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A paradoxical role for alarin in the nervous control of energy homeostasis and thermoregulation: orexigenic but hypermetabolic

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Alarin is a lately discovered member of the galanin family of peptides. Although it has orexigenic effects in the brain, alarin induces thermoregulatory responses, which promote an increase of core temperature in rats. With some delay intracerebroventricular injections of alarin causes a 15% rise in metabolic rate at an ambient temperature of 25°C and a pronounced fall in tail skin temperature, i.e. peripheral vasoconstriction, at 28°C.

The identification and characterization of thermoregulatory functions of alarin has been the central goal of the recently published study performed by Mikó et al.[1] Alarin is the latest discovered member of the galanin peptide family,[2] which includes galanin, galanin-message associated peptide (GMAP), galanin-like peptide (GALP) and alarin.[3] There are two reasons that may have caused the motivation to study effects of alarin on energy balance and temperature regulation. Firstly, other members of the galanin peptide family seem to be implicated in the control of energy balance. Namely, GALP has measurable effects on food intake and body temperature.[3] Secondly, centrally injected exogenous alarin stimulates gonadotropin release and food intake.[4] A role for alarin as an orexigenic stimulus would suggest that this peptide has anabolic properties. Thus, an inhibitory effect on energy expenditure/thermogenesis and a temporal hypothermia could have been expected. In contrast, injections of alarin into the lateral cerebral ventricle of rats evoked a slowly developing elevation of core body temperature (T_b) by about 0.5°C within 3 h, which was accompanied by a significant increase of oxygen consumption at sub-thermoneutral ambient temperatures, i.e. 25°C and lower. In a more thermoneutral environment, a similar developing rise of T_b was achieved by peripheral vasoconstriction rather than by stimulated thermogenesis. The experiments were well controlled. Neither central injections of scrambled or truncated alarin, nor peripheral injections of full-length, biologically active alarin evoked any thermoregulatory responses.[1]

What are the sites of action of the observed effects? The distribution of alarin immunoreactivity in the mouse brain was thoroughly studied.[5] Interestingly, brain sites with the strongest specific alarin staining included those, which are engaged in neuronal circuitries responsible for the central control of thermoregulation, food intake and metabolism.[6] With regard to thermoregulation, there is a specific population of brain neurons located in the median preoptic nucleus that regulates tail skin vasoconstriction via efferent projections to the rostral medullary raphe, which then directly contact preganglionic sympathetic neurons in the intermediolateral column of the spinal cord. Another group of neurons in the dorsolateral preoptic area regulates thermogenesis in brown adipose tissue via projections to the dorsomedial hypothalamus, medullary raphe and again the efferent sympathetic neuronal chain. The median preoptic nucleus, the medial preoptic area, and the dorsomedial hypothalamus belong to those brain sites with the strongest alarin immunoreactivity.[5] It is tempting to speculate that exogenous alarin might have activated the descending thermoregulatory pathways that mediate tail vasoconstriction and brown adipose tissue thermogenesis. Both of these responses were observed by Mikó et al[1] depending on the ambient temperature. It is worthwhile to mention that also brain sites implicated in the central nervous control of food intake[6] were strongly immunoreactive to alarin antiserum, i.e. the arcuate nucleus, the dorsomedial hypothalamus, the lateral hypothalamic area and the paraventricular nucleus.[5] These brain structures may be involved in the described stimulatory effect of alarin on food intake.[4]

What are the biological implications of the observed effects? Together with basal metabolic rate and energy required for physical activity, diet induced thermogenesis is a component of the daily energy expenditure. It consists of the energy used for digestion, absorption and storage of consumed nutrients. Excessive caloric intake, on the other hand, is thought to be sensed by the brain. The brain, in turn, activates thermogenesis as a strategy to prevent obesity. This type of heat production involves activation of the sympathetic nervous system and thereby brown adipose tissue.[7] The quantitative contributions of those signals, which operate in the brain to activate the sympathetic outflow to brown adipose tissue and thereby diet-induced thermogenesis, are still a matter of debate. Alarin exerts apparent

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Abbreviations: GALP, galanin-like peptide; GMAP, galanin-message associated peptide; T_b, body temperature

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stimulatory effects on food intake on the one hand[4] and on energy expenditure on the other hand.[1] Due to its strong presence within the central circuitries, which control food intake as well as sympathetically driven thermogenesis, it is tempting to speculate that endogenous alarin might contribute to diet-induced thermogenesis. Due to the fact that obesity is one of the most common health problems, such an effect of alarin might arouse broader interest.

What remains to be done? In the study of Mikó et al[1] the effects of exogenously administered alarin were analysed. Although the experiments were well controlled and the outcome was clear, a direct evidence for a role of endogenous alarin in thermoregulation and central control of metabolisnm is still missing. Pharmacological antagonism of alarin action within the brain under conditions of thermoregulatory and / or metabolic challenge might provide a tool to resolve this question. One prerequisite for such experiments would be the identification of the cognate receptor for alarin, especially within the brain sites involved in thermoregulation and central control of food intake. There are three galanin receptor subtypes, which have differences in their sites of expression and with regard to the activated intracellular signalling pathways upon receptor stimulation. According to the affinities of the four members of the galanin peptide family to the galanin receptor types 1–3, determined as K_i values in nM, just galanin and GALP seem to interact with the known galanin receptor subtypes. The 25 amino acid long peptide alarin, however, has no affinity towards either of all of the three receptor subtypes.[3] A successful search for the alarin receptor in the brain is necessary, before valid conclusions can be drawn on a putative role of alarin in thermoregulation, metabolism and other vital homeostatic functions. Another issue of interest relates to a possible function of alarin in inflammation. GALP, another member of the galanin peptide family, seems to have the capacity to induce interleukin-1 in the brain and thereby mediates febrile and anorectic effects.[3] According to the data provided by Micó et al.[1] and Boughton et al.,[4] alarin could readily contribute to inflammation-induced fever, but not to inflammation-induced anorexia. Many pieces of the puzzle related to the biological functions of the multifunctional neuropeptide alarin still have to be resolved; one important piece has been placed to the incomplete picture by the paper published in the first issue of *Temperature* by Micó et al.[1]

Disclosure of Potential Conflict of Interest

No potential conflicts of interest are disclosed.

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