Forgetting in obesity: the pregnenolone link

Luigi Bellocchio[1,2*] and Giovanni Marsicano[1,2*]

[1]INSERM, U1215 NeuroCentre Magendie, Endocannabinoids and Neuroadaptation, Bordeaux, France; [2]University of Bordeaux.

*Correspondence to: Luigi Bellocchio, luigi.bellocchio@inserm.fr

Giovanni Marsicano, giovanni.marsicano@inserm.fr

Cognitive dysfunction is often diagnosed in people with obesity and associated metabolic disorders. In the latest issue of *Cell Metabolism*, Ramirez et al. (2022) highlight an impaired production of the neurosteroid pregnenolone in the hypothalamus as a mechanism for obesity-induced cognitive impairment in both rodent models and patients with obesity.

"It's all in the head" is a sentence that has been used to describe obesity (Shefer et al., 2013). This concept indicates that the brain plays a key role in the pathogenesis and consequences of energy metabolism disorders, not only by processing psychological and environmental stimuli that favor energy accumulation, but also by undergoing obesity-induced changes and cognitive dysfunction (Shefer et al., 2013; Tanaka et al., 2020).

Several pieces of evidence point out that the metabolic alterations associated with obesity may underlie structural and functional changes in the brain. In particular, hypothalamic inflammation and gliosis, reduction in brain volume (especially of the

hippocampus), and sleep alterations have all been proposed as the possible culprits for cognitive dysfunction associated with metabolic disorders (Shefer et al., 2013; Tanaka et al., 2020). However, the identification of the specific metabolic alterations contributing to obesity-induced brain changes and cognitive impairments has never been properly addressed, and the involved biological mechanisms are still mysterious. Among different hypotheses, obesity-induced alterations in cholesterol metabolism, with its downstream derivatives pregnenolone and neurosteroids, represent a plausible candidate to participate in these processes. Indeed, a strong reciprocal crosstalk exists between metabolic disorders and brain cholesterol metabolism (Bruce et al., 2017), whereas perturbations in neurosteroid production can in turn be involved in the pathogenesis of neurological and neuropsychiatric disorders (Ratner et al., 2019).

In this issue of *Cell Metabolism*, Ramirez et al. (2022) elegantly pinpoint the hypothalamic arcuate nucleus (ARC), and in particular Pro-opiomelanocortin (POMC)-expressing neurons, as the anatomical and functional brain sites linking an obesogenic environment to cognitive impairments *via* reduced local pregnenolone production. The authors show that short-term exposure to a high-fat/high-carbohydrate Western diet did not induce significant metabolic disorder, but it nevertheless resulted in the disruption of hippocampal long-term potentiation (LTP) and impairment of object recognition memory in mice. This phenomenon was accompanied with a reduction of pregnenolone levels exclusively in the ARC and not in other brain regions involved in memory processes such as hippocampus and perirhinal cortex. Then, Ramirez et al. (2022) provided a causal link across the aforementioned observations: acute pregnenolone injections into the ARC were able to revert diet-induced memory impairment. As expected, longer

exposure to the same type of diet resulted in dramatic metabolic perturbations including obesity and insulin resistance. Obese mice were also characterized by object recognition memory deficits and reduced pregnenolone levels selectively in the ARC. Similar to mice, the concentration of pregnenolone in the cerebrospinal fluid (CSF) of patients with obesity negatively correlated with the body mass index (BMI). Interestingly, Mini-Mental Status Examination studies (MMSE) performed in the same subjects, showed that cognitive performances positively correlated with CSF pregnenolone levels. These results further indicate that obesity-induced reduction in central pregnenolone content are associated with cognitive impairment both in rodent models and patients.

But what is the functional link between pregnenolone, ARC and hippocampal LTP/recognition memory? In order to answer this question Ramirez et al. (2022) employed a genetic strategy to target pregnenolone synthesis in two well-known ARC neuronal populations (POMC- and AgRP-expressing cells, respectively). Conditional deletion of one key enzyme for neurosteroid production, Stard1, in POMC neurons but not in AgRP ones, while not altering metabolic parameters, reduced pregnenolone content in the ARC. This was accompanied by impaired hippocampal LTP and recognition memory deficits, which interestingly were both reverted by intra-ARC infusions of pregnenolone. Furthermore, the authors showed that pregnenolone infusions resulted in the activation of POMC neurons and, interestingly, pharmacogenetic inhibition of this cell type in the ARC was sufficient to mimic the amnesic phenotype of Stard1 deletion and of diet-induced obesity.

