UNIVERSIDAD SAN FRANCISCO DE QUITO USFQ

Colegio de Ciencias Biológicas y Ambientales

Molecular Physiology of Temperature Regulation and Perception in Vertebrates: A Systematic Literature Review of activated-TRPs on Genes and Intracellular Proteins.

Proyecto de investigación

Mateo Alejandro Flores Sánchez

Licenciatura en Biología

Trabajo de titulación presentado como requisito
para la obtención del título de
Licenciado en Biología

Quito, 23 de mayo de 2019

UNIVERSIDAD SAN FRANCISCO DE QUITO USFQ

COLEGIO DE CIENCIAS BIOLÓGICAS Y AMBIENTALES

HOJA DE CALIFICACIÓN
DE TRABAJO DE TITULACIÓN

Molecular Physiology of Temperature Regulation and Perception in Vertebrates: A Systematic Literature Review of activated-TRPs on Genes and Intracellular Proteins.

Mateo Alejandro Flores Sánchez

Calificación:

Nombre del profesor, Título académico — Diego F. Cisneros – Heredia, PhD.

Firma del profesor _____

Nombre del profesor, Título académico — Andrés Caicedo, PhD.

Firma del profesor _____

Quito, 23 de mayo de 2019

Derechos de Autor

Por medio del presente documento certifico que he leído todas las Políticas y Manuales de la Universidad San Francisco de Quito USFQ, incluyendo la Política de Propiedad Intelectual USFQ, y estoy de acuerdo con su contenido, por lo que los derechos de propiedad intelectual del presente trabajo quedan sujetos a lo dispuesto en esas Políticas.

Asimismo, autorizo a la USFQ para que realice la digitalización y publicación de este trabajo en el repositorio virtual, de conformidad a lo dispuesto en el Art. 144 de la Ley Orgánica de Educación Superior.

Firma del estudiante: _____

Nombres y apellidos: Mateo Alejandro Flores Sánchez

Código: 00123572

Cédula de Identidad: 1721830295

Lugar y fecha: Quito, 23 de mayo del 2019

Agradecimientos

Agradezco a todas las personas que contribuyeron al desarrollo de este trabajo; en especial a Pamela Vega, Diego Cisneros y mi familia por su apoyo, mentoría y paciencia, respectivamente.

Resumen

Los Canales de Potencial Receptor Transitorio (TRP, por sus siglas en inglés) son capaces de contrarrestar directamente los estímulos de temperatura en una variedad diversa de células al promover la activación de varios genes y proteínas intracelulares. Su sensibilización corriente abajo de los receptores acoplados a la proteína G, el receptor tirosina quinasa y la reciente conexión con otras máquinas moleculares hacen posible su influencia en diversos procesos fisiológicos distintos de la percepción de la temperatura. La complejidad de su función y la cantidad de literatura producida por aproximadamente 20 años de investigación ha dificultado la conexión de los puntos que podrían ayudar a comprender cómo estos canales pueden influir en las respuestas celulares a los estímulos de temperatura en los vertebrados. El objetivo de este estudio es consolidar y abordar la investigación que ha establecido una relación entre la función de los TRP activados sobre los genes y las proteínas intracelulares que responden a la regulación de la temperatura y la percepción de la temperatura en los vertebrados. Para abordar esto, hemos realizado una revisión sistemática de la literatura (SLR) según las directrices Cochrane para revisiones sistemáticas. Se evaluaron un total de 4662 documentos de las bases de datos Scopus® y MEDLINE®. De los 41 manuscritos elegidos, siete procesos estuvieron dentro de la percepción de la temperatura y uno dentro de la regulación de la temperatura. En conjunto, la percepción de la temperatura (34,1%) se investigó menos que la regulación de la temperatura (78,0%). Las familias más estudiadas fueron TRPV (90.3%) y TRPM (53.7%). Los resultados de esta revisión impiden un meta-análisis. La síntesis narrativa muestra la función de estos canales en la respuesta celular a la percepción de la temperatura y la regulación de la temperatura. De igual manera, expone las posibles conexiones que explican los efectos de los TRPs sobre las proteínas intracelulares que median la respuesta de los vertebrados a los estímulos de temperatura.

Abstract

Transient Receptor Potential (TRPs) channels are capable to directly counter back temperature stimuli in a diverse array of cells by promoting the activation of several genes and intracellular proteins. Its sensitization downstream of G protein-coupled receptors, receptor tyrosine kinase, and the recent connection with other molecular machinery make feasible its influence on various physiological processes other than temperature perception. The complexity of its function and the amount of literature produced by approximately 20 years of investigation has made difficult to connect the dots that could further the understanding of how these channels can influence over cellular responses to temperature stimuli in vertebrates. The objective of this study is to consolidate and addressed the research that has made a relationship between the function of activated-TRPs on genes and intracellular proteins that respond to temperature regulation and temperature perception in vertebrates. To approach this, we have performed a systematic literature review (SLR) under the Cochrane guidelines for systematic reviews. A total of 4662 documents from Scopus® and MEDLINE® databases were assessed. From the 41 manuscripts elected, seven processes were within temperature perception and one within temperature regulation. Collectively, temperature perception (34.1%) were less investigated than temperature regulation (78.0%). The more studied families were TRPV (90.3%) and TRPM (53.7%). The results of this SLR precludes a meta-analysis but a narrative synthesis is presented. The narrative synthesis shows the function of these channels on cellular response to temperature perception and temperature regulation. It also exposes the possible connections that explain the effects of TRPs on intracellular proteins mediating the vertebrates' response to temperature stimuli.

Table of Contents

List of Appendixes

List of Tables

List of Figures

Molecular Physiology of Temperature Regulation and Perception in Vertebrates: A Systematic Literature Review of activated-TRPs on Genes and Intracellular Proteins.

[1]Mateo A. Flores-Sánchez; Andrés Caicedo[2]; [1,3]Diego F. Cisneros-Heredia

[1]Universidad San Francisco de Quito, Colegio de Ciencias Biológicas y Ambientales, Laboratorio de Zoología Terrestre, Quito 170901, Ecuador.
[2]Universidad San Francisco de Quito, Colegio de Ciencias de la Salud, Laboratorio de Biomedicina, Quito 170901, Ecuador.
[3]King's College of London, Department of Geography, London, UK.

Glossary

TRP: Transient Receptor Potential Channel
GPCR: G Protein-Coupled Receptor
RTK: Receptor Tyrosine Kinase
STIM1: Stromal Interaction Molecule 1
SLR: Systematic Literature Review
SOCE: Store-Operated Calcium Entry
CRAC: Calcium Release-Activated Channels
BA: Brown Adipocytes
WA: White Adipocytes
BR: Brite Adipocytes
BAT: Brown Adipose Tissue
WAT: White Adipose Tissue
UCP1: Uncoupling Protein 1
PGC1α: Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PPARγ: Peroxisome proliferator-activated receptor gamma coactivator
PRDM16: PR domain containing 16
β-AR: Beta-Adrenergic Receptors
SNS: Sympathetic Nervous System
CREB: cAMP response element-binding protein
SCN: Suprachiasmatic Nucleus
RTK: Receptor Tyrosine Kinase
Clock: Circadian Locomotor Output Cycles Kaput
Bmal1: Brain and Muscle ARNT-Like 1
Per1/2: Period gene 1 or 2
HSF1: Heat Shock Factor 1
HSP90aa1: Heat shock protein 90kDa alpha (cytosolic), class A member 1
CIRBP: Cold-inducible RNA-binding protein
SRSF5: Serine/arginine-rich splicing factors
RBM3: RNA-binding motif protein 3
CIPs: Cold Inducible Proteins
ROS: Reactive Oxygen Species
VMH: Ventral Medial Hypothalamic Nucleus

Abstract

Transient Receptor Potential (TRPs) channels are capable to directly counter back temperature stimuli in a diverse array of cells by promoting the activation of several genes and intracellular proteins. Its sensitization downstream of G protein-coupled receptors, receptor tyrosine kinase, and the recent connection with other molecular machinery make feasible its influence on various physiological processes other than temperature perception. The complexity of its function and the amount of literature produced by approximately 20 years of investigation has made difficult to connect the dots that could further the understanding of how these channels can influence over cellular responses to temperature stimuli in vertebrates. The objective of this study is to consolidate and addressed the research that has made a relationship between the function of activated-TRPs on genes and intracellular proteins that respond to temperature regulation and temperature perception in vertebrates. To approach this, we have performed a systematic literature review (SLR) under the Cochrane guidelines for systematic reviews. A total of 4662 documents from Scopus® and MEDLINE® databases were assessed. From the 41 manuscripts elected, seven processes were within temperature perception and one within temperature regulation. Collectively, temperature perception (34.1%) were less investigated than temperature regulation (78.0%). The more studied families were TRPV (90.3%) and TRPM (53.7%). The results of this SLR precludes a meta-analysis but a narrative synthesis is presented. The narrative synthesis shows the function of these channels on cellular response to temperature perception and temperature regulation. It also exposes the possible connections that explain the effects of TRPs on intracellular proteins mediating the vertebrates' response to temperature stimuli.

Introduction

Mathematical representations and implications of particles reacting towards certain environmental or specific conditions are well-understood. Yet, how living organisms perceive and counter back towards external cues such as touch[1], chemicals[2] or innocuous and noxious temperature[3–5] has exhaustively been investigated by physiologists. From the bulk of stimuli that can have repercussions on animals physiology, the environmental and internal temperature stimuli have proven a critical influence over vertebrate's homeostasis[4]. In fact, resulting from evolution, vertebrates adaptations facing temperature challenge are manifested as the behavioural temperature seeking[6] and the ability to perform thermoregulation[7,8].

It was not until the discovery of the Transient Receptor Potential channels (TRPs) that an open door allowed the investigation to look at how these stimuli are internalized by vertebrates and other organisms at the molecular scale[9–14]. TRPs are integral membrane proteins that function as selective and non-selective cation channels with the same gating mechanism among vertebrates[15]. These ion channels, mainly transporters[16] of Ca^{2+}, are a superfamily of 30 proteins subdivided into the following seven subfamilies: TRPC, for canonical; TRPV, for vanilloids; TRPA, for ankyrin; TRPM, for melastatin; TRPP, for polycystic; TRPML, for mucolipin; and TRPN, for non-mechanoreceptor[17,18]. The TRPV, TRPA, and TRPM subfamilies, currently known as thermo-TRPs, are reported to be strongly implicated in the innocuous and noxious temperature sensation[19]. In addition to these so call thermos-TRPs, a member of the TRPC subfamily is also part of the

temperature sensing repertoire[20]. The four subfamilies have shown to be activated in a specific but overlapping temperature range, depending on the organism[15,21,22].

Initially, the discovery of TRPV1 being capable of integrating spiciness and heat[10] guide literature focus on identifying thermo-TRPs and its role in temperature perception at the nervous system[23–26]. Further interest in a second gating mechanism produced by activation through protein G coupled receptors[27,28](GPCRs) was studied. Parallel, TRPs structural analyses confirmed that temperature can independently function as an agonist for these receptors[29–32]. At this point, research allowed to think of these channels as the on-off switches present at the nerve endings of afferent neurons[33,34] that enable the integration of innocuous and noxious temperature at the hypothalamus. Its presence at the hypothalamus and efferent neurons also present modulation of physiological reactions towards temperature[35].

Recent scientific production is elucidating temperature influence over TRPs in a variety of different cells. For instance, activation of TRPV3[36,37] and TRV4[37,38] in keratinocytes is proposed to contribute to temperature sensation. Immunology research, also, suggested implications of temperature on activated-TRPs in innate cells modulation of thermal and obesity produced inflammation[39,40]. Evidence of temperature influence over TRPs in a variety of cells has also shown influence in many other aspects of vertebrates' physiology going beyond temperature perception. The first of these processes with an already plethora of studies is the triggered adaptive thermogenesis after abiotic temperature integration[41,18] or chemical agonists. Studies like the those exhibited by Jeong and Seong[42] and Castrucci group[43,44,45] have exposed the participation of the heat sensing TRPV1 and cold sensing TRM8 participation in the circadian clock molecular machinery activation. Other processes like the upregulation of cold-inducible proteins, CIPs, essential to secure correct splicing and translation of a complete mature mRNA, have proven to be TRPV4-dependent in mammalian cells[46,47].

While information of TRPs in a miscellaneous of biological processes, its presence in an array of different cells, its gating by GPCRs and temperature are reviewed, a systematic literature review (SLR) that consolidate this knowledge in the vertebrates' physiological reaction to temperature stimuli is lacking. The absence of connection between this vast information subjected to influence TRPs and the scarce literature addressing cellular processes that are connected with TRPs that underlay vertebrate's reaction to temperature are limiting the advance of research in vertebrates' temperature physiology. For these reasons, the primary aim of this systematic literature review (SLR) is to consolidate and addressed the research that has made a relationship between the function of activated-TRPs over genes and intracellular proteins that respond to temperature regulation and temperature perception in vertebrates.

Materials and Methods

The conduction of this review employs a systematic search that utilizes a defined algorithm attached to Cochrane guidelines[48]. The aim of the review relapse to appraise and integrate all known research on this topic. The potential omission of relevant data, trends, preference for a specific topic or lack or reproducibility were avoided for the critical appraisal and synthesis [49,50]. Therefore, the eligibility of found literature was subjected to inclusion criteria. The criteria were addressed under the scope of the established objective.

Search Strategy

The study question of this review was undertaken using the Cochrane Handbook for Systematic Literature Reviews[48](SLR). Therefore, the study question was defined using the Population, Intervention, Comparison, Study type, PICOS framework, see Table No. 1. The question approached the effects of activated-TRPs by thermal stimuli on genes and intracellular proteins by using the following physiological processes: temperature regulation, facultative thermogenesis, environmental and internal body temperature perception. Relevant peer-reviewed documents search was made using Scopus[51–53], the Elsevier abstract and citation database, and MEDLINE database, which was used through the PubMed search engine. The term's search was delimited by the population and intervention defined in the PICOS. The algorithm executed in Scopus used an exact same word search, see Appendix No. 1., while the algorithm used for PubMed used MeSHTerms and terms tagged with All Fields, see Appendix No. 2. The manuscript search was set until 31 of December of 2018 and constructed without language restriction. In addition, manuscripts that had been previously read and satisfied the inclusion criteria or add relevant information were considered to complement the review and were included as hand-search.

Definition of the concepts and Manuscript Selection

For processes undelaying temperature perception any molecular mechanisms within cellular reactions that respond to ambient or internal temperature are considered as part of temperature perception. The molecular actions within cells that facilitate the production or dissipation of energy are considered as part of temperature regulation.

Evident eligible manuscripts were chosen using a two-step process. First, a title and abstract examination were done. Documents were eligible if they talk about the link between temperature and vertebrates TRPs structure, its molecular pathway activation, its gene regulation, its post-transduction modifications, its down or up-regulation, its post-translational regulations, its gene variation, its transcriptional modifications and its influence over other genes and proteins that permit the understanding of the TRPs function in physiological processes related to the body and ambient temperature perception, body temperature regulation or facultative thermogenesis, see Table No. 2. Second, a title, abstract, methods and results screening were assessed; nevertheless, for reviews and book chapters' subtitles involved in the interested processes were complete read. Documents included were those that talk about the link between temperature and vertebrates activated-TRPs on the genes and intracellular proteins that contribute with the molecular pathway activation, gene regulation, post-transduction modifications, down or up-regulation, post-translation modifications that has any effect on the body and ambient temperature perception, body temperature regulation or facultative thermogenesis, see Table No. 3. It is important to mention that single tissue studies performed on established cell lines and isolated cell lines of vertebrates were included in both processes. Elected manuscripts were retrieved for full-text reading and data extraction using Universidad San Francisco the Quito electronic resources, Google or Google Scholar search engines. Furthermore, the inclusion process is resumed by the Preferred Reporting Item for Systematic Reviews and Meta-Analysis[54], PRISMA to see the flow diagram Figure No. 1.

Quality Assessment

For quality assessment, a second reviewer examined 5% of the population of documents retrieved for the title-abstract screening process. After a consensus was met in documents were the same criteria was not the same, a joint-probability agreement and a Cohen's Kappa Coefficient[55,56] test were implemented by using the "irr" R package[57] .

Data Extraction

The information was extracted from the second screening (title, abstract, methods and results examination) and full-text reading. The data extracted from the second screening used a wider amount of information addressing the following nine criteria: 1. Physiological Processes; 2.TRP Activation Pathway and activated Proteins 3. Cell Type; 4. Co-activated Receptors; 5. Transcription Factors; 6. Nervous System Location; 7. Temperature Activation;8. Type of TRP; and 9. Type of Vertebrate. The more necessarily detailed information was subcategorized and numerical ligated with the corresponding criteria, see Appendix No. 3 and Table No. 4. It was not possible to predict all the results that could be obtained, as a consequence, a subcategory called "Others" for each of the criteria presented was filled textually if it was needed. From full-text reading, the academic information and more synthesize data was extracted. The information extracted was directed for the following thirteen criteria: 1. Type of Article; 2. First Author Name; 3. Physiological Process; 4. Cell Type; 5. Cell Line; 6. Nervous System Location; 7. Stimuli, temperature and chemicals; 8. Type of TRP; 9. Co-activated Receptor; 10. Kinase/Phosphatase; 11. Gene or Intracellular Protein; 12. Transcription factors or Transcription co-regulator; 13. Type of Vertebrate, see Table No.5.

Results

Search Strategy and Quality Assessment

The combined amount of manuscripts obtained by the electronic databases was of 4662 documents. After citations went through title-abstract screening a total of 661 citations were left. The examination of title, abstract, methods and results gave a total of 60 manuscripts, excluding 22 documents that were not possible to asses. These 22 documents were not part of the USFQ electronic resources scope and authors did not respond to the manuscript request. The final number of articles after full-text examination, including those added by hand search (n=4), results in 41, see Figure No. 1. All retrieved articles were written in English. The heterogeneity of the data restrains this systematic review to perform a meta-analysis[48]; as a result, a narrative synthesis[58] of the data is developed. Finally, the joint-probability agreement showed a 99.6% of agreement and the Cohen's Kappa Coefficient test value of 0.995 with a p-value < 0.05.

Studies Characteristics

Articles engaged physiological processes that underlay within temperature perception and temperature regulation. Temperature perception was assessed by various studies representing a total percentage of (n=14/41;34.1%), see Figure No. 2. A set of physiological process responding to temperature was solely seen in this subject, see Figure No. 3. The studies coupled warm and cold temperature perception within manuscripts addressing temperature-evoked stress, adaptive thermogenesis, temperature

perception over vertebrates' circadian cycle, SOCE temperature perception and muscle contraction. Temperature regulation was the subject with the biggest number of literature (n=32/41 78.0%) for this SLR, see Figure No. 2. The TRP families with the biggest numbers were TRPV (n=37/41; 90.3%) with TRPV1(n=20/41; 49.0%) being the most representative and TRPM (n=22/41; 53.7%) with TRPM8(n=20/41; 49.0%), see Figure No. 4.

Temperature Perception

None manuscript engaged temperature perception independently. It is noteworthy that narrative reviews and book chapters aiming to expose the contemporary knowledge of TRPs on temperature perception did not present any result of interest and were excluded[3,18,35,59–64] (n=9/41; 22.0 %) for this theme. From these eleven reviews, five[18,35,62–64] remain in this SLR as they were useful for adaptive thermogenesis. Reviews mainly present the research evidencing specific location and function of TRPs in sensory nerves. The corresponding results for the objective of this SLR on temperature perception were evidenced with all the other physiological processes presented for both warm and cold perception. The set with the largest number of articles was with temperature stress[42,45–47,65] (n=5/14; 35.7%) follow by documents coupled with adaptive thermogenesis[43,44,65–67] (n=5/14; 35.7%) and SOCE temperature perception[68–70] (n=3/14; 21.4%), see Figure No. 5. One document[71] (n=1/14; 7.14%) was reported to involve cold perception with muscle contraction. A specific trend for cells is not clearly seen, but the major number of documents studied adipose cells (n=5/14; 35.7%). The other reported cells used presented an equal percentage. For neurons, embryonic, muscle, and lung cells (n=2/14; 14.3%) and for hepatocytes, osteocytes, lymphocytes, keratinocytes, and male germ cells (n=1/14; 7.14%), see Figure No. 6.The major studied TRPs were TRPV1 (n=6/14; 42.9%) and TRPM8 (n=5/14; 35.7%) follow by TRPV3 and TRPV4 (n=3/14; 21.4%) the other TRPs represented the lower percentage (n=1/14; 7.14%), see Figure No. 7. No particular trend was seen for kinases, phosphatases, genes, molecules or transcription factors and transcription co-regulators in warm and cold temperature perception. However, the particular trends for these categories are reported below in the processes with which temperature perception is coupled. The vertebrates more studied were mice (n=8/14; 57.1%) and human cells (n=4/14; 28.6%) follow by rats (n=3/14; 21.4%) Fish, *Danio rerio*, and hibernating ground squirrel, *Spermophilus undulatus*, (n=1/14; 7.14%) were also present, see Figure No. 8.

Warm Perception

Eight documents[42–45,65,69,70,72] (n=8/14; 57.1%) correspond to warm temperature. It was predominantly coupled with adaptive thermogenesis (n=4/8; 50%) followed by heat-evoked temperature stress (n=3/8; 37.5%) and SOCE temperature perception (n=2/8; 25%) see Figure No. 9 and Table No. 5. Accordingly, BA was the greater studied cell (n=4/8; 50%). The reported hepatocytes, lymphocytes, keratinocytes, neurons and embryonic cells had the same percentage (n=1/8; 12.5%), see Figure No. 10. For TRPs, the most studied in the warm temperature extent was TRPV1(n=6/8; 75%) follow by TRPV3 (n=2/8; 25%) and TRPV4 (n=1/8; 12.5 %). Presence of one manuscript (n=1/8; 12.5 %) assessing TRPM8 was also reported, see Figure No. 11. Similar to the overall count, mice were the representative value (n=4/8; 50%), but human cells and fish (n=1/8; 12.5%) were overcome by rats (n=2/8; 25%), see Figure No. 12.

Heat-evoked temperature stress

Temperature stress evoked by heat stimuli was reported by three documents[42,45,65] (n=3/8; 37.5%). TRPV1 was the only channel assessed, seeFigure No. 13, and HSF1[65], HSP90aa1[45], UCP1, and COX IV[65],see Figure No. 14,were the only proteins presenting changes in transcription in the fish, *Danio rerio*, and rats, respectively, percentages for each was (n=1/3; 33.3%), see Figure No. 15.

Cold Perception

Manuscripts directed to aboard cold perception were a total of six[46,47,66,68,71,73] (n=6/14; 42.9%). In contrast with manuscripts addressing warm perception adaptive thermogenesis, SOCE temperature perception and cold-induced muscle contraction receive the same lower percentage (n=1/6; 16.7%). The left three manuscripts coupled with cold-evoked temperature stress (n=3/6; 50%), see Figure No. 16 . From this group lung and muscle cells were present in two, respectively (n=2/6; 33.3%) and the same percentage (n=1/6; 16.7%) resulted to neurons, adipocytes, osteocytes, germ and embryonic cells, see Figure No. 17 . The percentages for ion channels were TRPM8 (n=4/6; 66.7%), TRPV4 (n=2/6; 33.3%) and TRPV3, TRPA1 and TRPC1-7(n=1/6; 16.7%) each, see Figure No. 18. Similar to the overall count for temperature perception mice (n=4/6; 66.7%) and human cells (n=3/6;50%) were the vertebrates in the majority of the studies. Ground squirrel *Spermophilus undulatus*, (n=1/6; 16.7%) were also assessed for this subject, see Figure No. 19.

Cold-evoked temperature stress

Three manuscripts assessed the cold-evoked temperature stress[46,47,73](n=3/6; 50%). The major type of cells used was related to lung (n=2/3; 66.7%), bronchial cells and lung epithelial cells. Male germ cells and osteocytes were also utilized, and their percentage were equal (n=1/3; 33.3%), see Figure No. 20. TRPM8 and TRPV4 (n=2/3; 66.7%) results were the same and TRPV3 percentage was the lowest (n=1/3; 33.3%), see Figure No. 21. The interest on intracellular proteins was ligated to SRSF5, RBM3, CIRBP (n=2/3; 66.7%) and IL-6 and IL-8(n=1/3; 33.3%), see Figure No. 22. The number for vertebrates in this subject broke the trend seen for mice. The human cells (n=3/3;100%) denoted a slightly major percentage compared to mice (n=2/3; 66.7%), see Figure No. 23

SOCE Temperature Perception

One study[68] retrieved from all the elected documents reported a relationship of TRPs with endoplasmic reticulum proteins involved in Ca^{2+} movement, SERCA and STIM1(n=1/41; 2.44%). Two additional studies[69,70] that presented a relationship between TRPs and proteins mediating SOCE were added as hand search (n=3/41; 7.32%), see Figure No. 24. From these three studies, two (n=2/3; 66.7%) addressed a relationship of TRPV3 and STIM1-Orai1 in a warm temperature context, and only one (n=1/3; 33.3%) referenced an interaction with TRPV4 and TRPA1 in the same temperature *milieu,* see Figure No. 25. The remaining document engaged an association of TRPC1-7 expression with STIM1-Orai1 and SERCA functioning in a cold environment[47]. The effects of activated TRPs and STIM1-Orai1 over intracellular proteins were uniquely reported by one study[70]. The transcription factors reported in this study were NFAT and AP-1 in a warm challenge environment, see.Figure No. 26. No particular interest was present for a type of cell. The

vertebrates more used to seek for a relationship between TRPs and SOCE were mice (n=2/3; 66.7 %) followed by an equivalent quantity (n=1/3; 33.3 %) of studies for human cells, rats and ground squirrels (*Spermophilus undulatus*), see Figure No. 27.

Temperature Perception over the vertebrates' circadian cycle

The intervention of TRPs in the vertebrates circadian cycle is accosted by a total of four research manuscripts[42–45] (n=4/41; 9.76%). Half of the documents (n=2/4; 50%) presented the influence of TRPs in the brown adipocytes light-dark circadian cycle, adaptive thermogenesis[43,44]. The remaining documents[42,45] (n=2/4; 50%) aboard the relationship of TRPs and circadian molecular machinery in heat-evoked temperature stress, see Figure No. 28.The research articles engaging heat-evoked temperature stress used embryonic zebrafish cells, hepatocytes and neurons, see Figure No. 29. The intracellular proteins in all manuscripts using BA included Per1/2, Bmal1 from circadian cycle genetic hallmark and Rev-erb-α and UCP1 from adaptive thermogenesis related genes. From these two articles, only one included PPARγ, PPARα genes and only one the CLOCK gene. Similar to articles using BA, the effects on intracellular proteins for heat-evoked temperature addressed Per2 gene function but included HSP90aa1 and HSF1, respectively see Figure No. 30. Taking together these results the Per2 gene was the more assessed (n=3/4;75.0%). All articles aimed to understand the role of TRPV1 and only one added TRPM8[44], see Figure No. 31. Vertebrates used were mice, rats and Fish (*Danio rerio*). Mice were uniquely used by articles (n=2/4; 50%) presenting the influence of TRPs in the BAs circadian cycle while *Danio rerio* (n=1/4; 25%) and rat (n=1/4; 25%) were used in heat-evoked temperature stress, see Figure No. 32.

Temperature Regulation

Adaptive Thermogenesis

For this subject, the research articles[40,43,44,65,66,72,74–86] (n=19/32; 59.4%) showed a difference of six manuscripts with those found as review articles[4,18,35,41,62–64,87–92] (n=13/32; 40.6%), see Figure No. 33. The greater number (n=14/32; 43.8%) approached adaptive thermogenesis activation presenting the adipogenesis of BA and WA or the trans-differentiation of WA into BR in parallel. The studies that displayed effects by activated-TRPs on adaptive thermogenesis coupled with temperature perception was (n=11/32; 34.4%). Energy expenditure through the sole function of adaptive thermogenesis was assessed by (n=6/32; 18.8%) and 6.25% corresponded to two documents, see Figure No. 34. One document that used the C2C12 muscle cell line to evaluate the thermogenic profile caused by menthol stimulation of the skeletal muscles TRPM8 and the other one aimed to see the effects of TRPV4 KO mice in oxidative muscles and brown adipose tissue.

