NEUROPHARMACOLOGICAL BASIS OF HYPOTHALAMIC INTERACTION OF THERMO- AND OSMOREGULATORY SIGNALS: INTEGRATIVE ROLE OF THE MEDIAN PREOPTIC NUCLEUS

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The hypothalamus contains nuclei/regions involved in the perception and integration of systemic and central signals important for body temperature homeostasis. Thermosensory function resides in preoptic hypothalamic regions like the medial preoptic area (MPA) and the median preoptic nucleus (MnPO). The organum vasculosum laminae terminalis (OVLT) outside the blood-brain barrier is identified as initiating the fever response to circulating cytokines. Pyrogenic factors either directly contact OVLT neurons or indirectly activate anterior hypothalamic structures *via* stimulation of cyclooxygenase-2 (COX-2) in their vascular endothelium or induction of endothelial or neuronal nitric oxide synthase (eNOS, nNOS) with formation of nitric oxide (NO). Neurons in the posterio-lateral hypothalamus (LHA) are involved in energy balance linked to metabolic cold defense, and MPA neurons control thermoregulatory effectors. According to expression patterns of immediate-early-genes (*c-fos*), both mild heat acclimation (33°C, 48 h) and heat stress (39°C, 1 h) reveal distinct and differential activation of neurons in the MPA, MnPO, septum and LHA, whereas mild dehydration (24 h) causes neuronal stimulation in the magnocellular paraventricular (mPVN) and supraoptic nucleus (SON), subfornical organ (SFO) and MnPO. Using microtranssection, transsynaptic viral as well as classical neuronal tracing techniques, the parvocellular PVN and MnPO can be regarded as integrative structures for afferent signals of various autonomic control circuits. A myriad of potential neurotransmitters has been discussed to convey thermosensory signals and facilitate neuronal integration. Recently, the NO-system has evolved as a major key player in hypothalamic control of thermoregulation and is discussed in detail, based on physiological and histochemical approaches. Nitrergic neurons are densily concentrated in the PVN, SON, OVLT, SFO, MPA and MnPO as revealed by nNOS mRNA in situ hybridization, immuno- and enzyme cytochemistry as well as Western blotting. Heat acclimation, heat stress and endotoxin-induced fever are accompanied by enhanced nNOS activity and partially also nNOS mRNA expression in the MPA, MnPO and LHA but not PVN, SON or SFO. Central application of NO donor substances stimulates cutaneous and vascular heat defense reactions in rats and rabbits. Central enzymatic blockade of nNOS by subtype-specific inhibitors reduces endurance, elevates theshold temperatures for salivation and tail skin vasodilation, and finally leads to a rise in core temperature under conditions of heat stress in eu- and/or dehydrated rats. In addition, dehydration and angiotensin II (AngII) stimulated drinking is reduced. Congruent results can be obtained after central suppression of nNOS mRNA expression employing long-term icv infusion of nNOS mRNA antisense deoxynucleotides. As indicated by Fos immunostaining, osmoregulatoratory signals (dehydration, AngII) preferentially activate nitrergic neurons within the MnPO, whereas heat stimuli induce *c-fos* expression in cells possibly representing direct targets of neuronally released NO. Complex interneuronal wiring appears therefore to underly the NO-mediated thermoregulatory heat defense and replenishmemt of extracellular fluid volume under conditions of high environmental temperature.

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