REVIEW

Survey and critical appraisal of pharmacological agents with potential thermo-modulatory properties in the context of artificially induced hypometabolism

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ABSTRACT

A reduction in body temperature can be achieved by a downward adjustment of the termoneutral zone, a process also described as anapyrexia. Pharmacological induction of anapyrexia could enable numerous applications in medicine. However, little is known about the potential of pharmacological agents to induce anapyrexic signaling. Therefore, a review of literature was performed and over a thousand pharmacologically active compounds were analyzed for their ability to induce anapyrexia in animals. Based on this analysis, eight agents (helium, dimethyl sulfoxide, reserpine, (oxo)tremorine, pentobarbital, (chlor) promazine, insulin, and acetaminophen) were identified as potential anapyrexia-inducing compounds and discussed in detail. The translational pitfalls were also addressed for each candidate compound. Of the agents that were discussed, reserpine, (oxo)tremorine, and (chlor) promazine may possess true anapyrexic properties based on their ability to either affect the thermoneutral zone or its effectors and facilitate hypothermic signaling. However, these properties are currently not unequivocal and warrant further examination in the context of artificially-induced hypometabolism.

1. Introduction

An organism's core body temperature (T_b) is of key importance to its physiological function, as reflected by the meticulous regulation of T_b. The plasticity of thermal regulation is demonstrated by numerous pathological conditions, such as the increase in T_b (pyrexia) during an infection. A lesser known, but potentially equally important thermal adaptation mechanism, is regulated decrease in T_b (anapyrexia). Anapyrexia can be described as the opposite of fever, namely a lowering of the boundaries between which the body considers itself thermoneutral (the thermoneutral zone, Z_{tn}), and concurs with the inhibition of thermogenic processes and the activation of heat loss mechanisms (Figure 1).

The ability to lower the Z_{tn} is an established feature of poikilothermic animals, one that is only starting to be recognized in homeothermic animals [1]. The integration and processing of thermoregulatory signals is believed to involve several intricate neural pathways encompassing both peripheral sensory neurons and central hypothalamic neurons and nuclei [2-5], including the preoptic anterior hypothalamus (POAH) [3, 4, 6-8]. Together these pathways manage the Z_{tn}, which in turn manages thermogenesis (e.g., shivering, activation of brown adipose tissue (BAT), vasoconstriction, tachycardia, tachypnea, piloerection, and behavioral accommodation) and heat loss (e.g., vasodilation, sweating, panting, and changes in

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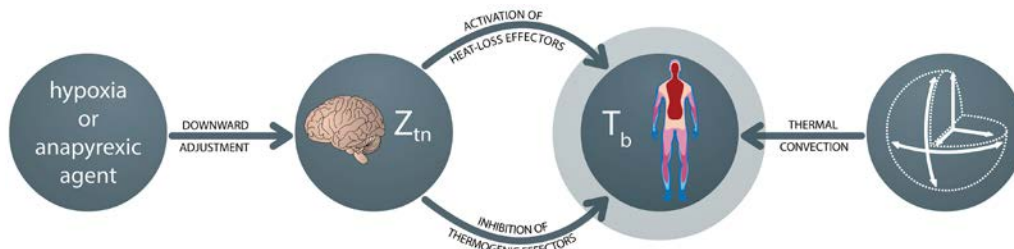E-mail: marcel.dirkes@philips.com

Figure 1. Regulation of body temperature (T_b) through change of the thermoneutral zone (Z_{tn}). The first sphere on the left indicates an initial external trigger, which may be an environmental stimulus such as hypoxia or a pharmacological agent with anapyrexic properties. These triggers can lead to a downward adjustment of the Z_{tn} (second sphere). In turn, the reduction of the Z_{tn} leads to activation of heat loss mechanisms (sweating, behavioral adaptation, panting, vasodilation) and inhibition of thermogenesis (shivering, activation of brown adipose tissue, behavioral adaptation, vasoconstriction, piloerection), resulting in a reduction of T_b (third sphere). The extent of T_b reduction is dependent on the rate of thermal convection, which in turn is dependent on the body surface:volume ratio (fourth sphere).

behavioral patterns such as the pursuit of lower environmental temperatures (T_a)) (Figure 1) [8,9]. Readers interested in the neuroanatomical networks that govern mammalian thermoregulation via the POAH are referred to a panel of excellent papers by Morrison and Nakamura on this subject [10-13].

A method to induce anapyrexia in small animals is by subjecting the animals to hypoxia, which triggers regulated hypothermia and corollary hypometabolism in some species as a countermeasure against the hypoxic, and thus potentially lethal, conditions [14-17]. One of the putative regulatory mechanisms is centered on carotid body sensing [18, 19]. Carotid bodies are clusters of chemoreceptors and cells near the bifurcation of the carotid artery that detect changes in oxygenation-related parameters, including partial pressure of oxygen and carbon dioxide as well as pH and temperature [20, 21]. When hypoxia is sensed, anapyrexia is induced through the inhibition of thermogenic effectors and activation of cooling effectors [1,16,22-24], which are under control of the POAH [7, 8,11,25]. This protective mechanism (Figure 1) is believed to be rooted in evolution, and there is evidence that such a mechanism is preserved in man, at least to an extent [14, 26]. However, hypoxia is generally not employed in the clinical setting as a patient's already compromised state may be exacerbated at low oxygen tensions. Nevertheless, the artificial modulation of a patient's Z_{tn} is of great interest because of the protective effects that are associated with hypometabolism [17].

Inasmuch as artificial (clinical) regulation of anapyrexia via the hypoxia-Z_{tn} axis does not constitute the most suitable and practical means, alternative methods have been explored. One interesting and potentially viable approach is pharmacological modulation of thermoregulatory cold receptors in the skin [27, 28]. Studies published by Andrej Romanovsky's Fever Lab have demonstrated that selective inhibition of the transient receptor potential melastatin-8 (TRPM8) channel (cutaneous cold receptor) with M8-B effectively decreases the T_b in mice and rats via several thermal effectors (thermopreferential behavior, tailskin vasoconstriction, and brown adipose tissue) [27]. Alternative strategies aimed at gaining control

over the Z_{tn} by pharmacological means at intervention sites other than cutaneous cold receptors also appear promising and encompass several proposed compounds such as arginine, vasopressin, lactate, adenosine, histamine, delta- and kappa opioids, nitrogen monoxide, and carbon monoxide [1]. Although these agents harness potential for clinical application, most of the compounds are associated with undesired side-effects that have confined their use to the experimental setting.

The pharmacological induction of hypothermia through modulation of the Z_{tn} has proven quite difficult in practice, particularly since the number of reports on methods to induce anapyrexia is limited. Nevertheless, the downward adjustment of the Z_{tn} by pharmacological agents may have numerous beneficial implications for medicine and biotechnology, but also for sports and aviation/space travel. Consequently, the identification of new anapyrexic agents or re-evaluation of established compounds for their anapyrexic properties has become increasingly important. Subjecting all known pharmacological agents to specific empirical investigations, however, would be exhaustive and comprehensive.

2. Aim of the study

In order to provide an accessible summary of potentially useful pharmacological agents for the induction of anapyrexic signaling, we performed a review of literature and analyzed over a thousand pharmacologically active compounds for their ability to induce anapyrexia in animals. The most viable candidates were identified on the basis of the magnitude of the reported heat loss and critically appraised in the context of the Z_{tn}-mediated heat loss mechanisms (Figure 1). In this study we focused specifically on the most studied compounds that potentially harness anapyrexic properties and addressed the candidate drugs against a backdrop of empirical evidence related to mainly pharmacodynamics and toxicology. The secondary purpose of this review was to guide novel research with 'old compounds' in the context of anapyrexic signaling by elaborating on the discrepancies in reported data and knowledge gaps. Subsequent reviews will focus on the physiological, biochemical, and neurological mechanisms of anapyrexic signaling in terms of hypometabolism-inducing pharmacological

agents (manuscript submitted) and the role of hypoxic sensing via e.g., carotid and aortic bodies with respect to POAH-mediated thermoregulation (manuscript in preparation).

3. Visualizing drug-induced changes in body temperature

Between 1979 and 1986 eight extensive reviews on changes in T_b after exposure to pharmacological agents were published by Wesley G. Clark in Neuroscience and Biobehavioral Reviews [29-36]. According to the author, "this survey … intended to provide an immediate source of information on drug-induced changes in thermoregulation" [31]. Published prior to the coining of the term 'anapyrexia,' the reviews furnish relevant information on 1,295 agents in 48 mammalian species, although the size of the data compilation makes it difficult to effectively assess the anapyrexic potential of all agents. Therefore, we have created a visual tool to assist in the analysis of data by plotting the T_b change per compound and per species in a single diagram (Figure 2, see legend for methods). In short, a blue sphere indicates a reduction in T_b,
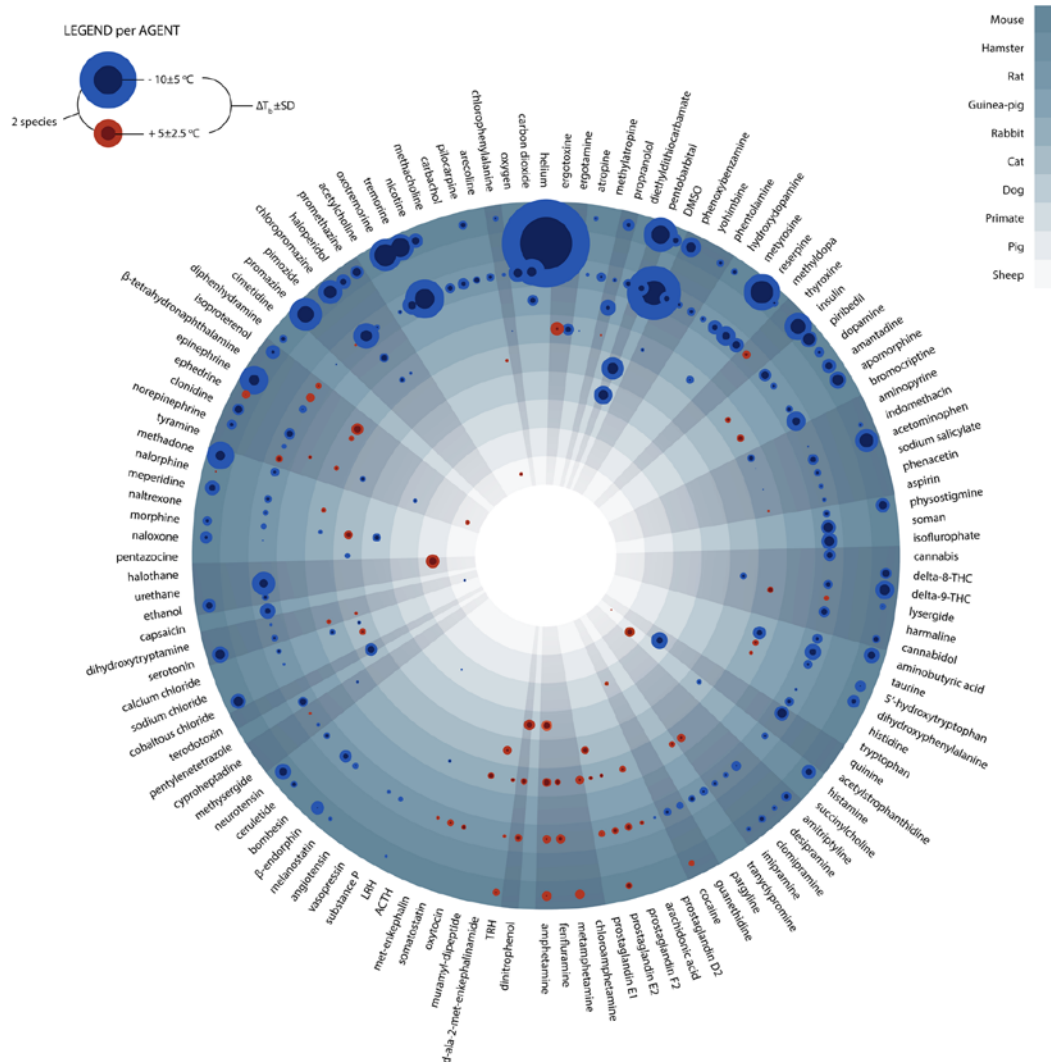

