COMMENTARY ON: **From sensory circumventricular organs to cerebral cortex: neural pathways controlling thirst and hunger. MCKINLEY NJ, DENTON DA, RYAN PJ, YAO ST, STEFANIDIS A, OLDFIELD BJ. *J Neuroendocrinol.* 2019. DOI: 10.1111/jne.12689**

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As a part of the 30th anniversary edition of the Journal of Neuroendocrinology, several leaders in the field present a comprehensive and whole-covering review of neural and endocrine pathways associated with thirst and hunger. These include sensory circumventricular organs (CVOs) mediating the sensation of ionic and humoral milieu of the circulating blood to cortical pathways responsible for the generation of conscious awareness of thirst and hunger (McKinley et al., 2019). The authors highlight the progress that has been made in the field during the past 30 years, facilitated by the development of new techniques such as human brain imaging, neuronal pathway tracing using viral tools, gene knockout, opto- and chemogenetics, and single-cell transcriptomics.

The sensory circumventricular organs (CVOs) of the mammalian brain, which include the organum vasculosum of the lamina terminalis (OVLT), the subfornical organ (SFO) and the area postrema (AP), are best-known for their role in osmoregulation, thirst, energy metabolism, and hunger. The authors overview neural pathways originating in the OVLT and the SFO, which mediate different types of thirst, including relaxin- and angiotensin-induced thirst, as well as osmotic and circadian drinking. Notably, although the SFO and OVLT show a high degree of redundancy, and activation of glutamatergic neurons in each respective nucleus triggers immediate drinking, some stimulus-specific differences are found between the OVLT and SFO. It appears that inactivation of SFO (but not OVLT) completely abolishes relaxin- and angiotensin-induced drinking, while osmotic and circadian drinking are fully eliminated upon inactivation of OVLT (but not SFO).

The authors also focus on the function of the median preoptic nucleus (MnPO) acting as a relay centre for neural outputs from both OVLT and SFO. A recent elegant study by the Oka group found that excitatory SFO neurons form monosynaptic connections with excitatory OVLT and MnPO neurons, and stimulation of any of these three neuronal populations is sufficient to drive drinking behaviour, while ablation of excitatory MnPO neurons causes significant reductions in both OVLT- and SFO-stimulated drinking (Augustine et al., 2018). Thus, neural signals arising from osmotic, angiotensin or relaxin activation of the SFO and OVLT, are relayed onward through glutamatergic synapses within the MnPO to other areas in the brain, including thalamic nuclei (e.g. thalamic paraventricular nucleus and mediodorsal thalamic nucleus), and then to cortical regions (cingulate and insular cortex) responsible for the conscious awareness of thirst.

In addition to thirst, the authors summarize recent advances in the understanding of the cessation of drinking/satiety, which appear to be associated with a subpopulation of GABAergic neurons in the MnPO and SFO. Recent studies reveal that MnPO sends inhibitory GABAergic inputs to SFO neurons to regulate drinking cessation (Abbott et al., 2016). Stimulation of GABAergic neurons in the MnPO is sufficient to inhibit drinking behaviour in dehydrated mice, but not feeding behaviour in starved mice (Abbott et al., 2016). Likewise, ablation of inhibitory MnPO neurons causes overdrinking (Augustine et al., 2018). In addition, neurons in the MnPO can sense changes in extracellular osmolality through the expression of a sodium-sensitive Na_X channel (Grob et al., 2004), raising the possibility that the MnPO acts not only as a relay station for thirst signals originating from CVOs, but also as a site of potential signal potentiation. Despite these recent advances, the precise circuitry underlying the satiety of thirst and their interplay with drinking-promoting excitatory neurons, as well as whether the cortical signals that correlate

with satiety of thirst are relayed from sensory CVOs via thalamic nuclei, remain unknown and should be the subject of future investigations.

McKinley and colleagues also review the role of CVOs in hunger and energy metabolism, specifically focusing on the SFO and the AP. Recent studies revealed that amylin, the satiety hormone, and ghrelin, the hunger hormone, activate distinct populations of neurons in the SFO. However, the contribution of these neuronal populations to the regulation of food intake is unclear and requires further examination. On the contrary, the AP has been classically described as the chemosensory area triggering emesis (Miller and Leslie, 1994, McKinley et al., 2019), and more recently, involved in energy metabolism. Neurons in the AP are activated in response to amylin and co-express receptors for leptin and amylin, both peripheral satiety signals (McKinley et al., 2019, Liberini et al., 2016). Similarly, another study by the Ferguson group found that amylin and leptin have an additive effect in increasing the level of cAMP compared to responses from amylin or leptin alone (Smith et al., 2016). In line with the idea that the MnPO can act as a potentiation centre for thirst signalling, these previous studies highlight the possibility of the AP acting as a relay station for hunger and satiety, which in turn transmits these metabolic neuronal signals to higher brain regions in the cortex. More research should be done to study the synergistic effects of both satiety agents, as well as how they may trigger interacting intracellular pathways in AP neurons.

This publication by McKinley and colleagues accompanies an earlier review published by the same group which describes the structure, function, and cellular expression profile of the sensory CVOs (McKinley et al., 2003). These complementary reviews provide the field of neuroendocrinology with a comprehensive and detailed overview of both the structure and functions of key hypothalamic areas that act as an initial point of contact between the brain and the circulation, as well as crucial insights into the efferent connections to the higher cortical regions of the central nervous system that process the physical sensation of thirst and hunger.

References:

ABBOTT, S. B. G., MACHADO, N. L. S., GEERLING, J. C. & SAPER, C. B. 2016. Reciprocal Control of Drinking Behavior by Median Preoptic Neurons in Mice. *The Journal of Neuroscience,* 36**,** 8228.

AUGUSTINE, V., GOKCE, S. K., LEE, S., WANG, B., DAVIDSON, T. J., REIMANN, F., GRIBBLE, F., DEISSEROTH, K., LOIS, C. & OKA, Y. 2018. Hierarchical neural architecture underlying thirst regulation. *Nature,* 555**,** 204.

GROB, M., DROLET, G. & MOUGINOT, D. 2004. Specific Na+ sensors are functionally expressed in a neuronal population of the median preoptic nucleus of the rat. *J Neurosci,* 24**,** 3974-84.

LIBERINI, C. G., BOYLE, C. N., CIFANI, C., VENNIRO, M., HOPE, B. T. & LUTZ, T. A. 2016. Amylin receptor components and the leptin receptor are co-expressed in single rat area postrema neurons. *European Journal of Neuroscience,* 43**,** 653-661.

MCKINLEY, M. J., DENTON, D. A., RYAN, P. J., YAO, S. T., STEFANIDIS, A. & OLDFIELD, B. J. 2019. From sensory circumventricular organs to cerebral cortex: neural pathways controlling thirst and hunger. 0**,** e12689.

MCKINLEY, M. J., MCALLEN, R. M., DAVERN, P., GILES, M. E., PENSCHOW, J., SUNN, N., USCHAKOV, A. & OLDFIELD, B. J. 2003. The sensory circumventricular organs of the mammalian brain. *Adv Anat Embryol Cell Biol,* 172**,** III-XII, 1-122, back cover.

MILLER, A. D. & LESLIE, R. A. 1994. The Area Postrema and Vomiting. *Frontiers in Neuroendocrinology,* 15**,** 301-320.

SMITH, P. M., BRZEZINSKA, P., HUBERT, F., MIMEE, A., MAURICE, D. H. & FERGUSON, A. V. 2016. Leptin influences the excitability of area postrema neurons. *Am J Physiol Regul Integr Comp Physiol,* 310**,** R440-8.