Review articles were not fully committed with the objective of this SLR but used most of the chosen research articles for its development; therefore, results from documents that performed an experimental approach will provide more insightful results. The research manuscripts presented a majority of documents boarding the effects of activated TRPs in any combination of adipose cells. The results, excluding the one using C2C12 muscle cell line, were BA and WA (n=4/18; 22.2%); BA, WA and BR (n=4/18; 22.2%); and BA alone (n=9/18; 50.0%). Independent study of muscles and muscles with BA represented (n= 1/18; 5.55%) each, see Figure No. 35. The TRPs more studied by research articles,

as well as for review articles, were TRPV1 (n=10/19; 52.6%); TRPM8 (n=7/19; 36.8%) and TRPV4 (n=2/19; 10,5%), see Figure No. 36 . The research manuscripts did not show a particular activated kinase/phosphatase as it was viewed when review manuscripts were added. The higher value was for PKA, Protein Kinase A, (n=7/32; 21.9%), see Figure No. 37. In the case of the intracellular proteins, transcription co-regulator or transcription factors UCP1(n=15/19; 79.0%), PGC1α (n=9/16; 56%), PPARγ (n=7/16; 44%), and PRDM16 (n=3/16; 19%) demonstrated to be the most present molecules addressed by research manuscripts, see Figure No. 38, the same trend was seen in review articles. Finally, the literature in research articles presented mouse (n=16/19; 84.2%) and humans (n=4/19; 21.0%) as the most used vertebrates for studying, in an overall count mouse (n=29/32; 89.3%) and humans (n=14/32; 43.8%) remained as the most studied, see Figure No. *39*.

Discussion

Overview

Search Strategy

The literature search strategy identified a considerable number of information addressing the function of activated-TRPs on genes and intracellular proteins that are part of an array of processes regarding temperature perception and regulation in vertebrates. The values from the joint-probability agreement and Cohen's Kappa Coefficient test suggest the high quality of the inclusion criteria by presenting almost the perfect value established for both tests.

Studies Characteristics

Articles investigated a combination of physiological processes within and among studies as a consequence of temperature's determining influence in the over-all organism's homeostasis. Lack of sole interest in temperature perception falls on the particular interest to evidence a specific TRP in nociceptors to address better therapeutics measurements for temperature-provoked pain related diseases[3,60,93–97]. Similarly, the elevated number in adaptive thermogenesis goes by hand with the interest of using TRP's ability to enhance temperature regulation to tackle metabolic diseases[18,41,62,85,86,91]. The greater use of TRPV1 and TRPM8 response to the overwhelming literature stating their function as temperature transductors.

Temperature Perception

The lack of particular trends for cells, especially neurons, and genes or intracellular proteins downstream of activated-TRPs seems to rely on a major interest to understand temperature detection. The interest to comprehend the intricate nature of the nervous system to better treat temperature-related pain pathways seems to delimit the knowledge of TRPs in this subject [3,18,35,59–64]. The greater number of manuscripts coupling warm and cold perception with temperature stress may also be explained under the interest for comprehend pain. Coupling with adaptive thermogenesis is not only explained by the overwhelming interest to use the effects of activated-TRPs over energy expenditure but also by the role of neurons to trigger this effect. For cells type, the heterogeneity of the processes with which temperature perception is coupled explains the lack of trends. The

higher number exposed for adipocytes may also be explained by the interest to treat obesity and the fact that the second greater percentage with which temperature perception is coupled is adaptive thermogenesis. The same effect of heterogeneity explains the lack of a particular trend for kinases, phosphatases, genes, molecules or transcription factors and transcription co-regulators. TRPV1[10] and TRPM8[98] results are explained by the fact that these channels were the first ones to be reported as warm and cold transducers, respectively. The advantages of mice as a model organism and the objective to understand the effects of temperature in humans, especially in the medical aspect, explains the resulted proportion of these vertebrates. It is important to mention that the particular trends for warm and cold temperature perception exposed need to be considered with caution due to the small number of manuscripts.

Warm perception and heat-evoked temperature stress

Possible reasons to justify the interest in themes like SOCE are scarce due to the small number of documents. The interest in SOCE falls into the research done by Patapoutian's group to relate the activation of TRPV3 with STIM1 function. As stated above the major interest to find medical alternatives to obesity explains the greater proportion of the adaptive thermogenesis in this context. BA cells as the major cell assessed go well with this result since the energy misbalance causing obesity is treated enhancing energy expenditure. The proportion of TRPV1 is also explained by the knowledge stating that this channel enhances and react towards UCP1 expression and mediate heat-evoked temperature stress, respectively. The aim of Moraes, M. N. et al.,[44] to see the effects of TRPM8 within the circadian cycle at a constant ambient temperature of 22°C explains the presence of this channel. Complete understanding of heat shock proteins mediating heat stress is the reason for the presence of HSP90aa1 and HSF1. The utility of *Dani rerio*, commonly known as zebrafish would explain the presence of this animal in this subject.

Cold perception and cold-evoked temperature stress

The small number of manuscripts for each particular subject connected to cold temperature may state that any particular interest is present. The major number of documents present in cold-evoked temperature stress is a consequence of the interest of Fujita, T., et al.[46,47] to understand the activation of proteins reacting to mild hypothermia. The results presented by Fujita, T., et al. [46,47] showed that TRPM8, TRPV3 and TRPV4 are necessary to the activation of CIPs, SRSF5, RBM3 and CIRBP, responding to cold-evoked temperature stress. Presence of TRPM8 is probably due to its known role mediating cold temperature. However, the novel presence of TRPC3 family in a mild cold context is connected to its possible complementary function for cardiac contractibility[68]. The numbers for mice and humans rely on the reasons already stated above and the interest in ground squirrel *Spermophilus undulatus* falls in Nakipova, O. V., et al[68] to spot cardiac adaptations of hibernators.

SOCE Temperature Perception

The small number of retrieved studies in this theme exposed no relevant interest to understand the interaction of TRPs with STIM1 or Orai channels in the temperature perception context. The absence of previous evidence reporting an interaction between STIM1 and TRPs to catalyse a cellular response towards any temperature stimuli may

explain these results. However, as a consequence of the findings by Xiao, B., et al[70], presenting STIM1 capability to detect warm temperature, the few studies available for this theme exhibited a greater interest for warm perception[69,70]. The scarce interest prevented the option to evidence a particular trend over transcription factors. Similar to the other processes the use-fullness of mice as a model organism and the understanding of its cell-physiology delimited the knowledge to this animal.

Temperature Perception over the vertebrates' circadian cycle

Connecting the function of activated-TRPs by heat or cold with the circadian cycle molecular machinery fall into a medical and physiological-evolutionary interest. The medical interest responds to the entanglement of the circadian clock with transcription factors regulating different biological functions[99–102]. The regulation of energy expenditure by central and peripheral clocks in SCN and adipocytes[100,103] expose possible paired contribution of TRPs and clock genes to treat metabolic disorders. The full percentage of manuscripts analysing Per2 and TRPV1 is related to the reported impacts of both molecules over temperature stimuli and especially lipid metabolism[18,85,89,104–107]. Light can also stimulate TRPs downstream of opsins activation[108,109]. Therefore, light-independent interactions between temperature, circadian genes and TRPs is also of interest for treating metabolic disorders[43,44]. The physiological-evolutionary interest is related to the organism's homeostasis and the determining effect of temperature over its niche colonizing capacity. Proper adjustment of enzymatic dynamics responds to daily temperature and light shifts[4,109] that guide core body temperature, locomotor activity, etc[103,110,111]. The established relationship between chaperones HSP90aa1[49], its transcription factor HSF1[39] and TRPs may help to comprehend responses of animal enzymatic dynamics within delayed natural rhythms due to climate change. The aim to understand the effects of climate change may also explain the presence of animals other than mice and human cells.

Temperature Regulation

Adaptive thermogenesis

Research investment in TRPs effects on adaptive thermogenesis relies on mainly three conditions. First, the interest in defying the worldwide growing prevalence of obesity[112], type two diabetes mellitus[113], cardiac diseases[114] and other human metabolic illnesses[115] with a high economic burden. Second, the reported ability of BA and BR to mitigate the energy disbalance[116–118].Third and last, the presence of TRPs in BA, WA and BR and its capacity to stimulate these cells for energy expenditure[76,78,86,119].The complexity of the first two conditions explains why the major quantity of review articles do not fully engage TRPs function on temperature regulation and limit them to the broad aspect of these metabolic diseases. Accordingly, the parallel presences of adipogenesis evaluation with adaptive thermogenesis are due to the fact of WA trans-differentiation to the thermogenic cell type BR under thermal stimuli[120–122].Adaptive thermogenesis and adipogenesis interest are, also, caused by the ability of mature BA to produce metabolic heat[117,123]. The entanglement of adrenergic receptors[123,124] with thermogenic cells answers to the high percentage of manuscripts evaluating the effect of the neurological function with adipocytes stimulated by TRPs. The greater attention for addressing BA and BR, respectively, is explained by its function to enhance energy expenditure. Studies utilizing muscles is due to the muscle's characteristic of being thermogenic cells.

The principal appearance of TRPV1 is generated by the overwhelming literature evidencing its functioning for inducing thermogenesis[18,62,89,91] ,see Figure No.4.For TRPM8 the value is explained for the stated ability of this thermo-TRP to induce adipogenesis and adaptive thermogenesis under mild cold challenge[78]. Investigator's interest in TRPV4 is not markedly clear but its presented value might be responded by the greater mRNA expression of this protein in adipocytes when evaluated in assays. The narrowed evaluation to UCP1 and transcriptional co-regulators like PGC1α, PPARγ, and PRDM16 is produced by its entailing in both adaptive thermogenesis and adipose differentiation[92]. The PKA's suggestive tendency for the combined total is justified by reviews discussing the kinase stimulated function in thermogenesis by GPCRs, like β-ARs[125]. Finally, vertebrate's restricted information to murine models is ligated to the more precise information can be extracted due to its evolutionary closeness to humans[126].

Literature Synthesis and Critical Appraisal

Temperature Perception

The literature synthesis and critical appraisal for warm and cold perception will be done together. Current understanding of temperature perception is thought to rely on TRPs and other ion-channels located in sensory nerve endings embedded in epithelium[3]. This idea is challenged by two facts. First, the reports exposing activity of TRPV3[36,37], TRPV4[37,38] and STIM1[69] in the skin in front of warm stimuli. Second and last, adipocytes ability to independent and autonomously react to temperature[127]. The restricted transduction of stimuli to keratinocytes is solved by reports proving secretion of nerve agonists by these cells after activation of TRPs[37,38]. For instance, with the exception of Liu, X. *et al.*, 2019[69] several studies state that neurons are ATP sensitive[128–131]. Secretion and sensitivity by other cells responding and reacting to temperature through TRPs is also reported. TRPs capacity to be sensitized downstream of GPCRs and RTK protein open the possibility to a wider range of agonists capable to induce neurons reactions[27,132,28]. The sensitization downstream GPCRs and RTKs connect with the evidence stating that TRPs mediates environmental temperature-transduction within neurons. The lack of synapsis between keratinocytes and neurons could possibly be responded by the proposal of true synapses between skin and nerves by Chateau, Y. and Misery, L.[133]

The expected effects over almost all physiological processes with which temperature perception is paired were not necessarily seen when a specific TRPs were blocked[3,60,134,135]. Similar to neurons and adipocytes, the answer to these unexpected results could possibly fall into the presence of more than one kind of TRP responding to the same stimuli. In fact, the presence of TRPM8 and TRPV1 in the same neurons[136,137] could explain why they can have the same effect on adaptive thermogenesis after environmental or chemical-induced temperature perception. Redundant functions[138] due to overlapping temperature ranges can also respond to why effects are not abolished at all when a specific TRP is blocked[134]. Reports evidencing a substantial loss of $[Ca^{2+}]_i$ and behavioural reactions to temperature stimuli when various TRPs are blunted support this idea[134]. The necessity of various TRPs to mediate the activation of a specific intracellular profile or response could also be explained by the formation of heteromeric channels[139,140].
The formation of heteromeric channels by TRPs is reported to show changes in temperature sensitivity[140]. These changes in temperature would explain why the investigations approaching effects of TRPs under different temperature ranges show

positive effects. The shifts of temperature ranges in TRPs and their effects over genes and intracellular proteins are also affected by intracellular molecules, like ROS[141,142], that are part of the same or other physiological processes[143]. It has to be considered that temperature perception for cells corresponding to internal organs may expose different temperature thresholds. The structure variation of individual TRPs among tissue adds another explanation to the activation of TRPs in different temperature ranges from the reported ones[73,144–146]. This idea is supported by the reported shift of type of temperature perception by TRPA1 in frogs[15,22]. The tissue-specific structure in pair with the interaction of both the N-terminal and C-terminal with molecules allowing cell signal could also explain tissue-specific functions[147]. In fact, Gracheva, E., et al[146], exposed that TRPV1 mediating infrared perception in bats has a truncated C-terminal domain. It also opens the idea that TRPs responses can be context specific, like Toll-Like Receptors by cytokines.

Heat and cold-evoked temperature stress

The effects of activated-TRPs were reported to influence differently molecular machinery for heat and cold-evoked temperature stress. Heat-evoked temperature stress is reported to function through a TRPV1- heat shock proteins axis[148]. The activation of this axis showed no correlation at the gene transcription level in ZEM-2S cells subjected to a heat pulse of 33°C[45]. Possible answers may rely on the need for more perpetual stimuli and the fact that noxious temperature shifts in nature are mostly coupled with increases in UV stimuli[45]. In neonatal mice, the relationship between TRPV1 and HSF1 was evidence[42]. Early treatment of mice with capsaicin presented decreased expression of TRPV1 in neurons[42,65] and negative effects over HSF1 expressed in the hypothalamus. The delayed compartmental withdrawal to noxious heat supports this effect. The treatment with capsaicin not only diminished expression and reaction to heat stimuli but also altered the expression of hepatic Per2 gene[42]. The increased core body temperature at the non-active state of the animals corroborate these effects. The shifts and increased body temperature relapse on the decreased number of neurons[65]. TRPM8 presence within the same neurons expressing TRPV1 can also contribute to the increased core body temperature and rat's body temperature rhythm shift.

Fujita, T., et al[46,47], recently exposed a relationship between TRPs and CIPs responding to cold-evoked temperature stress. The two manuscripts of Fujita, T., et al,[46,47] state that the activation of SRSF5, RBM3, CIRBP by activated-TRPs is not dependent on the ability of TRPs to perceive temperature. The mechanical sensitive of TRPV4[149] and other TRPs[150,151] coupled with the effects of temperature on membrane fluidity[152–154] are possible options to explain this phenomenon and innocuous temperature perception. Compensatory effects by TRPV3 are only seen when TRPV4 is genetically blocked but not chemical. Taking in count that GPCRs and thus TRPs activation is compromised by membrane fluidity this effects can contribute with the temperature activation of CIPs by TRPs mechanical activation[154].

SOCE Temperature Perception

Temperature perception has shown to rely on TRPs and other ion channels to convey temperature cues to the brain and enhanced physiological responses[3]. Intracellular proteins mediating calcium movement and storage like SERCA and STIM1 has also indicated involvement in cellular responses towards temperature[35,47,48]. Yet, the scarce

literature evidenced in this review exposes that little is known about the interactions of TRPs and these molecules in front of temperature challenges. Functioning of STIM1-Orai-TRPC in cold temperature context has been suggested as a compensatory mechanism of the hibernator ground squirrel. Nakipova, O. V., et al[68], evidence that protein expression of TRPC3/6 was strongly increased in cardiac papillary muscles (PM) of squirrels in winter compared to rats. This expression took relevance when SERCA mechanism for cardiac contractibility was compromised by cold in both squirrels and rats. More intriguing, expression of TRPC3 protein was significantly decreased in the PM of squirrels in the summer opening the idea of a relationship between circadian temperature rhythm and changes of cardiac contraction mechanisms.

Besides the possible function of STIM1 and TRPCs in cardiac contractility of hibernators, the temperature has also proved to independently be capable of activating extracellular Ca^{2+} entry in other cells. The intervention of STIM1-Orai1 in warm temperature stimuli of 35°C was evidenced as a heat-off response due to cooling of Jurak T-cells. This heat-off intervention was strictly manifested at 35°C and ligated to Orai1 rather than TRPV3, the TRP subjected to investigation. Nevertheless, two results suggest that STIM1 could possible present interactions with other TRPs. First, STIM1-Orai1 Ca^{2+} mediated influx $[Ca^{2+}]_i$ was blocked at a temperature above and below 35°C while STIM1 still showed 50% of the maximal temperature response of its function 8°C above 35°C. Second, the Q_{10} value of temperature change from 37°C - 43°C was 6.8, consistent with most of TRPs in the vanilloid and some in the canonical family Q_{10} values[155] in the similar temperature range.

The independent warm activation of STIM1 is also reported in keratinocytes and not only mediating the heat-off response but also a heat-on response coupled with Orai3[156]. Contradictory to the reported ability of keratinocytes to perceive heat through TRPV3/4[37] and promote ATP release,$[Ca^{2+}]_i$ induced by STIM1 temperature activity was not altered when TRPV3 and TRPV4 were genetically silenced. Nonetheless, the action of TRPs in this context may not only be related to the integration of the stimuli but also with the translation of the warm stimuli to neurons. It is possible that keratinocytes contribute with warm sensation by a paracrine signal produced either through TRPs, STIM1 or both. Previously demonstrated sensitization of TRPs through GPCRs and RTK makes feasible the possibility of its activation by a diverse group of molecules[26,27]. TRPA1 was tested in Liu, X., et al[35] and showed no action caused by ATP, NO, PGE2 or Endothelin-1. However, since TRPA1 is present in TRPV1 expressing neurons a better understanding could be evidenced if interactions with TRPV1, TRPM2, TRPM3 are assessed.

Temperature Perception over the vertebrates' circadian cycle

Synchronization of physiological functions with natural rhythms depends on the circadian molecular machinery. The understanding of this relationship is commonly ligated to light and dark cycles, yet temperature has also proved to be determining for circadian function[157,158]. The integration of light-dark cycles by SCN and core body temperature shifts by VMH implicate that effects of activated-TRPs are not only caused by its abiotic stimulation but also by its role in a specific tissue. TRPs activation in light-dark cycles contributes with the cellular clock in the SCN through its sensitization downstream of rhodopsin in the eye. Core body and environmental temperature perception affect thermogenic tissue through β-ARs and circadian genes in the VMH. However, the activation of TRPs, circadian genes and its effect caused by temperature may be more

complicated for three reasons. First, the reported disruption of Bmal-1 within VMH changes β-ARs expression in adipocytes. Taking in count the interactions of TRPs with β-ARs in adipocytes, effects on VMH's clock may alter the reactions evaluated in fat cells. Second, the ability of fat cells to independently perceive and respond to temperature shifts, possibly through activated-TRPs. Together with the autonomous regulation of adipocyte's clock using temperature cues these facts may present interactions of TRPs and circadian genes in fat tissue independent of CNS. Third and last, the complementary effects of circadian genes and thermic regulators to stimulate the E-box domain for a thermic response. Difficult interpretation of Moraes, M. N. et al.,[43,44] results for TRPV1 and TRPM8 may be due to these facts. Results of these manuscripts must be managed with caution given the fact that protein levels and confirmation of the channels function are not assessed. Comparison between TRPM8 and TRPV1 roles may also need attention. Results of TRPV1 and TRPM8 are compared towards wild type mice mRNA smallest value in complete dark and with wild type mice mRNA smallest value in light-dark, respectively. TRPV1 results also need to consider the fact that disposed environmental temperature for mice subjected to the study is not consistent with TRPV1 reported range.

Castrucci's group has also aimed to understand the effect of noxious heat in natural environments over the relationship of TRPs and circadian genes. Similar to studies done in adipocytes, period genes expression, specially Per2, changes within light-dark cycles rather than in the complete darkness. The effect of the heat shock was the same for both cycles but the blockage of TRPV1 has no effect in the complete dark or light-dark cycles. The complex relationship between temperature and light cycles and its coupled effects represent the major difficulty to understand the temperature independent effects. Although regulation by HSE on Per2 gene in a short-term heat shock is reported[159], a better understanding of the relationship between temperature effects, circadian genes and TRPs may be exposed in prolonged or repetitive temperature stimulus. The relationship between transcription factors that correlate light and temperature stimuli are understood through its E-box point of convergence. The molecular pathway that connects the effects of activated-TRPs with the molecular machinery responding to temperature and light shifts is still blurry[148]. The connection between activated-TRPs, a circadian cycle and the temperature are not only related to warm or heat. Response to mild cold by CIRBP also showed effects on CLOCK[160] gene and Fujita, T., et al. presented that activation of CIRB, SRSF5 and RBM3 is dependent of TRPV4, TRPV3 and TRPM8. This function of activate-TRPs over cold inducible proteins may connect the effect of cold temperature over the circadian cycle. Temporal changes of TRPCs expression and possible function of SOCE using these channels in ground squirrel's heart in winter also propose interactions between TRPs, temperature and circadian cycle.

Temperature Regulation

Adaptive Thermogenesis

Research made clear the usefulness of TRPs activating the thermogenic profile of adaptive thermogenesis. The data supporting BA as the most capable cells to engage thermogenesis has guided investigations trying to elucidate the role of activated TRPs in this process. However, the presence of WA differentiation into BR and its equal capability to potentiate fat mass loss with improved metabolic functioning after TRP stimulation is a parallel striking trend. The positive effect of TRPs to enhance browning of WA need further investigation, especially because WAT accumulate fat and is the greater

proportion of fat tissue in obese humans[161]. Evidence states that high peaks of gene expression of TRPVs in adipocytes are similarly present in different cell stages[40,75,76,81,82]. A higher expression of TRPV1/2/4[37,56,57] is reported in fully differenced BA and WA as well as for TRV1-4/6[82,119] in pre-adipocytes. Even if there is high gene-expression in both stages of cell development, the study presented by Bishnoi, M.,et al.,[119] showed a significant difference of some TRP's mRNA number in un-differentiated and differenced cells. Nevertheless, this trend of a major gene-expression in distinct stages of cell development is not seen in TRPM8. Research reported that TRPM8 major expression happens primarily in mature adipocytes[78,79,84].

More importantly, the high expression in both early and mature stages of the cells is reported to entail distinct effects in adipogenesis and especially in adaptive thermogenesis, since only differentiated BA and BR can perform this function. Particular studies like those conducted by Ye, Li., et al[40]; Cheung, SY., et al[82]; Zhang, LL., et al[81]; Sun, W., *et al;*[76,162] showed that TRPVs activation by distinct agonists inhibits adipose cells differentiation and that it's suppression potentiate adaptive thermogenesis and adipogenesis. The suppressing functions for adipocytes differentiation and therefore it's inhibition of the thermogenic capacity are unexpected since strong evidence has presented TRPV1 and TRPM8 as positive regulators of the processes[75,52]. This expected function, however, is caused by the well-proved effect of these two TRPs in adipocytes through the SNS[58]. Further, the inhibitory effect in adipose cells differentiation is explained by the biphasic functions of Ca^{2+} in cell development[163–165].This results demand a more profound investigation to better engage these world health problems.

The presence of various TRP and the high expression of more than one channel in the same cell suggest redundant functions not only in its role in temperature sensation but also in adipogenesis. The existence of distinct TRPs with similar temperature thresholds also presented compensatory effects as Ye, Li., et al[40] reported for TRPC3 and TRPC6. The compensatory effect, however, must be managed with caution since a contradiction by results presented by Krout, D., et al, [166] stated that TRPC1 inhibits positive effects of physical activity in obesity.

Ye, L. *et al.* [127] has proved in fat cells an autonomous capacity for sensing temperature without the functioning of the canonical adaptive thermogenesis pathway, cAMP/Protein Kinase A/CREB, activated downstream of stimulated-β-ARs. This explains why the interactions between TRPs and β-ARs is limited to the evaluation of the distinctive thermogenic proteins, UCP1, PGC1α, PPARγ, and PKA activity. Yet, additive or multiplicative effects between β-ARs and TRPs-activated adaptive thermogenesis for either of the pathways is not evidenced. Intriguingly, Zhu, Z. Z., *et al;*[79] and Sun, W., *et al;*[57]reported that in TRPV2KO and TRPM8KO mice,respectively, the induction of thermogenesis is ablated even with activation of β-ARs. Zhu, Z. Z., *et al;*[79] also reported that PKA function was independent of β-ARs.

The aim to understand the interactions between molecules allowing the cellular response towards the stimuli created by activated-TRPs is put aside and only committed to the evaluation of the adaptive thermogenesis protein hallmark. The enhanced expression is corroborated by improved metabolic signs like low insulin resistance, core body temperature, oxygen consumption, fat loss and others; yet, mitochondria genes for oxidative phosphorylation chain are scarcely addressed Likewise, the race to tackle the raising metabolic diseases has limited the understanding of activated-TRPs on cellular

physiology to murine models and human cells. Vertebrates with striking characteristics for temperature adaptations like hibernators or desert animals can contribute with substantial and unrevealed insights. In fact, the presence of BAT and the thermogenic marker UCP is present in all vertebrates[167]. The presence of BAT in ectotherms living in cold nocturnal or extremely cold environments coupled with the function of thermos-TRPs may suggest a heterothermic view for these animals.

Study Limitations

The aim of this SLR is to specifically understand the effects of activated-TRPs on genes and intracellular proteins mediating cellular responses to temperature stimuli. However, the scope of this objective could be limited by three facts. First, the lack of chemical agonists capable to produce temperature sensation through activation of TRPs in the algorithm. Second, the presence of TRPs in different cells and the determining effect of temperature over all organisms' physiological process also represent a limitation to understand the total effects of TRPs. To improve the scope of this SLR the algorithm could include vocabulary engaging oxidative metabolism. Third and last, the capacity of these ion channels to mediate and integrate a wide variety of stimuli can also hide possible effects of activated-TRPs over genes and proteins that respond to temperature stimuli.