Figure 2. Change in T_b upon exposure to pharmacological agents. All presented data are derived from reviews published by Clark *et al.* [29-36]. These reviews total 18,808 reports on changes in T_b (ΔT_b) following exposure to a biochemical agent. All avian (628 reports), aquatic (46 reports), reptilian (31 reports), and naturally hibernating species (164 reports) were excluded on the basis that they are intrinsically endowed with different mechanisms regarding thermoregulation and hypometabolism [37]. All reports of human ΔT_b (1,285 reports) were excluded on the basis that they are not likely to be performed under standardized or controlled circumstances. All reports including a pre-existing febrile state (2,680 reports) were excluded on the rationale that these do not reflect an effect on healthy individuals and possibly only affect an increased Z_{tn}. All reports with no quantitative data were excluded (6,591 reports). In case of multiple data points, the largest ΔT_b was included. To improve the validity of T_b values, all agents that had < 10 reports within one species were also excluded. The final dataset, consisting of ≥10 reports/agent/species, was used for analysis and visualization. Data analysis was performed in Matlab R2011a (Mathworks) and graphically processed in Adobe InDesign CS5 (Adobe). The ΔT_bs are plotted as bicolored spheres, whereby cooling is indicated in blue and heating in red. The mean ΔT_b of each agent per species (n ≥10) is represented by the inner diameter of the sphere. The difference between the inner and outer diameter of the sphere represents the standard deviation. All spheres are projected against a layered concentric background, whereby each layer (separated by different shades of gray) represents a species as indicated in the legend (upper right). The agents are grouped according to the classification used in the original manuscripts, delineated by the outward radiating gray areas. For better viewing, the figure is also provided online as supplemental Figure 1.

which reflects the inability to maintain thermal homeostasis and hence points to potential anapyrexic properties of the agent. Contrastingly, a red sphere indicates an increase in T_b and thus pyretic properties of the agent. The size of the sphere is proportional to the magnitude of the change in T_b. Before elaborating on the most promising anapyrexia-inducing agents, it is important to outline some limitations of the analysis.

4. Limitations of the analytical method

The data in Figure 2 have four important limitations. Firstly, although each data point (sphere) represents the average of ≥ 10 reports, the number of animals in each report was not taken into account simply because the sample size was not indicated in every report, making a weighted analysis impossible. This may skew the data insofar as the result from one animal bears equal weight as the mean of results acquired with a larger group size.

Secondly, the change in T_b was not corrected for the T_a, which can have a considerable effect on convection and therefore the measured depth of hypothermia, particularly in small species [38]. Although most experiments were conducted at an average T_a that was within a normally accepted range (~18-25 °C), a few exceptions must be noted, such as for helium and DMSO, where the experiments were performed at an average T_a of 10.0 ± 13.3 °C and 12.5 ± 10.3 °C, respectively. The complete list of T_as and the quantitative data of Figure 2 can be found in supplemental Table S1.

Thirdly, the dosage and administration route, which can affect the disposition of a pharmacological agent, were not accounted for in the analysis. An example of a dose-dependent effect on T_b can be seen with morphine (Figure 2). Morphine has the potential to both increase (cat) and decrease (dog) the T_b. These opposite findings may originate from differences in

dosing since low concentrations of morphine (≤ 5 mg/kg intravenous bolus) cause a rise in T_b, whereas high concentrations (≥ 10 mg/kg intravenous bolus) cause a marked decrease in T_b [39].

Lastly, the manner in which experiments were performed was discounted. The reports from which the data were collected were published between 1979 to 1987, i.e., just after the introduction of 'good laboratory practice' criteria in the late 1970's [40]. This may have had an impact on the accuracy of the obtained and published results.

5. Thermal convection: the importance of surface:volume ratio and metabolic rate

In addition to the evident thermomodulatory effects induced by some of the compounds, the data in Figure 2 is subject to two important principles that may affect anapyrexia, namely the body surface:volume ratio and Kleiber's law (discussed in [38]). With respect to the former, small animals cool down at a faster rate than larger animals because their relatively large surface:volume ratio facilitates more extensive heat exchange with the environment (Figure 1). Corroboratively, the largest changes in T_b are found in mice and rats (Figure 3A). Kleiber's law is an allometric law that describes an inverse relationship between metabolic rate and body size [41]. One of the pillars of this law is that smaller species need proportionally more energy than larger species to sustain their metabolism. Both principles essentially dictate that a reduction in Z_{tn} can manifest itself faster and more profoundly in small species compared to larger species. Unfortunately, the distribution of the data in Figure 2 is slightly biased towards the smaller species (supplemental Table S2), which clouds the unequivocal manifestation of these principles across all species included in the analysis.
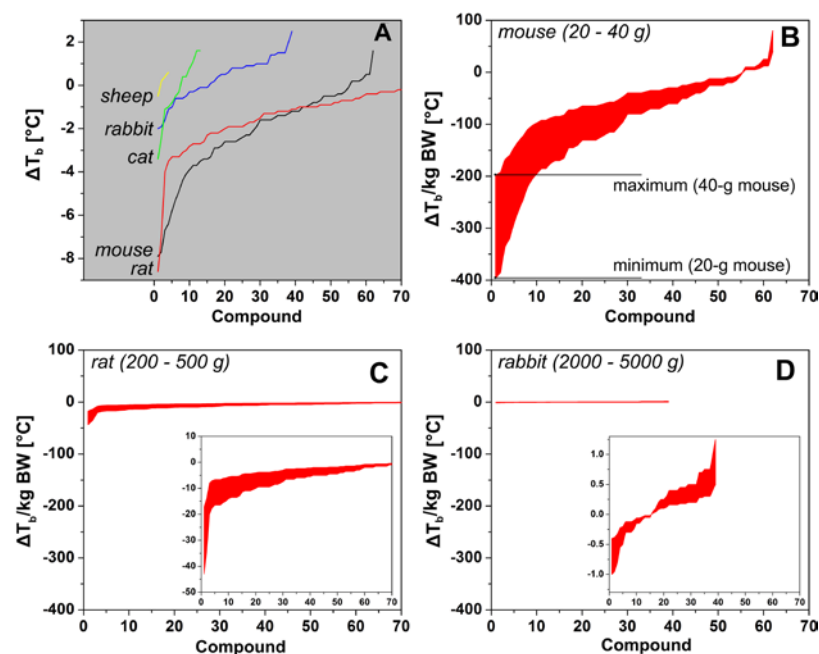
Figure 3. (A) Change in core body temperature (ΔT_b) per species plotted as a function of compound with the most profound effect on T_b (1, *x*-axis) to the compound with the least effect on T_b (up to 70, *x*-axis). The ΔT_b represents the mean of all ΔT_bs reported for the respective compound in the respective species that were included in the analysis. Research data were included on the basis of the criteria described in section 3 and the legend of Figure 2. The complete data set containing all the species is provided in Table S3. The data were normalized to the maximum and minimum common body weights (BW) of laboratory mice (B), rats (C), and rabbits (D) and should be read vertically per compound, whereby the upper limit is the minimum ΔT_b for the heaviest animals. The actual recorded values fall between the upper and lower bounds per compound. Note the different *y*-axis scaling of the inset plots. Common body weights were obtained from the internet (e.g., laboratory animal providers such as Harlan and Charles River).

Nevertheless, a good illustration can be provided on the basis of mice (N = 62), rats (N = 96), and rabbits (N = 39) alone, as shown in Figure 3B-D, where the change in T_b was organized from greatest to lowest and plotted per compound following normalization to body weight (in kg). The upper limit and lower limit weights of these laboratory animals were used to demarcate the maximum and minimum boundaries of the T_b change per unit weight. This was done to semi-standardize the data because a considerable fraction of the articles from which the data were derived did not report the mean body weight or weight range of the animals used in the experiments. When normalized to body weight, the heat loss per kg body weight is most sizeable in mice and smallest in rabbits, confirming the observations in Figure 2 and clearly illustrating both principles described above. A complete list with the categorized variables is provided in Table S3.

6. Compounds with anapyrexic potential

To identify anapyrexic agents, the data in Figure 2 were plotted according to the magnitude of T_b change, from the greatest decrease to the greatest increase in T_b (Figure 4). The magnitude of T_b decrease was used as the standard parameter to gauge anapyrexic signaling potential insofar as a downward modulation of T_b is the most important hallmark of anapyrexic signaling and does not occur in hibernators and non-hibernators in the absence of a Z_{tn} adjustment under non-stimulatory circumstances (e.g., under conditions of normoxia, abundant food supply, $T_a \approx T_b$, etc.) [37-42]. Based on this figure, eight agents (eleven agent-species combination) with the largest T_b decrease were selected as the most promising agents in terms of anapyrexic potential. These agents include helium (hamster, $\Delta T_b = -18.0 \pm 12.7$ °C), dimethyl sulfoxide (DMSO, rat, $\Delta T_b = -8.6 \pm 10.5$ °C), reserpine (mouse, $\Delta T_b = -7.9 \pm 4.8$ °C), (oxo)tremorine (oxotremorine, mouse, $\Delta T_b = -7.7 \pm 3.6$ °C;

tremorine, rat, $\Delta T_b = -6.9 \pm 6.9$ °C, mouse, $\Delta T_b = -6.7 \pm 2.7$ °C), pentobarbital (mouse, $\Delta T_b = -6.4 \pm 5.6$ °C), (chlor)promazine (chlorpromazine, mouse, $\Delta T_b = -4.4 \pm 4.1$ °C; promazine, mouse, $\Delta T_b = -5.8 \pm 5.8$ °C), insulin (mouse, $\Delta T_b = -5.3 \pm 4.4$ °C), and acetaminophen (mouse, $\Delta T_b = -4.9 \pm 3.3$ °C).

The observed reduction in T_b for these agents raises an important question: should the observed T_b reduction be diagnosed as anapyrexia or hypothermia, their sole difference being that the decrease in T_b is the result of a downward adjustment of the Z_{tn} in case of anapyrexia? A direct measurement of the Z_{tn} following administration of an agent would constitute the ultimate method to determine anapyrexic potential. However, due to the fact that we currently neither fully understand the body's temperature integration system nor have the means to monitor it, direct measurement of the boundaries that make up the Z_{tn} is impossible. Consequently, the gold standard in determination whether an organism is within the Z_{tn} boundaries is based on the activity of thermal effectors (Figure 1).

Therefore, in the next sections the eight most promising agents are addressed in the context of their effect on thermogenic and heat loss effectors such as shivering, BAT activity, sweating, vasoconstriction/vasodilation, and behavioral accommodation (Figure 1).