In summary, the study by Ramirez et al. (2022) indicates that an obesogenic diet is able to interfere with pregnenolone metabolism in POMC neurons in the ARC. This causes a

perturbation of hippocampal LTP and an impairment of object recognition memory. These findings are novel and rather important in the field for several reasons: i) they link hypothalamic cholesterol metabolism and especially pregnenolone to metabolic disorders; ii) they reveal a novel role for hypothalamic POMC neurons in cognitive processes; and iii) given the high therapeutic potential of neurosteroids (Zorumski and Mennerick, 2013), they pave the way for new treatments of obesity-associated cognitive disorders.

One important question raised by this study is how changes in pregnenolone levels in POMC neurons are able to modulate hippocampal activity. Direct projections from ARC-POMC neurons to the hippocampal subiculum have been previously described (Wang et al., 2015) and confirmed in the present study. Using opto- and/or pharmaco-genetic tools to manipulate selected neuronal circuits, it will be interesting to decipher the neuroanatomical and neurochemical phenotype(s) of POMC neurons projecting to the hippocampus and their role in modulating synaptic plasticity and memory processes. POMC neurons in the ARC have been recently shown to encompass a high molecular, functional and neuroanatomical heterogeneity (Quarta et al., 2021), which might help explain the functional link discovered in the present study. For instance, at least one subpopulation of POMC neurons contain cannabinoid type-1 receptors (CB_1) (Saucisse et al., 2021), and pregnenolone has been shown to be an important endogenous allosteric modulator of CB_1 (Vallée et al., 2014). The effect of CB_1 activation in neurons is generally a presynaptic reduction of neurotransmission and pregnenolone is able to block the memory-impairment effects of exogenous cannabinoids (Raux et al., 2021; Vallée et al., 2014). It is, therefore, tempting to speculate that, by increasing CB_1

4

signaling, the obesity-induced decrease of pregnenolone levels might dampen the hippocampal outputs of POMC neurons. This scenario would fit with the observation of Ramirez et al that inhibition of POMC neurons mimics the decrease of pregnenolone. In other words, less pregnenolone would unleash CB_1 receptors to reduce the activity of hippocampal-projecting POMC neurons.

Within the heterogeneity of the ARC (Quarta et al. 2021), it will be interesting to investigate whether specific POMC neuronal subsets mediate cognitive *versus* energy-related functions. The striking observations of Ramirez et al. (2022) show that pregnenolone signaling regulated by energetic state can modulate cognitive function, further highlighting the complex and diverse roles for POMC neurons in the context of energy metabolism.

References

Bruce, K.D., Zsombok, A., and Eckel, R.H. (2017). Lipid Processing in the Brain: A Key Regulator of Systemic Metabolism. Front. Endocrinol. (Lausanne). *8*.

Quarta, C., Claret, M., Zeltser, L.M., Williams, K.W., Yeo, G.S.H., Tschöp, M.H., Diano, S., Brüning, J.C., and Cota, D. (2021). POMC neuronal heterogeneity in energy balance and beyond: an integrated view. Nat. Metab. *3*, 299–308.

Ratner, M.H., Kumaresan, V., and Farb, D.H. (2019). Neurosteroid Actions in Memory and Neurologic/Neuropsychiatric Disorders. Front. Endocrinol. (Lausanne). *10*.

Raux, P., Drutel, G., Revest, J., and Vallée, M. (2021). New perspectives on the role of the neurosteroid pregnenolone as an endogenous regulator of type-1 cannabinoid receptor (CB1R) activity and function. J. Neuroendocrinol.

Saucisse, N., Mazier, W., Simon, V., Binder, E., Catania, C., Bellocchio, L., Romanov, R.A., Léon, S., Matias, I., Zizzari, P., et al. (2021). Functional heterogeneity of POMC neurons relies on mTORC1 signaling. Cell Rep. *37*, 109800.

Shefer, G., Marcus, Y., and Stern, N. (2013). Is obesity a brain disease? Neurosci. Biobehav. Rev. *37*, 2489–2503.

Tanaka, H., Gourley, D.D., Dekhtyar, M., and Haley, A.P. (2020). Cognition, Brain Structure, and Brain Function in Individuals with Obesity and Related Disorders. Curr. Obes. Rep. *9*, 544–549.

Vallée, M., Vitiello, S., Bellocchio, L., Hébert-Chatelain, E., Monlezun, S., Martin-Garcia, E., Kasanetz, F., Baillie, G.L., Panin, F., Cathala, A., et al. (2014). Pregnenolone can protect the brain from cannabis intoxication. Science *343*, 94–98.

Wang, D., He, X., Zhao, Z., Feng, Q., Lin, R., Sun, Y., Ding, T., Xu, F., Luo, M., and Zhan, C. (2015). Whole-brain mapping of the direct inputs and axonal projections of POMC and AgRP neurons. Front. Neuroanat. *9*.

Zorumski, C.F., and Mennerick, S. (2013). Neurosteroids as Therapeutic Leads in Psychiatry. JAMA Psychiatry *70*, 659.

Acknowledgments