References

1. Poirier, C. C. & Iglesias, P. A. An integrative approach to understanding mechanosensation. *Briefings in Bioinformatics* (2007). doi:10.1093/bib/bbm025
2. Nei, M., Niimura, Y. & Nozawa, M. The evolution of animal chemosensory receptor gene repertoires: Roles of chance and necessity. *Nature Reviews Genetics* (2008). doi:10.1038/nrg2480
3. Vriens, J., Nilius, B. & Voets, T. Peripheral thermosensation in mammals. *Nat. Rev. Neurosci.* **15**, 573–589 (2014).
4. Seebacher, F. & Little, A. G. Plasticity of performance curves can buffer reaction rates from body temperature variation in active endotherms. *Front. Physiol.* **8**, 1–8 (2017).
5. Dubin, A. E. & Patapoutian, A. Nociceptors: The sensors of the pain pathway. *Journal of Clinical Investigation* (2010). doi:10.1172/JCI42843
6. Flouris, A. D. Functional architecture of behavioural thermoregulation. *European Journal of Applied Physiology* (2011). doi:10.1007/s00421-010-1602-8
7. Angilletta, M. J., Cooper, B. S., Schuler, M. S. & Boyles, J. G. The evolution of thermal physiology in endotherms. *Front. Biosci. E* (2010). doi:10.2741/E148
8. Clarke, A. & Pörtner, H. O. Temperature, metabolic power and the evolution of endothermy. *Biological Reviews* (2010). doi:10.1111/j.1469-185X.2010.00122.x
9. COSENS, D. J. & MANNING, A. Abnormal Electroretinogram from a Drosophila Mutant. *Nature* **224**, 285–287 (1969).
10. Caterina, M. J. *et al.* The capsaicin receptor: A heat-activated ion channel in the pain pathway. *Nature* **389**, 816–824 (1997).
11. McKemy, D. D., Neuhausser, W. M. & Julius, D. Identification of a cold receptor reveals a general role for TRP channels in thermosensation. *Nature* **416**, 52–58 (2002).
12. Clapham, D. E. TRP channels as cellular sensors. *Nature* (2003). doi:10.1038/nature02196
13. Montell, C. The history of TRP channels, a commentary and reflection. *Pflugers*

Arch. **461**, 499–506 (2011).
14. Voets, T., Talavera, K., Owsianik, G. & Nilius, B. Sensing with TRP channels. *Nature Chemical Biology* (2005). doi:10.1038/nchembio0705-85
15. Laursen, W. J., Anderson, E. O., Hoffstaetter, L. J., Bagriantsev, S. N. & Gracheva, E. O. Species-specific temperature sensitivity of TRPA1. *Temperature* (2015). doi:10.1080/23328940.2014.1000702
16. Mulier, M., Vriens, J. & Voets, T. TRP channel pores and local calcium signals. *Cell Calcium* (2017). doi:10.1016/j.ceca.2017.04.007
17. Ambudkar, I. S., Liu, X. & Paria, B. Transient Receptor Potential Channels. in *Encyclopedia of Biological Chemistry* 412–417 (Elsevier, 2013). doi:10.1016/B978-0-12-378630-2.00154-7
18. Bishnoi, M., Khare, P., Brown, L. & Panchal, S. K. Transient receptor potential (TRP) channels: a metabolic TR(i)P to obesity prevention and therapy. *Obesity Reviews* (2018). doi:10.1111/obr.12703
19. Vay, L., Gu, C. & McNaughton, P. A. The thermo-TRP ion channel family: properties and therapeutic implications. *Br. J. Pharmacol.* **165**, 787–801 (2012).
20. Zimmermann, K. *et al.* Transient receptor potential cation channel, subfamily C, member 5 (TRPC5) is a cold-transducer in the peripheral nervous system. *Proc. Natl. Acad. Sci. U. S. A.* **108**, 18114–18119 (2011).
21. Chen, J. *et al.* Species differences and molecular determinant of TRPA1 cold sensitivity. *Nat. Commun.* (2013). doi:10.1038/ncomms3501
22. Saito, S., Fukuta, N., Shingai, R. & Tominaga, M. Evolution of vertebrate transient receptor potential vanilloid 3 channels: opposite temperature sensitivity between mammals and western clawed frogs. *PLoS Genet.* **7**, e1002041 (2011).
23. Li, H. S., Xu, X. Z. S. & Montell, C. Activation of a trpc3-dependent cation current through the neurotrophin bdnf. *Neuron* (1999). doi:10.1016/S0896-6273(00)80838-7
24. Caterina, M. J. Transient receptor potential ion channels as participants in thermosensation and thermoregulation. *Am. J. Physiol. Integr. Comp. Physiol.* **292**, R64-76 (2007).
25. Bandell, M., Macpherson, L. J. & Patapoutian, A. From chills to chilis: mechanisms for thermosensation and chemesthesis via thermoTRPs. *Curr. Opin. Neurobiol.* **17**, 490–497 (2007).
26. Talavera, K., Nilius, B. & Voets, T. Neuronal TRP channels: thermometers, pathfinders and life-savers. *Trends Neurosci.* **31**, 287–295 (2008).
27. Kwon, Y., Shim, H. S., Wang, X. & Montell, C. Control of thermotactic behavior via coupling of a TRP channel to a phospholipase C signaling cascade. *Nat. Neurosci.* (2008). doi:10.1038/nn.2170
28. Veldhuis, N. A., Poole, D. P., Grace, M., McIntyre, P. & Bunnett, N. W. The G protein-coupled receptor-transient receptor potential channel axis: molecular insights for targeting disorders of sensation and inflammation. *Pharmacol. Rev.* **67**, 36–73 (2015).
29. Brauchi, S. A Hot-Sensing Cold Receptor: C-Terminal Domain Determines Thermosensation in Transient Receptor Potential Channels. *J. Neurosci.* (2006). doi:10.1523/jneurosci.5080-05.2006
30. Yao, J., Liu, B. & Qin, F. Modular thermal sensors in temperature-gated transient receptor potential (TRP) channels. *Proc. Natl. Acad. Sci.* **108**, 11109–11114 (2011).
31. Saito, S. *et al.* Heat and noxious chemical sensor, chicken TRPA1, as a target of bird repellents and identification of its structural determinants by multispecies

functional comparison. *Mol. Biol. Evol.* **31**, 708–722 (2014).
32. Lishko, P. V., Procko, E., Jin, X., Phelps, C. B. & Gaudet, R. The Ankyrin Repeats of TRPV1 Bind Multiple Ligands and Modulate Channel Sensitivity. *Neuron* (2007). doi:10.1016/j.neuron.2007.05.027
33. Morrison, S. F. & Madden, C. J. Central nervous system regulation of brown adipose tissue. *Compr. Physiol.* (2014). doi:10.1002/cphy.c140013
34. Patapoutian, A., Peier, A. M., Story, G. M. & Viswanath, V. Thermotrp channels and beyond: Mechanisms of temperature sensation. *Nat. Rev. Neurosci.* **4**, 529–539 (2003).
35. Blaszkiewicz, M. & Townsend, K. L. Adipose Tissue and Energy Expenditure: Central and Peripheral Neural Activation Pathways. *Curr. Obes. Rep.* **5**, 241–250 (2016).
36. Moqrich, A. *et al.* Impaired thermosensation in mice lacking TRPV3, a heat and camphor sensor in the skin. *Science* **307**, 1468–1472 (2005).
37. Mandadi, S. *et al.* TRPV3 in keratinocytes transmits temperature information to sensory neurons via ATP. *Pflugers Arch.* **458**, 1093–1102 (2009).
38. Gifford, J. R., Heal, C., Bridges, J., Goldthorpe, S. & Mack, G. W. Changes in dermal interstitial ATP levels during local heating of human skin. *J. Physiol.* **590**, 6403–6411 (2012).
39. Shutov, L. P. *et al.* The Complement System Component C5a Produces Thermal Hyperalgesia via Macrophage-to-Nociceptor Signaling That Requires NGF and TRPV1. *J. Neurosci.* **36**, 5055–5070 (2016).
40. Ye, L. *et al.* TRPV4 is a regulator of adipose oxidative metabolism, inflammation, and energy homeostasis. *Cell* **151**, 96–110 (2012).
41. Uchida, K. *et al.* Involvement of thermosensitive TRP channels in energy metabolism. *J. Physiol. Sci.* **67**, 549–560 (2017).
42. Jeong, K.-Y. Y. & Seong, J. Neonatal capsaicin treatment in rats affects TRPV1-related noxious heat sensation and circadian body temperature rhythm. *J. Neurol. Sci.* **341**, 58–63 (2014).
43. Moraes, M. N. *et al.* TRPV1 participates in the activation of clock molecular machinery in the brown adipose tissue in response to light-dark cycle. *Biochim. Biophys. Acta - Mol. Cell Res.* (2017). doi:10.1016/j.bbamcr.2016.11.010
44. Moraes, M. N. *et al.* Cold-sensing TRPM8 channel participates in circadian control of the brown adipose tissue. *Biochim. Biophys. Acta - Mol. Cell Res.* (2017). doi:10.1016/j.bbamcr.2017.09.011
45. Jerônimo, R. *et al.* Thermal stress in Danio rerio: a link between temperature, light, thermo-TRP channels, and clock genes. *J. Therm. Biol.* (2017). doi:10.1016/j.jtherbio.2017.02.009
46. Fujita, T. *et al.* Involvement of TRPV3 and TRPM8 ion channel proteins in induction of mammalian cold-inducible proteins. *Biochem. Biophys. Res. Commun.* **495**, 935–940 (2018).
47. Fujita, T. *et al.* TRPV4-dependent induction of a novel mammalian cold-inducible protein SRSF5 as well as CIRP and RBM3. *Sci. Rep.* 1–11 (2017). doi:10.1038/s41598-017-02473-x
48. Higgins, J. P. & Green, S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. *Cochrane Collab.* (2011). doi:10.1002/9780470712184.ch4
49. Grant, M. J. & Booth, A. A typology of reviews: an analysis of 14 review types and associated methodologies. *Health Info. Libr. J.* (2009). doi:10.1111/j.1471-1842.2009.00848.x

50. Dixon-Woods, M., Agarwal, S., Jones, D., Young, B. & Sutton, A. Synthesising qualitative and quantitative evidence: A review of possible methods. *Journal of Health Services Research and Policy* (2005). doi:10.1258/1355819052801804
51. Burnham, J. F. Scopus database: A review. *Biomedical Digital Libraries* (2006). doi:10.1186/1742-5581-3-1
52. Elsevier. Scopus fact sheet. *An eye on global research* 1–2 (2018). Available at: https://www.elsevier.com/__data/assets/pdf_file/0008/208772/ACAD_R_SC_FS.pdf.
53. Elsevier B.V. Scopus: Content Coverage Guide. 28 (2017).
54. Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G. & PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. *Open Med.* **3**, e123-30 (2009).
55. Hallgren, K. A. Computing Inter-Rater Reliability for Observational Data: An Overview and Tutorial. *Tutor. Quant. Methods Psychol.* (2012).
56. McHugh, M. L. Interrater reliability: the kappa statistic. *Biochem. medica* (2012).
57. Gamer, M., Lemon, J., Fellows, I. & Singh, P. Various Coefficients of Interrater Reliability and Agreement. *Http://Cran.R-Project.Org/Web/Packages/Irr/Irr.Pdf* (2012). doi:https://cran.r-project.org/package=irr%0A
58. Rodgers, M. *et al.* Testing methodological guidance on the conduct of narrative synthesis in systematic reviews: Effectiveness of interventions to promote smoke alarm ownership and function. *Evaluation* (2009). doi:10.1177/1356389008097871
59. Tan, C.-H. H. & McNaughton, P. A. The TRPM2 ion channel is required for sensitivity to warmth. *Nature* **536**, 460–463 (2016).
60. Jeon, S. & Caterina, M. J. Molecular basis of peripheral innocuous warmth sensitivity. *Handb. Clin. Neurol.* **156**, 69–82 (2018).
61. Glauser, D. A. & Goodman, M. B. Molecules empowering animals to sense and respond to temperature in changing environments. *Curr. Opin. Neurobiol.* **41**, 92–98 (2016).
62. Señarís, R., Ordás, P., Reimúndez, A. & Viana, F. *Mammalian cold TRP channels: impact on thermoregulation and energy homeostasis*. *Pflugers Archiv European Journal of Physiology* 761–777 (Pflügers Archiv - European Journal of Physiology, 2018). doi:10.1007/s00424-018-2145-9
63. Kruse, V., Neess, D. & Færgeman, N. J. The Significance of Epidermal Lipid Metabolism in Whole-Body Physiology. *Trends in Endocrinology and Metabolism* (2017). doi:10.1016/j.tem.2017.06.001
64. Whittle, A., Relat-Pardo, J. & Vidal-Puig, A. Pharmacological strategies for targeting BAT thermogenesis. *Trends in Pharmacological Sciences* (2013). doi:10.1016/j.tips.2013.04.004
65. Yamashita, H. *et al.* Impaired basal thermal homeostasis in rats lacking capsaicin-sensitive peripheral small sensory neurons. *J. Biochem.* **143**, 385–393 (2008).
66. Tajino, K. *et al.* Cooling-sensitive TRPM8 is thermostat of skin temperature against cooling. *PLoS One* **6**, e17504 (2011).
67. Alawi, K. M. *et al.* Transient receptor potential canonical 5 (TRPC5) protects against pain and vascular inflammation in arthritis and joint inflammation. *Ann. Rheum. Dis.* **76**, 252–260 (2017).
68. Nakipova, O. V. *et al.* Store-operated Ca2+ entry supports contractile function in hearts of hibernators. *PLoS One* **12**, e0177469 (2017).
69. Liu, X. *et al.* STIM1 thermosensitivity defines the optimal preference

temperature for warm sensation in mice. *Cell Res.* **29**, 95–109 (2019).
70. Xiao, B., Coste, B., Mathur, J. & Patapoutian, A. Temperature-dependent STIM1 activation induces Ca2+influx and modulates gene expression. *Nat. Chem. Biol.* (2011). doi:10.1038/nchembio.558
71. Sun, J. *et al.* Activation of cold-sensing transient receptor potential melastatin subtype 8 antagonizes vasoconstriction and hypertension through attenuating RhoA/Rho kinase pathway. *Hypertens. (Dallas, Tex. 1979)* **63**, 1354–1363 (2014).
72. Alawi, K. M. *et al.* The sympathetic nervous system is controlled by transient receptor potential vanilloid 1 in the regulation of body temperature. *FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol.* **29**, 4285–4298 (2015).
73. Sabnis, A. S., Shadid, M., Yost, G. S. & Reilly, C. A. Human lung epithelial cells express a functional cold-sensing TRPM8 variant. *Am. J. Respir. Cell Mol. Biol.* **39**, 466–474 (2008).
74. Kim, M. *et al.* 10-oxo-12(Z)-octadecenoic acid, a linoleic acid metabolite produced by gut lactic acid bacteria, enhances energy metabolism by activation of TRPV1. *FASEB J.* **31**, 5036–5048 (2017).
75. Kida, R. *et al.* Direct action of capsaicin in brown adipogenesis and activation of brown adipocytes. *Cell Biochem. Funct.* **34**, 34–41 (2016).
76. Sun, W. *et al.* Lack of TRPV2 impairs thermogenesis in mouse brown adipose tissue. *EMBO Rep.* **17**, 383–399 (2016).
77. Kim, M. *et al.* Fish oil intake induces UCP1 upregulation in brown and white adipose tissue via the sympathetic nervous system. *Sci. Rep.* **5**, 18013 (2015).
78. Rossato, M. *et al.* Human white adipocytes express the cold receptor TRPM8 which activation induces UCP1 expression, mitochondrial activation and heat production. *Mol. Cell. Endocrinol.* **383**, 137–146 (2014).
79. Zhu, Z. Z. *et al.* Activation of the cold-sensing TRPM8 channel triggers UCP1-dependent thermogenesis and prevents obesity. *J. Mol. Cell Biol.* **4**, 88–96 (2012).
80. Kusudo, T. *et al.* TRPV4 deficiency increases skeletal muscle metabolic capacity and resistance against diet-induced obesity. *J. Appl. Physiol.* **112**, 1223–1232 (2012).
81. Zhang, L. L. *et al.* Activation of transient receptor potential vanilloid type-1 channel prevents adipogenesis and obesity. *Circ. Res.* (2007). doi:10.1161/01.RES.0000262653.84850.8b
82. Cheung, S. Y., Huang, Y., Kwan, H. Y., Chung, H. Y. & Yao, X. Activation of transient receptor potential vanilloid 3 channel suppresses adipogenesis. *Endocrinology* (2015). doi:10.1210/en.2014-1831
83. Li, C. *et al.* TRPM8 activation improves energy expenditure in skeletal muscle and exercise endurance in mice. *Gene* (2018). doi:10.1016/j.gene.2017.10.045
84. Clemmensen, C. *et al.* Coordinated targeting of cold and nicotinic receptors synergistically improves obesity and type 2 diabetes. *Nat. Commun.* **9**, 4304 (2018).
85. Baskaran, P. *et al.* TRPV1 activation counters diet-induced obesity through sirtuin-1 activation and PRDM-16 deacetylation in brown adipose tissue. *Int. J. Obes.* **41**, 739–749 (2017).
86. Goralczyk, A. *et al.* TRP channels in brown and white adipogenesis from human progenitors: new therapeutic targets and the caveats associated with the common antibiotic, streptomycin. *FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol.* **31**, 3251–3266 (2017).

87. Yang, L. *et al.* Targeting Transient Receptor Potential Channels in Cardiometabolic Diseases and Myocardial Ischemia Reperfusion Injury. *Curr. Drug Targets* (2016). doi:10.2174/1389450116666151019102052
88. Birerdinc, A., Jarrar, M., Stotish, T., Randhawa, M. & Baranova, A. Manipulating molecular switches in brown adipocytes and their precursors: A therapeutic potential. *Prog. Lipid Res.* **52**, 51–61 (2013).
89. Ahern, G. P. Transient receptor potential channels and energy homeostasis. *Trends Endocrinol. Metab.* **24**, 554–560 (2013).
90. Panchal, S. K. K., Bliss, E. & Brown, L. Capsaicin in metabolic syndrome. *Nutrients* (2018). doi:10.3390/nu10050630
91. Uchida, K., Sun, W., Yamazaki, J. & Tominaga, M. Role of Thermo-Sensitive Transient Receptor Potential Channels in Brown Adipose Tissue. *Biol. Pharm. Bull.* **41**, 1135–1144 (2018).
92. Liu, J., Wang, Y. & Lin, L. Small molecules for fat combustion: targeting obesity. *Acta Pharm. Sin. B* (2018). doi:10.1016/j.apsb.2018.09.007
93. Salat, K., Moniczewski, A. & Librowski, T. Transient Receptor Potential Channels - Emerging Novel Drug Targets for the Treatment of Pain. *Curr. Med. Chem.* **20**, 1409–1436 (2013).
94. Brederson, J.-D. D., Kym, P. R. & Szallasi, A. Targeting TRP channels for pain relief. *Eur. J. Pharmacol.* **716**, 61–76 (2013).
95. Jardín, I. *et al.* TRPs in pain sensation. *Frontiers in Physiology* (2017). doi:10.3389/fphys.2017.00392
96. Thiel, G. *et al.* Transient receptor potential TRPM3 channels: Pharmacology, signaling, and biological functions. *Pharmacol. Res.* **124**, 92–99 (2017).
97. Vriens, J. & Voets, T. Sensing the heat with TRPM3. *Pflugers Archiv European Journal of Physiology* (2018). doi:10.1007/s00424-017-2100-1
98. Peier, A. M. *et al.* A TRP channel that senses cold stimuli and menthol. *Cell* **108**, 705–715 (2002).
99. Sulli, G. *et al.* Pharmacological activation of REV-ERBs is lethal in cancer and oncogene-induced senescence. *Nature* (2018). doi:10.1038/nature25170
100. Stenvers, D. J., Scheer, F. A. J. L., Schrauwen, P., la Fleur, S. E. & Kalsbeek, A. Circadian clocks and insulin resistance. *Nature Reviews Endocrinology* (2019). doi:10.1038/s41574-018-0122-1
101. Savvidis, C. & Koutsilieris, M. Circadian Rhythm Disruption in Cancer Biology. *Mol. Med.* (2012).
102. Labrecque, N. & Cermakian, N. Circadian clocks in the immune system. *Journal of Biological Rhythms* (2015). doi:10.1177/0748730415577723
103. Onder, Y. & Green, C. B. Rhythms of metabolism in adipose tissue and mitochondria. *Neurobiology of Sleep and Circadian Rhythms* (2018). doi:10.1016/j.nbscr.2018.01.001
104. Husse, J., Hintze, S. C., Eichele, G., Lehnert, H. & Oster, H. Circadian Clock Genes Per1 and Per2 Regulate the Response of Metabolism-Associated Transcripts to Sleep Disruption. *PLoS One* (2012). doi:10.1371/journal.pone.0052983
105. Grimaldi, B. *et al.* PER2 controls lipid metabolism by direct regulation of PPARγ. *Cell Metab.* (2010). doi:10.1016/j.cmet.2010.10.005
106. Bonney, S. *et al.* Cardiac Per2 Functions as Novel Link between Fatty Acid Metabolism and Myocardial Inflammation during Ischemia and Reperfusion Injury of the Heart. *PLoS One* (2013). doi:10.1371/journal.pone.0071493
107. Uchida, K., Sun, W., Yamazaki, J. & Tominaga, M. Ion Channels as Therapeutic

Targets for the Immune , Inflammatory , and Metabolic Disorders Role of Thermo-Sensitive Transient Receptor Potential Channels in Brown Adipose Tissue. **41**, 1135–1144 (2018).
108. Hardie, R. C. Photosensitive TRPs. *Handb. Exp. Pharmacol.* (2014). doi:10.1007/978-3-319-05161-1_4
109. Poletini, M. O. *et al.* TRP channels: a missing bond in the entrainment mechanism of peripheral clocks throughout evolution. *Temp. (Austin, Tex.)* **2**, 522–534 (2015).
110. Cambras, T. *et al.* Circadian desynchronization of core body temperature and sleep stages in the rat. *Proc. Natl. Acad. Sci.* (2007). doi:10.1073/pnas.0702424104
111. Ki, Y. *et al.* Warming Up Your Tick-Tock. *Neurosci.* (2015). doi:10.1177/1073858415577083
112. Tremmel, M., Gerdtham, U. G., Nilsson, P. M. & Saha, S. Economic burden of obesity: A systematic literature review. *International Journal of Environmental Research and Public Health* (2017). doi:10.3390/ijerph14040435
113. Zheng, Y., Ley, S. H. & Hu, F. B. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nature Reviews Endocrinology* (2018). doi:10.1038/nrendo.2017.151
114. Andersson, C. & Vasan, R. S. Epidemiology of cardiovascular disease in young individuals. *Nature Reviews Cardiology* (2018). doi:10.1038/nrcardio.2017.154
115. Saklayen, M. G. The Global Epidemic of the Metabolic Syndrome. *Current Hypertension Reports* (2018). doi:10.1007/s11906-018-0812-z
116. Scheja, L. & Heeren, J. Metabolic interplay between white, beige, brown adipocytes and the liver. *Journal of Hepatology* (2016). doi:10.1016/j.jhep.2016.01.025
117. Sidossis, L. & Kajimura, S. Brown and beige fat in humans: Thermogenic adipocytes that control energy and glucose homeostasis. *Journal of Clinical Investigation* (2015). doi:10.1172/JCI78362
118. Wu, J., Cohen, P. & Spiegelman, B. M. Adaptive thermogenesis in adipocytes: Is beige the new brown? *Genes and Development* (2013). doi:10.1101/gad.211649.112
119. Bishnoi, M., Kondepudi, K. K., Gupta, A., Karmase, A. & Boparai, R. K. Expression of multiple Transient Receptor Potential channel genes in murine 3T3-L1 cell lines and adipose tissue. *Pharmacol. Reports* (2013). doi:10.1016/S1734-1140(13)71055-7
120. Moisan, A. *et al.* White-to-brown metabolic conversion of human adipocytes by JAK inhibition. *Nat. Cell Biol.* (2015). doi:10.1038/ncb3075
121. Giralt, M. & Villarroya, F. White, brown, beige/brite: Different adipose cells for different functions? *Endocrinology* (2013). doi:10.1210/en.2013-1403
122. Petrovic, N. *et al.* Chronic peroxisome proliferator-activated receptor γ (PPARγ) activation of epididymally derived white adipocyte cultures reveals a population of thermogenically competent, UCP1-containing adipocytes molecularly distinct from classic brown adipocytes. *J. Biol. Chem.* (2010). doi:10.1074/jbc.M109.053942
123. CANNON, B. & NEDERGAARD, J. Brown Adipose Tissue: Function and Physiological Significance. *Physiol. Rev.* (2004). doi:10.1152/physrev.00015.2003
124. Romanovsky, A. A. The thermoregulation system and how it works. in *Handbook of Clinical Neurology* **156**, 3–43 (Elsevier B.V., 2018).

125. Cao, W., Medvedev, A. V., Daniel, K. W. & Collins, S. β-adrenergic activation of p38 MAP kinase in adipocytes: cAMP induction of the uncoupling protein 1 (UCP1) gene requires p38 map kinase. *J. Biol. Chem.* (2001). doi:10.1074/jbc.M101049200
126. Waterston, R. H. *et al.* Initial sequencing and comparative analysis of the mouse genome. *Nature* (2002). doi:10.1038/nature01262
127. Ye, L. *et al.* Fat cells directly sense temperature to activate thermogenesis. 1–6 (2013). doi:10.1073/pnas.1310261110/-/DCSupplemental.www.pnas.org/cgi/doi/10.1073/pnas.1310261110
128. Burnstock, G. Purinergic cotransmission. in *Experimental Physiology* (2009). doi:10.1113/expphysiol.2008.043620
129. North, R. A. Molecular physiology of P2X receptors. *Physiol. Rev.* (2002). doi:10.1152/physrev.00015.2002
130. Khakh, B. S. & North, R. A. Neuromodulation by Extracellular ATP and P2X Receptors in the CNS. *Neuron* (2012). doi:10.1016/j.neuron.2012.09.024
131. Burnstock, G. Purine and pyrimidine receptors. *Cellular and Molecular Life Sciences* (2007). doi:10.1007/s00018-007-6497-0
132. Yao, X., Kwan, H. Y. & Huang, Y. Regulation of TRP channels by phosphorylation. *NeuroSignals* (2006). doi:10.1159/000093042
133. Chateau, Y. & Misery, L. Connections between nerve endings and epidermal cells: Are they synapses? *Exp. Dermatol.* **13**, 2–4 (2004).
134. Vandewauw, I. *et al.* A TRP channel trio mediates acute noxious heat sensing. *Nature* **555**, 662–666 (2018).
135. Yarmolinsky, D. A. *et al.* Coding and Plasticity in the Mammalian Thermosensory System. *Neuron* **92**, 1079–1092 (2016).
136. Kobayashi, K. *et al.* Distinct expression of TRPM8, TRPA1, and TRPV1 mRNAs in rat primary afferent neurons with adelta/c-fibers and colocalization with trk receptors. *J. Comp. Neurol.* **493**, 596–606 (2005).
137. Story, G. M. *et al.* ANKTM1, a TRP-like channel expressed in nociceptive neurons, is activated by cold temperatures. *Cell* **112**, 819–829 (2003).
138. Mori, N. *et al.* Intragastric administration of allyl isothiocyanate increases carbohydrate oxidation via TRPV1 but not TRPA1 in mice. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **300**, R1494-505 (2011).
139. Cheng, W., Yang, F., Takanishi, C. L. & Zheng, J. Thermosensitive TRPV Channel Subunits Coassemble into Heteromeric Channels with Intermediate Conductance and Gating Properties. *J. Gen. Physiol.* (2007). doi:10.1085/jgp.200709731
140. Cheng, W. *et al.* Heteromeric heat-sensitive transient receptor potential channels exhibit distinct temperature and chemical response. *J. Biol. Chem.* **287**, 7279–7288 (2012).
141. Nesuashvili, L., Hadley, S. H., Bahia, P. K. & Taylor-Clark, T. E. Sensory Nerve Terminal Mitochondrial Dysfunction Activates Airway Sensory Nerves via Transient Receptor Potential (TRP) Channels. *Mol. Pharmacol.* (2013). doi:10.1124/mol.112.084319
142. Kozai, D., Ogawa, N. & Mori, Y. Redox Regulation of Transient Receptor Potential Channels. *Antioxid. Redox Signal.* (2013). doi:10.1089/ars.2013.5616
143. Moparthi, L. *et al.* Human TRPA1 is a heat sensor displaying intrinsic U-shaped thermosensitivity. *Sci. Rep.* **6**, 28763 (2016).
144. Cordero-Morales, J. F., Gracheva, E. O. & Julius, D. Cytoplasmic ankyrin repeats of transient receptor potential A1 (TRPA1) dictate sensitivity to thermal

and chemical stimuli. *Proc. Natl. Acad. Sci. U. S. A.* **108**, E1184-91 (2011).
145. Matos-Cruz, V. *et al.* Molecular Prerequisites for Diminished Cold Sensitivity in Ground Squirrels and Hamsters. *Cell Rep.* **21**, 3329–3337 (2017).
146. Gracheva, E. O. *et al.* Ganglion-specific splicing of TRPV1 underlies infrared sensation in vampire bats. *Nature* (2013). doi:10.1038/nature10245.Ganglion-specific
147. Thiel, G., Lesch, A., Rubil, S., Backes, T. M. & Rossler, O. G. Regulation of Gene Transcription Following Stimulation of Transient Receptor Potential (TRP) Channels. *Int. Rev. Cell Mol. Biol.* **335**, 167–189 (2018).
148. Bromberg, Z., Goloubinoff, P., Saidi, Y. & Weiss, Y. G. The Membrane-Associated Transient Receptor Potential Vanilloid Channel Is the Central Heat Shock Receptor Controlling the Cellular Heat Shock Response in Epithelial Cells. *PLoS One* (2013). doi:10.1371/journal.pone.0057149
149. Fernandes, J. *et al.* IP3 sensitizes TRPV4 channel to the mechano-and osmotransducing messenger 5′-6′-epoxyeicosatrienoic acid. *J. Cell Biol.* (2008). doi:10.1083/jcb.200712058
150. Nozadze, I., Tsiklauri, N., Gurtskaia, G. & Tsagareli, M. G. Role of thermo TRPA1 and TRPV1 channels in heat, cold, and mechanical nociception of rats. *Behav. Pharmacol.* **27**, 29–36 (2016).
151. Yin, J. & Kuebler, W. M. Mechanotransduction by TRP channels: General concepts and specific role in the vasculature. *Cell Biochemistry and Biophysics* (2010). doi:10.1007/s12013-009-9067-2
152. Traxlmayr, M. W. *et al.* Strong Enrichment of Aromatic Residues in Binding Sites from a Charge-neutralized Hyperthermostable Sso7d Scaffold Library. *J. Biol. Chem.* **291**, 22496–22508 (2016).
153. Malekar, V. C. *et al.* Effect of elevated temperature on membrane lipid saturation in Antarctic notothenioid fish. *PeerJ* (2018). doi:10.7717/peerj.4765
154. Gudi, S., Nolan, J. P. & Frangos, J. A. Modulation of GTPase activity of G proteins by fluid shear stress and phospholipid composition. *Proc. Natl. Acad. Sci.* (1998). doi:10.1073/pnas.95.5.2515
155. Clapham, D. E. & Miller, C. A thermodynamic framework for understanding temperature sensing by transient receptor potential (TRP) channels. *Proc. Natl. Acad. Sci.* (2011). doi:10.1073/pnas.1117485108
156. Liu, X. *et al.* STIM1 thermosensitivity defines the optimal preference temperature for warm sensation in mice. *Cell Res.* (2019). doi:10.1038/s41422-018-0129-0
157. Buhr, E. D., Yoo, S. H. & Takahashi, J. S. Temperature as a universal resetting cue for mammalian circadian oscillators. *Science (80-.).* (2010). doi:10.1126/science.1195262
158. Sokabe, T., Chen, H. C., Luo, J. & Montell, C. A Switch in Thermal Preference in Drosophila Larvae Depends on Multiple Rhodopsins. *Cell Rep.* (2016). doi:10.1016/j.celrep.2016.09.028
159. Tamaru, T. *et al.* Synchronization of circadian Per2 rhythms and HSF1-BMAL1:clock interaction in mouse fibroblasts after Short-Term heat shock pulse. *PLoS One* (2011). doi:10.1371/journal.pone.0024521
160. Morf, J. *et al.* Cold-inducible RNA-binding protein modulates circadian gene expression posttranscriptionally. *Science (80-.).* (2012). doi:10.1126/science.1217726
161. Parlee, S. D., Lentz, S. I., Mori, H. & MacDougald, O. A. Quantifying size and number of adipocytes in adipose tissue. in *Methods in Enzymology* (2014).

