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ExActa

Thermoregulation

Mammals and birds are endothermic animals that control their body temperature very tightly. Keeping the central body temperature within a narrow range allows many essential mechanisms such as kidney function and central nervous activity to operate with high precision. Further, this type of thermoregulation allows mammals and birds to be physically active for hunting and travelling with lesser dependence on environmental temperatures, which in turn increases the degrees of freedom for living and thus evolutionary fitness.

So it was a real surprise when researchers found the first warm-bodied fish in 2015 (Wegner *et al.* 2015). The increased temperature of *Lampris guttatus* allows the fish being faster than its prey in cold water, which is obviously an evolutionary advantage. It was known before that predator fish may heat up their muscles by continuous moving to prepare for hunting. However, the mechanism in *Lampris guttatus* is completely different. They have a major energy-saving mechanism that can be found in the structure of the gills where the blood vessels are organized as a countercurrent network acting as a heat exchanger which is typically not seen in other fish species.

One of the enigmas of thermoregulation is the understanding of the 'sensors' in the control system. The challenge is that the temperature has to be kept constant over long time. Peripheral 'warm' and 'cold' receptors adapt quickly and are seen from control theory not perfectly suited to serve for the regulator as sensory 'input' at a first glance. A detailed review on the role of the skin was given by Romanovsky (2014) with a discussion of feed-back and feed-forward signals and the impact on response time of the thermoregulatory system in hairy and non-hairy mice.

One candidate for a sensor of body temperature, the TRP4, was studied by means of a pharmacological approach in rats (Vizin *et al.* 2015). They observed a rise in body temperature accompanied by higher oxygen consumption once a potent pharmacological inhibitor (HC-067047) of TRP4 was administered and hypothermia once a TRPV agonist was administered topically. However, this work misses experiments in TRP4 knockout animals to exclude possible off-target effects of the TRP4 inhibitor (Garami & Romanovsky 2015).

Muscle work contributes significantly to heat generation in the body. The thermoregulatory system uses this mechanism also as a heat source during shivering, for example in the ascending phase of fever. From the standpoint of control theory, it might be of advantage to know early the fact that a muscle generated heat well before that heat reaches the central body. In this context, we see the work by Todd *et al.* (2014) who investigated the relationship between muscle temperature and eccrine sweating in exercising. As conclusion, they put forward the notion of an intramuscular thermoreceptor. However, the physical identity of that remains still to be established (Kenny 2014).

Sweating is an important mechanism for heat dissipation. In humans, the volume of water lost via sweat can be in the order of litres under very hot conditions and/or physical activity. As evolution has not 'produced' a water pump, the transport of water can only be accomplished along osmotic gradients. Those gradients are generated typically by active salt transport that itself requires energy and produces thermal energy. If under certain conditions the heat dissipation via sweating is smaller than the heat production required for generating the osmotic gradients, we would find a positive feedback that is potentially life-threatening if other dissipative routes such as conduction and radiation are less effective. This might be the reason for the epidemiological observation that the risk for sudden infant death is increased among infants that had more thermal insulation than was necessary to maintain the lower critical temperature (Williams *et al.* 1996).

Sweating is less effective for heat dissipation in humid climate and we can observe a humid-heat acclimation. Patterson *et al.* investigate the question whether or not plasma volume is selectively defended during exercise- and heat-induced dehydration following humid-heat acclimation. Patterson *et al.* (2014) concluded from their study that the plasma volume was not defended more vigorously following humid-heat acclimation and a greater fluid loss may well underlie the mechanisms for enhancing plasma volume recovery when heat acclimation is induced using the controlled-hyperthermia technique. Sweating at higher rate will ultimately lead to increased thirst. Temperature of drinking water seems to be important for hemodynamic aspects. Low temperature of drinking water temperature leads to a reduction of heart rate possibly by an augmented vagal tone (Girona *et al.* 2014, Grasser *et al.* 2015). However, some aspects of this work were challenged by McMullen (2015).

One of the important central nervous structures in regulating body temperature is the median pre-optic nucleus (MnPO) as reviewed in detail by McKinley *et al.* (2015) with regard to central connections and other physiological functions such as homoeostasis of body fluid, sodium, temperature and sleep.

