Sexually dimorphic development of hypothalamic feeding-circuits
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Feeding is crucial for life and alteration of this behavior by environmental signals such as social pressure and daily stress can precipitate the onset of anorexia nervosa or obesity. Individuals are not equal facing these stress- and eating-related disorders, and women are at higher risk to develop these pathologies than men. Whereas stress and feeding are intertwined, developmental, and genetic determinants of the sexually dimorphic stress-related control of food intake are still poorly described.

Several brain areas are known to control energy metabolism, and accumulating evidence converges towards a central role of the hypothalamus. A particularly important metabolic function has been given to the hypothalamic arcuate nucleus (ARH) which contains two functionally antagonistic neuronal populations, the pro-opiomelanocortin (POMC)- and the agouti-related peptide (AgRP)-expressing neurons that suppress and stimulate feeding, respectively. These neurons are sensors of the nutritional status and integrate diverse peripheral signals including hormonal, metabolic, and sensory information to control the balance between energy intake and energy expenditure via complex neuroendocrine, and autonomic regulatory pathways. Arcuate POMC and AgRP neurons, often seen as first-order neurons which maintain energy balance through downstream hypothalamic and extra-hypothalamic targets, are actually integrated in more complex neuronal networks. Indeed, they receive central information through inputs coming from a plethora of brain areas including telencephalic, and hypothalamic structures. My group notably showed that arcuate POMC and AgRP cells are innervated by neurons found in the bed nucleus of the stria terminalis (BNST), **a sexually dimorphic forebrain area** well connected to the stress-related amygdala. Whereas the BNST is known to integrate stress information and to control energy balance through hypothalamic targets, how these neuronal networks develop and connect to key-feeding neurons have not been thoroughly explored.

The proper formation of such neuronal circuits is critical for long-lasting metabolic functions, and relies on various processes including axon growth, and synaptogenesis. During the wiring process, proteins expressed at the pre- and post-synaptic levels interact to trigger synapse formation, and stabilization. **The proper development of synapses is achieved through timely-regulated expression of these molecules belonging notably to Semaphorin and Ephrin families.** My work has been pioneering in showing the role of Ephrins in orchestrating the postnatal development of excitatory neuronal inputs into POMC neurons. However, the molecular mechanisms underlying the formation of inhibitory inputs into POMC and AgRP neurons, notably those coming from the BNST, is still unknown.

Beyond our interest to decipher the molecular mechanisms underlying the sexually dimorphic development of the inhibitory connections from BNST to ARH neurons, this project will provide a developmental basis for the sexual dimorphism observed in the stress-induced control of feeding behavior. To reach our objective, we will employ multidisciplinary techniques ranging from histological, and in vitro assays to optogenetics combined with behavioral approaches.