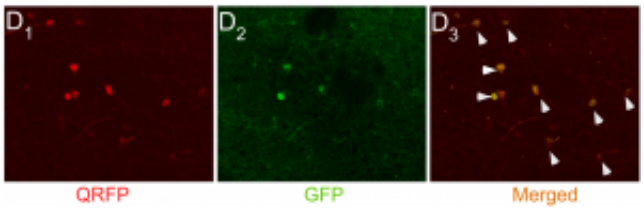
The hypothalamic QRFP—a neuropeptide between food and mood

December 13 2016, by Giuseppe Gangarossa



Localization of QRFP in the mouse hypothalamus. Credit: Okamoto et al., 2016

The hypothalamus is a brain region implicated in several vital functions such as feeding, thermoregulation, reproduction, stress and metabolic regulation. Dozens of hypothalamic neuropeptides have been shown to be involved in the regulation of food intake and body weight homeostasis. The extreme heterogeneity of these chemical signals and the complex sub-architecture of the hypothalamus participate in regulating homeostatic adaptations.

Information about the body's energy store is gathered by the arcuate nucleus (Arc), a small hypothalamic nucleus, and then transmitted to second order neurons, including ones localized in the paraventricular nucleus (PVN) and others in the lateral hypothalamic area (LHA), to evoke hunger sensation and feeding behavior. Since the seminal study of Anand and Brubeck (1951), the LHA has been identified as the "feeding center of the brain". However, the exact contribution of each hypothalamic nucleus remains poorly understood and far from fully

explored.

QRFP, a recently identified hypothalamic neuropeptide, has emerged as an interesting chemical signal in the LHA and adjacent regions. What is the function of this novel peptide?

In a recent PLOS ONE article, Okamoto and colleagues from the Kanazawa University in Japan, decided to explore the functions of this neuropeptide. Here is what they found.

QRFP, feeding and energy homeostasis

To examine the physiological role of QRFP, the authors generated a transgenic mouse line (Qrfp-/-) by replacing the entire prepro-QRFP sequence with the enhanced green fluorescent protein (eGFP) gene. Interestingly, under standard diet the body weight of Qrfp-/- mice was significantly lower than that of wildtype littermates. This phenotype was also maintained when the mice were exposed to high-fat diet, a protocol known to induce obesity and metabolic disorders. These experiments strongly suggest that QRFP may play a critical role in influencing feeding behavior and central energy homeostasis.

The two major neuronal populations that control food intake are the arcuate POMC and AgRP neurons. Taking advantage of the eGFP expression of QRFP-expressing LHA neurons, the authors observed that arcuate AgRP neurons were able to contact those cells, thus suggesting a synaptic link. Interestingly, "the area of distribution of AgRP fibers in the hypothalamus overlapped with that of QRFP-positive neurons", say Kitaro Okamoto, the leading author of the study.

QRFP: not only food but also mood

Interestingly, most substances that affect food intake show effects on mood and motivation simultaneously, and eating disorders are often accompanied by mood or behavioral disorders. To address whether QRFP may impact mood and emotional states, the authors conducted a battery of behavioral experiments to further elucidate this possibility. Using the elevated plus maze and the open field tests, two behavioral paradigms which rely on the aversion of rodents to open spaces, Okamoto and colleagues showed that genetic inactivation of the hypothalamic QRFP was able to induce anxiety and hypo-activity. "Behavioral tests revealed that Qrfp null mice showed increased anxiety-like behavior", concluded Takeshi Sakurai, the senior author of the study. In agreement with this behavioral phenotype, QRFP receptors, notably GPR103A and GPR103B, are expressed in regions implicated in the regulation of feeding behavior and mood. "These observations", report the authors, "suggest that QRFP exerts its activity through these regions, and this factor is likely to be involved in emotional aspects of feeding".

Science is not science without caveats

It must be mentioned that QRFP peptides are not only expressed in the brain, but also in peripheral organs such as in adrenal cortex and adipocytes. "Since our present mouse model is a conventional QRFP knockout, the peripheral actions of QRFP might also contribute to metabolic phenotype of these mice", cautiously add the authors. Indeed, future studies taking advantage of optogenetic/pharmacogenetic approaches might further reveal the central mechanisms by which QRFP promotes feeding and mood.

Although there is need for further investigations, this study points to QRFP as a potential pharmacological target for metabolic as wells as emotional disorders, thus opening exciting hypotheses to be tested and verified in the near future.

More information: Kitaro Okamoto et al. QRFP-Deficient Mice Are Hypophagic, Lean, Hypoactive and Exhibit Increased Anxiety-Like Behavior, *PLOS ONE* (2016). DOI: 10.1371/journal.pone.0164716