The odorous hydrogen sulphide (H_2S) has been established as an endogenous mediator and was reported be involved in the CO_2 respiratory response (da Silva *et al.* 2014). One mechanism by which this gas acts on the cellular level is the inhibition of the phosphorylation of p38 (Li *et al.* 2016, 12). During hypoxia, H_2S is produced in the anteroventral pre-optic region that is regarded to be an important integrating site of thermal and cardiorespiratory responses to hypoxia (Kwiatkoski *et al.* 2014). This in turn inhibits also the hypoxic ventilator response (Lopes *et al.* 2014). How thermoregulation interferes with this process is still unknown.

Thermoregulation may be deeply impacted by hormones that modulate metabolic rate such as thyroid hormones and leptin (Taylor *et al.* 2014). Excess of thyroid hormone makes patients flee warm situations such as sunlight. People with hypothyroidism feel typically 'cold' and seek warm places. The role of another hormone, the neuropeptide Y, was studied in catecholaminergic-specific overexpressing NPY neurons in a mice model by Vähätalo *et al.* (2015). They observe in those mice severe obesity with impaired glucose tolerance. Brown adipose tissue thermogenic capacity was decreased, and brown adipocytes filled with lipids. Decreased lipolysis leads to adipocyte hypertrophy accompanied by low catecholaminergic activity.

In contrast to white adipose tissue, brown adipose tissue is able to generate heat by shortcutting the proton gradient in the mitochondria. This shortcut is accomplished by the mitochondrial transmembrane proteins, uncoupling proteins (UCP) UCP1-UCP5. Thermogenic brown adipose tissue is regarded to be of great importance for thermoregulation after birth. Here the newborn is in a complete new environment. Gas exchange over lungs contributes to heat loss as well as heat loss over the body surface that was prenatally kept in 'isothermal' condition in the mother. In this context, embryonal development of brown adipose tissue was studied in sheep in a paper that appeared in Acta Physiologica (Pope *et al.* 2014). They identified four distinct phases of development, each associated with pronounced changes in tissue histology and in distribution of the brown adipose tissue-specific uncoupling protein 1. Interestingly, within 12 h after birth, lipid storage depots were depleted and uncoupling protein 1 and others showed peak expression. By 1 month, uncoupling protein 1 disappeared and the depot contained lipid droplets again.

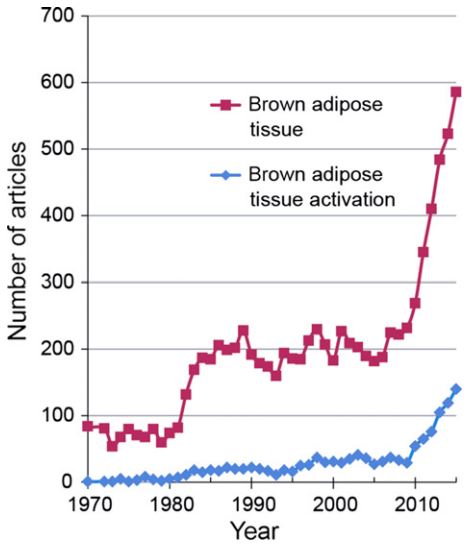

Figure 1 Number of published articles with the keywords 'brown adipose tissue' and its activation as they appeared in NCBI PubMed database in the years 1970–2015. Data were obtained in 2016 from the site with the respective keywords in the search query.

The authors conclude that the brown adipose tissue undergoes profound compositional changes in early life (Pope *et al.* 2014). Brown fat and its activation have been of increasing interest in the recent years. An analysis of the number of articles that have been published in that topic shows a steep increase after the year 2008 (Fig. 1). Inducing weight loss in obesity by pharmacological approaches might be an interesting concept in fighting associated morbidity of obesity such as type 2 diabetes mellitus, hypertension (Haslam & James 2005) and complications thereof, such as chronic kidney disease. Brown adipose tissue with its uncoupling mechanism seems to be an interesting key target for pharmacological intervention (Lidell & Enerbäck 2010) from this perspective.

Conflict of interest

None.

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References

Garami, A. & Romanovsky, A.A. 2015. The transient receptor potential vanilloid-4 channel: detecting body temperatures that drive defences against mild warmth. *Acta Physiol* **214**, 154–156.

  doi: 10.1111/apha.12664

Girona, M., Grasser, E.K., Dulloo, A.G. & Montani, J.P. 2014. Cardiovascular and metabolic responses to tap water ingestion in young humans: does the water temperature matter?. *Acta Physiol* **211**, 358–370.

Grasser, E.K., Girona, M., Dulloo, A.G. & Montani, J.P. 2015. It is likely that the drinking of cold and room temperature water decreases cardiac workload. *Acta Physiol* **213**, 5–6.