6.1. Helium

Helium is a noble gas with minimal direct biological activity [43]. Due to its biological inertness it is unlikely that helium induces cooling (Figure 2) via direct impact on the Z_{tn}. Instead, the thermoregulatory mechanism of helium may be based on its ability to augment the rate of heat convection.

The thermal conductivity of helium is 5.75 times higher than that of nitrogen [44]. When inhaling a gas mixture in which nitrogen is replaced by helium (e.g., Helox), the

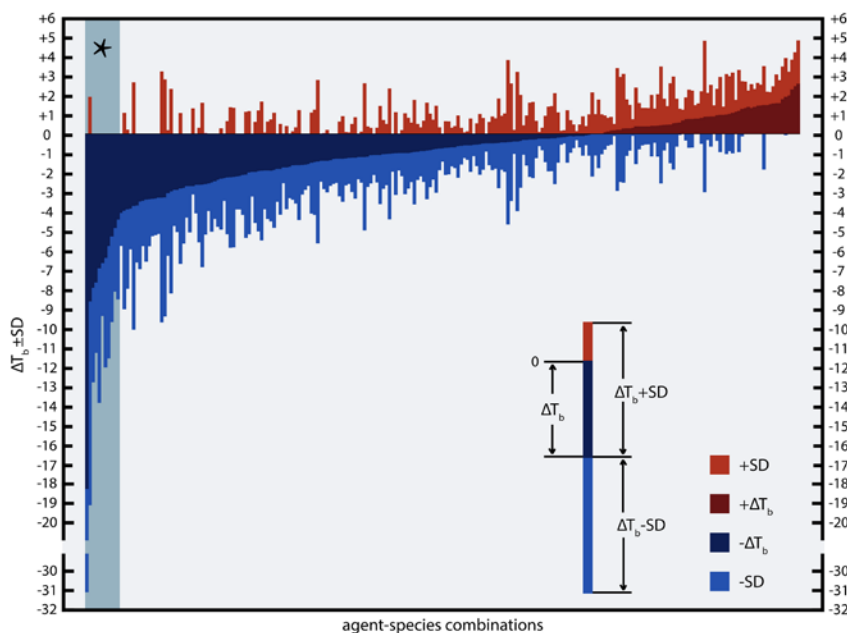**Figure 4**. Ranked effect size of the change in T_b following exposure of an animal to a pharmacological agent. For the source of the data and inclusion criteria see the legend of Figure 2. All agent-species combinations (*x*-axis) were ranked by mean effect size (*y*-axis) with standard deviations (see legend within panel). The section marked with an asterix (*, top left) marks the agents that are discussed in more detail.

increased thermal conductivity of helium can accelerate changes in T_b in a proportional manner to T_a. The efficiency with which the pulmonary vascular bed is able to exchange heat is reflected by the clinical use of helium gas as a tool to accelerate the rewarming of hypothermic patients in combination with regular heating therapy [45]. An important prerequisite for helium-mediated reduction in T_b, as shown in Figure 2, is that it must be accompanied by a low T_a, which indeed averaged 10.0 ± 13.3 °C (supplemental Table S1).

Accelerated heat convection as the mechanism behind helium-induced hypothermia is further supported by the absence of change in behavioral thermoregulation in animals. In mice exposed to normoxic normobaric helium, there is no increase in heat avoidance, suggesting that helium does not have an effect on the Z_{tn} [46]. The mechanism of helium-induced hypothermia is therefore ascribable to its biophysical rather than its biochemical properties.

6.2. Dimethyl sulfoxide

DMSO has been widely exploited as an analgesic, anti-inflammatory agent, cryoprotectant, radioprotectant, transcutaneous transporter, barbiturates enhancer, and organ preservative [47-50]. However, the clinical use of DMSO was banned in 1965 by the Food and Drug Administration, restricting its applicability to experimental use. In the experimental setting the hypothermic effects of DMSO are markedly evident without inducing notable arterial and neuronal damage following systemic administration [51], suggesting that DMSO may be an anapyrexic agent.

In rats, exposure to DMSO resulted in a decreased T_b with a simultaneous decrease in oxygen consumption and respiratory quotient, which are characteristic of a hypometabolic state [52]. The reduction in metabolism was likely triggered by a reduction in Z_{tn}, as a sustained Z_{tn} would initiate a temporary increase in oxygen consumption (a thermogenic effector mechanism) in an attempt to bring the T_b back to a thermoneutral level.

Besides anapyrexic effects, it has been suggested that DMSO has the potential to act via the thyroid gland. Normally, the thyroid gland is under hypothalamic control to produce metabolism-promoting thyronines, which require iodine (I) for their synthesis. Upon exposure of mice to DMSO via intraperitoneal injection, the uptake of ^{131}I was shown to be attenuated, suggesting that the mechanism of DMSO-induced hypometabolism may be co-regulated by the thyroid gland [52]. However, it cannot be excluded that the observed dose-dependent reduction in ^{131}I uptake was a result of DMSO-induced reduction in T_b, or that it originated from a change in hypothalamic control (e.g., due to changes in Z_{tn}).

Nevertheless, the question remains whether the decline in T_b is anapyrexic in nature or mediated by peripheral factors. In an experiment focused on behavioral thermoregulation in rats, exposure to DMSO, which had a lowering effect on T_b, led to a 2-fold increase in the need for external heat reinforcement [53]. This finding is in direct contradiction to anapyrexia, in which the lowered T_b would manifest itself by heat avoidance rather than reinforcement. In addition, the experiments performed in rats were performed in a temperature range of 0-26 °C [32]. The observation that DMSO caused such a large change in T_b in a small species such as a rat (Figure 3A, C) may in part be explained by the heavy cold thermal load. Finally, the interaction between DMSO and H_2O is exothermic in nature, causing erythema when applied on the skin [48]. In spite of the initial warm sensation, the accompanying vasodilation can considerably augment the rate of heat loss, which may be further exacerbated by a DMSO-induced decrease in shivering [52].

It therefore appears that the physiological effects of DMSO do not completely fit the physiological response profile of an anapyrexic agent.

6.3. Reserpine

Reserpine is prescribed to patients as an antipsychotic or anti-hypertensive drug. In the experimental setting the drug is often avoided because it induces hypothermia in small animals (Figure 2).

The mechanism of reserpine-mediated hypothermia is supposedly based on massive depletion of monoamines. Experiments in which cerebral monoamine concentrations were measured following reserpine administration revealed that reserpine depletes dopamine, norepinephrine, and serotonin levels [54, 55]. More specifically, reserpine was shown to decrease monoamine levels in the hypothalamus, an important part of the thermoregulatory system, suggesting anapyrexic potential [56].

Several studies have attempted to narrow down specific monoamines that may be involved in reserpine-induced hypothermia. These demonstrated that the reduction in cerebral serotonin levels by para-chlorphynylalanine was not accompanied by hypothermia [54]. Similarly, no hypothermic response was observed following a reduction in cerebral dopamine and norepinephrine levels by α-methyl-*m*-tyrosine [54].

However, exposure of reserpine-induced hypothermic mice to SKF-38393, a D_1-like (dopamine) receptor agonist, led to a significant reversal of hypothermia [57]. Subsequent addition of SCH-23390, a D_1-like receptor antagonist, abrogated the T_b raising effects of SKF-38393, suggesting a central role for the D_1-like receptor in reserpine-induced hypothermia [57]. On the other hand, apomorphine, a non-specific dopamine receptor agonist, had the ability to induce hypothermia to a similar depth as reserpine, altogether indicating that the dopamine receptor plays an ambivalent but prominent role in the observed hypothermia following reserpine exposure [58].

The inconsistencies in reserpine-induced hypothermia mechanisms have been the focus of numerous reports [59]. However, most reports predominantly address augmentation of monoamines and their associated receptors of the central nervous system, while only a few reports describe the effects

on (peripheral) thermogenic effectors. Reserpine has important inhibitory effects on thermogenic effectors such as BAT, where it has been shown to deplete norepinephrine stores [60]. As BAT is under adrenergic control, depleted norepinephrine stores can lead to severely impaired thermogenic activity [61].

Considering the current knowledge on reserpine, it could be postulated that reserpine constitutes the proverbial cannon to kill a mosquito. Generally, monoamine depletion causes many depressive effects that may encompass the POAH, and may therefore cause anapyrexia by a direct effect on the Z_{tn}. Irrespective of the central effects, reserpine's inhibitory effect on BAT will promote hypothermia indirectly by its inhibitory effect on thermogenesis through local norepinephrine depletion. These favorable properties notwithstanding, more specific knowledge on reserpine's mechanism of action is required, particularly with respect to central effects, before it can be categorized as a legitimate anapyrexic agent and clinically implemented as such.

6.4. (Oxo)tremorine

The use of tremorine and its metabolite oxotremorine are limited to the experimental setting. Exposure to tremorine does not only lead to hypothermia, but also induces generalized tremor and rigidity, owing to its muscarinic acetylcholine transport agonism [62].

Induction of hypothermia with (oxo)tremorine coincides with an important anapyrexic-like change in thermoregulatory behavior in animals, namely the active search for a cooler environment [63, 64]. This effect can be readily reversed by addition of atropine, a muscarinic acetylcholine receptor antagonist, suggesting involvement of cholinergic receptors in the management of Z_{tn} and T_b [63]. Further evidence supporting the anapyrexic effect of (oxo)tremorine is the profound hypothermia upon injection of tremorine directly into the POAH, a regulatory site involved in management of the Z_{tn}. A hypothermic response is absent when tremorine is injected into other cerebral regions [65]. Cholinergic receptors are putatively associated with T_b control. However, as they have been shown to trigger both pyretic and anapyrexic responses, their exact role in T_b control remains unclear [66-68].

Contrary to the central anapyrexia-like effects of (oxo)tremorine, the effects on peripheral effectors are equivocal. In larger animals, exposure to oxotremorine produces shivering, vasoconstriction, and signs of inhibited panting, altogether culminating in a T_b increase [69, 70]. Although the vasoconstrictive response does not necessarily imply pyretic signaling but rather an effect of low blood pressure associated with oxotremorine exposure, the shivering can be associated with pyrexia or constitute a local effect [71]. The increase in T_b could possibly be supported by BAT activity, albeit the direct effects of (oxo)tremorine on BAT are largely unexplored. However, due to the limited presence of cholinergic fibers in BAT and its predominantly adrenergic control, BAT most likely plays no role in the (oxo)tremorine-induced thermogen-esis [61, 72].

The capacity of (oxo)tremorine to induce both anapyrexia (i.e., thermoregulatory behavioral patterns, POAH-specific effects) and pyrexia (i.e., shivering, inhibition of panting) gives rise to the clinically relevant question whether its pyretic responses are centrally or peripherally regulated. The emphasis on the underlying mechanism of the pyretic responses is related to the possibility to control one of the thermogenic effectors, namely shivering, by the use of muscle relaxants. If shivering accounts for the majority of thermogenesis after (oxo)tremorine administration, anapyrexia could be effectively induced by (oxo)tremorine during hypothermic surgery on the condition it is co-administered with muscle relaxants to suppress the shivering.

Unfortunately, the amount of data on the peripheral mechanisms of (oxo)tremorine is very limited. To assess the anapyrexic potential of (oxo)tremorine, its mechanism on peripheral thermal effectors must be elucidated first.

