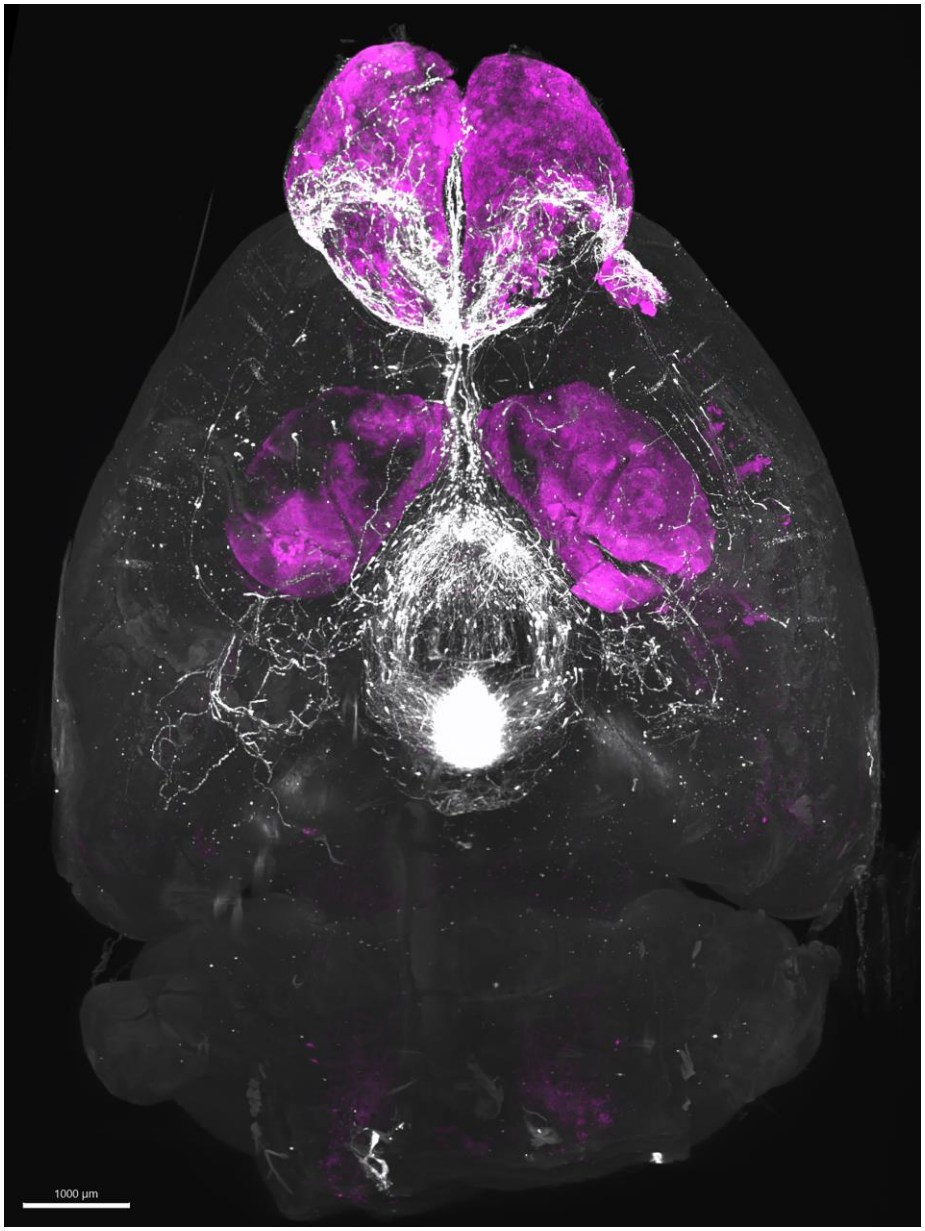
SNE Impacts 2024



Localization of the distribution of GnRH neurons (immunolabelled in white) and catecholaminergic neurons (labelled with tyrosine hydroxylase in magenta) in the transparent adult mouse brain.
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A summary of breakthroughs in Neuroendocrinology in 2024
https://www.neuroendocrinologie.fr/

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Alexandre Benani & Nathalie Bancod (website), Sebastien Bouret (LinkedIn), Elodie Desroziers (X), Giuseppe Gangarossa (Bluesky), Clara Sanchez (Facebook/Instagram)

List of selected papers

Bentefour Y and Bakker J. Stress during pubertal development affects female sociosexual behavior in mice. ***Nat Commun.*** *2024 Apr 30;15(1):3610. doi: 10.1038/s41467-024-47300-w.*

Borie A, Dromard Y, Chakraborty P, Fontanaud P, Andre E, François A, Colson P, Muscatelli F, Guillon G, Desarménien M, Jeanneteau F. Neuropeptide therapeutics to repress lateral septum neurons that disable sociability in an autism mouse model. ***Cell Rep Med****. 2024 Nov 19;5(11):101781. doi: 10.1016/j.xcrm.2024.101781.*