Haslam, D.W. & James, W.P.T. 2005. Obesity. *Lancet* **366**, 1197–1209.

Kenny, G.P. 2014. Muscle temperature and sweating during exercise: a new link? *Acta Physiol* **212**, 11–13.

Kwiatkoski, M., Soriano, R.N., da Silva, G.S.F., Francescato, H.D., Coimbra, T.M., Glass, M.L., Carnio, E.C. & Branco, L.G.S. 2014. Endogenous preoptic hydrogen sulphide attenuates hypoxia-induced hyperventilation. *Acta Physiol* **210**, 913–927.

Li, C., Liu, Y., Tang, P., Liu, P., Hou, C., Zhang, X., Chen, L., Zhang, L. & Gu, C. 2016. Hydrogen sulfide prevents OGD/R-induced apoptosis by suppressing the phosphorylation of p38 and secretion of IL-6 in PC12 cells. *NeuroReport* **27**, 230–234.

Lidell, M.E. & Enerbäck, S. 2010. Brown adipose tissue–a new role in humans? *Nat Rev Endocrinol* **6**, 319–325.

Lopes, L.T., Biancardi, V., Vieira, E.B., Leite-Panissi, C., Bícego, K.C. & Gargaglioni, L.H. 2014. Participation of the dorsal periaqueductal grey matter in the hypoxic ventilatory response in unanaesthetized rats. *Acta Physiol* **211**, 528–537.

McKinley, M.J., Yao, S.T., Uschakov, A., McAllen, R.M., Rundgren, M. & Martelli, D. 2015. The median preoptic nucleus: front and centre for the regulation of body fluid, sodium, temperature, sleep and cardiovascular homeostasis. *Acta Physiol* **214**, 8–32.

McMullen, M.K. 2015. It is unlikely that the drinking of cold and room temperature water decreases cardiac workload. *Acta Physiol* **213**, 3–4.

Patterson, M.J., Stocks, J.M. & Taylor, N.A.S. 2014. Whole-body fluid distribution in humans during dehydration and recovery, before and after humid-heat acclimation induced using controlled hyperthermia. *Acta Physiol* **210**, 899–912.

Pope, M., Budge, H. & Symonds, M.E. 2014. The developmental transition of ovine adipose tissue through early life. *Acta Physiol* **210**, 20–30.

Romanovsky, A.A. 2014. Skin temperature: its role in thermoregulation. *Acta Physiol* **210**, 498–507.

da Silva, G.S.F., Soriano, R.N., Kwiatkoski, M., Giusti, H., Glass, M.L. & Branco, L.G.S. 2014. Central hydrogen sulphide mediates ventilatory responses to hypercapnia in adult conscious rats. *Acta Physiol* **212**, 239–247.

Taylor, P.D., Samuelsson, A.-M. & Poston, L. 2014. Maternal obesity and the developmental programming of hypertension: a role for leptin. *Acta Physiol* **210**, 508–523.

Todd, G., Gordon, C.J., Groeller, H. & Taylor, N.A.S. 2014. Does intramuscular thermal feedback modulate eccrine sweating in exercising humans? *Acta Physiol* **212**, 86–96.

Vähätalo, L.H., Ruohonen, S.T., Mäkelä, S., Kovalainen, M., Huotari, A., Mäkelä, K.A., Määttä, J.A., Miinalainen, I., Gilsbach, R., Hein, L. *et al.* 2015. Neuropeptide Y in the noradrenergic neurones induces obesity and inhibits sympathetic tone in mice. *Acta Physiol* **213**, 902–919.

Vizin, R.C.L., Scarpellini Cda, S., Ishikawa, D.T., Correa, G.M., de Souza, C.O., Gargaglioni, L.H., Carrettiero, D.C., Bícego, K.C. & Almeida, M.C. 2015. TRPV4 activates autonomic and behavioural warmth-defence responses in Wistar rats. *Acta Physiol* **214**, 275–289.

Wegner, N.C., Snodgrass, O.E., Dewar, H. & Hyde, J.R. 2015. Animal physiology. Whole-body endothermy in a mesopelagic fish, the opah, *Lampris guttatus*. *Science* **348**, 786–789.

Williams, S.M., Taylor, B.J. & Mitchell, E.A. 1996. Sudden infant death syndrome: insulation from bedding and clothing and its effect modifiers. The National Cot Death study Group. *Int J Epidemiol* **25**, 366–375.

