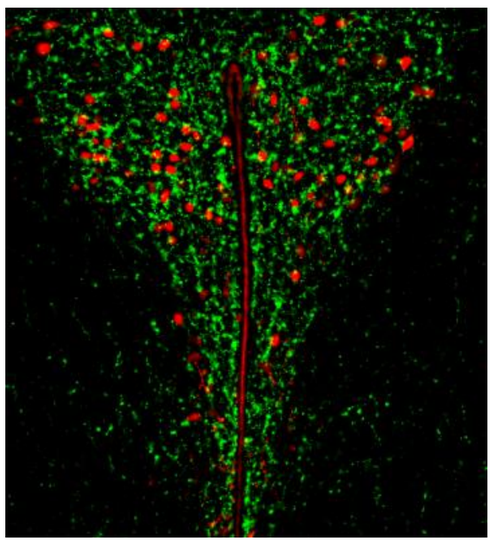
Increased innervation of the hypothalamic para-ventricular nucleus by the AgRP and α-MSH axonal projections in female germ-free mice



Oarii Vahirua[1,2], Mouna El Mehdi[1,2], Florent Zysk[1,2], Sylvie Rabot[3], Sergueï O. Fetissov[1,2]

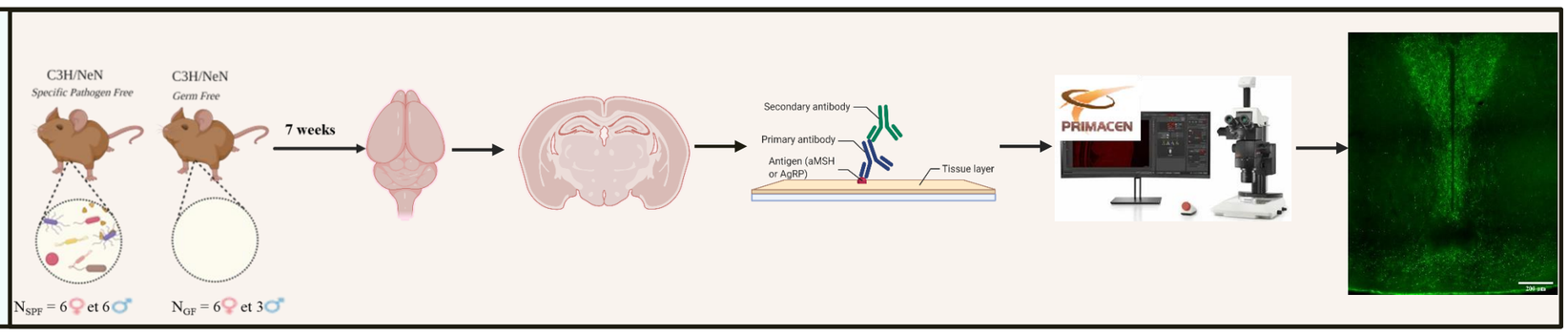
1: Inserm UMR1239, Regulatory Peptides – Energy Metabolism and Motivated Behavior Team, 76130, Mont-Saint-Aignan, France;
2: Normandie Univ, UNIROUEN, INSERM, Neuroendocrine, Endocrine and Germinal Differentiation and Communication Laboratory , 76000, Rouen, France;
3: Université Paris-Saclay, INRAE, AgroParisTech, Micalis Institute, 78350 Jouy-en-Josas, France.

INTRODUCTION

Innervation of the paraventricular hypothalamic nucleus (PVN) by the orexigenic agouti-related protein (AgPR) and anorexigenic α-melanocyte-stimulating hormone (α-MSH) neurons of the arcuate nucleus (ARC), represents a key element in the appetite-regulating circuitry. Insufficient development of such circuitry has been found in mice with an early onset of anorexia and body weight loss. Recent studies also show that gut microbiota can be involved in regulation of feeding behavior by activation of both intestinal and central satiety pathways. Moreover, altered composition of gut microbiota is present in patients with anorexia and bulimia nervosa, the eating disorders which are 10 times more prevalent in females *vs.* males. However, it is unknown if the gut microbiota may influence the development of the ARC /PVN appetite circuitry.

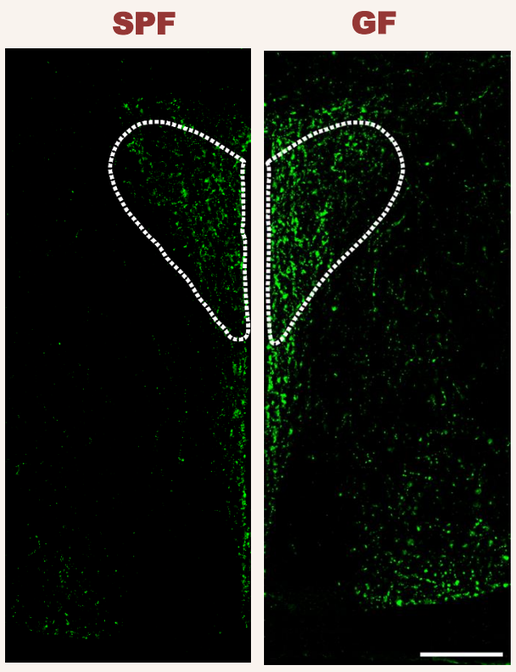
OBJECTIVES & METHODS

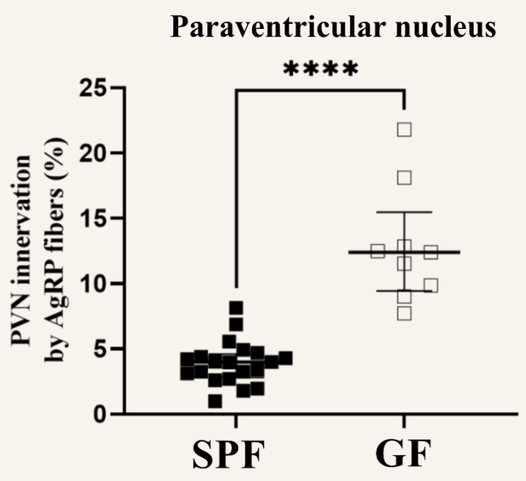
To respond to this question, in the present study, we used immunohistochemistry to compare AgRP and α-MSH innervation of the PVN between germ-free (GF) and specific pathogen free (SPF) 7-week-old C3H/HeN female mice.