6.5. Pentobarbital

Pentobarbital-induced hypothermia is believed to be facilitated by an increase in heat loss via dilation of cutaneous blood vessels [73]. The lack of Z_{tn} involvement in pentobarbital-induced hypothermia is supported by studies in rats, where no hypothermic response was observed following injection of pentobarbital into the POAH [73, 74]. However, intracerebroventricular injection of a 6-fold higher pentobarbital concentration resulted in a T_a-dependent hypothermic response that was accompanied by cutaneous vasodilation [75]. Accordingly, the T_a-dependent decrease in T_b and vasodilation imply that high intracerebroventricular pentobarbital concentrations produce systemic triggers that result in hypothermia, but not via the Z_{tn}. The absence of an anapyrexic effect is further supported by the lack of changes in thermoregulatory behavior in mice and rats [76].

Despite the widespread view that pentobarbital has no anapyrexic effects, more recent studies suggest that γ-aminobutyric acid (GABA) receptors, the main target of pentobarbital, may play a role in thermal homeostasis [77]. An *in vitro* study using hypothalamic medial preoptic slices revealed that both $GABA_A$ and $GABA_B$ receptor agonists inhibit neuronal tonic activity, implying a potential of GABA receptor agonists to modulate the Z_{tn} [78]. In murine $GABA_B$ knockout and partial knockdown models, hypothermic responses were observed in $GABA_B^{+/-}$ and wild type ($GABA_B^{+/+}$) mice but remained absent in $GABA_B^{-/-}$ mice, supporting the notion that GABA receptors regulate temperature homeostasis via the Z_{tn} [77]. Despite the established pentobarbital-GABA signaling link and the apparent relationship between GABA receptor agonism and T_b control, the evidence is presently too scant to classify pentobarbital as an anapyrexic agent.

6.6. (Chlor)promazine

Both chlorpromazine and promazine are drugs with anti-

psychotic effects. Chlorpromazine is used to treat schizophrenia, although promazine is the major metabolite found in chlorpromazine-treated schizophrenic patients and therefore constitutes the pharmacodynamically active compound. In rats chlorpromazine does not undergo metabolism as extensively as in in humans inasmuch as dechlorination results in less than 1/20 of the promazine plasma concentration in schizophrenic patients [79].

Chlorpromazine acts as an antagonist of dopamine-, serotonin-, adrenergic-, and muscarinic acetylcholine receptors. With respect to muscarinic acetylcholine receptors, chlorpromazine has an opposite effect of that of oxotremorine, which is a muscarinic acetylcholine receptor agonist. Considering that both (oxo)tremorine and chlorpromazine can induce hypothermia, it is unlikely that the induction of hypothermia is mediated solely by muscarinic receptors.

The effects of chlorpromazine on thermal effectors are inconsistent. On the one hand, chlorpromazine injection into the POAH of primates led to hypothermia with concomitant cutaneous vasodilation and respiratory acceleration (panting), which is suggestive of anapyrexia [80]. The intraperitoneal administration of chlorpromazine in rats resulted in a T_b reduction, characterized by inhibition of thermogenic shivering and piloerection and an increase in heat loss mechanisms such as augmented blood flow in the tail [81]. On the other hand, intracerebral injection of chlorpromazine into the POAH of rats produced a T_b increase [82, 83]. In mice, chlorpromazine was shown to substantially increase BAT activity [84]. This observation is particularly interesting since chlorpromazine has no sympathicomimetic properties, indicating possible central control.

Based on these contrasting reports, chlorpromazine does not unequivocally qualify as an anapyrexic agent. However, some of the pharmacodynamic features impart strong effects on the T_b, making them an important focus of further research.

6.7. Insulin

Hypothermia is a common response to systemic insulin exposure as an anticipatory coping mechanism for an impending hypoglycemic state [85]. Hypoglycemia-induced hypothermia is not only prevalent in many small animals, but is also observed in humans following e.g., insulin shock therapy [86]. Infusion of 2-deoxyglucose, a metabolically inert glucose analogue, also results in lowering of T_b in humans, implying that hypoglycemia-induced hypothermia may comprise an evolutionary conserved mechanism across different species [87].

The main question, however, is whether hypothermia following (insulin-induced) hypoglycemia is anapyrexic in nature. In terms of anapyrexia, insulin should exert an inhibitory effect on thermogenesis in combination with stimulation of heat loss mechanisms. In ectothermic toads, for instance, induction of hypoglycemia via both insulin and 2-deoxyglucose is associated with a behavioral drift towards lower temperatures [88]. This behavioral pattern ultimately causes a reduction in T_b and

constitutes one of the hallmarks of Z_{tn}-mediated thermoregulation. Similarly, humans who become hypoglycemic at the expense of insulin or 2-deoxyglucose activate heat loss mechanisms such as sweating, vasodilation, and hyperventilation [87, 89, 90].

The major thermogenic effector BAT is under control of insulin, which stimulates its anabolic (endothermic) rather than its catabolic (thermogenic) activity [61]. It may, however, be the hypoglycemic state itself rather than the insulin that inhibits thermogenic signaling. Hypoglycemia-mediated inhibition of thermogenesis is in agreement with the finding that shivering is attenuated in cold-exposed human subjects who have become hypoglycemic [90].

It therefore appears that hypoglycemia, and not insulin per se, has anapyrexic potential. At this stage, however, hypoglycemia-induced anapyrexia is difficult to translate to a clinical application without understanding the underlying mechanism of action in the context of thermoregulation.

6.8. Acetaminophen

Acetaminophen is a well-known and widely used analgesic and antipyretic drug. Most research on the pharmacodynamics of acetaminophen is therefore mainly focused on the antipyretic properties. However, its role as an anapyrexic agent has been proposed, but remains controversial and inconclusive. Clinical studies have demonstrated a significant reduction in T_b following acetaminophen treatment of stroke, head trauma, and subarachnoid hemorrhage [91, 92]. However, these findings are inconsistent with other reports, in which acetaminophen treatment of stroke and administration after cardiac bypass surgery showed no significant effect on T_b [93, 94]. The latter reports do not preclude the possibility that higher dosages may exhibit a thermomodulatory effect, but the amount of data on acetaminophen-induced anapyrexic T_b reduction is too limited to draw solid conclusions at this point [95].

The thermoregulatory pharmacodynamics of acetaminophen remain elusive, although several advances in recent years have implicated the involvement of cyclooxygenase, peroxidase, nitric oxide synthase, canabinoid receptors, and serotonin receptors [95]. In an effort to elucidate the pharmacological mechanism of acetaminophen, a study in mice revealed that acetaminophen can reduce T_b from euthermic levels, which is in support of anapyrexic properties [96]. However, the underlying mechanisms remain obscure, with data suggesting an effect on anti-glutamate and anti-oxidant capacities rather than on thermoregulatory mechanisms [96]. Moreover, the T_b-downmodulatory properties of acetaminophen may have been falsely ascribed in instances where the thermoregulatory system was already activated, or functionally compromised. These instances include underlying disease or clinical trauma (e.g., cancer or stroke, such as cited in the previous paragraph [91]) and bacterial and viral infections [97]. Finally, the hypothermic effect of acetaminophen has only been demonstrated in mice. Rats exposed to increasing acetaminophen dosages did not exhibit heat-avoiding behavior, indicat-

ing that no pharmacological modulation of the Z_{tn} had occurred [98]. Accordingly, the effect of acetaminophen on behavioral thermoregulation pleads against its classification as an anapyrexic agent, and it is unclear whether this class of drugs would induce hypothermia in a normal subject.

7. Concluding remarks

Anapyrexia has yet to gain widespread acceptance as a clinically functional state. Acknowledgement of its implementation through clinical pharmacology will largely depend on three factors: the development of efficient methods to adjust the Z_{tn} downward, the ability to accurately measure the boundaries of the Z_{tn}, and the simultaneous use of external T_b control.

As indicated in the sections on the pharmacological agents above, there are various agents such as reserpine, (oxo)tremorine, and (chlor)promazine that exhibit specific aspects suggestive of an anapyrexic potential. However, due to the primary research focus on aspects other than anapyrexia, the anapyrexic potential of these agents requires further examination. Combinational therapy and translation to larger animal models constitute important steps towards the elucidation and optimization of the anapyrexic candidate drugs.

Ultimately, for clinical application, the simultaneous use of external T_b control alongside anapyrexic agents will be essential. Due to the high body surface:volume ratio of humans, passive lowering of T_b is too inefficient to support the depth of hypothermia that is dictated by the Z_{tn} under conditions of anapyrexia. Therefore, the advantage of anapyrexic agents lies in the facilitation of hypothermic therapy by optimizing thermal effectors (i.e., inhibition of thermogenic effectors and activation of heat loss effectors), thereby preventing the manifestation of Z_{tn}-T_b mismatch-induced stressors during the induction of hypothermia.

Acknowledgements

References

[1] Steiner AA, Branco LG. Hypoxia-induced anapyrexia: implications and putative mediators. Annu Rev Physiol 2002; 64: 263-288.

[2] Cerri M, Zamboni G, Tupone D, Dentico D, Luppi M, Martelli D, Perez E, Amici R. Cutaneous vasodilation elicited by disinhibition of the caudal portion of the rostral ventromedial medulla of the free-behaving rat. Neuroscience 2010; 165: 984-995.

[3] Maingret F, Lauritzen I, Patel AJ, Heurteaux C, Reyes R, Lesage F, Lazdunski M, Honore E. TREK-1 is a heat-activated background K(+) channel. EMBO J 2000; 19: 2483-2491.

[4] Crawshaw L, Grahn D, Wollmuth L, Simpson L. Central nervous regulation of body temperature in vertebrates: comparative aspects. Pharmacol Ther 1985; 30: 19-30.

[5] Cerri M, Mastrotto M, Tupone D, Martelli D, Luppi M, Perez E, Zamboni G, Amici R. The inhibition of neurons in the central

[6] Parmeggiani PL, Azzaroni A, Calasso M. Behavioral state-dependent thermal feedback influencing the hypothalamic thermostat. Arch Ital Biol 2000; 138: 277-283.

[7] He Z, Yamawaki T, Yang S, Day AL, Simpkins JW, Naritomi H. Experimental model of small deep infarcts involving the hypothalamus in rats: changes in body temperature and postural reflex. Stroke 1999; 30: 2743-2751.

[8] Boulant JA. Role of the preoptic-anterior hypothalamus in thermoregulation and fever. Clin Infect Dis 2000; 31 Suppl 5: S157-S161.

[9] Romanovsky AA, Ivanov AI, Shimansky YP. Selected contribution: ambient temperature for experiments in rats: a new method for determining the zone of thermal neutrality. J Appl Physiol (1985) 2002; 92: 2667-2679.

[10] Morrison SF, Nakamura K, Madden CJ. Central control of thermogenesis in mammals. Exp Physiol 2008; 93: 773-797.

[11] Nakamura K. Central circuitries for body temperature regulation and fever. Am J Physiol Regul Integr Comp Physiol 2011; 301: R1207-R1228.

[12] Morrison SF, Nakamura K. Central neural pathways for thermoregulation. Front Biosci (Landmark Ed) 2011; 16: 74-104.

[13] Nakamura K, Morrison SF. Central efferent pathways for cold-defensive and febrile shivering. J Physiol 2011; 589: 3641-3658.

[14] Kottke FJ, Phalen JS. Effect of hypoxia upon temperature regulation of mice, dogs, and man. Am J Physiol 1948; 153: 10-15.

[15] Hayden P, Lindberg RG. Hypoxia-induced torpor in pocket mice (genus: Perognathus). Comp Biochem Physiol 1970; 33: 167-179.