doi:10.1016/B978-0-12-411619-1.00006-9
162. Sun, W. *et al.* Activation of TRPV2 negatively regulates the differentiation of mouse brown adipocytes. *Pflugers Arch. Eur. J. Physiol.* (2016). doi:10.1007/s00424-016-1846-1
163. SHI, H., HALVORSEN, Y.-D., ELLIS, P. N., WILKISON, W. O. & ZEMEL, M. B. Role of intracellular calcium in human adipocyte differentiation. *Physiol. Genomics* (2017). doi:10.1152/physiolgenomics.2000.3.2.75
164. He, Y. Y. H. Y. *et al.* The calcium-sensing receptor promotes adipocyte differentiation and adipogenesis through PPARγ pathway. *Mol. Cell. Biochem.* (2012). doi:10.1007/s11010-011-1118-5
165. Jensen, B., Farach-Carson, M. C., Kenaley, E. & Akanbi, K. A. High extracellular calcium attenuates adipogenesis in 3T3-L1 preadipocytes. *Exp. Cell Res.* (2004). doi:10.1016/j.yexcr.2004.08.030
166. Krout, D. *et al.* The TRPC1 Ca2+-permeable channel inhibits exerciseinduced protection against high-fat diet-induced obesity and type II diabetes. *J. Biol. Chem.* (2017). doi:10.1074/jbc.M117.809954
167. Jastroch, M., Oelkrug, R. & Keipert, S. Insights into brown adipose tissue evolution and function from non-model organisms. *J. Exp. Biol.* (2018). doi:10.1242/jeb.169425

Acknowledgements

We thank USFQ for providing access to Scopus and other magazines and Pamela Vega to allow us to confirm the reproducibility of 5% of the obtained results.

APPENDIX

Appendix No. 1. Search Terms for Scopus Database.

Term Groups	#	Search Term
Transient Receptor Potential Channel (Population)	1	(trp* OR {Transient Potential Receptor Channel} OR {TRP channel} OR {Transient Potential Receptor Cation Channel} OR {TRP Membrane Proteins} OR {TRP Membrane} OR {TRP Cation Channel} OR {TRP Protein} OR {TRP ion channel} OR {Thermo TRP} OR trpa OR {TRPA Cation Channel} OR trpc OR {TRPC Cation Channel} OR trpm OR {TRPM Cation Channel} OR trpn OR {TRPN Cation Channel} OR trpv OR {TRPV Cation Channel} OR trpp OR {TRPP Cation Channel} OR trpml OR {TRPML Cation Channel} OR {TRPA1 Cation Channel} OR {TRPC1 Cation Channel} OR {TRPC2 Cation Channel} OR {TRPC3 Cation Channel} OR {TRPC4 Cation Channel} OR {TRPC5 Cation Channel} OR {TRPC6 Cation Channel} OR {TRPC7 Cation Channel} OR {TRPM1 Cation Channel} OR {TRPM2 Cation Channel} OR {TRPM3 Cation Channel} OR {TRPM4 Cation Channel} OR {TRPM5 Cation Channel} OR {TRPM6 Cation Channel} OR {TRPM7 Cation Channel} OR {TRPM8 Cation Channel} OR {TRPN1 Cation Channel} OR {TRPV1 Cation Channel} OR {TRPV2 Cation Channel} OR {TRPV3 Cation Channel} OR {TRPV4 Cation Channel} OR {TRPV5 Cation Channel} OR {TRPV6 Cation Channel} OR {TRPP2 Cation Channel} OR {TRPP3 Cation Channel} OR {TRPP5 Cation Channel} OR {TRPML1 Cation Channel} OR {TRPML2 Cation Channel} OR {TRPML3 Cation Channel} OR trpa1 OR trpc1 OR trpc2 OR trpc3 OR trpc4 OR trpc5 OR trpc6 OR trpc7 OR trpm1 OR trpm2 OR trpm3 OR trpm4 OR trpm5 OR trpm6 OR trpm7 OR trpm8 OR trpn1 OR trpv1 OR trpv2 OR trpv3 OR trpv4 OR trpv5 OR trpv6 OR trpp2 OR trpp3 OR trpp5 OR trpml1 OR trpml2 OR trpml3)
Vertebrates (Population)	2	(vertebrate OR mammal OR reptile OR fish OR amphibian OR bird)

Temperature Process (Intervention)	3	({thermal regulation} OR {thermal perception} OR {thermal acclimation} OR {thermic regulation} OR {thermogenesis} OR {metabolic heat production} OR {physiological heat production} OR {physiological heat generation} OR {metabolic heat generation} OR {muscle heat production} OR {muscle heat generation} OR {heat generation} OR {heat production} OR {physiological heat synthesis} OR {thermosensation} OR {thermosensitive} OR {thermoperception} OR {thermorecognition} OR {thermoregulation} OR {facultative thermogenesis} OR {thermogenesis} OR {thermosensing} OR {temperature generation} OR {temperature control} OR {temperature perception} OR {temperature sensation} OR {temperature recognition} OR {non-shivering thermogenesis} OR {non-shivering thermoregulation} OR {shivering thermoregulation} OR {shivering thermogenesis} OR {hot perception} OR {cold perception} OR {hot sensation} OR {cold sensation} OR {heat acclimation} OR {cold acclimation} OR acclimation OR acclimatization OR {body temperature regulation} OR torpor OR shivering OR estivation OR thermogeneses OR {thermosensing} OR {hot sensation} OR {cold sensation} OR {heat sensation} OR {heat perception} OR {corporal heat generation} OR {corporal heat regulation} OR {corporal temperature regulation} OR {corporal heat production} OR {corporal temperature generation} OR {body temperature generation} OR {body temperature production} OR {body temperature perception} OR {body heat perception} OR {body cold perception} OR {corporal temperature perception} OR {corporal heat perception} OR {corporal cold perception})

NOTE: The algorithm used for the advance search was (#1 AND #2 AND #3). The use of brackets {} in Scopus mean search the exact phrase or word and asterisk * is used for all kinds of words beginning with e.g. trp.

Appendix No. 2. Search Terms for PubMed Algorithm.

Term Groups	#	Search Term
Transient Receptor Potential Channel (Population)	1	((TRP[All Fields]) OR Transient Receptor Potential Channels[All Fields]) OR TRP channel[All Fields]) OR TRP Membrane Proteins[All Fields]) OR Transient Receptor Potential Cation Channels[All Fields]) OR TRP Cation Channel[All Fields]) OR TRP Protein[All Fields]) OR TRP ion channel[All Fields]) OR Thermo TRP[All Fields]) OR TRPA[All Fields]) OR TRPC[All Fields]) OR TRPM[All Fields]) OR TRPN[All Fields]) OR TRPV[All Fields]) OR TRPML[All Fields]) OR TRPA1 Cation Channel[All Fields]) OR TRPC1 Cation Channel[All Fields]) OR TRPC2 Cation Channel[All Fields]) OR TRPC3 Cation Channel[All Fields]) OR TRPC4 Cation Channel[All Fields]) OR TRPC5 Cation Channel[All Fields]) OR TRPC6 Cation Channel[All Fields]) OR TRPC7 Cation Channel[All Fields]) OR TRPM1 Cation Channel[All Fields]) OR TRPM2 Cation Channel[All Fields]) OR TRPM3 Cation Channel[All Fields]) OR TRPM4 Cation Channel[All Fields]) OR TRPM5 Cation Channel[All Fields]) OR TRPM6 Cation Channel[All Fields]) OR TRPM7 Cation Channel[All Fields]) OR TRPM8 Cation Channel[All Fields]) OR TRPN1 Cation Channel[All Fields]) OR TRPV1 Cation Channel[All Fields]) OR TRPV2 Cation Channel[All Fields]) OR TRPV3 Cation Channel[All Fields]) OR TRPV4 Cation Channel[All Fields]) OR TRPV5 Cation Channel[All Fields]) OR TRPV6 Cation Channel[All Fields]) OR TRPP2 Cation Channel[All Fields]) OR TRPP3 Cation Channel[All Fields]) OR TRPP5 Cation Channel[All Fields]) OR (TRPP5 Cation Channel[All Fields])) OR TRPML1 Cation Channel[All Fields]) OR TRPML2 Cation Channel[All Fields]) OR TRPML3 Cation Channel[All Fields]) OR TRPA1[All Fields]) OR TRPC1[All Fields]) OR TRPC2[All Fields]) OR TRPC3[All Fields]) OR TRPC4[All Fields]) OR TRPC5[All Fields]) OR TRPC6[All Fields]) OR TRPC7[All Fields]) OR TRPM1[All Fields]) OR TRPM2[All Fields]) OR TRPM3[All Fields]) OR TRPM4[All Fields]) OR TRPM5[All Fields]) OR TRPM6[All Fields]) OR TRPM7[All Fields]) OR TRPM8[All Fields]) OR TRPN1[All Fields]) OR TRPV1[All Fields]) OR TRPV2[All Fields]) OR TRPV3[All Fields]) OR TRPV4[All Fields]) OR TRPV5[All Fields]) OR TRPV6[All Fields]) OR TRPP2[All Fields]) OR

		TRPP3[All Fields]) OR TRPP5[All Fields]) OR TRPML1[All Fields]) OR TRPML2[All Fields]) OR TRPML3[All Fields]))
Vertebrates (Population)	2	((((((Vertebrate[All Fields]) OR Mammal[All Fields]) OR Reptile[All Fields]) OR Fish[All Fields]) OR Amphibian[All Fields]) OR Bird[All Fields]))
Temperature Process (Intervention)	3	(((((corporal cold perception[All Fields]) OR (corporal cold perception[All Fields])) OR corporal heat perception[All Fields]) OR (corporal heat perception[All Fields])) OR (corporal temperature perception[All Fields])) OR corporal temperature perception[All Fields]) OR body cold perception[All Fields]) OR body heat perception[All Fields]) OR body temperature perception[All Fields]) OR body temperature production[All Fields]) OR body temperature generation[All Fields]) OR (corporal temperature generation[All Fields])) OR corporal temperature generation[All Fields]) OR corporal heat production[All Fields]) OR corporal temperature regulation[All Fields]) OR (corporal heat regulation[All Fields])) OR corporal heat regulation[All Fields]) OR corporal heat generation[All Fields]) OR (corporal heat generation[All Fields])) OR Acclimatization[All Fields]) OR Thermo[All Fields]) OR Thermal[All Fields]) OR acclimation[All Fields]) OR cold sensation[All Fields]) OR heat sensation[All Fields]) OR hot sensation[All Fields]) OR heat acclimation[All Fields]) OR cold acclimation[All Fields]) OR cold perception[All Fields]) OR hot perception[All Fields]) OR Shivering thermogenesis[All Fields]) OR Nonshivering thermogenesis[All Fields]) OR Shivering thermoregulation[All Fields]) OR Nonshivering thermoregulation[All Fields]) OR Metabolic heat production[All Fields]) OR Metabolic heat generation[All Fields]) OR Muscle heat generation[All Fields]) OR Muscle heat production[All Fields]) OR physiological heat synthesis[All Fields]) OR physiological heat generation[All Fields]) OR heat production[All Fields]) OR heat generation[All Fields]) OR physiological heat production[All Fields]) OR metabolic heat generation[All Fields]) OR thermic regulation[All Fields]) OR thermal acclimation[All Fields]) OR thermal perception[All Fields]) OR thermal regulation[All Fields]) OR Temperature Recognition[All Fields]) OR Thermosensing[All Fields]) OR Temperature Sensation[All Fields]) OR

		Temperature Perception[All Fields]) OR Temperature Control[All Fields]) OR Temperature Generation[All Fields]) OR Thermogeneses[All Fields]) OR thermogenesis[All Fields]) OR Facultative thermogenesis[All Fields]) OR Estivation[All Fields]) OR Estivation[All Fields]) OR Shivering[All Fields]) OR Torpor[All Fields]) OR Body Temperature Regulation[All Fields]) OR Thermoregulation[All Fields]) OR (Thermorecognition[All Fields])) OR Thermorecognition[All Fields]) OR Thermoperception[All Fields]) OR Thermosensitivity[All Fields]) OR Thermosensation[All Fields]

NOTE: The algorithm used for the advance search was (#1 AND #2 AND #3). The use of [All Fields] is equivalent to " " and it includes [MeSh Terms].

Appendix No. 3. Extraction Data of Title, Abstract, Methods and Results

Criteria	Objetive	Sub-category
1. Physiological Processes	This criterion aims to recognize the physiological-processes that are activated by TRP temperature stimulation.	100. Adaptive Thermogenesis
		101. SOCE Temperature Perception
		102. Cold-evoked Temperature Stress
		103. Heat-evoked Temperature Stress
		104. Warm Temperature Perception
		105. Cold Temperature Perception
		106. Circadian Cycle
		107. Temperature-Induced RNA Regulation
2.TRP Activation Pathway and activated Proteins	This criterion seek to detect the proteins and molecules that contribute to TRP temperature stimulation and are part of the activation of the molecular processes established in criteria 1	200. PKA
		201. PLC
		202. PKC
		203. PHOSPHOINOSITIDES (PIP2, IP3,etc)
		204. Citokines
		205. ERK1/2
		206. Calcineurin
		207. Calmodulin
		208. DAG
		209. AKAP
		210. CIRP/CIRBP(Cold Inducible RNA Biding Proteins)
		211. Elk
		212. JNK
		213. MAPK
		214. AMPK
		215. Per1/Per2
		216. Clock
		217. Cry
		218. UCP
		219. CGRP(Clacitocin Gene Related Peptide)
		220. Others
3.Cell Type		300. Neurons

	This criterion has as an objective to identify the cell type in which TRPs are located.	301. Myocytes
		302. Keratinocytes
		303. Adipocytes
		304. Beta Cells
		305. Others
4. Co-activated Receptors	This criterion look forward to establish the receptors by if which temperature activation of TRPs is paired happen.	400. mGluR1/mGluR5
		401. Beta Adrenergic receptor
		402. Orai/STIM1
		403. SERCA2B
		404. RyR
		405. CALCLR(calcitonin receptor-like receptor)
		406. Others
5. Transcription Factors	This criterion aims to detect transcription factors activated after temperature stimulation.	500. PPAR(Peroxisome Prolifeatore Activated Receptor)
		501. PGC1 (Peroxisome proliferator-activated receptor gamma coactivator)
		502. NRF(Nuclear Respiratory Factor)
		503. TFAM(Mitochondrial Transcription Factor)
		504. MRTF(Myocardin-related transcription factor A)
		505. EGR-1 (Early growth response protein 1) o NGFI-A(nerve growth factor-induced protein A)
		506. NFAT(Nuclear factor of activated T-cells)
		507. NFkB(nuclear factor kappa-light-chain-enhancer of activated B cells)
		508. CREB(cAMP response element-binding protein)
		509. Sp1(Specificity Protein1)

		510. BMAL1/MOP3/ARNTL (Aryl hydrocarbon receptor nuclear translocator-like protein 1)
		511. Others
6. Nervous System Location	This criterion tries to identify in what type of neurons TRPs are located in.	600. DRG(Dorsal Root Ganglia)
		601. TRG(Trigeminal Root Ganglia)
		602. Hypothalamic
		603. Others
7. Temperature Activation	This criterion seek to identify the specific temperature (℃)activation of TRPs.	700.(< 0)
		701.(0-10)
		702.(10-20)
		703.(20-30)
		704.(30-40)
		705.(40-50)
		706.(> 50)
8. Type of TRP	This criterion aims to identify the TRP that is activated.	TRPC1
		TRPC2
		TRPC3
		TRPC4
		TRPC5
		TRPC6
		TRPC7
		TRPV1
		TRPV2
		TRPV3
		TRPV4
		TRPV5
		TRPV6
		TRPA1
		TRPM1
		TRPM2
		TRPM3
		TRPM4
		TRPM5
		TRPM6
		TRPM7
		TRPM8
		TRPN1

		TRPP2
		TRPP3
		TRPP5
		TRPML1
		TRPML2
		TRPML3
9. Type of vertebrate	This criterion seek to identify the vertebrates.	900. Mouse/Mice
		901. Squirrel
		902. Camel
		903. Rat
		904. Frog
		905. Toad
		906. Lizzard
		907. Snake
		908. Fish
		909. Chicken
		910. Human
		911. Others

TABLES

Table No. 1.PICOS Framework used to define the research question.

Item	Definition
Population	Transient Receptor Potential Channels and Vertebrates.
Intervention	Temperature regulation and temperature perception physiological related processes.
Comparison	Not applicable.
Outcome	Any function on genes and intracellular protein that allows the cellular response to any temperature stimuli.
Study Type	Any primary and secondary academic literature that has passed through a peer-reviewed process.

Table No. 2. Eligibility Criteria for Title-Abstract Screening

Category	Exclusion Criteria	Description
0.Manuscript	01. Null Entries	No information is available in the abstract.
	02. Duplicate	The exact same content are present between two or more papers.
	03. Abstract and content that is reported elsewhere	Two documents or more has the exact same results and conclusions; demonstrating the manuscripts contain the same information.
	04. Missing abstract	The title suggest the outcome may be cover, but the abstract is no reported.
1.Study Population	10. Not animal	The subject of study is focused on bacteria/prokaryotes, fungi, plant, or any other unicellular eukaryote but not in animals. Also, manuscripts that do not include any cell, molecular component, organ or tissue component of multicellular animals, or are not based on cell cultures and cell lines from any invertebrate or vertebrate, are included under this criteria.
	11. Not vertebrate	The subject of study is focused in invertebrates.
	12. Not TRP Channel	The study does not include Transient Receptor Potential (TRP) channels. These criteria include all manuscripts that talk about the tryptophan amino acid diets, mutations in proteins or protein's structure that are not related to the Transient Receptor Potential Channel protein.
2.Intervention	21. Not including any function of TRPs in the perception of environmental, body temperature, regulation of animal's temperature or facultative thermogenesis.	The study does not manage to make any clear and direct relationship between the temperature and vertebrates TRPs effect in the body and ambient temperature perception, regulation of organism temperature or facultative thermogenesis; also, manuscripts that do intend to seek at any relationship but do not find any are included under this criteria.

3.Outcome	31. Pain	The study includes a relationship between any disease, pain treatment, pain nociceptive stimulation, nociceptive block, hyperalgesia, heat pain sensation, cold pain sensation, pain relief, inflammation, noxious stress or any associated pain sensation and vertebrates TRPs. Nonetheless, if it clearly and strictly reveals insights about the link between temperature and vertebrates TRPs structure on the molecular pathway activation, gene regulation, post-translation modifications, down-regulation, post-translation, gene variation, gene variation, transcription modifications and influence under other genes and proteins to understand TRPs function on the body temperature regulation, facultative thermogenesis and ambient and body temperature perception by the organism, **the manuscript will be tagged as potential.**
	32. Not including any impact of interest	Lack any relevant information about the link between temperature and vertebrates TRPs structure, the molecular pathway activation, gene regulation, post-transduction modifications, down or up regulation, post-translation, gene variation, transcription modifications and influence under other genes and proteins to understand the function of TRPs on body and ambient temperature perception, body temperature regulation or facultative thermogenesis.

4.Nature of Study	41. Not study type of interest but **may be useful for discussion**	The manuscript not treat or talk directly about any activation function of vertebrates TRPs in the body and ambient temperature perception, thermoregulation or facultative thermogenesis, but it does make valid points about the link between temperature and TRPs structure, the molecular pathway activation, gene regulation, post-transduction modifications, down or up-regulation, post-translation modifications, gene variation and influence under other genes and proteins that enrol TRPs function on body and ambient temperature perception, body temperature regulation or facultative thermogenesis; this criteria also include manuscripts that talk about the mentioned above but are performed by invertebrates. Also, manuscripts under this category may also include involvement of the vertebrates TRPs in other physiological aspects that directly contribute to performance thermoregulation, animals body or ambient temperature perception, or facultative thermogenesis of vertebrates. This documents must show a strict correlation with the body and ambient temperature perception, body temperature regulation or facultative thermogenesis. Finally, documents that provide knowledge and a basic understanding of TRPs molecular structure, evolution and structure gating properties must be included.
	42. Cannot Decide	Maybe potential because abstract highly suggest a TRPs function on the link between temperature and vertebrates TRPs structure, molecular pathway activation, gene regulation, post-transduction modifications, down or up-regulation, post-translation, post-transcription modifications, gene variation and influence under other genes and proteins that may contribute to understand the TRPs function on the body and ambient temperature perception, body temperature regulation

		or facultative thermogenesis. However, more information is needed for a conclusive decision.
	43. Potential	The manuscript has relevant information that directly and strictly talk about the link between temperature and vertebrates TRPs structure, its molecular pathway activation, its gene regulation, its post-transduction modifications, its down or up-regulation, its post-translation regulations, its gene variation, its transcription modifications and its influence over other genes and proteins that permit the understanding of the TRPs function in physiological processes related to the body and ambient temperature perception, body temperature regulation or facultative thermogenesis. It is important to mention that cell culture, single tissue or studies performed on cell lines of multicellular organisms that are vertebrates must be included.

Table No. 3. Eligibility Criteria for Title, Abstract, Methods and Results

Category	Exclusion Criteria	Description
0. Manuscript	01. Lack of availability	Manuscripts contents are not found using Google Search (Google Scholar) or available by Universidad San Francisco de Quito electronic resources nor by request.
1.Outcome	10. Not including any impact of interest	Lack any information about the link between temperature and vertebrates TRPs activation that contributes to gene regulation, post-transduction modifications, down or up-regulation, post-translation or transcription modifications of **proteins and genes that contribute to the body and ambient temperature perception, body temperature regulation or facultative thermogenesis of vertebrates**. Studies that make a vague mention and with no critical information to understand the TRPs and its molecular pathway activation function on the body and ambient temperature perception, body temperature regulation or facultative thermogenesis must be included under this criterion.
2. Nature of Study	21. Not study type of interest but **may be useful for discussion**	The manuscript not treat or talk directly about any link between temperature and the activation of vertebrates TRPs over the genes and proteins that are part of the body and ambient temperature perception, thermoregulation or facultative thermogenesis of vertebrates; but it does make valid points about the link between temperature and TRPs activation that complements gene regulation, post-transduction modifications, down or up-regulation, post-translation or transcription modifications that enrol functions on body and ambient temperature perception, body temperature regulation or facultative thermogenesis of vertebrates. Also, manuscripts under this category may also include involvement of the vertebrates TRPs in other physiological aspects that directly contribute to thermoregulation performance, animals body or ambient temperature perception, or facultative thermogenesis of vertebrates. This documents must show a strict correlation with the body and ambient temperature perception, body temperature regulation or facultative thermogenesis. Finally, documents that provide knowledge and a basic understanding of TRPs molecular structure, structure gating properties, evolution and localization must be included.

	22. Chosen	The manuscript has relevant information that directly and strictly talk about the link between temperature and vertebrate's activated-TRPs on the genes and intracellular proteins that contribute with the molecular pathway activation, gene regulation, post-transduction modifications, down or up-regulation, post-translational modifications that has any effect on the body´s and ambient temperature perception, body temperature regulation or facultative thermogenesis. It is important to mention that cell culture, single tissue or studies performed on cell lines of multicellular organisms that are vertebrates must be included.

Table No. 4. Extraction Data of Title, Abstract, Methods and Results

Criteria	Objective
1. Physiological Processes	This criterion aims to recognize the physiological-processes that are activated by TRP temperature stimulation.
2.TRP Activation Pathway and activated Proteins	This criterion seek to detect the proteins and molecules that contribute to TRP temperature stimulation and are part of the activation of the molecular processes established in criteria 1.
3.Cell Type	This criterion has as an objective to identify the cell type in which TRPs are located.
4. Co-activated Receptors	This criterion look forward to establish the receptors by if which temperature activation of TRPs is paired happen.
5. Transcription Factors	This criterion aims to detect transcription factors activated after temperature stimulation.
6. Nervous System Location	This criterion tries to identify in what type of neurons TRPs are located in.
7. Temperature Activation	This criterion seek to identify the specific temperature (°C)activation of TRPs.
8. Type of TRP	This criterion aims to identify the TRP that is activated.
9. Type of vertebrate	This criterion seek to identify the vertebrates.

Table No. 5. Evidence of data extracted from all retrieve manuscripts.