RESULTS

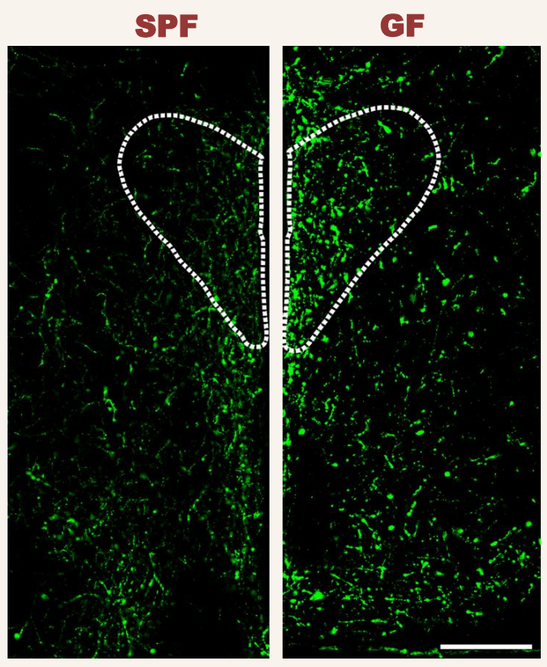
AgRP Innervation

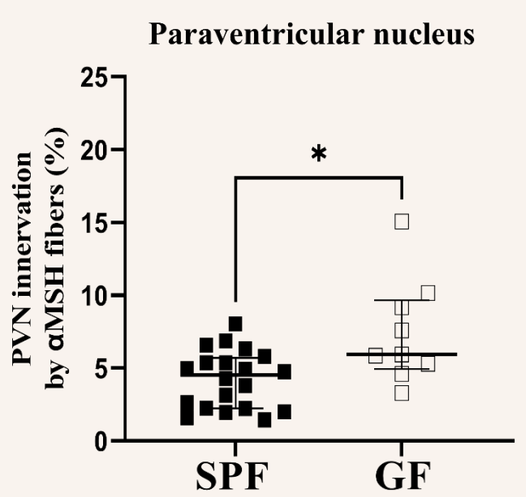




PVN innervation by orexigenic AgRP fibers is twice more important in GF than in SPF female mice

αMSH innervation

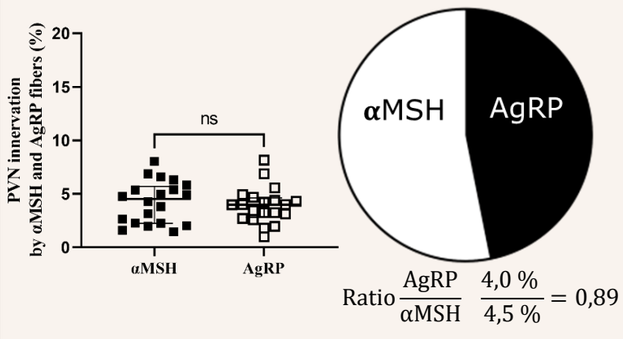




PVN innervation by anorexigenic α-MSH fibers is slightly more elevated in GF than in SPF female mice

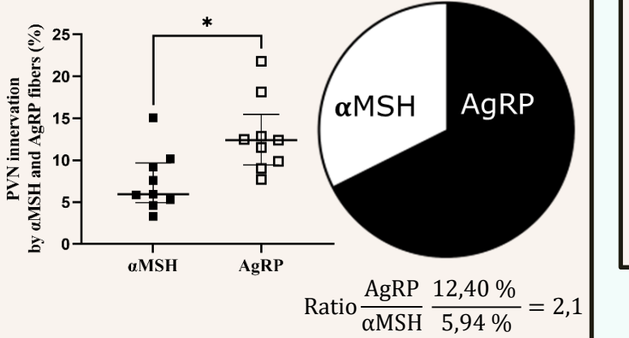
AgRP/αMSH relative innervation

SPF



$$\text{Ratio}\frac{\text{AgRP}}{\alpha\text{MSH}}\ \frac{4{,}0\ \%}{4{,}5\ \%} = 0{,}89$$

GF



$$\text{Ratio}\frac{\text{AgRP}}{\alpha\text{MSH}}\ \frac{12{,}40\ \%}{5{,}94\ \%} = 2{,}1$$

In SPF condition, the PVN of female mice is innervated equally by AgRP and α-MSH fibers

In the absence of microbiota there is a relative increase of AgRP innervation on the PVN

CONCLUSION

These data reveal that gut microbiota may play an inhibitory role in the development in ARC/PVN axonal projections of both AgRP and α-MSH neurons. The previous data have shown an increased food intake of GF mice. Thus, our data suggest that the increased innervation of the PVN by AgRP fibers may contribute to the development of hyperphagia in GF mice.

ACKNOWLEDGMENTS :

The study was supported by the EC H2020 “GEMMA” , ERAnet “MIGBAN” and Inserm TMP2 research programs.

Contact : Serguei.Fetissov@univ-rouen.fr