[16] Frappell P, Lanthier C, Baudinette RV, Mortola JP. Metabolism and ventilation in acute hypoxia: a comparative analysis in small mammalian species. Am J Physiol 1992; 262: R1040-R1046.

[17] Gordon CJ. The therapeutic potential of regulated hypothermia. Emerg Med J 2001; 18: 81-89.

[18] Peng YJ, Nanduri J, Raghuraman G, Souvannakitti D, Gadalla MM, Kumar GK, Snyder SH, Prabhakar NR. H2S mediates O2 sensing in the carotid body. Proc Natl Acad Sci U S A 2010; 107: 10719-10724.

[19] Prabhakar NR, Semenza GL. Gaseous messengers in oxygen sensing. J Mol Med (Berl) 2012; 90: 265-272.

[20] Buckler KJ, Williams BA, Honore E. An oxygen-, acid- and anaesthetic-sensitive TASK-like background potassium channel in rat arterial chemoreceptor cells. J Physiol 2000; 525 Pt 1: 135-142.

[21] Gonzalez C, Almaraz L, Obeso A, Rigual R. Carotid body chemoreceptors: from natural stimuli to sensory discharges. Physiol Rev 1994; 74: 829-898.

[22] Gordon CJ, Fogelson L. Comparative effects of hypoxia on behavioral thermoregulation in rats, hamsters, and mice. Am J Physiol 1991; 260: R120-R125.

[23] Madden CJ, Morrison SF. Hypoxic activation of arterial chemoreceptors inhibits sympathetic outflow to brown adipose tissue in rats. J Physiol 2005; 566: 559-573.

[24] Hinrichsen CF, Maskrey M, Mortola JP. Ventilatory and metabolic responses to cold and hypoxia in conscious rats with discrete hypothalamic lesions. Respir Physiol 1998; 111: 247-256.

[25] Heller HC. Hibernation: neural aspects. Annu Rev Physiol 1979; 41: 305-321.

[26] Robinson KA, Haymes EM. Metabolic effects of exposure to hypoxia plus cold at rest and during exercise in humans. J Appl

Physiol (1985) 1990; 68: 720-725.

[27] Almeida MC, Hew-Butler T, Soriano RN, Rao S, Wang W, Wang J, Tamayo N, Oliveira DL, Nucci TB, Aryal P, Garami A, Bautista D, Gavva NR, Romanovsky AA. Pharmacological blockade of the cold receptor TRPM8 attenuates autonomic and behavioral cold defenses and decreases deep body temperature. J Neurosci 2012; 32: 2086-2099.

[28] de Oliveira C, Garami A, Lehto SG, Pakai E, Tekus V, Pohoczky K, Youngblood BD, Wang W, Kort ME, Kym PR, Pinter E, Gavva NR, Romanovsky AA. Transient receptor potential channel ankyrin-1 is not a cold sensor for autonomic thermoregulation in rodents. J Neurosci 2014; 34: 4445-4452.

[29] Clark WG. Changes in body temperature after administration of amino acids, peptides, dopamine, neuroleptics and related agents. Neurosci Biobehav Rev 1979; 3: 179-231.

[30] Clark WG, Clark YL. Changes in body temperature after administration of acetylcholine, histamine, morphine, prosta-glandins and related agents. Neurosci Biobehav Rev 1980; 4: 175-240.

[31] Clark WG, Clark YL. Changes in body temperature after administration of adrenergic and serotonergic agents and related drugs including antidepressants. Neurosci Biobehav Rev 1980; 4: 281-375.

[32] Clark WG, Clark YL. Changes in body temperature after administration of antipyretics, LSD, delta 9-THC, CNS depressants and stimulants, hormones, inorganic ions, gases, 2,4-DNP and miscellaneous agents. Neurosci Biobehav Rev 1981; 5: 1-136.

[33] Clark WG, Lipton JM. Changes in body temperature after administration of amino acids, peptides, dopamine, neuroleptics and related agents: II. Neurosci Biobehav Rev 1985; 9: 299-371.

[34] Clark WG, Lipton JM. Changes in body temperature after administration of acetylcholine, histamine, morphine, prosta-glandins and related agents: II. Neurosci Biobehav Rev 1985; 9: 479-552.

[35] Clark WG, Lipton JM. Changes in body temperature after administration of adrenergic and serotonergic agents and related drugs including antidepressants. II. Neurosci Biobehav Rev 1986; 10: 153-220.

[36] Clark WG. Changes in body temperature after administration of antipyretics, LSD, delta 9-THC and related agents. II. Neurosci Biobehav Rev 1987; 11: 35-96.

[37] Geiser F, Ruf T. Hibernation versus daily torpor in mammals and birds-physiological variables and classification of torpor patterns. Physiological Zoology 1995; 68: 935-966.

[38] Dirkes MC, Milstein DM, Heger M, van Gulik TM. Absence of hydrogen sulfide-induced hypometabolism in pigs: a mechanistic explanation in relation to small nonhibernating mammals. Eur Surg Res 2015; 54: 178-191.

[39] Lotti VJ, Lomax P, George R. Temperature responses in the rat following intracerebral microinjection of morphine. J Pharmacol Exp Ther 1965; 150: 135-139.

[40] Goodwin M. Good laboratory practice 30 years on: challenges for industry. Ann Ist Super Sanita 2008; 44: 369-373.

[41] Kleiber M. Body size and metabolic rate. Physiol Rev 1947; 27: 511-541.

[42] Geiser F. Metabolic rate and body temperature reduction during hibernation and daily torpor. Annu Rev Physiol 2004; 66: 239-274.

[43] Trudell JR, Koblin DD, Eger EI. A molecular description of how noble gases and nitrogen bind to a model site of anesthetic action. Anesth Analg 1998; 87: 411-418.

[44] Piantadosi CA, Thalmann ED. Thermal responses in humans exposed to cold hyperbaric helium-oxygen. J Appl Physiol Respir Environ Exerc Physiol 1980; 49: 1099-1106.

[45] Danzl DF, Pozos RS. Accidental hypothermia. N Engl J Med 1994; 331: 1756-1760.

[46] Pertwee RG, Marshall NR, Macdonald AG. Effects of subanesthetic doses of inert gases on behavioral thermoregulation in mice. J Appl Physiol (1985) 1986; 61: 1623-1633.

[47] Armitage WJ, Dale W, Alexander EA. Protocols for thawing and cryoprotectant dilution of heart valves. Cryobiology 2005; 50: 17-20.

[48] Bradham GB, Sample JJ. The vascular and thermal effects of dimethyl sulfoxide. Ann N Y Acad Sci 1967; 141: 225-230.

[49] Kocsis JJ, Harkaway S, Snyder R. Biological effects of the metabolites of dimethyl sulfoxide. Ann N Y Acad Sci 1975; 243: 104-109.

[50] Rosenbaum EE, Herschler RJ, Jacob SW. Dimethyl sulfoxide in musculoskeletal disorders. JAMA 1965; 192: 309-313.

[51] Bakar B, Kose EA, Sonal S, Alhan A, Kilinc K, Keskil IS. Evaluation of the neurotoxicity of DMSO infused into the carotid artery of rat. Injury 2012; 43: 315-322.

[52] Orlando MM, Panuska JA. Dimethylsulfoxide and thermore-gulation: studies on body temperature, metabolic rate and thyroid function. Cryobiology 1972; 9: 198-204.

[53] Panuska JA. The effect of dimethylsulfoxide on behavioral temperature regulation. Proc Soc Exp Biol Med 1968; 127: 169-173.

[54] Somerville AR, Whittle BA. The interrelation of hypothermia and depletion of noradrenaline, dopamine and 5-hydroxytryptamine from brain by reserpine, para-chlorophenylalanine and alpha-methylmetatyrosine. Br J Pharmacol Chemother 1967, 31: 120-131.

[55] Tricklebank MD, Forler C, Fozard JR. The involvement of subtypes of the 5-HT1 receptor and of catecholaminergic systems in the behavioural response to 8-hydroxy-2-(di-n-propylamino) tetralin in the rat. Eur J Pharmacol 1984; 106: 271-282.

[56] Brodie BB, Finger KF, Orlans FB, Quinn GP, Sulser F. Evidence that tranquilizing action of reserpine is associated with change in brain serotonin and not in brain norepinephrine. J Pharmacol Exp Ther 1960; 129: 250-256.

[57] Duterte-Boucher D, Panissaud C, Michael-Titus A, Costentin J. Stimulation of central D1 dopamine receptors reverses reserpine-induced hypothermia in mice. Neuropharmacology 1989; 28: 419-421.

[58] Lin MT, Chern YF, Wang Z, Wang HS. Effects of apomorphine on thermoregulatory responses of rats to different ambient tempera-tures. Can J Physiol Pharmacol 1979; 57: 469-475.

[59] Cox B. Pharmacologic control of temperature regulation. Annu Rev Pharmacol Toxicol 1977; 17: 341-353.

[60] Weiner N, Perkins M, Sidman RL. Effect of reserpine on noradrenaline content of innervated and denervated brown adipose tissue of the rat. Nature 1962; 193: 137-138.

[61] Cannon B, Nedergaard J. Brown adipose tissue: function and physiological significance. Physiol Rev 2004; 84: 277-359.

[62] Cho AK, Haslett WL, Jenden DJ. The peripheral actions of oxotremorine, a metabolite of tremorine. J Pharmacol Exp Ther 1962; 138: 249-257.

[63] Cox B, Tha SJ. The role of dopamine and noradrenaline in temperature control of normal and reserpine-pretreated mice. J Pharm Pharmacol 1975; 27: 242-247.

[64] Gordon CJ, Mohler FS, Watkinson WP, Rezvani AH. Temperature regulation in laboratory mammals following acute toxic insult. Toxicology 1988; 53: 161-178.

[65] Lomax P, Jenden DJ. Hypothermia following systematic and intracerebral injection of oxotremorine in the rat. Int J Neuropharmacol 1966; 5: 353-359.

[66] Avery DD. Intrahypothalamic adrenergic and cholinergic injection effects on temperature and ingestive behavior in the rat. Neuropharmacology 1971; 10: 753-763.

[67] Myers RD, Yaksh TL. Control of body temperature in the unanaesthetized monkey by cholinergic and aminergic systems in the hypothalamus. J Physiol 1969; 202: 483-500.

[68] Lomax P, Foster RS, Kirkpatrick WE. Cholinergic and adrenergic interactions in the thermoregulatory centers of the rat. Brain Res 1969; 15: 431-438.

[69] Decima EE, Rand RW. Oxotremorine induced tremor in the decorticated cat. Int J Neuropharmacol 1965; 4: 139-148.

[70] Johnson KG. Thermoregulatory changes induced by cholinomimetic substances introduced into the cerebral ventricles of sheep. Br J Pharmacol 1975; 53: 489-497.

[71] Dage RC. A centrally mediated prolonged hypotension produced by oxotremorine or pilocarpine. Br J Pharmacol 1979; 65: 15-21.

[72] Giordano A, Frontini A, Castellucci M, Cinti S. Presence and distribution of cholinergic nerves in rat mediastinal brown adipose tissue. J Histochem Cytochem 2004; 52: 923-930.

[73] Lomax P. The hypothermic effect of pentobarbital in the rat: sites and mechanisms of action. Brain Res 1966; 1: 296-302.

[74] Humphreys RB, Hawkins M, Lipton JM. Effects of anesthetic injected into brainstem sites on body temperature and behavioral thermoregulation. Physiol Behav 1976; 17: 667-674.