Type of Article	First Author Name	Physiological Process	Cell Type	Cell Line	Nervous System Location	Stimuli	Type of TRP	Co-activated Receptors/Integral Membrane Protein	Kinase / Phosphatase	Gene or Intracellular Protein	Transcription Factor or Transcription Co-regulator	Type of vertebrate
Research	Li C., et al.	Energy Expenditure	Myocytes	C2C12	-	Cold (Menthol)	TRPM8	-	-	UCP1	PGC1α	Mice
Research	Clemmensen, Christoffer., et al.	Adaptive Thermogenesis-Adipogenesis	Adipocytes (BA and WA), Neurons	Isolated	Hypothalamus Paraventricular Nucleus	Cold (Icilin) at 30ºC	TRPM8	β-ARs, MC4R	-	UCP1, Cox2,Cox4,Atpb5,CytC ,Gamt	PGC1α	Mice, Human
Research	Baskaran, P.,et al.	Adaptive Thermogenesis	Adipocytes (BA)	Isolated	-	(Capsaicin) at 22ºC	TRPV1	-	CAMKII, AMPK	Sirtuin-1, BMP8b,GLP-1, Cox2,Cidea,Dio2	PPARγ,PPARα,FOXC2, PRDM16	Mice
Research	Goralczyk, Anna., et al.	Adaptive Thermogenesis - Adipogenesis	Adipocytes (BA, WA and BR)	Induced	-	Cold (Menthol)	TRPM8, TRPP3	-	-	UCP1, FABP-4 (aP-2)	PGC1α	Human
Research	Kim M., et al.	Adaptive Thermogenesis - Adipogenesis	Adipocytes (BA, WA and BR), Neurons	Isolated	Dorsal Root Ganglia	KetoA [10-oxo-12(Z)-octadecenoic acid]	TRPV1	β3-AR	-	UCP1,Cpt1b, Leptin	PGC1α,PRDM16	Mice
Research	Kida, Ryosuke., et al.	Adaptive Thermogenesis - Adipogenesis	Adipocytes (BA)	HB2	-	Heat(Capsaicin)	TRPV1	-	-	UCP1,FABP-4 (aP-2)	PPARγ,PGC1α	Mice
Research	Sun W., et al.	Adaptive Thermogenesis - Adipogenesis	Adipocytes (BA and WA)	Isolated	-	2APB,LPC	TRPV2	α1-AR,β-3AR	-	UCP1	PPARγ,PGC1α	Mice
Research	Alawi, Khadija M., et al.	Adaptive Thermogenesis - Warm Temperature Perception	Adipocytes (BA)	Isolated	-	AMG9810	TRPV1(Blocked)	α1-AR,β-3AR	-	UCP1,UCP3,Dio2	PPARγ,PGC1α	Mice
Research	Kim M., et al.	Adaptive Thermogenesis - Adipogenesis	Adipocytes (BA, WA and BR)	Isolated	-	Eicosapentaenoic acid and docosahexaenoic acid	TRPV1	β3-AR	-	UCP1,Adrb3,Fgf21(Indirectly),Cidea(Indirectly),Cpt1b(Indirectly)	PGC1α(Indirectly),PRDM16(Indirectly)	Mice
Research	Rossato, Marco., et al.	Adaptive Thermogenesis - Adipogenesis	Adipocytes (WA and BR)	Isolated	-	Cold (Menthol and Icilin), 26ºC	TRPM8	-	-	UCP1,Cidea, Leptin, FABP-4	PPARγ,PRDM16	Human
Research	Ma, Shuangtao., et al.	Adaptive Thermogenesis	Adipocytes (BA)	Isolated	-	Cold (Menthol)	TRPM8	-	PKA	UCP1	-	Mice
Research	Kusudo T., et al.	Adaptive Thermogenesis -	Myocytes, Hepatocytes, Adipocytes(BA and WA)	Isolated	-	High Fat Diet	TRPV4(Blocked)	-	CaN	PECK,ACO,CPT1,AdipoR-1,TRPC3,TRPC6	PPARδ,PPARα,LXRα, Myogenic	Mice

		Energy Expenditure										
Research	Yamashita, Hitoshi., et al.	Adaptive Thermogenesis - Warm Temperature Perception (stress)	Adipocytes(BA), Neurons	Isolated	Dorsal Root Ganglia	Heat(Capsaicin)	TRPV1	-	-	UCP1(Dowregulated), COXIV	-	Rat
Research	Li Ye.,et al.	Adaptive Thermogenesis - Adipogenesis	Adipocytes (BA, WA and BR)	Isolated, 3T3-F442A	-	AMG9810 (TRPV1/4 antagonist), BCTC(TRPV1/4 antagonist)	TRPV4(Blocked), TRPV1 (Blocked)	β-ARs	ERK1/2	UCP1,CytC,CoxIII, Cox4il, Cox5b, Cox7a, and Cox8b,Adrb3,Cidea / Downregulated chemokines and cytokines: MCP1, MIP1a, CXCL1, IL6, and RANTES (see more in paper)	PGC1α	Mice
Research	Cheung SY., et al.	Adaptive Thermogenesis s-Adipogenesis	Adipocytes (BA)	3T3-L1	-	Epicatechin	TRPV3(Blocked)	-	PI3K/Akt(Dowregulated inTRPV3blocked)	-	FOXO1,C/EBPα,PPARγ(activated when TRPV3 Blocked)	Mice
Research	Tajino, K.,et al.,	Adaptive thermogenesis-Cold Temperature Perception	Adipocytes(BA),Embrionic kidney	Isolated, HEK293	-	Cold(10ºC, Menthol)	TRPM8	-	-	UCP1	NFkB	Mice
Research	Li Li Zhang., et al.,	Adaptive Thermogenesis - Adipogenesis	Adipocytes (BA and WA)	Isolated, 3T3-L1	-	Heat(Capsaicin)	TRPV1	-	-	-	PPARγ	Mice, Human
Review	Panchal S.K., et al.	Adaptive Thermogenesis - Adipogenesis	Adipocytes (BA, WA and BR)	Isolated, HB2,3T3-L1,3T3-F442A	-	Heat(Capsaicin)	TRPV1	-	-	UCP1,GLP-1	PPARα,PGC1α	Mice, Rat, Human
Review	Señarís R., et al.	Adaptive Thermogenesis - Temperature Perception	Adipocytes (BA and WA), Neurons	Isolated, HB2,3T3-L1,3T3-F442A	Dorsal Root Ganglia, Hypothalamus	Cold(Menthol, Icillin,) 20-30ºC(TRPM8)	TRPM8, TRPA1	β3-AR	PKA(TRPM8)	UCP1	-	Mice, Human
Review	Uchida K., et al.	Adaptive Thermogenesis - Adipogenesis	Adipocytes (WA and BR)	Isolated, HB2,3T3-L1,3T3-F442A	-	Heat(Capsaicinoids,2APB,LPC, LPI)	TRPV1,TRPV1(Blocked), TRPV2,TRPV2(Blocked), TRPV3, TRPV4,T	β3-AR	CaN,PKA	UCP1, FABP-4,BMP7(Upregulated), Adiponectin(TRPC5 negative regulated)	PPARγ, PGC1α	Mice, Human

							RPM4,TRPM8,TRPC5 and TRPA1					
Review	Liu J., et al.	Adaptive Thermogenesis	Adipocytes (BA, WA and BR)	Isolated, HB2,3T3-L1,3T3-F442A	-	Heat(Capsinoids),42ºC(TRPV1) Monoacylglycerol, 52ºC(TRPV2), Cold(Menthol), 20ºC(TRPM8),Allylisothiocyannate(TRPA1),cinnamaldehyde(TRPA1)	TRPV1,TRPV2,TRPA1,TRPM8	-	-	UCP1	-	Mice, Human, Rat
Review	Bishnoi M., et al.	Adaptive Thermogenesis - Temperature Perception	Adipocytes (BA, WA and BR), Neurons	Isolated, 3T3-L1	Hypothalamus, and Nociceptors(TRPM8)	Heat,TRPV1 (>42°C) and TRPV2 (>52°C); TRPV3 (>32°C); Basal body temp, TRPV4 (>27–41°C), TRPM2 (>36°C), Cold TRPM8 (<27°C, Menthol, Eucalyptol, Icillin,),TRPA1 (<17°C) and TRPC5(<35–25°C)	TRPV1,TRPV2,TRPV3,TRPM2,TRPM8,TRPC5, TRPA1	-	PI3K/Akt(Downregulated inTRPV3blocked)	UCP1(TRPV2,TRPV4, TRPM8)	PPARγ(TRPV1,TRPM2,activated when TRPV3 Blocked)C/EBPα,(activated when TRPV3 Blocked,TRPV1); PGC1α(TRPM2,TRPV2),FOXO1(activated when TRPV3 Blocked)	Mice, Human, Rat
Review	Uchida, Kunitoshi., et al.	Adaptive Thermogenesis	Adipocytes (BA, WA and BR)	Isolated, HB2,3T3-L1	-	2APB, LPC, LPI, Cold(menthol), AMG9810(TRPV4), BCTC(TRPV4)	TRPV2, TRPM8,TRPV4(Blocked)	β3-AR	ERK1/2(TRPV4),PKA(TRPM8)	UCP1,LPL	PGC1α	Mice, Human
Review	Seebacher F., et al.	Adaptive Thermogenesis	Adipocytes (BA, WA and BR)	Isolated, 3T3-F442A	-	<26ºC(TRPM8)	TRPV4,TRPM8	-	-	UCP1	PGC1α	Mice
Review	Kruse V., et al.	Adaptive Thermogenesis - Temperature Perception	Adipocytes (BA, WA and BR)	Isolated	Dorsal Root Ganglia, Hypothalamus(Preoptic-sub nucleus)	Cold <27ºC (TRPM8) , Cold 17ºC(TRPA1)	TRPM8, TRPA1	β1-AR, β3-AR	-	UCP1	-	Mice, Human
Review	Ma J., et al.	Adaptive Thermogenesis - Adipogenesis	Adipocytes(BA)	Isolated	-	Heat(Capsaicin), Monoacylglycerol(TRPV1),	TRPV1,TRPM8, TRPA1	-	PKA(TRPM8)	UCP1(TRPM8,TRPV1)	-	Rat, Mice

						Cold(Menthol), Cold(Cinnamaldehyde TRPA1)						
Review	Blaszkiewicz, Magdalena., et al.	Adaptive Thermogenesis - Temperature Perception	Adipocytes (BA, WA and BR), Neurons	Isolated Adipocytes,3T3-L1	Dorsal Root Ganglia, Trigeminal Ganglia, Hypothalamus	Heat (Capsaicin),AMG9810(TRPV1), DPBA,Epicatechin(TRPV3)	TRPV1, TRPV1(Blocked), TRPV3(Blocked), TRPV2	α1-AR,β-3AR(TRPV1)	-	UCP1	PGC1α(TRPV1), FOXO1,C/EBPα,PPARγ(activated when TRPV3 Blocked)	Mice
Review	Birerdinc, Aybike., et al.	Adaptive Thermogenesis	Adipocytes (BA and WA)	Isolated, 3T3-L1	-	Heat(Capsaicinoids), monoacylglycerols	TRPV1	-	-	UCP1	-	Mice, Human
Review	Whittle A., et al.	Adaptive Thermogenesis - Temperature Perception	Adipocytes (BA), Neurons	Isolated	Dorsal Root Ganglia	Heat(Capsaicin), Cold(Menthol)	TRPV1,TRPM8	-	PKA(TRPM8)	UCP1	-	Mice, Human
Review	Ahern G.P.	Adaptive Thermogenesis - Temperature Perception-Adipogenesis	Adipocytes (BA, WA and BR)	Isolated, HB2,3T3-L1,3T3-F442A	Afferent and Efferent Neurons	TRPV1/4 Heat(Capsaicin), TRPM2 cADP-ribose, H2O2, TRPM8 Cold(Menthol), TRPC1/5 Ca depletion/PLC, TRPA1 Cold(icillin, mustard oil, garlic,PLC)	TRPV1,TRPV4,TRPM2, TRPM8, TRPC1, TRPC5, TRPA1	β-ARs	PKA,PKC, ERK1/2,PLC	UCP1,AdipoR-1	PPARα,PGC1α	Mice, Human
Research	Moraes, Maria Nathalia, et al.,	Adaptive Thermogenesis-Warm Temperature Perception	Adipocytes (BA)	Isolated	-	Light and Dark at Cold 22ºC	TRPV1	-	-	UCP1, Per1, Per2	Rev-erbα, Bmal1,Clock	Mice
Research	Moraes, Maria Nathalia, et al.,	Adaptive Thermogenesis-Warm Temperature Perception	Adipocytes (BA), Neurons	Isolated	SCN, Eyes nerve endings	Light and Dark at Cold 22ºC	TRPV1, TRPM8	-	-	UCP1, Per1, Per2	Rev-erbα, Bmal1,PPARγ,PPARα	Mice
Research	Jeronimo, Rodrigo, et al.,	Warm Temperature Perception (stress)	Embryonic	ZEM-2S	-	Light and Dark with heat shock at 33ºC	TRPV1	-	-	HSP90aa1,Per2	-	Fish (*Danio rerio*)
Research	Jeong, Keun-Yeong; Seong, Jinsil	Warm Temperature Perception (stress)	Neurons, Hepatocytes,	Isolated	Dorsal Root Ganglia, Hypothalamus	Heat(Capsaicin)	TRPV1	-	-	Per2	HSF1	Rats

Research	Xiao B, et al.,	Warm Temperature Perception (SOCE)	Lymphocyte (Jurak T-cell)	HEK293T, HeLa	-	Heat(35ºC<)	TRPV3	STIM1-Orai1	-	-	NFAT, AP-1	Human
Research	Liu, X, et al.,	Warm Temperature Perception (SOCE)	Keratinocytes	Isolated, HEK293T, HeLa	Dorsal Root Ganglia	Heat(33ºC<)	TRPA1, TRPV3,TRPV4	STIM1-Orai1/Orai3	-	-	-	Mice
Research	Nakipova, O.V., et al.,	Cold Temperature Perception (SOCE)	Cardiomyocytes	Isolated	-	Cold 7ºC, Heat 30ºC	TRPC3, TRPC1,2, 4-7	STIM1-Orai1, SERCA	-	-	-	Rats, Ground Squirrel (*Spermophilus undulatus*)
Research	Fujita, T., et al.	Cold Temperature Perception (Cold Induced Regulation, stress)	Male Germ Cells, Osteocytes	Isolated, U-O2S, NIH 3T3, NC65, HEK293	-	Mild Cold (32ºC)	TRPV4	-	-	SRSF5,RBM3,CIRBP	-	Mice, Human
Research	Fujita, T., et al.	Cold Temperature Perception (Cold Induced Regulation, stress)	Lung fibroblast	Isolated, U-O2S	-	Mild Cold (32ºC)	TRPV4,TRPV3,TRPM8	-	-	SRSF5,RBM3,CIRBP	-	Mice, Human
Research	Sun, Jing.,et al	Cold Temperature Perception (Cold Induced Contraction)	Endothelial	Isolated	-	Cold(Menthol)	TRPM8	-	RhoA/Rho (attenuated), MYPT-1(attenuated)	-	-	Mice
Research	Sabnis, Ashwini S.,et al.,	Cold Temperature Perception (stress)	Bronchial epithelial	BEAS-2B,NHBE	-	Cold(Menthol, 18ºC)	TRPM8	-	-	IL-6, IL-8	-	Human

FIGURES

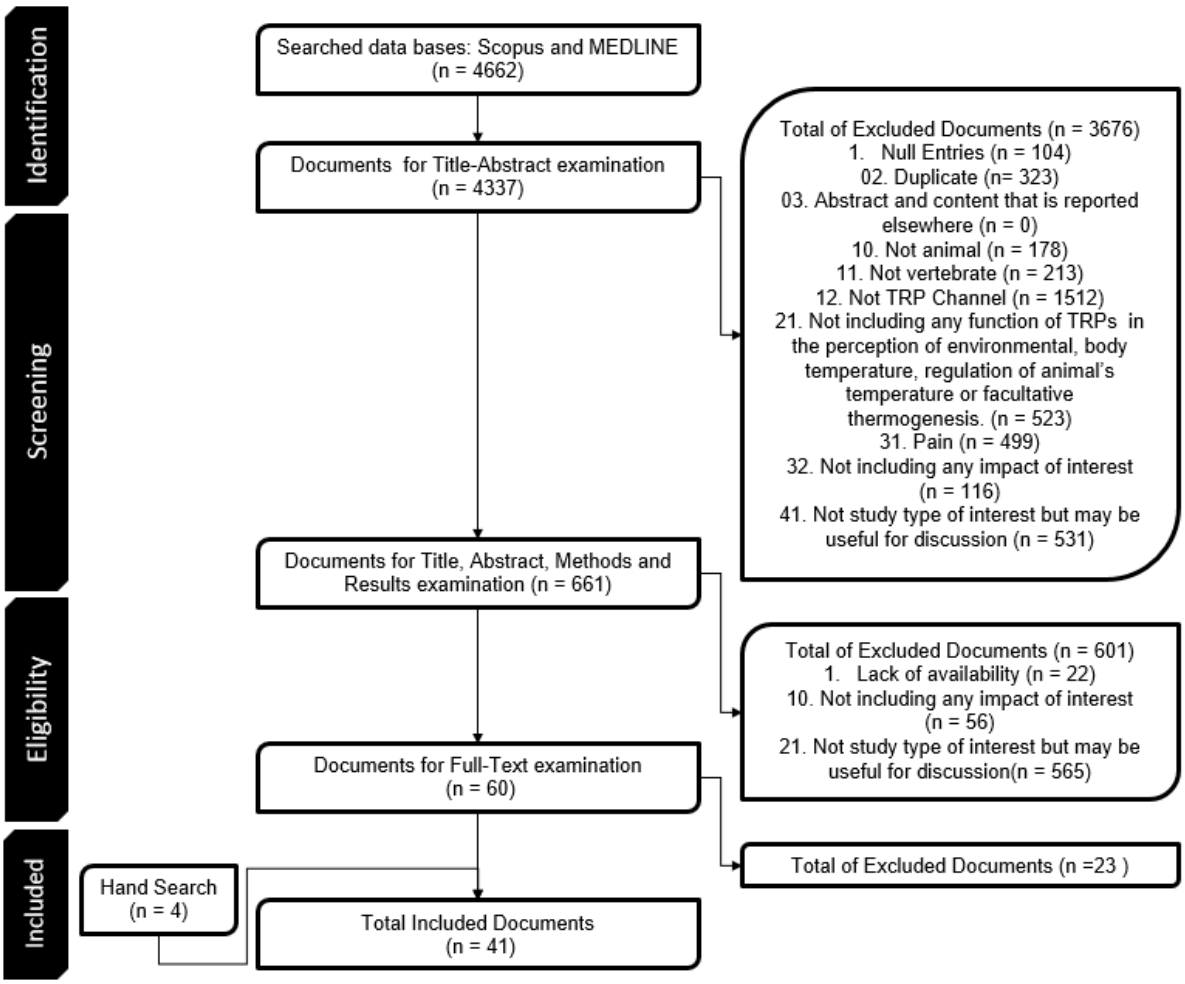

Figure No. 1. PRISMA Flow Diagram

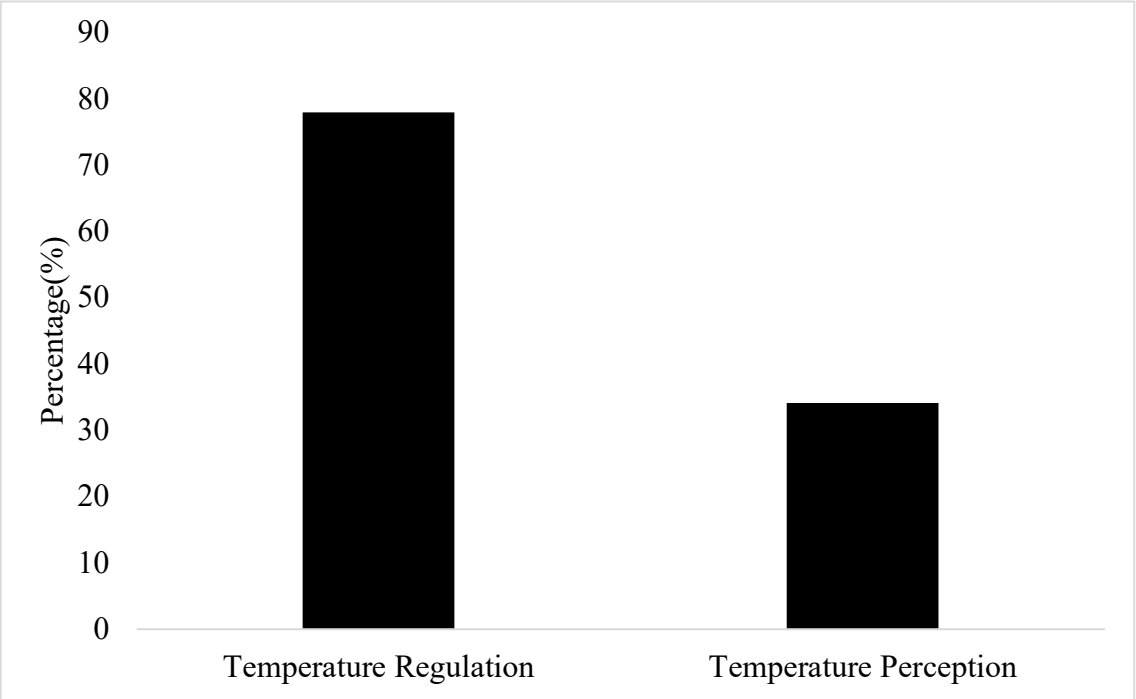

Figure No. 2.Percentages for Temperature Regulation and Temperature Perception relative to the total number of documents used.

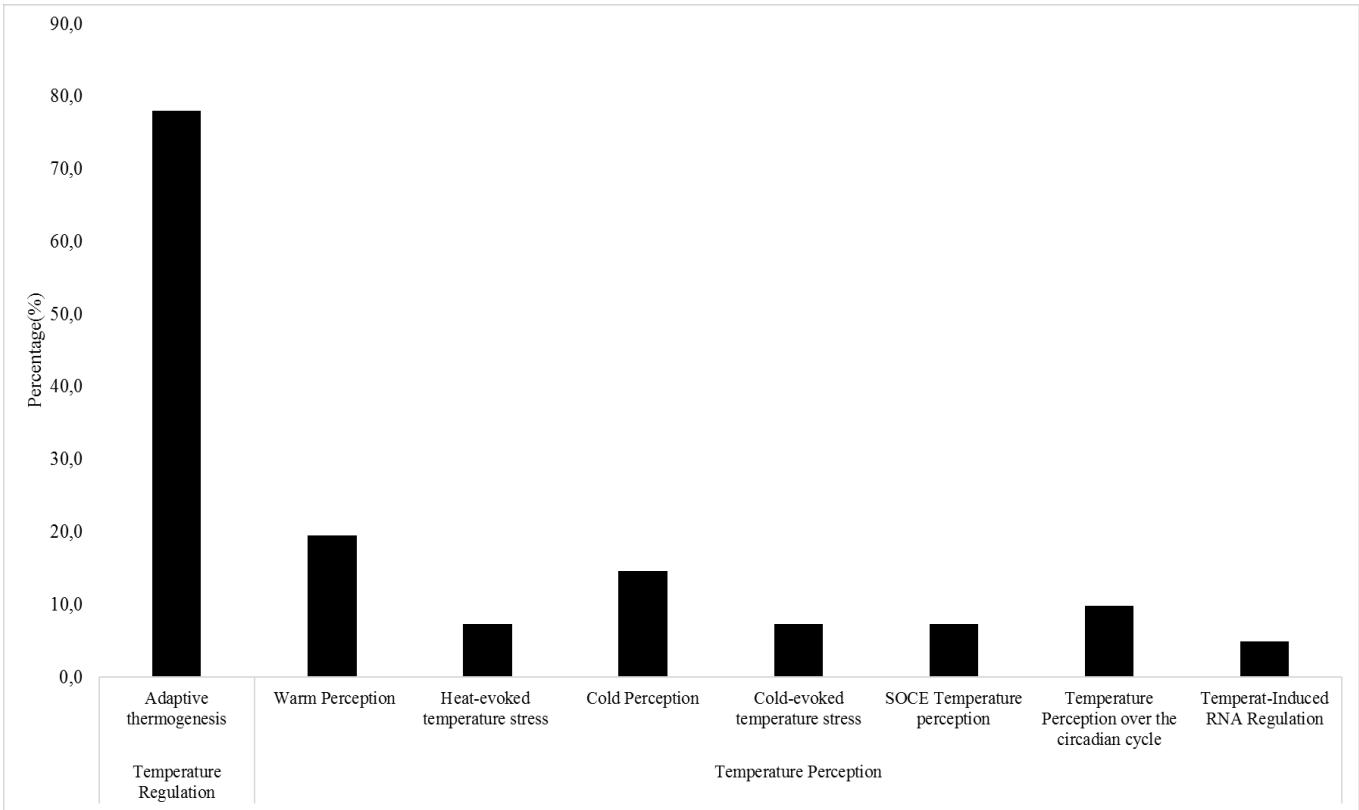

Figure No. 3. Percentage for each of the addressed physiological processes relative to the total number of documents used.

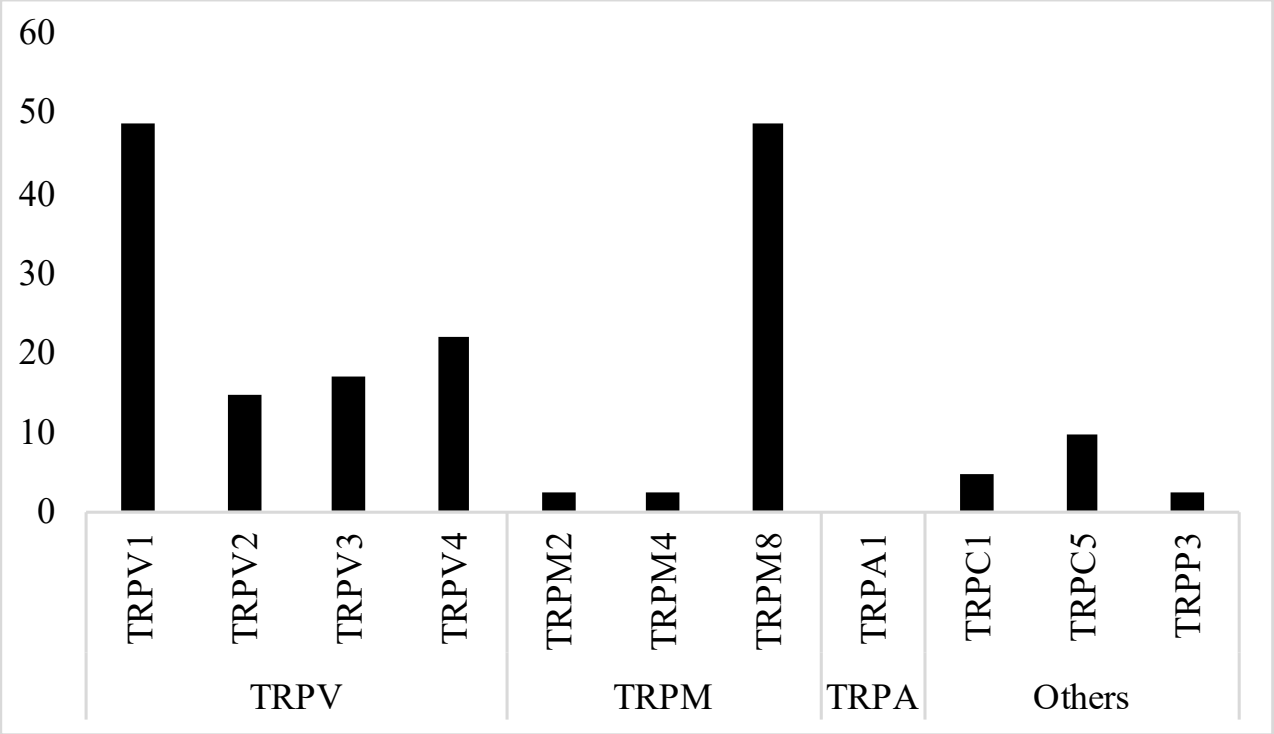

Figure No. 4.Families of TRPs with their most reported individual relative to the total number of documents used.

