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NEUROACTIVE STEROIDS AND METABOLIC AXIS

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Neuroactive steroids (i.e., steroids synthesised both in peripheral glands and in nervous system) are important physiological regulators of the nervous functions. In particular, they are involved in the control of many physiological aspects of reproduction, stress response, and metabolism, as well as in several pathologies including depression, obesity, feeding and reproduction disorders (Panzica and Melcangi, 2008, Melcangi et al., 2011, Melcangi and Panzica, 2013).

Due to the large diffusion of metabolic diseases the study of the interaction between metabolic axis and nervous function represents a really hot topic in biomedical research.

For this reason, we have collected in this special issue some reviews exploring the relationships among neuroactive steroids and the metabolic axis that originated from the lectures presented at a satellite symposium of the 9th International meeting "Steroids and Nervous System " (February 2017, Torino, Italy).

The reviews by Chowen et al. (Chowen et al., 2017), and by Pinos et al. (Pinos et al., 2017) elucidate the role played by early exposure to sex steroids in later inducing metabolic alterations that could be the gate to obesity and metabolic syndrome. Sex differences have

been largely reported in response to high- or low-fat diets (Zammaretti et al., 2007; Mele et al., 2016), but what it is now emerging is that the early postnatal environment may play an important role in establishing these differences and that in addition to the neurons, glial cells have an important role (Chowen et al., 2016). Estradiol and thyroid hormones regulate the energy metabolism through the hypothalamic-pituitary-gonadal (HPG) and the hypothalamic-pituitary-thyroid (HPT) axis. In addition, they are important for the development of neuronal circuits directly controlling food intake and energy metabolism (in the hypothalamus), but also important for many other regions of the brain (Bernal, 2000; Bernal, 2005; Hedges et al., 2012; Adhya et al., 2017; Galea et al., 2017). Alterations of the environment through the exposure to metabolic disrupting chemicals (Heindel et al., 2015; Heindel et al., 2017) interfere directly with those two hormone systems inducing alterations of the brain development. These effects are summarized in the review of Zsarnovszky et al. (Zsarnovszky et al., 2017), with particular emphasis of the effects of phytoestrogens and other endocrine disruptors on *in vitro* models of the developing cerebellum.

The functions of HPG axis are strictly connected to the metabolic state of the organism, this is particularly evident for puberty and during pregnancy (Castellano and Tena-Sempere, 2013; De Bond and Smith, 2014). The review of Manfredi-Lozano et al. (Manfredi-Lozano et al., 2017) summarizes the major physiological mechanisms involved in the metabolic control of hypothalamic-pituitary-gonadal axis by discussing the roles of the major neuropeptidergic pathways that send metabolic information to the GnRH system.

In addition to the HPG and HPT axis, also the hypothalamic-pituitary-adrenal (HPA) axis is involved in the control of energy metabolism through the regulation of glucose and lipids metabolism (Garabedian et al., 2017; Gray et al., 2017; Legeza et al., 2017). The review of de Kloet and Herman (de Kloet and Herman, 2017) explores the fat-to-brain pathway based on the integration of psychogenic signals by the fat cells that give rise to feedback signals to the

HPA axis. This is particularly relevant in the connections between stress and metabolism, whose comorbidities are recognized as complicating factors in metabolic diseases and in neuropsychiatric conditions.

Finally, the last two reviews discuss the relationships of neuroactive steroids with diabetes and obesity. In fact the levels of neurosteroids are altered in pathological conditions (Melcangi et al., 2014). As reviewed by Giatti et al. (Giatti et al., 2017), neuroactive steroids levels are affected by the diabetes mellitus (a disease that can lead to important complications in central and peripheral nervous system) in a sex-dimorphic way. In addition, neuroactive steroids, such as metabolites of progesterone and testosterone, may act as protective agents against the damage induced by diabetes in the nervous system.

In the last review Holmberg et al. (Holmberg et al., 2017) discuss the roles of GABA to stimulate food intake by activation of GABA-A receptors in hypothalamus. Interestingly, increased levels of allopregnanolone (i.e., a progesterone metabolite able to interact with GABA-A receptors) are associated with increase in food intake, preference for energy-rich food and obesity.

In conclusion, the data discussed in these reviews support the idea that there is a very close link among neuroactive steroids (including both hormones produced by the endocrine peripheral glands and those synthetized within the central nervous system) and the control of metabolic axis. This opens new perspectives to understand the biological basis of many pathologies based on metabolic alterations, as the metabolic syndrome, obesity or diabetes.

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