[75] Lin MT. Effects of sodium pentobarbital on thermoregulatory responses in the rat. Neuropharmacology 1981; 20: 693-698.

[76] Strek KS, Long MD, Gordon CJ. Effect of sodium pentobarbital on behavioral thermoregulation in rats and mice. Pharmacol Biochem Behav 1986; 24: 1147-1150.

[77] Queva C, Bremner-Danielsen M, Edlund A, Ekstrand AJ, Elg S, Erickson S, Johansson T, Lehmann A, Mattsson JP. Effects of GABA agonists on body temperature regulation in GABA (B(1)) -/- mice. Br J Pharmacol 2003; 140: 315-322.

[78] Yakimova K, Sann H, Schmid HA, Pierau FK. Effects of GABA agonists and antagonists on temperature-sensitive neurones in the rat hypothalamus. J Physiol 1996; 494 (Pt 1): 217-230.

[79] Sgaragli G, Ninci R, Della CL, Valoti M, Nardini M, Andreoli V, Moneti G. Promazine. A major plasma metabolite of chlorpromazine in a population of chronic schizophrenics. Drug Metab Dispos 1986; 14: 263-266.

[80] Chai CY, Fann YD, Lin MT. Hypothermic action of chlorpromazine in monkeys. Br J Pharmacol 1976; 57: 43-49.

[81] Kollias J, Bullard RW. The influence of chlorpromazine on physical and chemical mechanisms of temperature regulation in the rat. J Pharmacol Exp Ther 1964; 145: 373-381.

[82] Kirkpatrick WE, Lomax P. Temperature changes induced by chlorpromazine and N-methyl chlorpromazine in the rat. Neuropharmacology 1971; 10: 61-66.

[83] Rewerski WJ, Jori A. Microinjection of chlorpromazine in different parts of rat brain. Int J Neuropharmacol 1968; 7: 359-364.

[84] Som P, Yonekura Y, Oster ZH, Meyer MA, Pelletteri ML, Fowler JS, MacGregor RR, Russell JA, Wolf AP, Fand I, McNally WP, Brill AB. Quantitative autoradiography with radiopharmaceuticals, Part 2: Applications in radiopharmaceutical research: concise communication. J Nucl Med 1983; 24: 238-244.

[85] Buchanan TA, Cane P, Eng CC, Sipos GF, Lee C. Hypothermia is critical for survival during prolonged insulin-induced hypoglycemia in rats. Metabolism 1991; 40: 330-334.

[86] Mayer-Gross W, Berliner F. Observations in hypoglycaemia: IV. Body temperature and coma. Br J Psychiatry 1942; 88: 419-427.

[87] Thompson DA, Lilavivathana U, Campbell RG, Welle SL, Craig AB. Thermoregulatory and related responses to 2-deoxy-D-glucose administration in humans. Am J Physiol 1980; 239: R291-R295.

[88] Branco LG. Effects of 2-deoxy-D-glucose and insulin on plasma glucose levels and behavioral thermoregulation of toads. Am J Physiol 1997; 272: R1-R5.

[89] Molnar GW, Read RC. Hypoglycemia and body temperature. JAMA 1974; 227: 916-921.

[90] Passias TC, Meneilly GS, Mekjavic IB. Effect of hypoglycemia on thermoregulatory responses. J Appl Physiol (1985) 1996; 80: 1021-1032.

[91] Dippel DW, van Breda EJ, van der Worp HB, van Gemert HM, Kappelle LJ, Algra A, Koudstaal PJ. Timing of the effect of acetaminophen on body temperature in patients with acute ischemic stroke. Neurology 2003; 61: 677-679.

[92] Mellergard P. Changes in human intracerebral temperature in response to different methods of brain cooling. Neurosurgery 1992; 31: 671-677.

[93] Kasner SE, Wein T, Piriyawat P, Villar-Cordova CE, Chalela JA, Krieger DW, Morgenstern LB, Kimmel SE, Grotta JC. Acetaminophen for altering body temperature in acute stroke: a randomized clinical trial. Stroke 2002; 33: 130-134.

[94] Stevens T, Fitzsimmons L. Effect of a standardized rewarming protocol and acetaminophen on core temperature after coronary artery bypass. Am J Crit Care 1995; 4: 189-197.

[95] Toussaint K, Yang XC, Zielinski MA, Reigle KL, Sacavage SD, Nagar S, Raffa RB. What do we (not) know about how paracetamol (acetaminophen) works? J Clin Pharm Ther 2010; 35: 617-638.

[96] Li S, Dou W, Tang Y, Goorha S, Ballou LR, Blatteis CM. Acetaminophen: antipyretic or hypothermic in mice? In either case, PGHS-1b (COX-3) is irrelevant. Prostaglandins Other Lipid Mediat 2008; 85: 89-99.

[97] Ayoub SS, Botting RM, Goorha S, Colville-Nash PR, Willoughby DA, Ballou LR. Acetaminophen-induced hypothermia in mice is mediated by a prostaglandin endoperoxide synthase 1 gene-derived protein. Proc Natl Acad Sci U S A 2004; 101: 11165-11169.

[98] Vitulli WF, Kaiser GA, Maranto DL, Blake SE, Storey TM, McPherson KP, Luper SL. Acetaminophen effects on behavioral thermoregulation in albino rats. Percept Mot Skills 1999; 88: 281-291.

Table S1 - Nummercial data

Agent	Catagory	n[1]	Species	ΔT$_b$±SD		ΔT$_a$±SD		n[2]
5'-Hydroxytryptophan	Amino acid	20	Rat	-1.0 ± 2.1	°C	23.1 ± 6.2	°C	19
5'-Hydroxytryptophan	Amino acid	10	Mouse	-0.4 ± 3.6	°C			<10
5'-Hydroxytryptophan	Amino acid	38	Rabbit	0.8 ± 1.3	°C	21.8 ± 1.3	°C	25
Acetaminophen	Antipyretic	13	Mouse	-4.9 ± 3.3	°C			<10
Acetaminophen	Antipyretic	10	Rat	-1.9 ± 2.0	°C			<10
Acetylcholine	Acetylcholine agonist	18	Rat	-0.7 ± 1.0	°C	18.9 ± 9.8	°C	17
Acetylstrophanthidin	Glycoside	11	Primate	-2.2 ± 3.6	°C	24.0 ± 0.0	°C	11
ACTH	Peptide	12	Rabbit	-0.6 ± 0.6	°C	22.7 ± 3.4	°C	12
Amantadine	Dopamine receptor agonist	12	Mouse	-2.5 ± 2.5	°C			
Aminobutyric Acid	Amino acid	54	Mouse	-2.6 ± 2.9	°C	22.0 ± 6.7	°C	21
Aminobutyric Acid	Amino acid	27	Rat	-1.1 ± 2.5	°C	24.6 ± 7.0	°C	17
Aminopyrine	Antipyretic	13	Rabbit	-1.6 ± 1.1	°C			<10
Amitriptyline	Tricyclic antidepressant	14	Mouse	-1.6 ± 2.0	°C			<10
Amphetamine	Amphetamine	197	Mouse	0.5 ± 3.0	°C	21.4 ± 5.4	°C	171
Amphetamine	Amphetamine	272	Rat	0.6 ± 2.4	°C	18.7 ± 9.1	°C	210
Amphetamine	Amphetamine	22	Rabbit	2.0 ± 1.2	°C	22.1 ± 1.6	°C	11
Amphetamine	Amphetamine	10	Dog	2.3 ± 1.5	°C			<10
Angiotensin	Peptide	15	Primate	-0.1 ± 0.6	°C			<10
Apomorphine	Dopamine receptor agonist	144	Mouse	-3.9 ± 2.1	°C	29.9 ± 1.5	°C	124
Apomorphine	Dopamine receptor agonist	145	Rat	-1.2 ± 1.3	°C	19.2 ± 7.4	°C	115
Apomorphine	Dopamine receptor agonist	37	Rabbit	1.5 ± 1.1	°C	21.4 ± 4.8	°C	24
Arachidonic Acid	Prostaglandin precursor	16	Rat	0.8 ± 0.8	°C	21.8 ± 0.8	°C	14
Arachidonic Acid	Prostaglandin precursor	11	Rabbit	1.0 ± 1.3	°C			<10
Arecoline	Acetylcholine agonist	54	Rat	-1.0 ± 1.8	°C			<10
Arecoline	Acetylcholine agonist	10	Cat	0.4 ± 0.9	°C			<10
Aspirin	Antipyretic	26	Rat	-0.6 ± 1.1	°C			<10
Aspirin	Antipyretic	12	Rabbit	0.1 ± 0.7	°C			<10
Atropine	Muscarinic blocking agent	22	Mouse	-0.5 ± 1.4	°C	22.2 ± 6.8	°C	18
Atropine	Muscarinic blocking agent	47	Rat	-0.1 ± 1.3	°C	19.7 ± 9.0	°C	44
Atropine	Muscarinic blocking agent	17	Rabbit	-0.1 ± 0.6	°C	20.7 ± 8.2	°C	14
Bombesin	Peptide	64	Rat	-1.9 ± 2.5	°C	13.5 ± 11	°C	61
Bromocriptine	Dopamine receptor agonist	16	Rat	-2.7 ± 4.1	°C			<10
Calcium Chloride	Cation	12	Rat	-1.0 ± 0.9	°C	22.6 ± 1.1	°C	12
Calcium Chloride	Cation	10	Rabbit	-1.0 ± 1.2	°C			<10
Calcium Chloride	Cation	12	Cat	-0.8 ± 0.7	°C			<10
Cannabidol	Hallucinogen	13	Mouse	-1.6 ± 1.3	°C			<10
Cannabis	Hallucinogen	14	Rat	-2.1 ± 2.0	°C			<10
Capsaicin	Capsaicinoid	11	Rat	-1.9 ± 3.6	°C			<10
Carbachol	Acetylcholine agonist	10	Rat	-1.5 ± 2.6	°C	19.3 ± 8.5	°C	10
Carbachol	Acetylcholine agonist	10	Sheep	0.6 ± 0.7	°C	21.5 ± 8.3	°C	10
Carbon Dioxide	Gas	28	Rat	-3.3 ± 6.1	°C	23.5 ± 13	°C	28
Carbon Dioxide	Gas	14	Guinea Pig	-1.7 ± 2.1	°C	21.4 ± 5.6	°C	14
Ceruletide	Peptide	20	Mouse	-1.4 ± 1.1	°C			<10
Chloroamphetamine	Amphetamine	14	Rabbit	1.0 ± 2.1	°C			<10
Chlorophenylalanine	Presynaptic aminergic altering agent	18	Mouse	-0.5 ± 1.6	°C	19.8 ± 7.4	°C	14
Chlorophenylalanine	Presynaptic aminergic altering agent	18	Rabbit	-0.2 ± 0.3	°C	21.5 ± 5.4	°C	15
Chlorophenylalanine	Presynaptic aminergic altering agent	50	Rat	-0.2 ± 1.3	°C	21.1 ± 8.9	°C	45
Chlorpromazine	Neuroleptic	101	Mouse	-4.4 ± 4.1	°C	23.6 ± 7.9	°C	82
Chlorpromazine	Neuroleptic	205	Rat	-4.0 ± 5.0	°C	21.5 ± 21	°C	157
Chlorpromazine	Neuroleptic	12	Guinea Pig	-2.0 ± 1.2	°C			<10
Chlorpromazine	Neuroleptic	46	Rabbit	-1.1 ± 1.0	°C	21.1 ± 5.9	°C	26
Cimetidine	H2 receptor antagonist	11	Rat	-0.3 ± 0.4	°C	21.3 ± 1.3	°C	11
Clomipramine	Tricyclic antidepressant	11	Mouse	-1.4 ± 1.3	°C			<10
Clomipramine	Tricyclic antidepressant	16	Rat	-0.6 ± 1.3	°C	21.5 ± 6.8	°C	21
Clonidine	adrenergic agonist	27	Mouse	-2.6 ± 1.4	°C	21.3 ± 1.0	°C	24
Clonidine	adrenergic agonist	72	Rat	-2.2 ± 1.7	°C	21.1 ± 7.5	°C	64