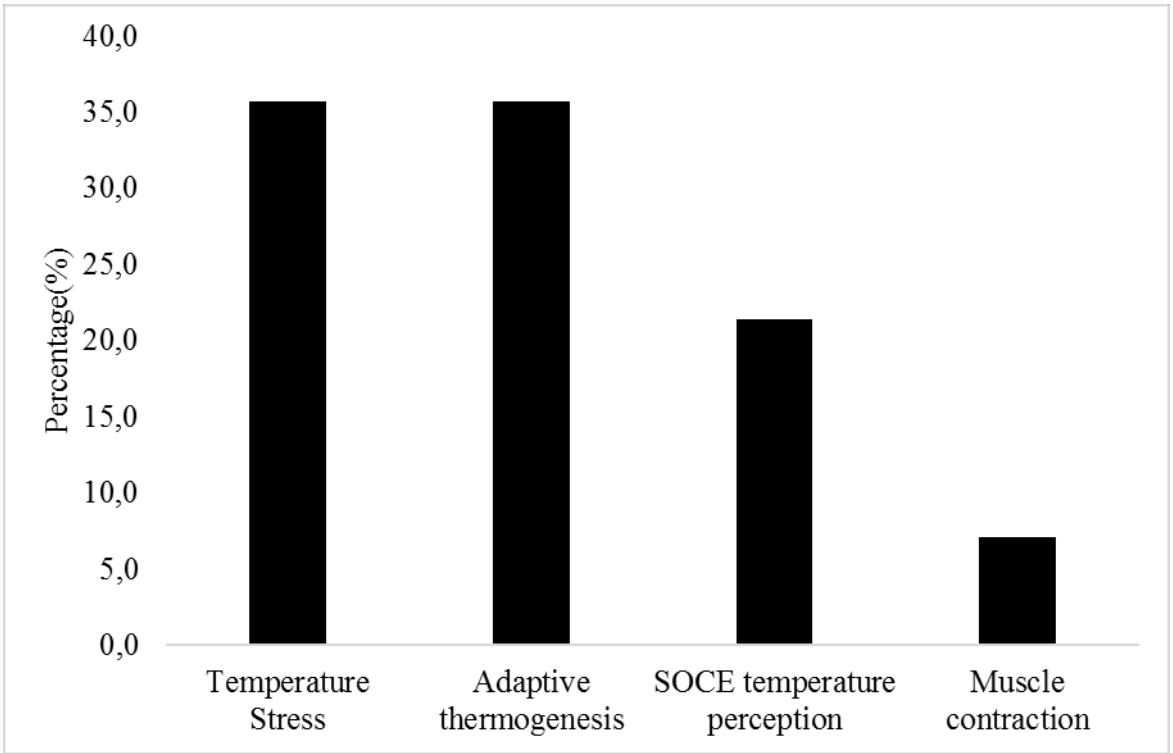

Figure No. 5. Percentages of physiological processes coupled with temperature perception relative to the total number of manuscripts found for temperature perception.

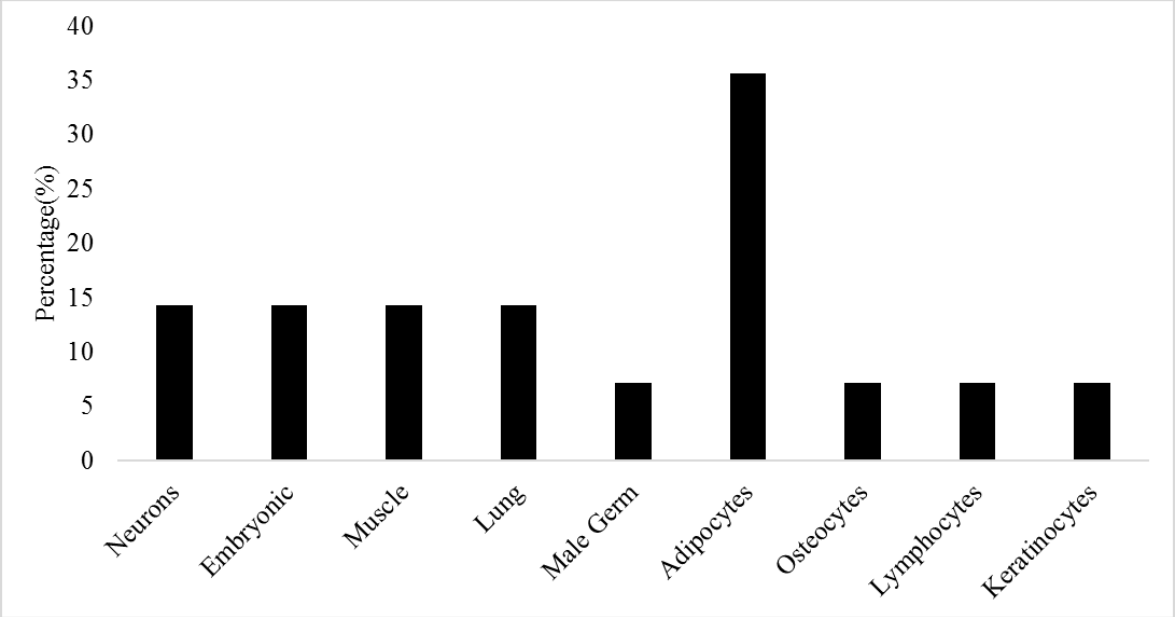

Figure No. 6. Percentages of cells addressed in temperature perception relative to the total number of manuscripts found for temperature perception.

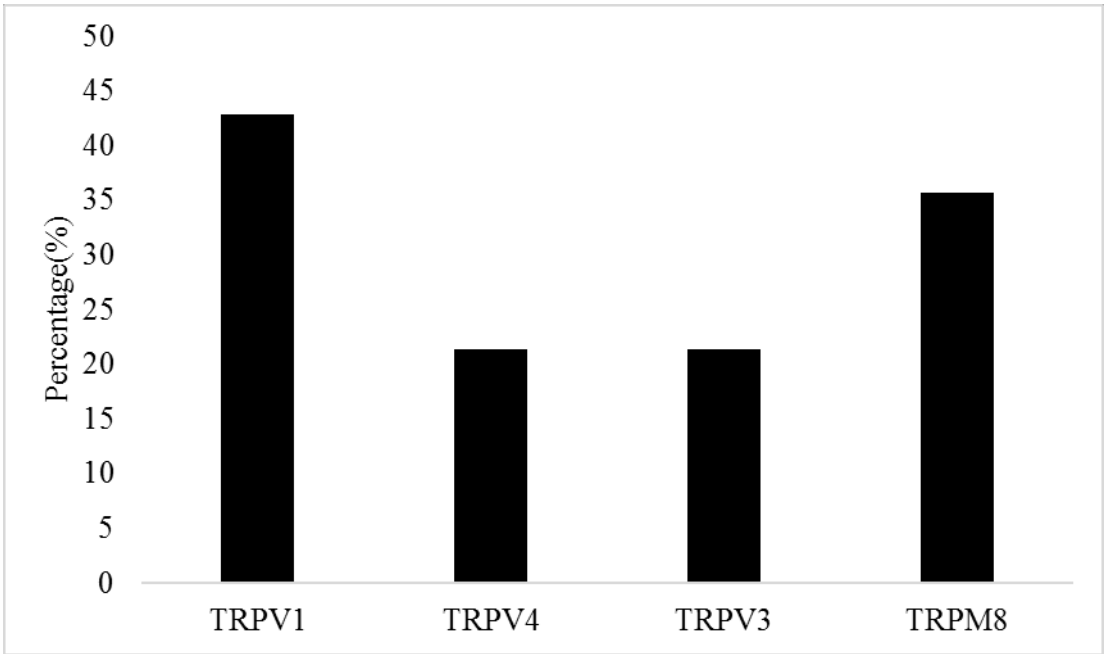

Figure No. 7. Percentage of TRPs addressed in temperature perception relative to the total number of manuscripts found for temperature perception.

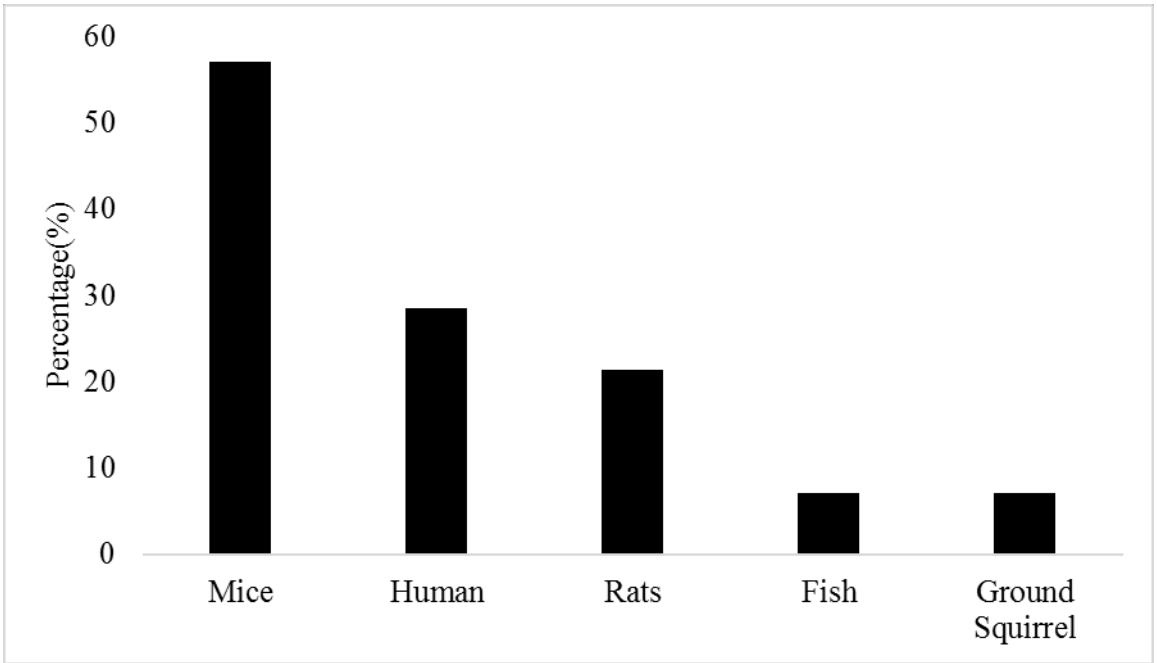

Figure No. 8. Percentages of vertebrates addressed in temperature perception relative to the total number of manuscripts found for temperature perception.

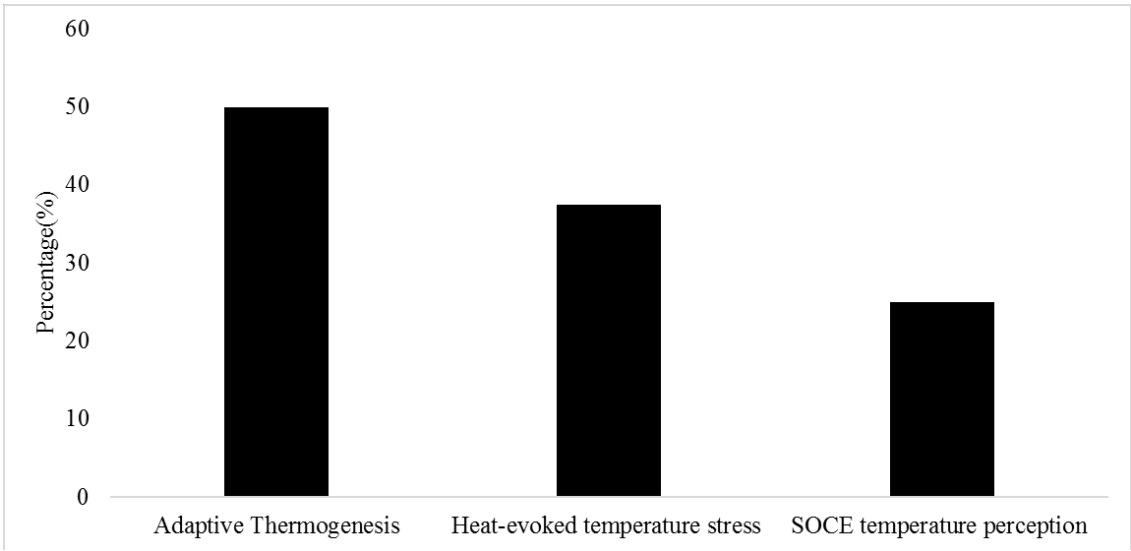

Figure No. 9. Percentages of physiological processes coupled with warm temperature perception relative to the total number of manuscripts found for warm temperature perception.

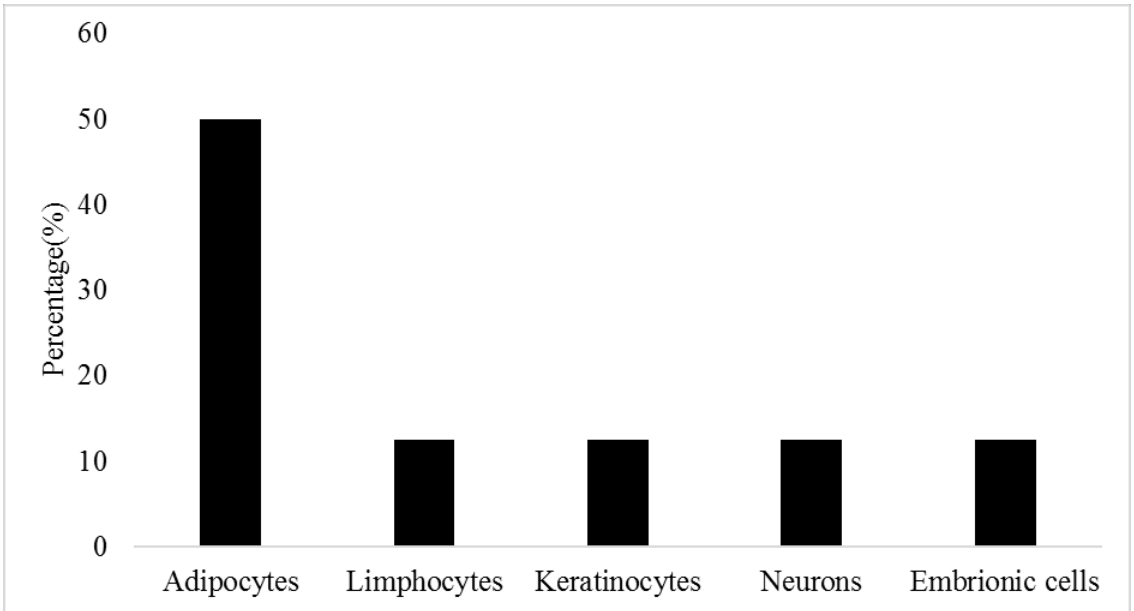

Figure No. 10. Percentages of cells addressed in warm temperature perception relative to the total number of manuscripts found for warm temperature perception.

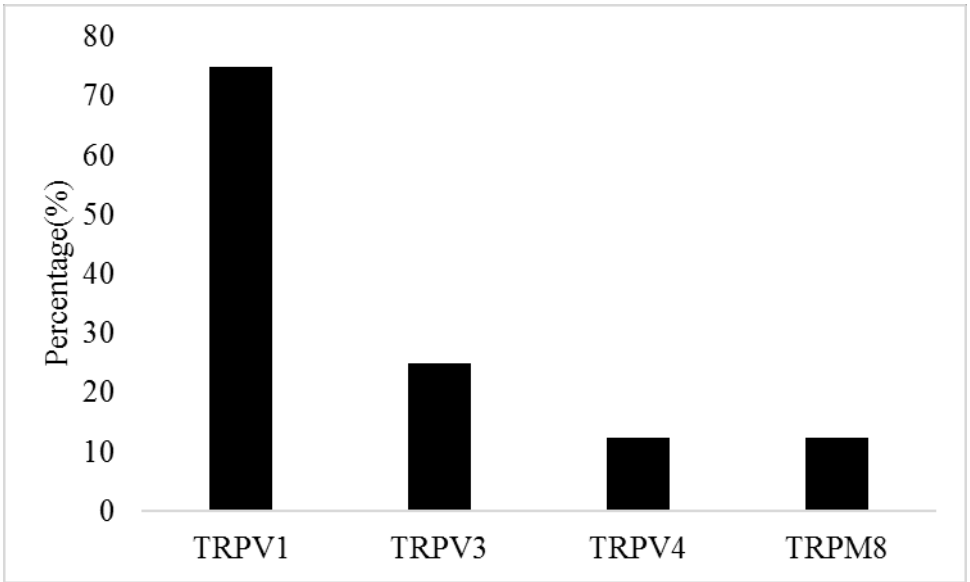

Figure No. 11.Percentages of TRPs addressed in warm temperature perception relative to the total number of manuscripts found for warm temperature perception.

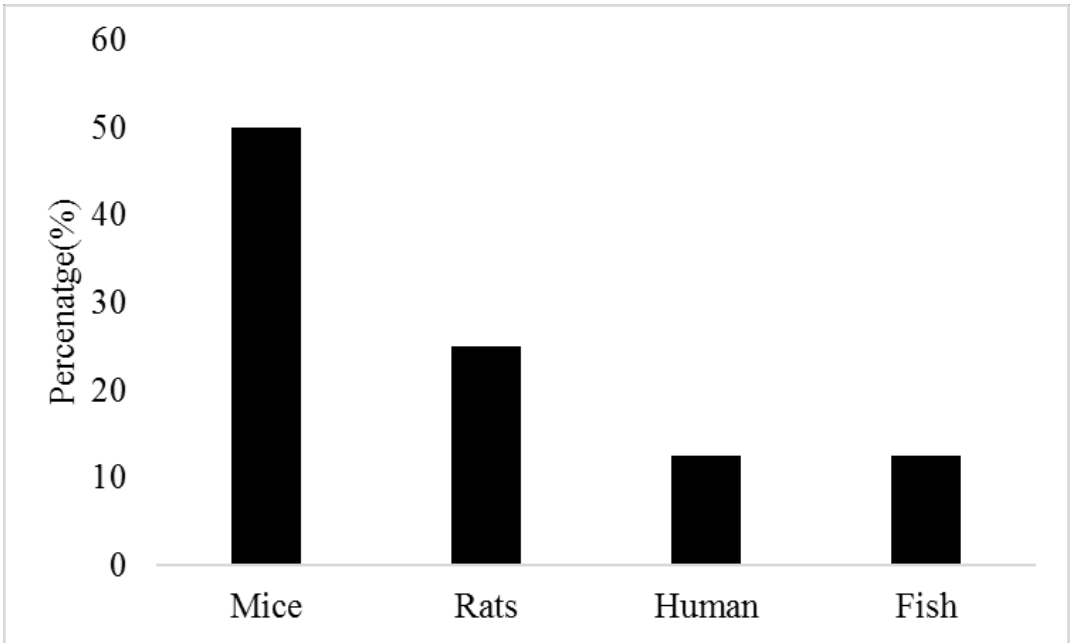

Figure No. 12.Percentages of vertebrates addressed in warm temperature perception relative to the total number of manuscripts found for warm temperature perception.

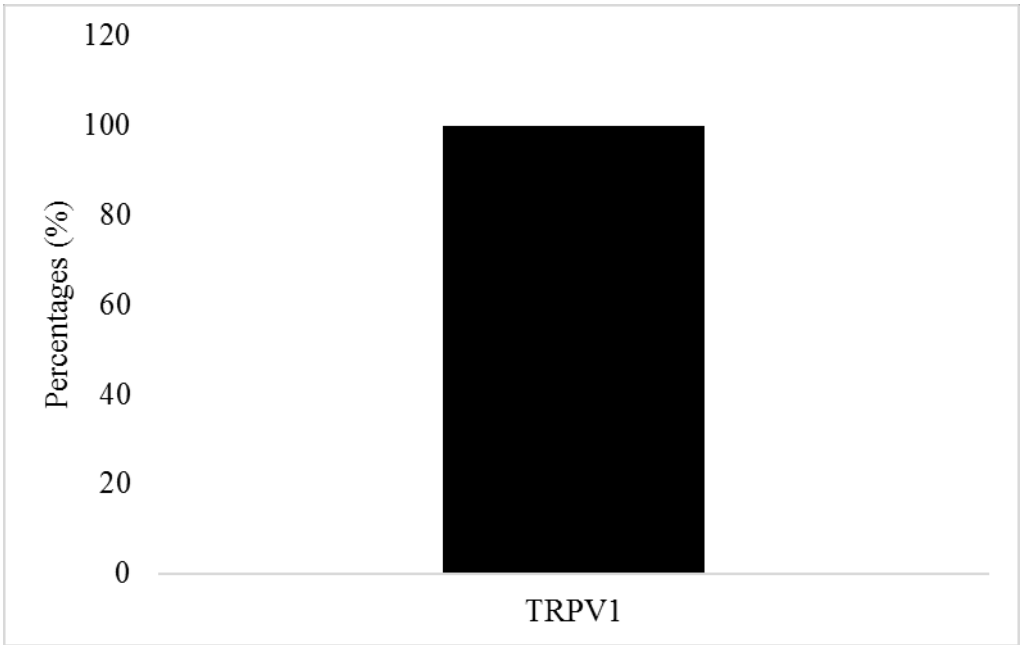

Figure No. 13. Percentages of TRPs in heat-evoked temperature stress relative to the total number of manuscripts found for heat-evoked temperature stress.

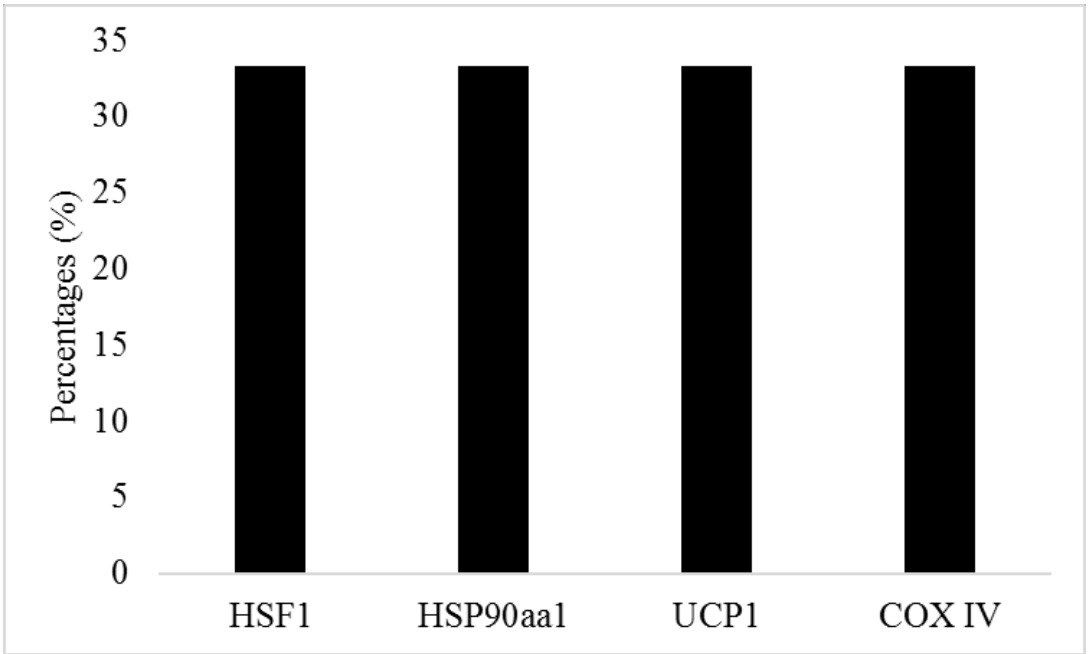

Figure No. 14. Percentages of intracellular proteins correlated with activated-TRPV1 in heat-evoked temperature stress relative to the total number of manuscripts found for heat-evoked temperature stress.

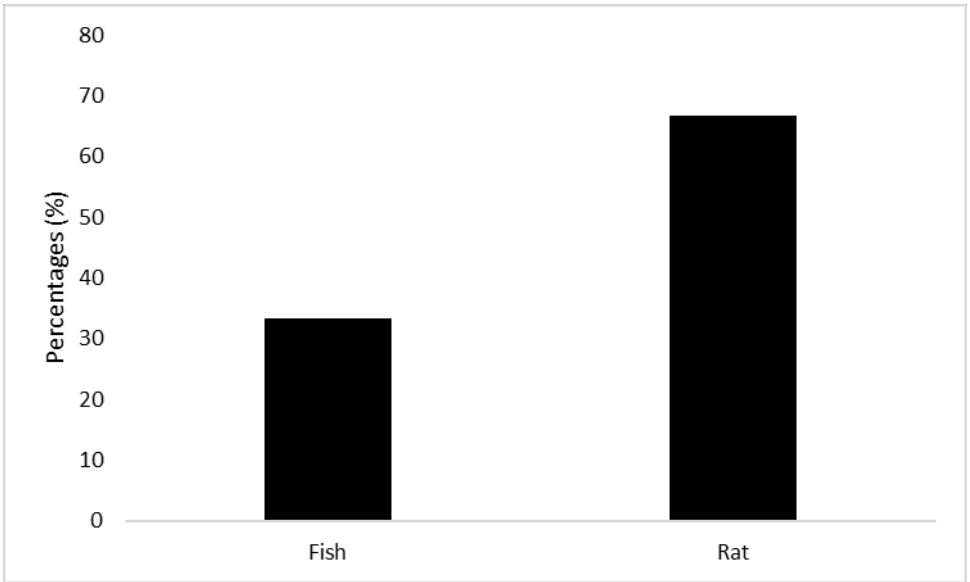

Figure No. 15. Percentages of vertebrates addressed in heat-evoked temperature stress relative to the total number of manuscripts found for heat-evoked temperature stress.

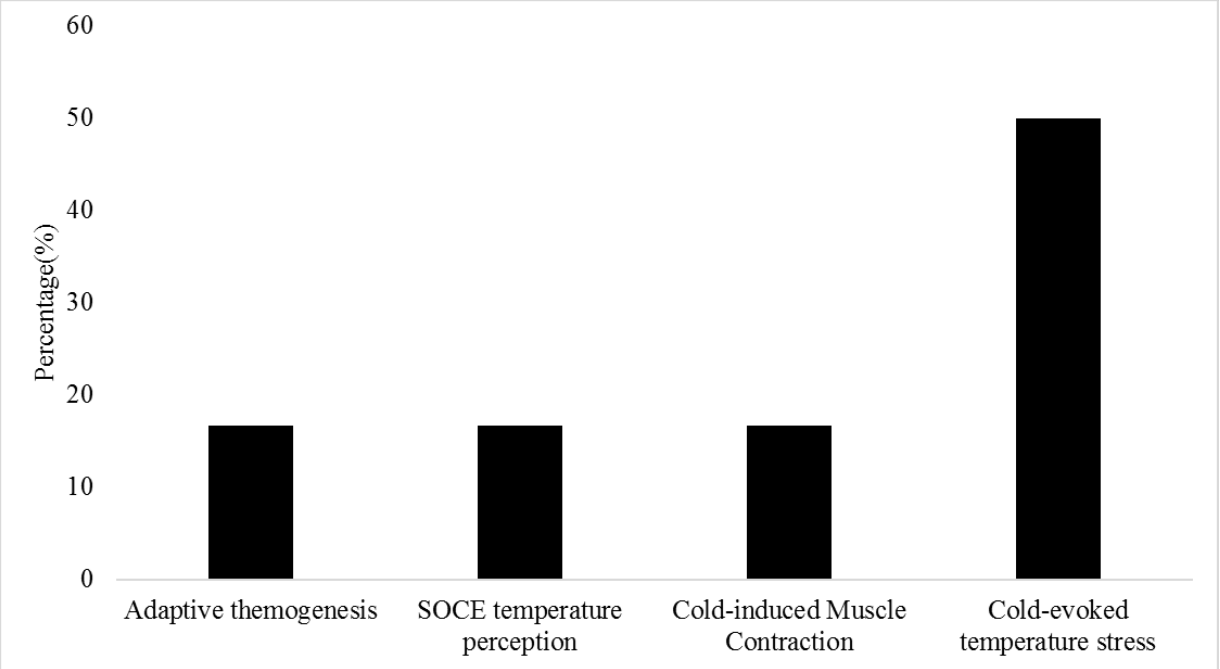

Figure No. 16. Percentages of physiological processes coupled with cold temperature perception relative to the total number of manuscripts found for cold temperature perception.

