Master de Sciences et Technologies
Mention Biologie Intégrative et Physiologie
Parcours : Neurosciences
Responsable : Professeur Régis Lambert

Internship Proposal
Academic Year 2018-2019

1. Host team :

Research Unit (e.g. Department or Institute) : Center of Psychiatry and Neuroscience, INSERM U894
Research Unit Director : Dr Thierry GALLI
Research Team Director : Pr Philip GORWOOD
Team name : Vulnerability of psychiatric and addictive disorder
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2. Internship project title:
Role of the ghrelin/GHS-R system in the dual regulation of the motivational and homeostatic brain circuits under chronic food restriction

3. Internship Description :

State of art: Anorexia nervosa (AN) is characterised by a severe and chronic food restriction, weight loss and inappropriate physical activity regarding the undernutrition state. The high mortality rate and high level of relapse challenge the care protocols, valuable prognostic markers lacking in clinical practice. Factors influencing the duration of recovery and the possibility of complete recovery constitute a research priority for AN. Among these factors, the ghrelin hormone might be a valuable candidate since its plasma levels are elevated in AN patients. The peak of ghrelin before the meal and its rapid decrease after the meal appears to be essential to regulate appetite and adapts the metabolism in response to nutritional and/or hedonic dysfunctions like the rewarding aspect of food and/or activity. Indeed, it modulates dopamine release in the meso-cortico-limbic circuit, is involved in the reinforcing actions of food and acutely alters food choice.

Objective The aim of this M2 program is to decipher the functional importance played by ghrelin in a situation of chronic food restriction and nutritional recovery to modulate in parallel the reward meso-cortico-limbic circuit and the homeostatic structures involved in the regulation of feeding behaviour.

Methods: we will submit WT mice to a protocol that combines chronic food restriction (D; 50% caloric restriction, 15 to 21 days) and physical activity (A; free access to a running wheel), followed by a nutritional recovery period (15 days). We will test two protocols of nutritional recovery: rapid (food *ad libitum* after the food restriction, rapid body weight gain) and progressive (slow body weigh gain). This DxA model, routinely used in our laboratory, mimics numerous alterations observed in AN and preliminary results have already validated the protocol of “rapid nutritional recovery” .

First set of experiments: we will 1) measure the plasma ghrelin concentrations around the meal (preliminary data not yet published) during the denutrition and during the renutrition period and 2) evaluate by qPCR the mRNA expression of hypothalamic neuropeptides involved in hunger and satiety, at the end of the nutritional recovery. Second set of experiments, we aim to perform a similar approach (according to the results obtained) but with a manipulation of the ghrelin signaling around the meal using an i.p. injection of ghrelin antagonist delivered two hours before meal. Mice will then be sacrificed just after the meal to evaluate the activation of hypothalamic and mesolimbic structures using dual

immunocytochemistry to identify the neurochemical phenotype of the population activated (c-Fos or delta FosB). We will assessed the following behavioral parameters: physical activity, meal pattern (food intake, number of meal..) thanks to appropriate automatized cages (TSE systems).

Conclusion and Perspectives: these fundamental data are of importance since similar evaluation of the role of ghrelin around the meal is currently evaluated in patients. We aim here to decipher the role of hypothalamic populations (like AgRP neurons) and mesolimbic dopaminergic neurons in the precise regulation of meal pattern in a situation of undernutrition and nutritional recovery. The data obtained will be a prerequisite to further examine the role of these neurons targeted by ghrelin in the rewarding aspect of food that is deregulated in AN.