Table S1 - Nummercial data

Cobaltous Chloride	Cation	11	Mouse	-3.4	± 1.9	°C	23.9 ± 3.8	°C	11
Cocaine	Uptake inhibitor	16	Rat	-1.0	± 1.8	°C	19.3 ± 6.6	°C	15
Cocaine	Uptake inhibitor	11	Mouse	0.2	± 2.0	°C	26.6 ± 4.9	°C	11
Cocaine	Uptake inhibitor	12	Primate	0.3	± 1.2	°C			<10
Cyproheptadine	Serotonin antagonist	10	Rabbit	-0.6	± 0.6	°C			<10
Cyproheptadine	Serotonin antagonist	20	Rat	0.0	± 1.1	°C	20.9 ± 6.5	°C	19
d-Ala-2-Met-Enkephalinamide	Peptide	20	Cat	1.1	± 2.0	°C	19.2 ± 8.7	°C	19
Desipramine	Tricyclic antidepressant	22	Mouse	-0.7	± 1.3	°C	22.8 ± 3.3	°C	19
Desipramine	Tricyclic antidepressant	21	Rat	-0.4	± 3.0	°C	18.4 ± 7.0	°C	17
Diethyldithiocarbamate	Dopamine β-hydroxylase inhibitor	12	Rat	-1.6	± 1.8	°C	22.5 ± 6.3	°C	12
Dihydroxyphenylalanine	Amino acid	13	Mouse	-1.6	± 2.8	°C	22.1 ± 1.6	°C	12
Dihydroxyphenylalanine	Amino acid	18	Rabbit	0.5	± 0.9	°C	21.2 ± 8.5	°C	15
Dihydroxytryptamine	Tryptamine	23	Rat	-0.1	± 1.0	°C	21.8 ± 9.2	°C	23
Dinitrophenol	Uncoupling agent	25	Rat	1.3	± 1.4	°C	22.0 ± 8.4	°C	19
Dinitrophenol	Uncoupling agent	24	Rabbit	1.4	± 0.9	°C			<10
Dinitrophenol	Uncoupling agent	18	Dog	1.9	± 2.0	°C			<10
Diphenhydramine	H1 receptor antagonist	15	Mouse	-1.4	± 1.4	°C	22.5 ± 2.6	°C	12
DMSO	Organosulfic	18	Rat	-8.6	± 10.5	°C	12.5 ± 10	°C	17
DMSO	Organosulfic	11	Mouse	-1.9	± 2.6	°C			<10
Dopamine	Dopamine receptor agonist	14	Mouse	-0.9	± 2.7	°C			<10
Dopamine	Dopamine receptor agonist	53	Rat	-0.9	± 1.4	°C	19.5 ± 4.7	°C	41
Dopamine	Dopamine receptor agonist	21	Rabbit	0.9	± 1.2	°C	21.5 ± 4.6	°C	21
Ephedrine	adrenergic agonist	15	Mouse	0.2	± 2.7	°C	24.4 ± 6.5	°C	14
Epinephrine	adrenergic agonist	18	Mouse	-3.7	± 6.4	°C	20.9 ± 6.5	°C	11
Epinephrine	adrenergic agonist	26	Rat	-0.4	± 2.4	°C	21.1 ± 6.2	°C	25
Epinephrine	adrenergic agonist	24	Rabbit	0.4	± 1.6	°C			<10
Ergotamine	Ergot alkaloid	13	Rabbit	-1.9	± 2.3	°C			<10
Ergotoxine	Ergot alkaloid	14	Rabbit	0.9	± 3.9	°C			<10
Ethanol	Anesthetic	52	Mouse	-2.4	± 2.4	°C	23.4 ± 4.9	°C	48
Ethanol	Anesthetic	28	Rat	-1.3	± 1.2	°C	23.4 ± 7.5	°C	12
Fenfluramine	Amphetamine	25	Rat	1.2	± 2.1	°C	25.6 ± 5.9	°C	23
Fenfluramine	Amphetamine	12	Rabbit	1.5	± 0.6	°C	22.6 ± 1.8	°C	12
Guanethidine	Uptake inhibitor	13	Rat	-0.2	± 2.3	°C	20.7 ± 8.2	°C	13
Haloperidol	Neuroleptic	28	Mouse	-2.3	± 2.9	°C	21.3 ± 4.0	°C	19
Haloperidol	Neuroleptic	69	Rat	-0.4	± 1.5	°C	19.3 ± 8.1	°C	56
Haloperidol	Neuroleptic	18	Rabbit	-0.3	± 0.7	°C	21.3 ± 6.8	°C	12
Halothane	Anesthetic	23	Pig	2.6	± 2.2	°C			<10
Harmaline	Hallucinogen	10	Rat	-2.2	± 1.7	°C	23.8 ± 0.9	°C	10
Helium	Gas	21	Hamster	-18.3	± 12.7	°C	10.4 ± 13	°C	21
Histamine	Neuromuscular blocking agent	21	Mouse	-2.3	± 2.6	°C	22.8 ± 4.9	°C	16
Histamine	Neuromuscular blocking agent	57	Rat	-0.9	± 1.6	°C	22.3 ± 4.7	°C	47
Histamine	Neuromuscular blocking agent	12	Cat	-0.5	± 1.3	°C	21.9 ± 7.2	°C	10
Histamine	Neuromuscular blocking agent	10	Sheep	0.2	± 0.3	°C			<10
Histidine	Amino acid	10	Rat	-0.4	± 0.6	°C			<10
Hydroxydopamine	Uptake altering agent	14	Mouse	-1.2	± 1.3	°C	20.7 ± 5.0	°C	14
Hydroxydopamine	Uptake altering agent	70	Rat	-0.7	± 1.6	°C	16.3 ± 12	°C	62
Imipramine	Tricyclic antidepressant	24	Rat	-0.9	± 1.3	°C	21.3 ± 7.3	°C	19
Imipramine	Tricyclic antidepressant	23	Mouse	-0.8	± 1.1	°C	22.4 ± 2.4	°C	16
Imipramine	Tricyclic antidepressant	12	Rabbit	1.0	± 1.9	°C			<10
Indomethacin	Antipyretic	11	Mouse	-0.5	± 1.3	°C	18.2 ± 14	°C	11
Indomethacin	Antipyretic	28	Rat	-0.3	± 0.6	°C	22.4 ± 4.7	°C	25
Indomethacin	Antipyretic	15	Rabbit	-0.1	± 0.2	°C	21.8 ± 1.7	°C	13
Insulin	Hormone	10	Mouse	-5.3	± 4.4	°C	24.1 ± 5.2	°C	10
Isoflurophate	Anticholinesterase	30	Rat	-3.5	± 2.3	°C	23.3 ± 2.8	°C	15
Isoproterenol	adrenergic agonist	14	Mouse	-1.2	± 3.8	°C	21.1 ± 6.7	°C	14
Isoproterenol	adrenergic agonist	56	Rat	0.4	± 1.6	°C	23.0 ± 5.3	°C	52
LRH	Peptide	10	Rat	-0.1	± 1.0	°C	20.4 ± 7.5	°C	10
Lysergide	Hallucinogen	10	Mouse	-0.3	± 2.0	°C			<10
Lysergide	Hallucinogen	25	Rat	0.3	± 1.5	°C	25.9 ± 7.9	°C	16
Lysergide	Hallucinogen	88	Rabbit	1.5	± 0.7	°C	22.7 ± 5.3	°C	48

