University of Fribourg / Faculty of Science and Medicine / Department of Medicine

**A glucose-sensing circuit in the insular cortex**

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The brain plays an important role in regulating energy homeostasis. However, in the natural environment, this mechanism frequently competes with concurrent survival-promoting behaviors. The goal of my thesis was to investigate brain circuits influencing behavioral choice in function of the organism's energy status. I decided to focus on the insular cortex (IC) as a potential hub for those interactions.

I first identified a metabolic hot-spot activated by glucoprivation in IC. To functionally characterize putative glucose-responding cells, I established a new method "TraGeTing", based on an activity reporter genetic mouse model that enables tagging metabolic-responsive neurons in vitro. Whole-cell electrophysiological recordings performed on cells labeled with this method indicated that they are glucose sensing neurons. Their response to glucose was cell-autonomous and followed a glucose-inhibited pattern driven by the opening of 2-pore domain potassium channels. Post-recording reconstructions identified them as a homogeneous and well-localized population of thick-tufted layer 5 pyramidal neurons.

I then questioned the physiological relevance of IC glucose-sensing neurons. Using the Fos-TRAP mouse model, I identified two projecting areas of those neurons, the lateral part of the central amygdala (CeL) and the juxta-capsular aspect of the bed nucleus of the stria terminalis (jcBNST). The fact that both output regions are involved in the fear response prompted me to investigate this behavior in my model. For that purpose, I used DREADD technology to reactivate IC glucose-sensing neurons in vivo. I defined an intersectional viral strategy to express activating DREADD hM3Dq in projection-specific glucose-sensing neurons. Activation of IC-CeL, but not IC-jcBNST, -projecting glucose-sensing cells led to a decrease in the innate fear response to a looming visual stimulus mimicking a predator bird approach.

Altogether, my work has led to the discovery of glucose-sensing neuronal circuits in IC that contribute to shifting the behavioral response to an environmental threat towards a higher risk-taking strategy in conditions of energy depletion.

Jury:
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