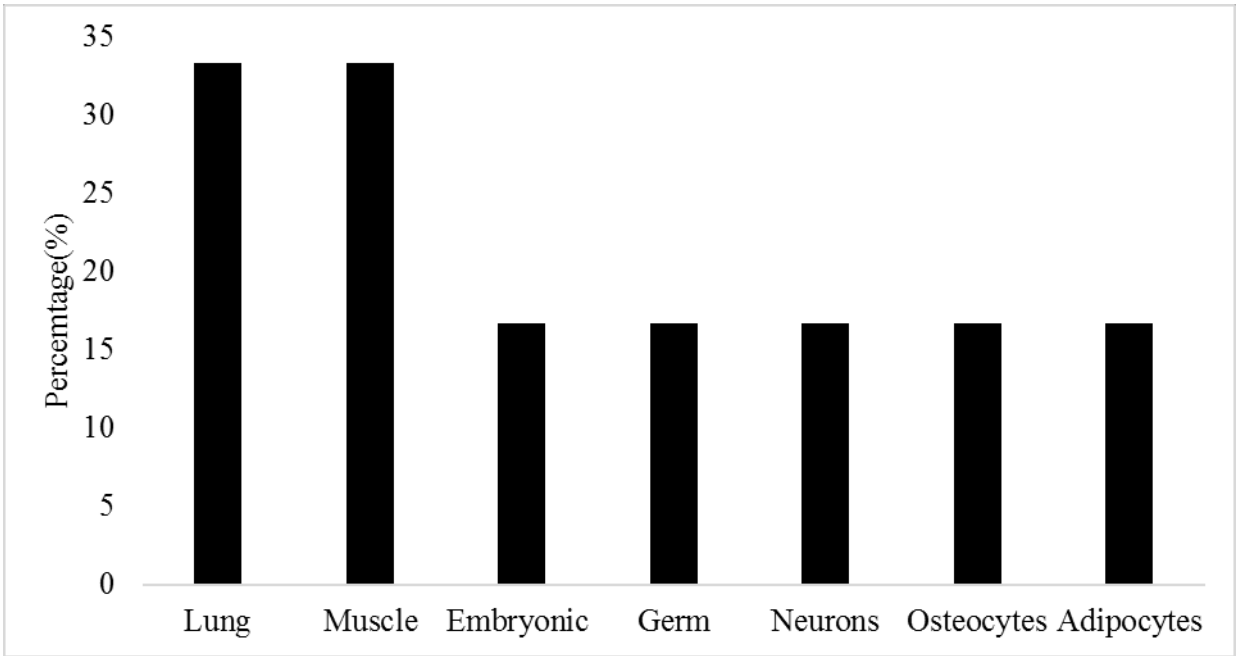

Figure No. 17. Percentages of cells addressed in cold temperature perception relative to the total number of manuscripts found for cold temperature perception.

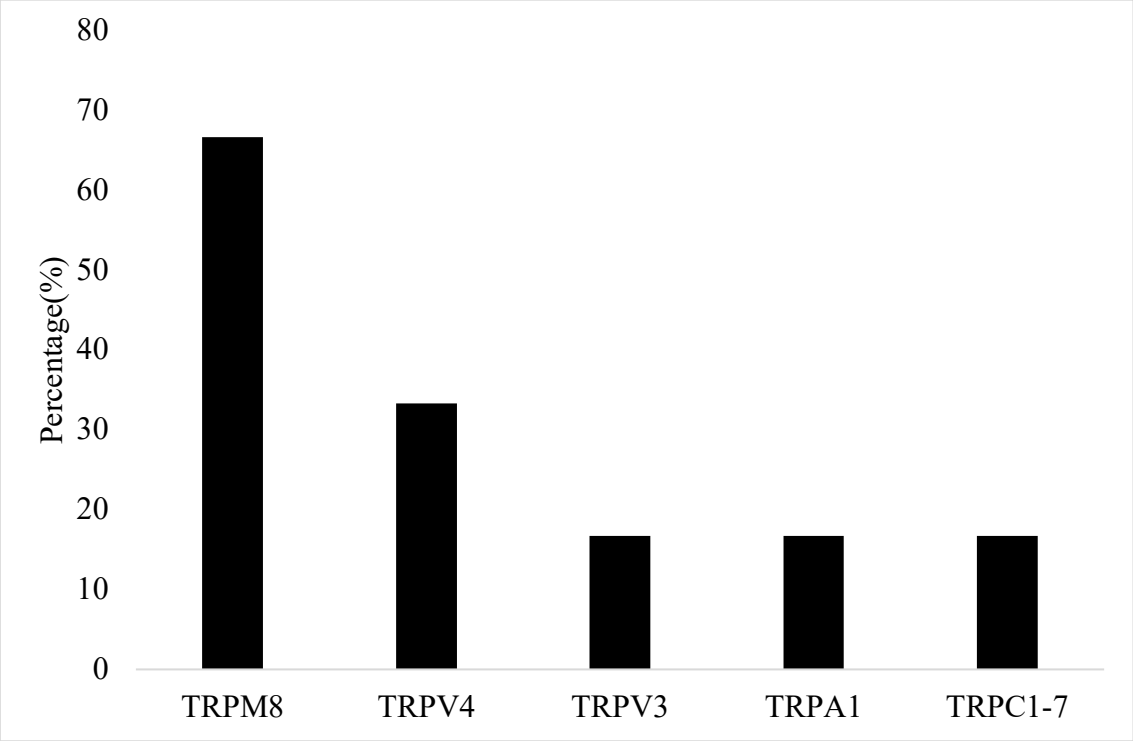

Figure No. 18. Percentages of TRPs addressed in cold temperature perception relative to the total number of manuscripts found for cold temperature perception.

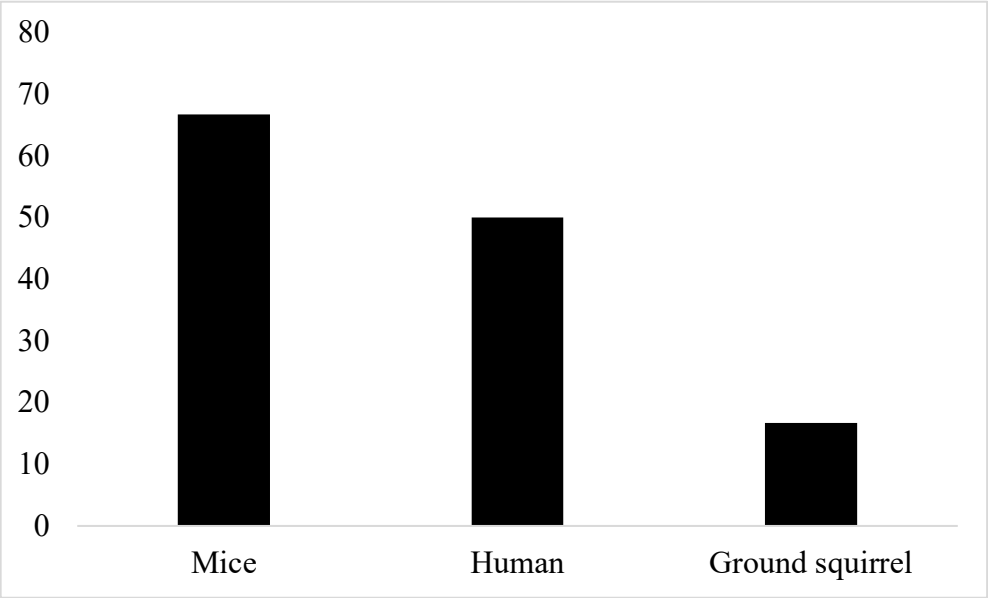

Figure No. 19. Percentages of vertebrates addressed in cold temperature perception relative to the total number of manuscripts found for cold temperature perception.

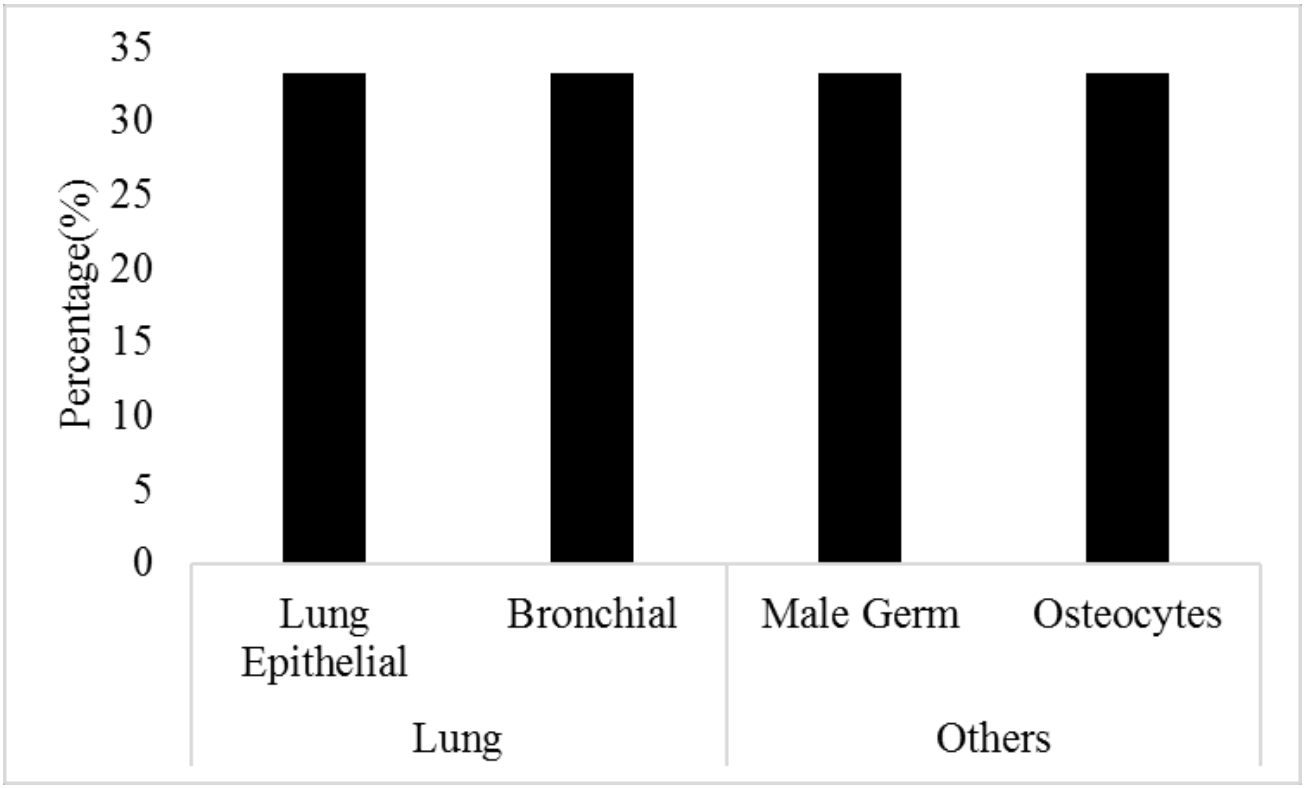

Figure No. 20. Percentages of cells addressed in cold-evoked temperature stress relative to the total number of manuscripts found for cold-evoked temperature stress.

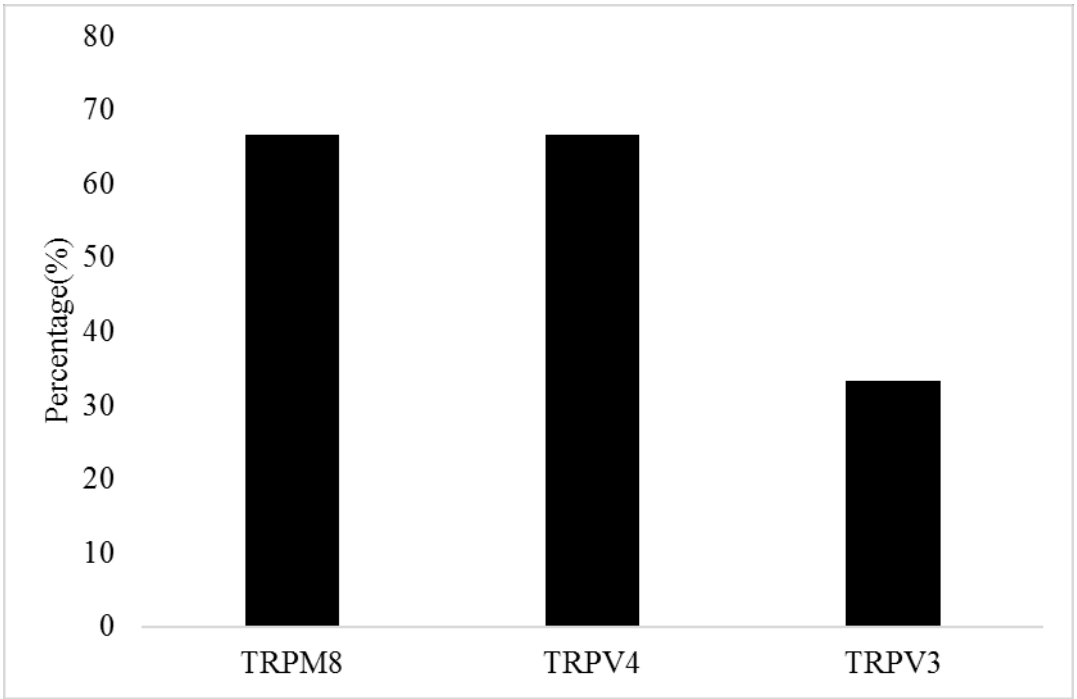

Figure No. 21. Percentages of TRPs addressed in cold-evoked temperature stress relative to the total number of manuscripts found for cold-evoked temperature stress.

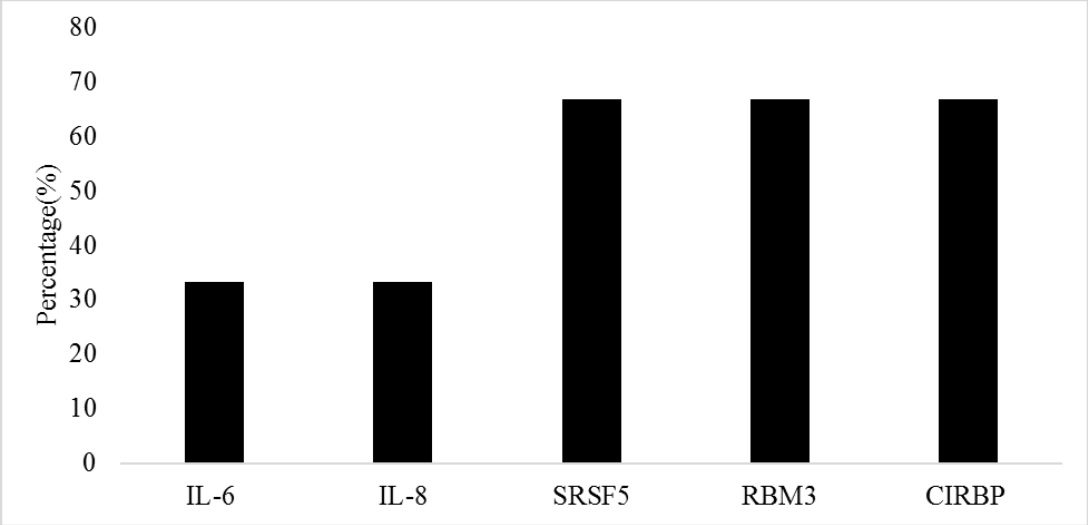

Figure No. 22. Percentages of intracellular proteins influenced by activated-TRPs in cold-evoked temperature stress relative to the total number of manuscripts found for cold-evoked temperature stress.

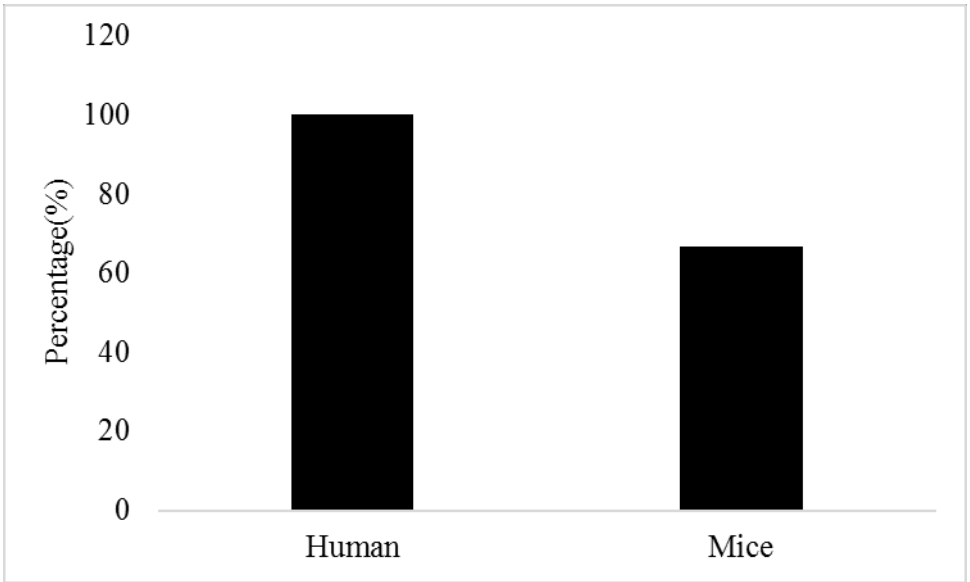

Figure No. 23. Percentages of vertebrates addressed in cold-evoked temperature perception relative to the total number of manuscripts found for cold-evoked temperature perception.

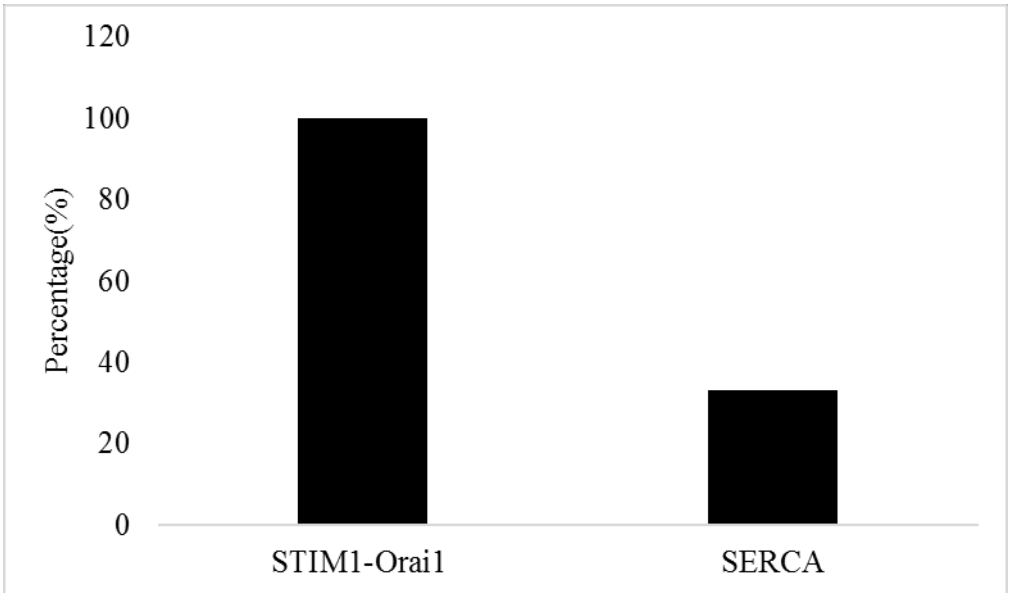

Figure No. 24. Percentages of receptors co-activated with TRPs in SOCE temperature perception relative to the total number of manuscripts found for SOCE temperature perception.

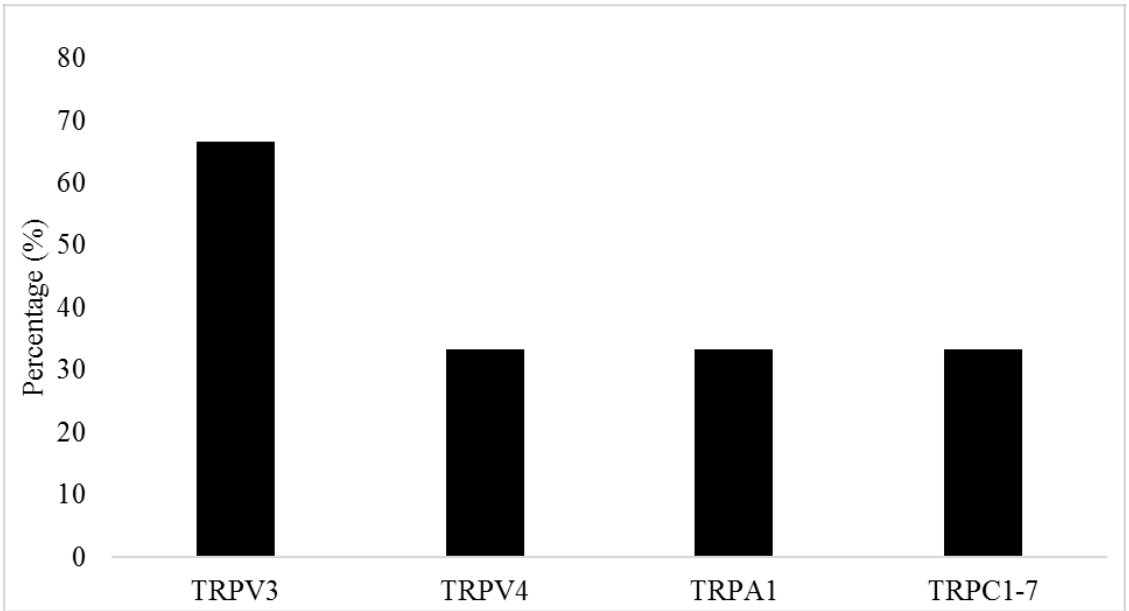

Figure No. 25. Percentages of TRPs in SOCE temperature perception relative to the total number of manuscripts found for SOCE temperature perception.

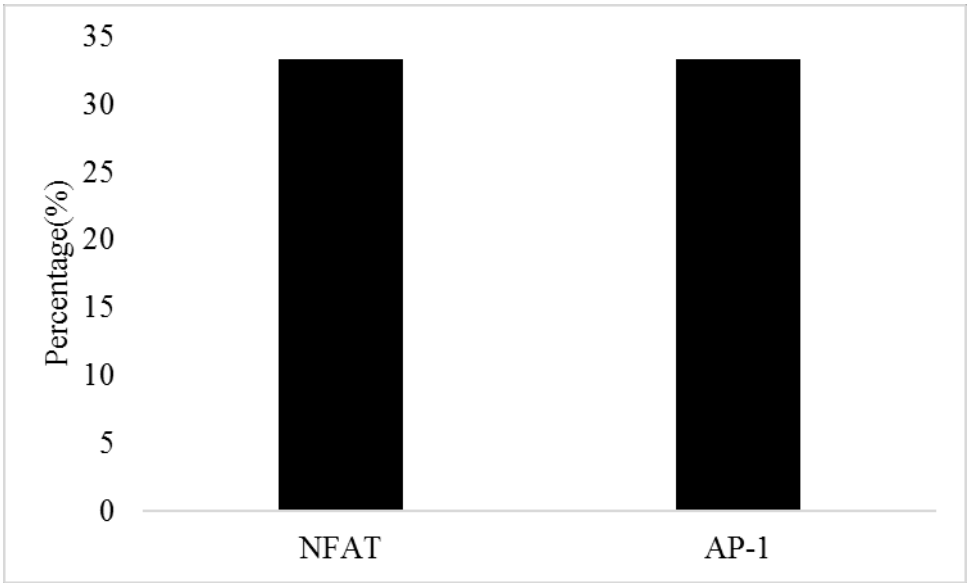

Figure No. 26. Percentages of intracellular proteins in proteins influenced by activated-TRPs in SOCE temperature perception relative to the total number of manuscripts found for SOCE temperature perception.

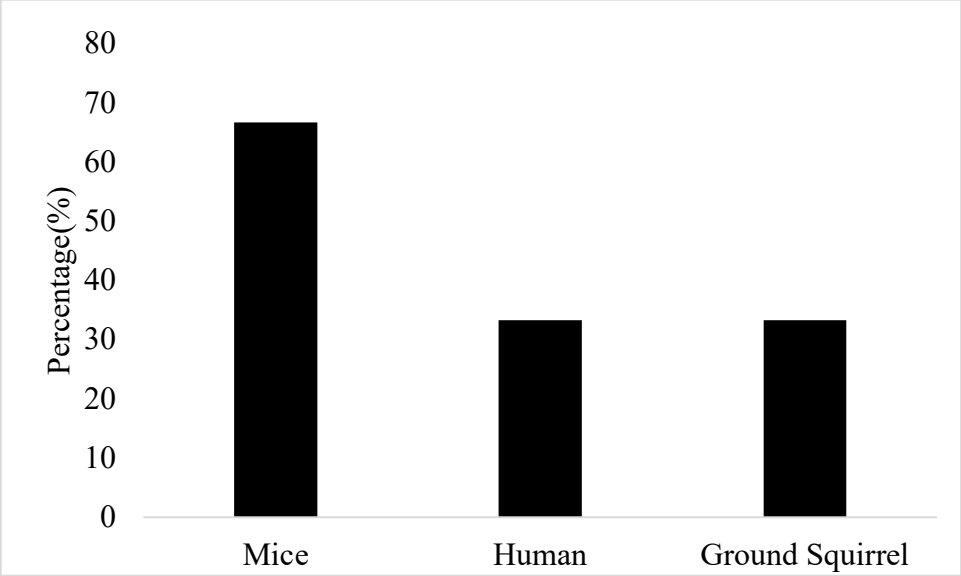

Figure No. 27. Percentages of vertebrates addressed in SOCE temperature perception relative to the total number of manuscripts found for SOCE temperature perception.