Table S1 - Nummercial data

Melanostatin	Peptide	10	Mouse	-0.5 ± 1.1 °C			<10
Meperidine	Narcotic analgesic	27	Mouse	-2.1 ± 3.2 °C	22.7 ± 5.3 °C	23	
Meperidine	Narcotic analgesic	13	Rat	-1.2 ± 1.5 °C	20.4 ± 2.9 °C	11	
Meperidine	Narcotic analgesic	11	Rabbit	0.6 ± 1.2 °C			<10
Met-Enkephalin	Peptide	11	Rat	0.4 ± 0.9 °C			<10
Metamphetamine	Amphetamine	23	Mouse	0.2 ± 3.2 °C	24.8 ± 5.4 °C	21	
Methacholine	Acetylcholine agonist	11	Rat	-1.8 ± 1.7 °C	20.5 ± 8.5 °C	11	
Methadone	Narcotic analgesic	10	Mouse	-3.3 ± 6.4 °C	23.9 ± 2.8 °C	11	
Methadone	Narcotic analgesic	41	Rat	-1.0 ± 2.1 °C	20.3 ± 6.7 °C	27	
Methylatropine	Muscarinic blocking agent	11	Rat	-0.9 ± 2.5 °C			<10
Methyldopa	Uptake altering agent	10	Rat	-2.7 ± 2.4 °C			<10
Methyldopa	Uptake altering agent	11	Mouse	-0.8 ± 1.9 °C			<10
Methysergide	Serotonin antagonist	28	Rat	-0.3 ± 0.9 °C	18.7 ± 8.3 °C	25	
Metyrosine	Uptake altering agent	41	Rat	-1.9 ± 3.1 °C	22.7 ± 7.5 °C	29	
Morphine	Narcotic analgesic	32	Dog	-1.4 ± 1.6 °C			<10
Morphine	Narcotic analgesic	108	Mouse	-1.2 ± 2.1 °C	23.0 ± 3.6 °C	92	
Morphine	Narcotic analgesic	330	Rat	-0.0 ± 2.1 °C	22.3 ± 5.1 °C	273	
Morphine	Narcotic analgesic	37	Cat	1.6 ± 1.4 °C	18.8 ± 8.7 °C	24	
Morphine	Narcotic analgesic	35	Rabbit	-0.3 ± 1.3 °C	21.7 ± 6.5 °C	15	
Muramyl-dipeptide	Peptide	25	Rabbit	1.4 ± 0.8 °C			<10
Nalorphine	Narcotic analgesic	11	Mouse	0.3 ± 0.4 °C	24.0 ± 6.6 °C	10	
Naloxone	Narcotic analgesic	29	Mouse	-1.0 ± 3.4 °C	21.7 ± 5.6 °C	25	
Naloxone	Narcotic analgesic	81	Rat	-0.1 ± 0.5 °C	19.4 ± 7.4 °C	67	
Naltrexone	Narcotic analgesic	11	Rat	-0.7 ± 1.4 °C			<10
Neurotensin	Peptide	40	Mouse	-2.8 ± 2.8 °C	20.1 ± 8.5 °C	40	
Neurotensin	Peptide	77	Rat	-1.2 ± 1.1 °C	18.8 ± 8.3 °C	59	
Nicotine	Acetylcholine agonist	26	Mouse	-2.6 ± 2.6 °C	20.7 ± 7.1 °C	24	
Norepinephrine	adrenergic agonist	35	Mouse	-1.3 ± 2.2 °C	20.9 ± 9.7 °C	32	
Norepinephrine	adrenergic agonist	38	Cat	-1.0 ± 0.9 °C	23.1 ± 4.8 °C	27	
Norepinephrine	adrenergic agonist	13	Primate	-0.6 ± 0.9 °C	22.7 ± 7.5 °C	10	
Norepinephrine	adrenergic agonist	223	Rat	-0.0 ± 1.8 °C	22.7 ± 7.9 °C	155	
Norepinephrine	adrenergic agonist	21	Sheep	0.4 ± 1.2 °C	21.4 ± 13 °C	21	
Norepinephrine	adrenergic agonist	15	Guinea Pig	0.7 ± 0.5 °C	26.2 ± 7.2 °C	14	
Norepinephrine	adrenergic agonist	55	Rabbit	0.8 ± 1.1 °C	24.3 ± 22 °C	42	
Oxotremorine	Acetylcholine agonist	89	Mouse	-7.7 ± 3.6 °C	21.4 ± 3.5 °C	86	
Oxotremorine	Acetylcholine agonist	33	Rat	-2.8 ± 3.9 °C	19.2 ± 4.8 °C	21	
Oxygen	Gas	11	Rat	-3.1 ± 3.2 °C			<10
Oxytocin	Peptide	11	Rat	1.1 ± 0.6 °C	20.0 ± 9.1 °C	10	
Pargyline	Monoamine oxidase inhibitor	20	Rat	-1.3 ± 1.3 °C	18.2 ± 10 °C	19	
Pentazocine	Narcotic analgesic	18	Cat	-0.3 ± 1.6 °C	17.6 ± 11 °C	17	
Pentobarbital	Barbiturate	16	Mouse	-6.4 ± 5.6 °C	21.9 ± 7.1 °C	11	
Pentobarbital	Barbiturate	12	Dog	-3.9 ± 4.1 °C			<10
Pentobarbital	Barbiturate	10	Cat	-3.4 ± 3.2 °C			<10
Pentobarbital	Barbiturate	35	Rat	-2.0 ± 3.2 °C	20.0 ± 9.6 °C	35	
Pentylenetetrazole	Analeptic	10	Rat	-2.3 ± 1.1 °C	21.9 ± 7.1 °C	10	
Phenacetin	Antipyretic	12	Rat	-0.5 ± 1.4 °C			<10
Phenoxybenzamine	α-adrenergic antagonist	20	Mouse	-3.5 ± 3.5 °C	23.0 ± 1.8 °C	18	
Phenoxybenzamine	α-adrenergic antagonist	26	Rat	-1.9 ± 2.9 °C	17.4 ± 8.0 °C	24	
Phenoxybenzamine	α-adrenergic antagonist	20	Rabbit	-0.6 ± 0.7 °C	21.8 ± 1.5 °C	15	
Phentolamine	α-adrenergic antagonist	65	Rat	-1.2 ± 1.7 °C	19.2 ± 8.4 °C	63	
Phentolamine	α-adrenergic antagonist	14	Mouse	-1.0 ± 1.6 °C	23.7 ± 5.1 °C	12	
Physostigmine	Anticholinesterase	12	Mouse	-2.9 ± 2.1 °C	22.1 ± 4.1 °C	12	
Physostigmine	Anticholinesterase	26	Rat	-1.3 ± 1.4 °C	22.1 ± 5.8 °C	18	
Pilocarpine	Acetylcholine agonist	29	Rat	-1.7 ± 0.8 °C	22.1 ± 3.7 °C	19	
Pilocarpine	Acetylcholine agonist	22	Mouse	-1.6 ± 1.5 °C	23.5 ± 5.2 °C	20	
Pimozide	Neuroleptic	54	Rat	0.1 ± 0.9 °C	18.2 ± 8.3 °C	51	
Piribedil	Dopamine receptor agonist	14	Mouse	-4.1 ± 1.7 °C			<10
Piribedil	Dopamine receptor agonist	16	Rat	-2.7 ± 1.6 °C	16.2 ± 8.9 °C	15	
Promazine	Neuroleptic	26	Mouse	-5.8 ± 5.8 °C	25.4 ± 8.1 °C	19	
Promethazine	Neuroleptic	10	Mouse	-2.9 ± 1.8 °C	22.8 ± 2.6 °C	10	

Table S1 - Nummercial data

Name	Class	n^1	Species	T_b			T_a			n^2
Propranolol	β-adrenergic antagonist	29	Mouse	-1.5	± 2.7	°C	19.8	± 10	°C	29
Propranolol	β-adrenergic antagonist	11	Guinea Pig	-1.4	± 4.2	°C	20.6	± 19	°C	11
Propranolol	β-adrenergic antagonist	67	Rat	-0.7	± 1.1	°C	18.9	± 8.5	°C	63
Propranolol	β-adrenergic antagonist	14	Rabbit	0.2	± 0.7	°C	21.5	± 2.9	°C	14
Prostaglandin D2	Prostaglandin	14	Rat	-0.1	± 0.8	°C	22.7	± 1.3	°C	13
Prostaglandin E1	Prostaglandin	43	Rat	0.4	± 2.0	°C	21.6	± 5.2	°C	33
Prostaglandin E1	Prostaglandin	52	Rabbit	0.9	± 0.5	°C	23.4	± 17	°C	42
Prostaglandin E1	Prostaglandin	24	Cat	1.6	± 1.2	°C	22.0	± 4.2	°C	22
Prostaglandin E2	Prostaglandin	16	Rabbit	1.0	± 0.4	°C	23.2	± 2.9	°C	15
Prostaglandin E2	Prostaglandin	57	Rat	1.4	± 1.2	°C	20.7	± 6.4	°C	41
Prostaglandin E2	Prostaglandin	11	Mouse	1.6	± 0.9	°C				<10
Prostaglandin F2	Prostaglandin	24	Rat	1.3	± 1.3	°C				<10
Quinine	Glycoside	11	Rat	-3.3	± 1.8	°C	19.2	± 8.1	°C	11
Reserpine	Uptake altering agent	152	Mouse	-7.9	± 4.8	°C	22.1	± 6.2	°C	56
Reserpine	Uptake altering agent	82	Rat	-2.6	± 4.2	°C	20.0	± 7.8	°C	66
Reserpine	Uptake altering agent	35	Rabbit	-0.5	± 2.3	°C	23.7	± 1.2	°C	20
Serotonin	Tryptamine	27	Mouse	-3.4	± 2.4	°C	23.0	± 4.0	°C	24
Serotonin	Tryptamine	114	Rat	-0.8	± 1.5	°C	21.9	± 6.8	°C	103
Serotonin	Tryptamine	20	Sheep	-0.5	± 0.4	°C	18.4	± 14	°C	19
Serotonin	Tryptamine	22	Cat	0.4	± 0.9	°C	25.1	± 6.3	°C	19
Serotonin	Tryptamine	54	Rabbit	0.5	± 1.3	°C	21.0	± 6.5	°C	40
Sodium Chloride	Cation	16	Rat	-0.0	± 1.0	°C	21.5	± 1.6	°C	15
Sodium Chloride	Cation	12	Cat	0.8	± 1.4	°C	20.1	± 9.9	°C	10
Sodium Salicylate	Antipyretic	34	Rat	-1.1	± 1.4	°C	23.0	± 6.3	°C	15
Sodium Salicylate	Antipyretic	17	Rabbit	-0.1	± 0.3	°C				<10
Soman	Anticholinesterase	18	Rat	-3.3	± 1.9	°C	22.2	± 4.0	°C	15
Somatostatin	Peptide	27	Rat	0.9	± 1.6	°C				<10
Substance P	Peptide	17	Rat	-0.2	± 1.7	°C	10.7	± 10	°C	10
Succinylcholine	Neuromuscular blocking agent	16	Pig	1.8	± 1.7	°C				<10
Taurine	Amino acid	18	rat	-2.2	± 3.6	°C	21.4	± 9.4	°C	16
Taurine	Amino acid	17	Rabbit	-2.0	± 2.6	°C	19.8	± 7.0	°C	16
Terodotoxin	Toxin	11	Cat	-2.4	± 1.9	°C	14.7	± 8.2	°C	10
Thyroxine	Hormone	12	Rat	1.0	± 1.9	°C	16.7	± 15	°C	13
Tranyclypromine	Monoamine oxidase inhibitor	19	Rat	-0.8	± 2.2	°C	21.6	± 1.9	°C	16
Tranyclypromine	Monoamine oxidase inhibitor	13	Rabbit	0.8	± 1.5	°C				<10
Tremorine	Acetylcholine agonist	12	Rat	-6.9	± 6.9	°C	15.5	± 11	°C	11
Tremorine	Acetylcholine agonist	35	Mouse	-6.7	± 2.7	°C	21.1	± 2.5	°C	35
TRH	Peptide	50	Rat	0.4	± 0.9	°C	19.3	± 7.8	°C	38
TRH	Peptide	35	Mouse	0.5	± 2.1	°C	19.3	± 6.7	°C	29
TRH	Peptide	25	Rabbit	0.8	± 0.7	°C				<10
Tryptophan	Amino acid	13	Rat	-1.3	± 1.9	°C	16.3	± 9.7	°C	13
Tyramine	adrenergic agonist	23	Rat	1.5	± 1.0	°C	24.9	± 8.3	°C	23
Urethan	Anesthetic	13	Rat	-3.0	± 5.2	°C	23.0	± 9.4	°C	12
Vasopressin	Peptide	23	Rat	-0.3	± 1.2	°C				<10
Yohimbine	α-adrenergic antagonist	15	Rat	-1.0	± 1.5	°C	22.1	± 2.6	°C	15
β-Endorphin	Peptide	34	Mouse	-0.4	± 4.2	°C	19.9	± 9.3	°C	30
β-Endorphin	Peptide	97	Rat	-0.3	± 1.9	°C	18.9	± 8.8	°C	82
β-Tetrahydronaphthalamine	adrenergic agonist	11	Rat	0.3	± 2.8	°C				<10
β-Tetrahydronaphthalamine	adrenergic agonist	21	Rabbit	2.5	± 1.7	°C				<10
Δ8-THC	Hallucinogen	18	Mouse	-2.6	± 1.4	°C	22.6	± 0.3	°C	18
Δ9-THC	Hallucinogen	103	Mouse	-3.7	± 2.9	°C	22.7	± 6.0	°C	90
Δ9-THC	Hallucinogen	75	Rat	-1.7	± 1.6	°C	22.3	± 3.6	°C	63
Δ9-THC	Hallucinogen	12	Cat	-1.1	± 1.4	°C	24.0	± 0.0	°C	14

T_b, body temperature
T_a, ambient temperature (in case of < 10 T_a reported values, no mean was calculated)
n^1, groupsize for T_b data
n^2, groupsize for T_a data

Table S2 - Species distribution

Species	Number of reports
Alpaca	9
Armadillo	1
Bear	2
Cat	720
Cattle	36
Crab	1
Crayfish	1
Deer	1
Desert rat	19
Dog	368
Duck	7
Echnida	9
Fish	42
Frog	3
Gerbil	44
Goat	65
Goose	2
Ground squirrel	86
Guinea pig	281
Hamster	101
Hedgehog	4
Horse	16
Human	1285
Leopard	1
Lion	1
Lizard	10
Lobster	1
Mouse	3549
Pigeon	238
Pig	78
Primate	328
Quail	5
Rabbit	2008
Rat	6154
Salamander	13
Scorpion	2
Sheep	251
Shrimp	1
Toad	1
Turkey	3
Turtle	2
Woodchuck	5
Zebu	1