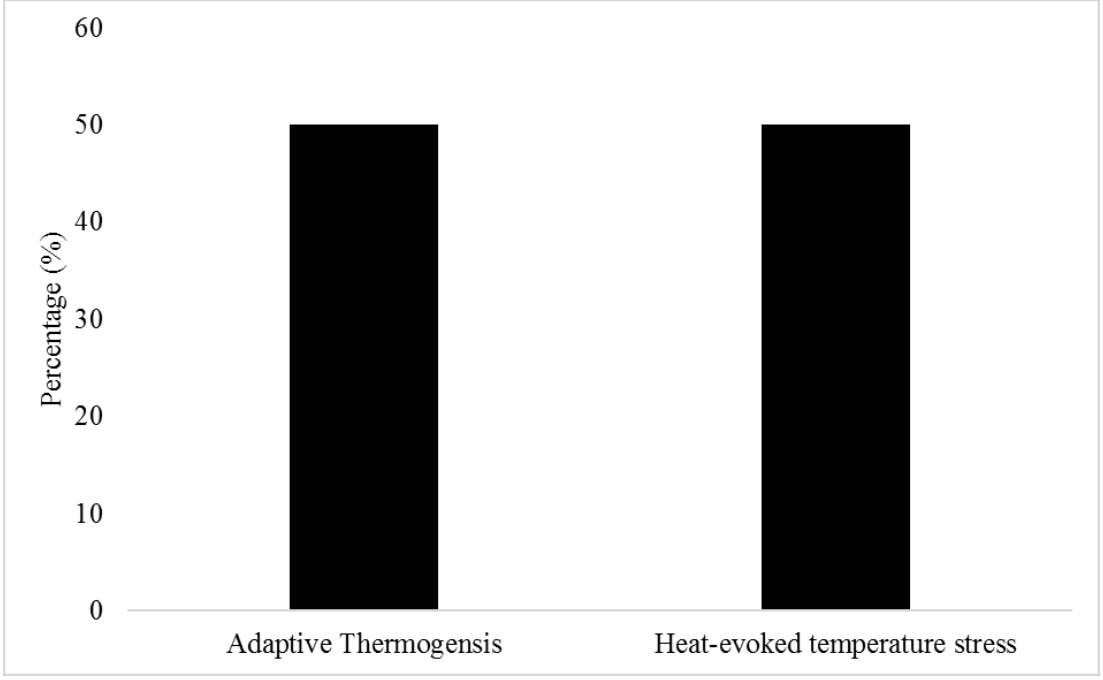

Figure No. 28. Percentage of physiological processes coupled with temperature perception over vertebrates' circadian cycle relative to the total number of manuscripts coupled with temperature perception over vertebrates' circadian cycle.

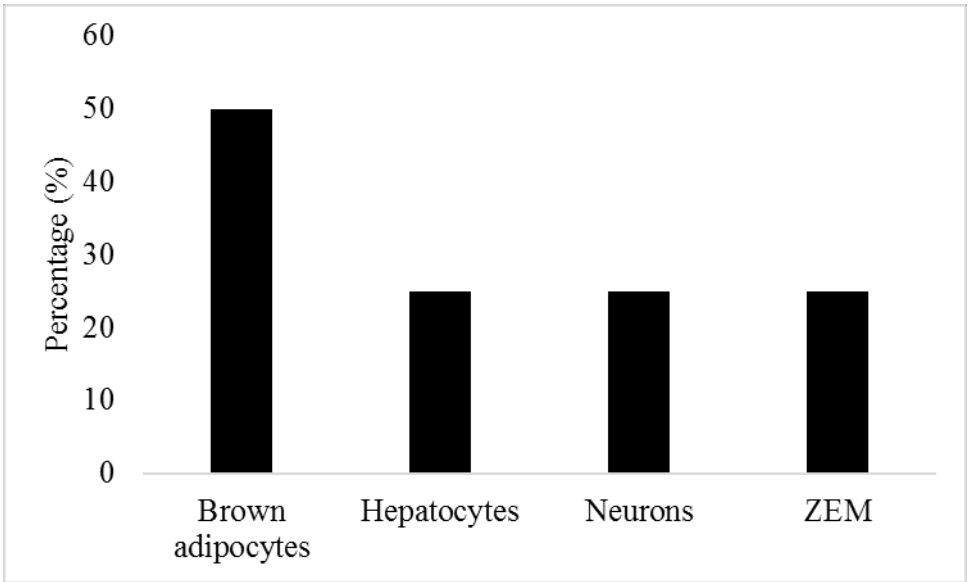

Figure No. 29. Percentages of cells addressed in in temperature perception over vertebrates' circadian cycles relative to the total number of manuscripts found for in temperature perception over vertebrates' circadian cycle.

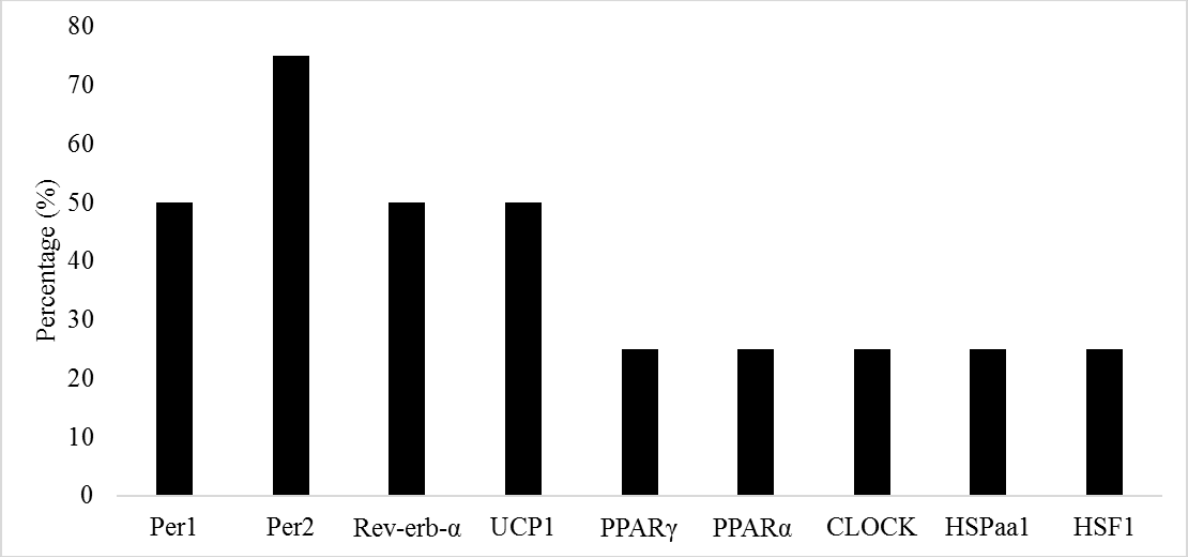

Figure No. 30. Percentages of intracellular proteins in temperature perception over vertebrates circadian cycle relative to the total number of manuscripts found for in temperature perception over vertebrates circadian cycle.

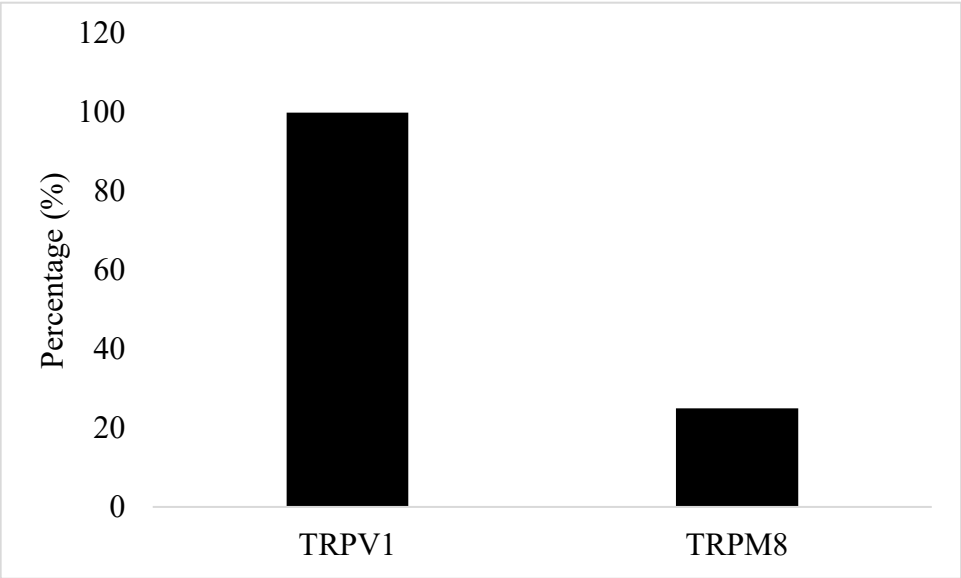

Figure No. 31.Percentages of TRPs in proteins in temperature perception over vertebrates' circadian cycle relative to the total number of manuscripts found for in temperature perception over vertebrates' circadian cycle.

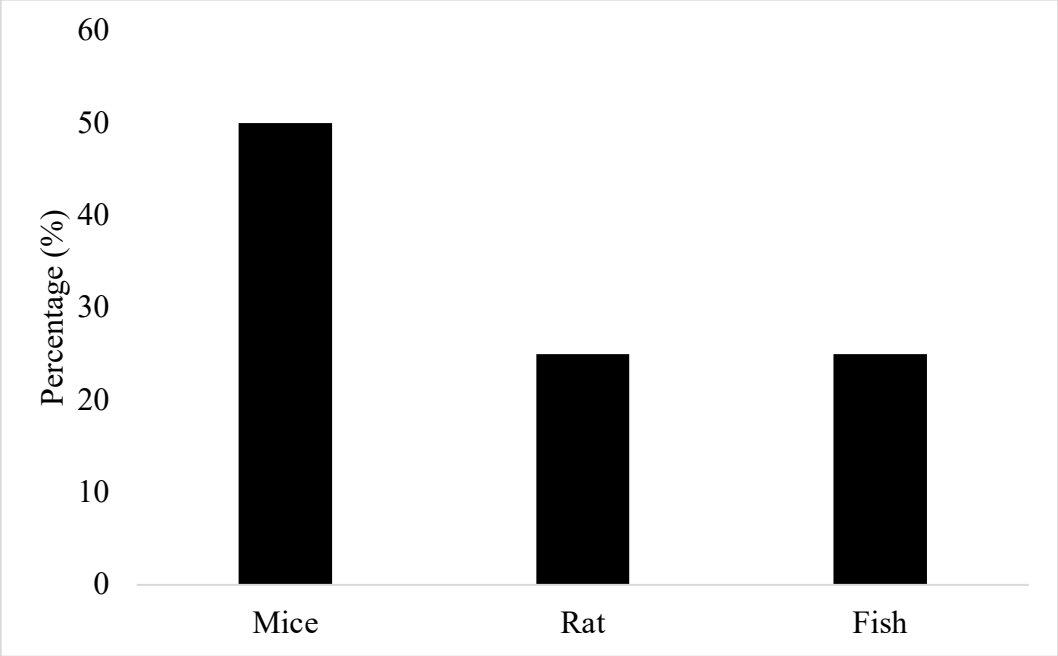

Figure No. 32. Percentages of vertebrates addressed in temperature perception over vertebrates' circadian cycle relative to the total number of manuscripts found for in temperature perception over vertebrates' circadian cycle.

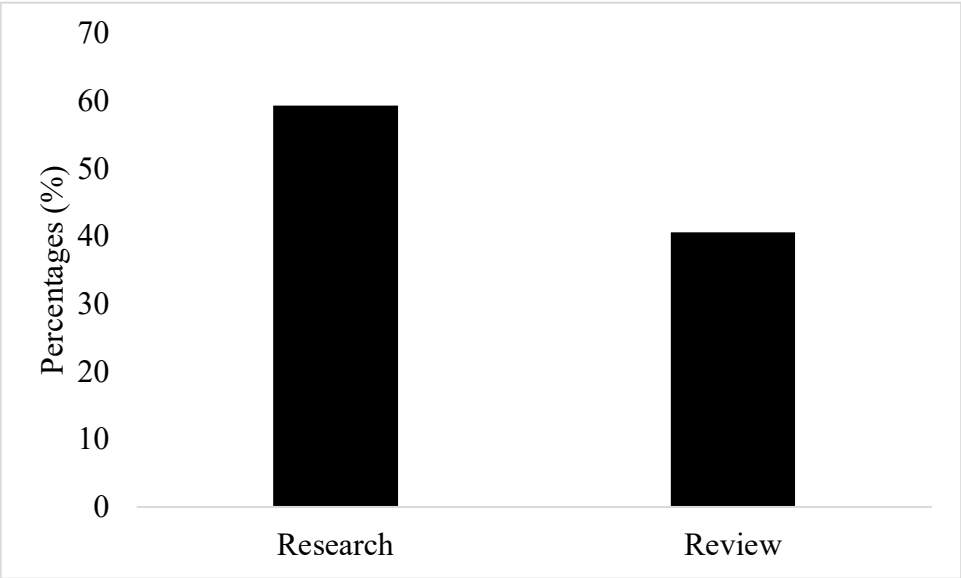

Figure No. 33. Percentages for type of academic literature assessing activated-TRPs functions on genes and intracellular proteins within temperature regulation of vertebrates relative to the total number of manuscripts found for temperature regulation.

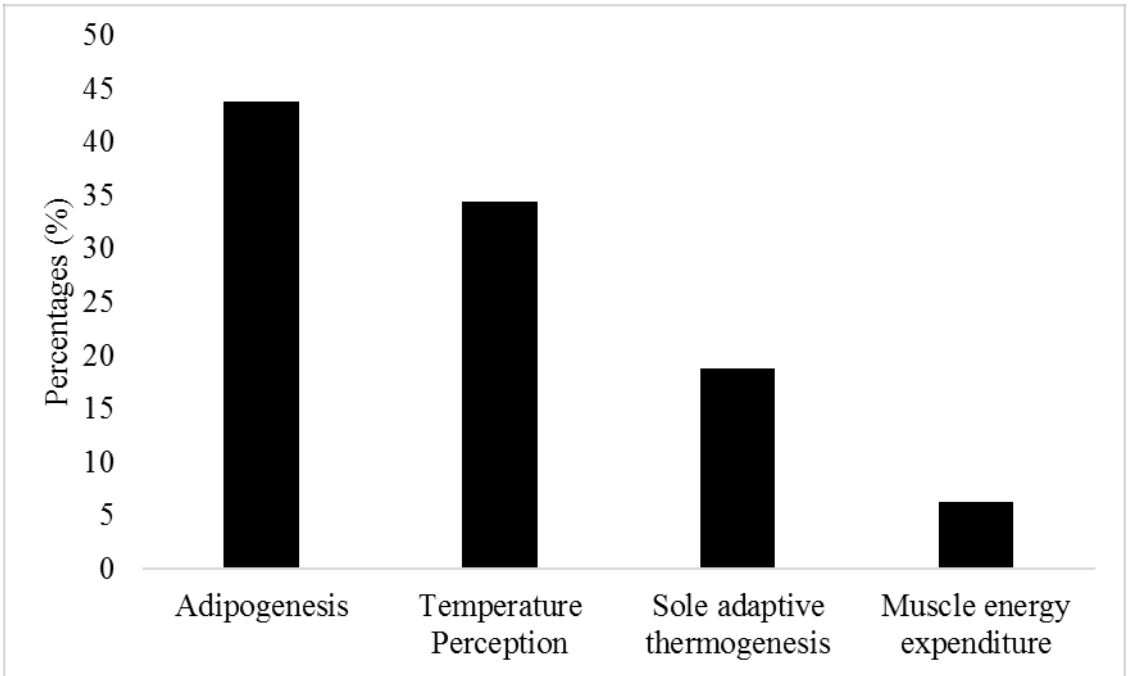

Figure No. 34. Percentages of processes coupled with adaptive thermogenesis relative to the total number of documents found for adaptive thermogenesis.

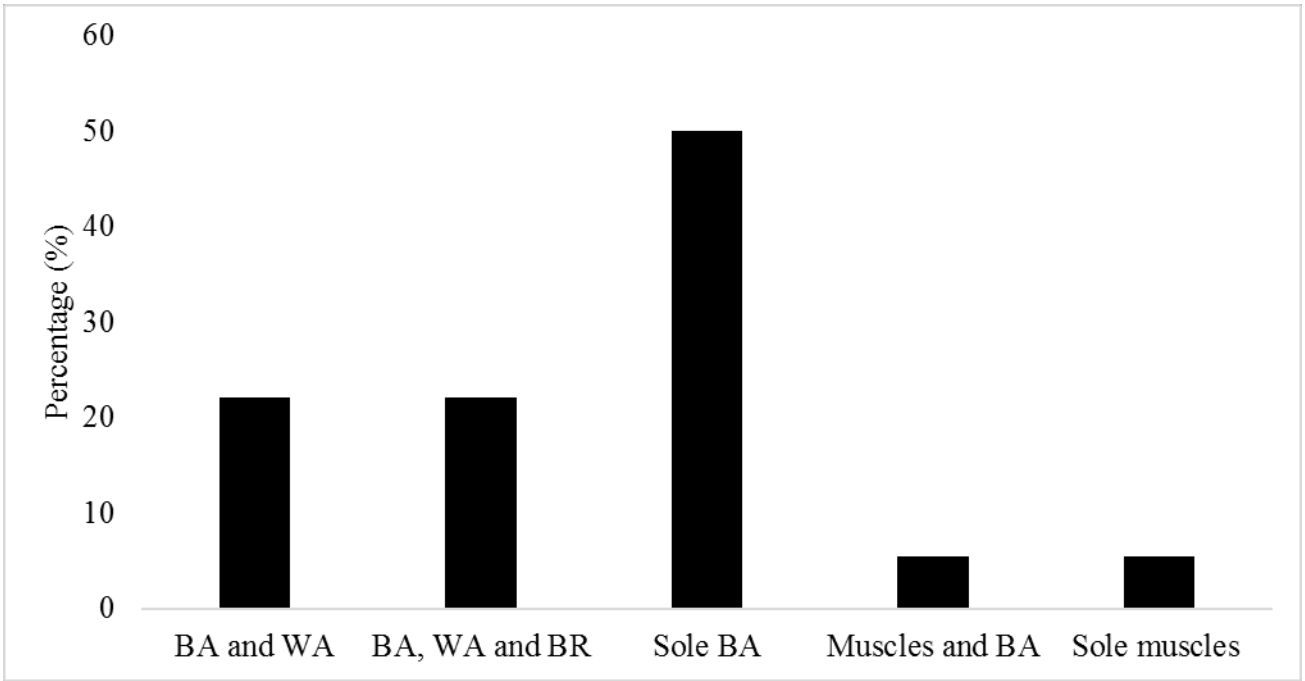

Figure No. 35. Percentage of cells addressed in adaptive thermogenesis relative to the total number of manuscripts found for adaptive thermogenesis.

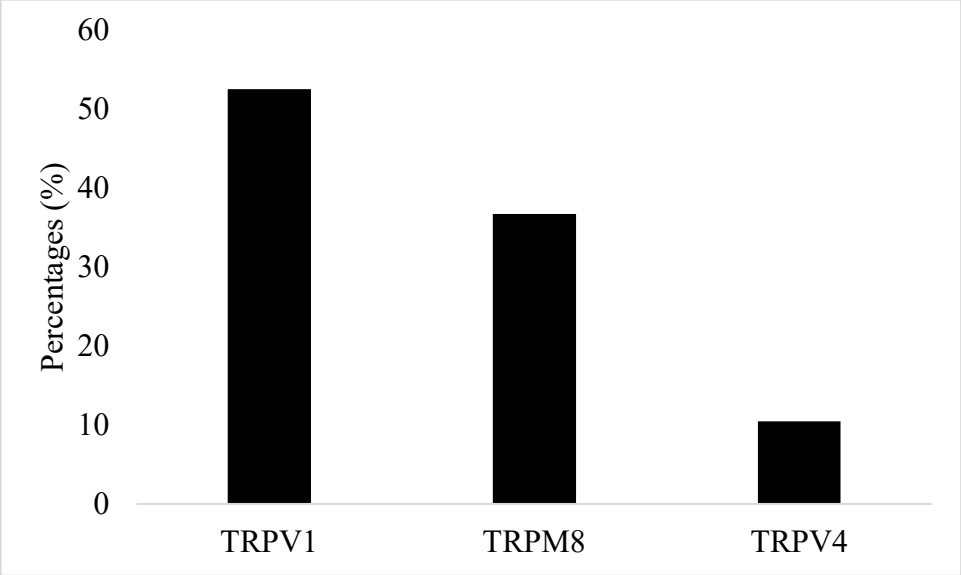

Figure No. 36. Percentage of TRPs addressed in adaptive thermogenesis relative to the total number of manuscripts found for adaptive thermogenesis.

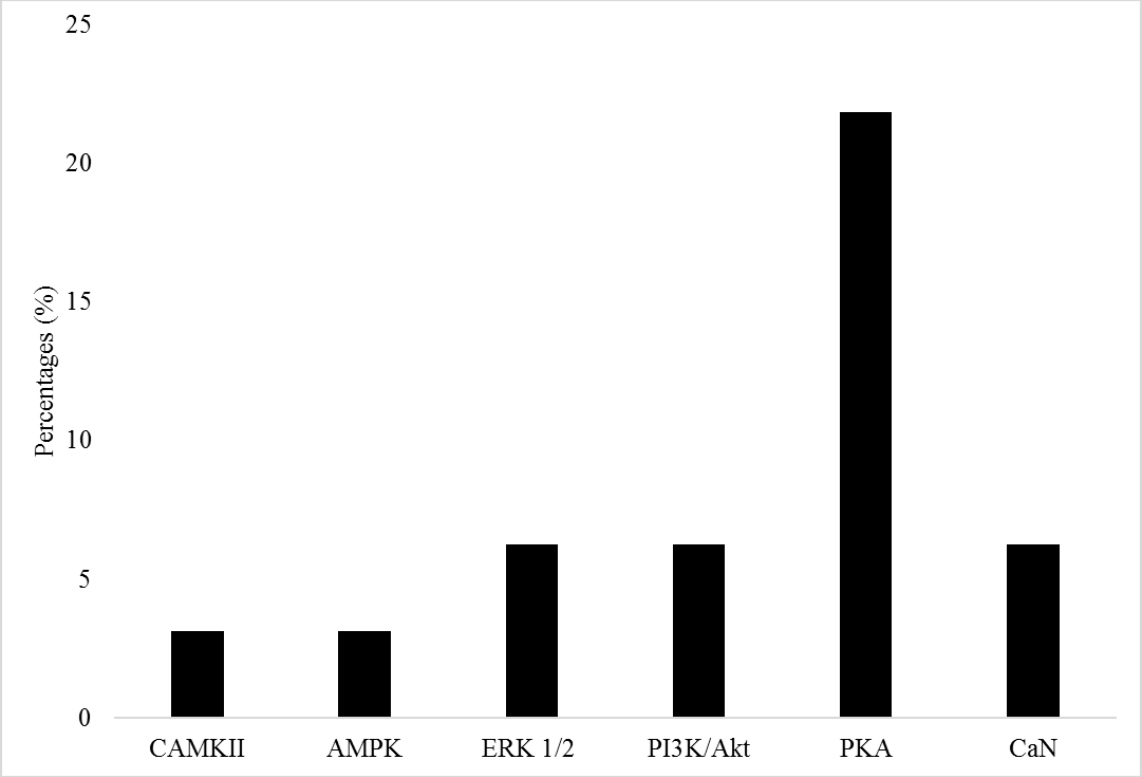

Figure No. 37.Percentages of proteins mediating cell signaling correlated with activated-TRPs in adaptive thermogenesis relative to the total number of documents found for adaptive thermogenesis.

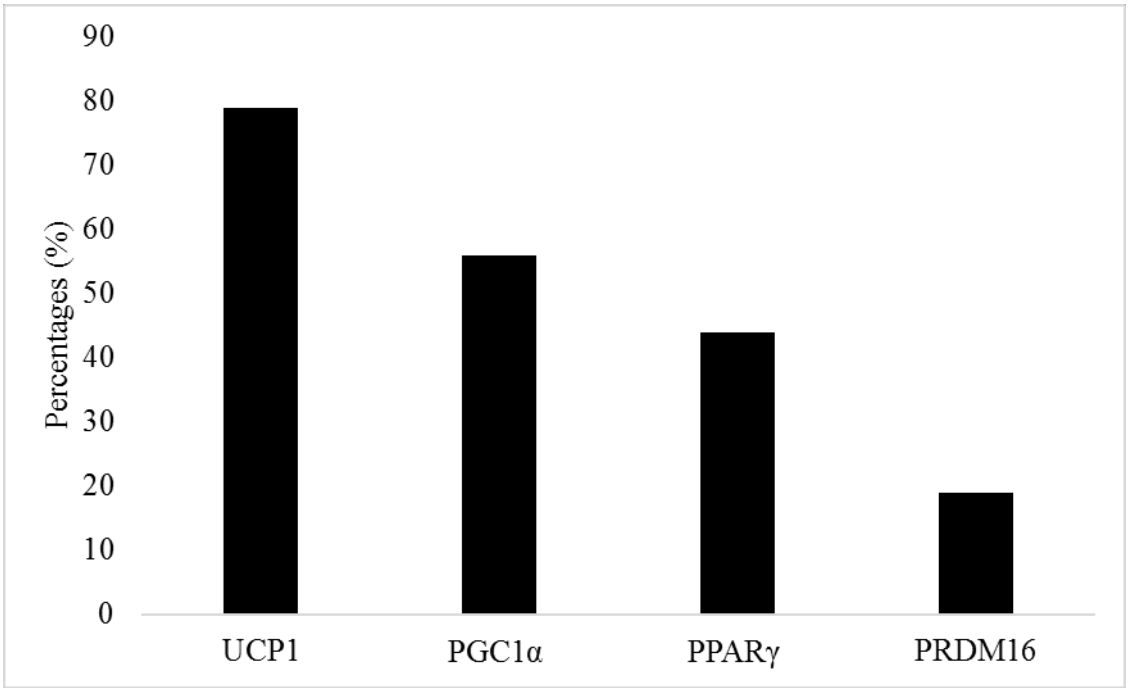

Figure No. 38. Percentages of intracellular proteins correlated with activated-TRPs in adaptive thermogenesis relative to the total number of documents found for adaptive thermogenesis.

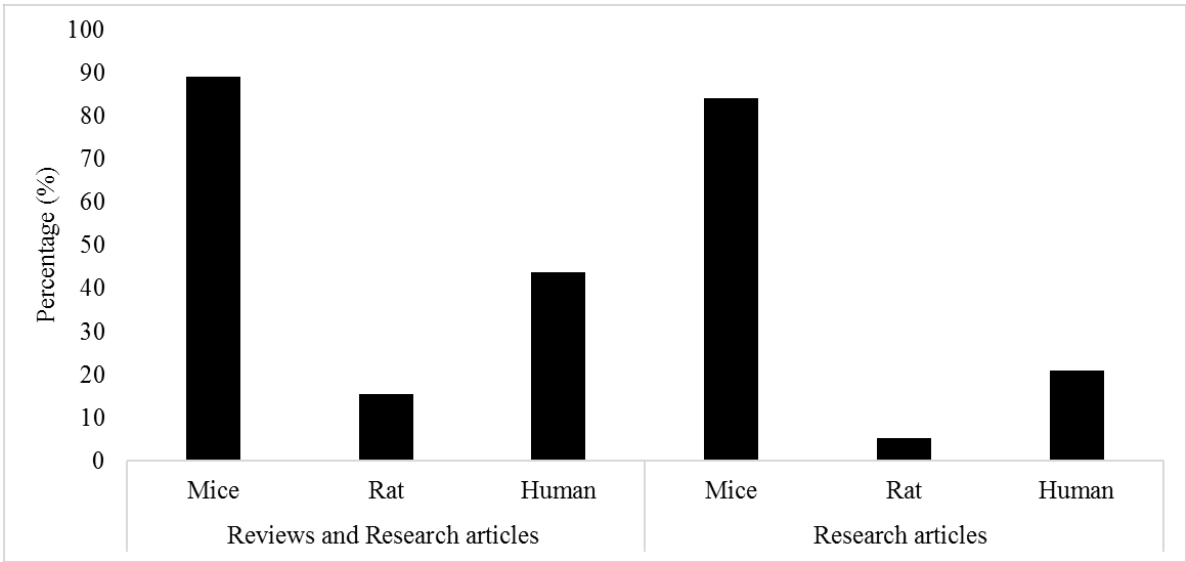

Figure No. 39. Percentages of vertebrates addressed in adaptive thermogenesis relative to the total number of documents found for adaptive thermogenesis.