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Duquenne M, Deligia E, Folgueira C, Bourouh C, Caron E , Pfrieger F, Schwaninger M, Nogueiras R, Annicotte JS, Imbernon M, Prévot V. Tanycytic transcytosis inhibition disrupts energy balance, glucose homeostasis and cognitive function in male mice. ***Mol Metab.*** *2024 Sep:87:101996. doi: 10.1016/j.molmet.2024.101996. Epub 2024 Jul 22.*

Estrada-Meza J, Videlo J, Bron C, Duchampt A, Saint-Béat C, Zergane M, Silva M, Rajas F, Bouret SG, Mithieux G, Gautier-Stein A. Intestinal gluconeogenesis controls the neonatal development of hypothalamic feeding circuits. ***Mol Metab****. 2024 Nov;89:102036. doi: 10.1016/j.molmet.2024.102036. Epub 2024 Sep 18.PMID: 39304064*

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*Leon S, Simon V, Lee TH, Steuernagel L, Clark S, Biglari N, Lesté-Lasserre T, Dupuy N, Cannich A, Bellocchio L, Zizzari P, Allard C, Gonzales D, Le Feuvre Y, Lhuillier E, Brochard A, Nicolas JC, Teillon J, Nikolski M, Marsicano G, Fioramonti X, Brüning JC, Cota D and Quarta C. Single cell tracing of Pomc neurons reveals recruitment of "Ghost" subtypes with atypical identity in a mouse model of obesity****. Nat. Commun.*** *2024 Apr 24;15(1):3443. doi: 10.1038/s41467-024-47877-2.*

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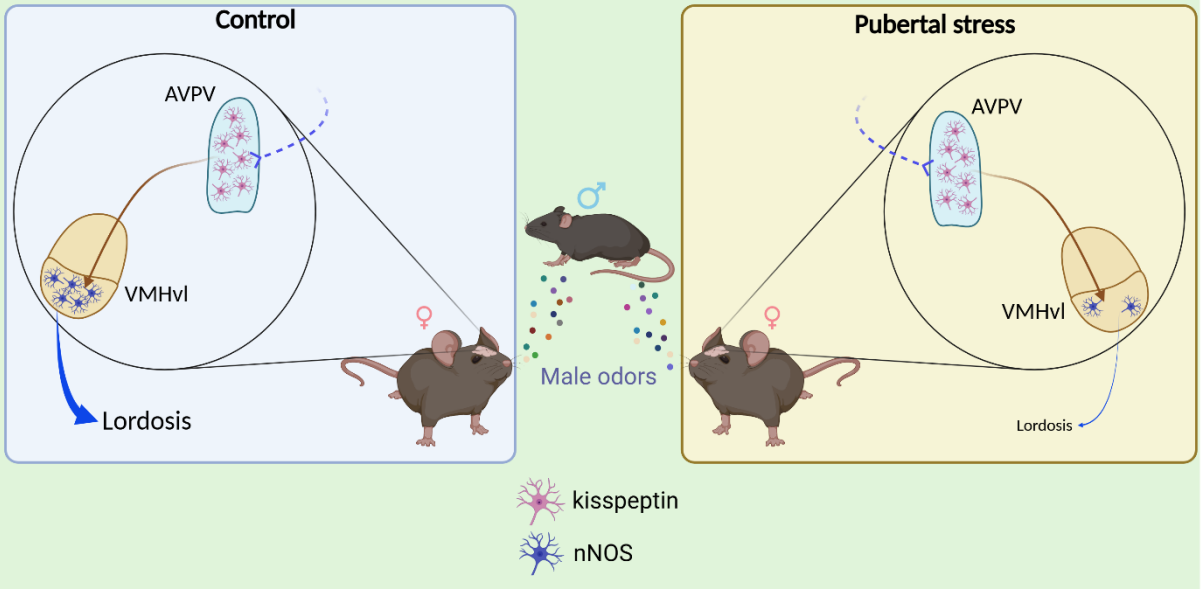
Zizzari P, Castellanos-Jankiewicz A, Yagoub S, Simon V, Clark S, Maître M, Dupuy N, Leste-Lasserre T, Gonzales D, Schoonjans K, Fénelon VS, Cota D. TGR5 receptors in SF1-expressing neurons of the ventromedial hypothalamus regulate glucose homeostasis. ***Mol Metab.*** *2025 Jan;91:102071. doi: 10.1016/j.molmet.2024.102071. Epub 2024 Nov 26.PMID: 39603503.*

Stress during pubertal development affects female sociosexual behavior in mice

Low sexual desire is a deleterious condition that causes marked distress and interpersonal difficulties. It has a general negative impact on the quality of life. The prevalence of low sexual desire is high: up to 39.5% of women aged between 18 and 44 years old reported deficient or absent sexual fantasies, sexual arousal, and orgasm. Puberty is defined as the transition to a mature reproductive state and is a crucial phase in the development of female sexual functioning. There is growing evidence that exposure to stress during puberty might lead to sexual dysfunction. Therefore, in the present study, the effects of chronic stress over the pubertal period on the neural circuit regulating female sexual behavior was investigated. It was found that pubertal stress permanently disrupted sexual performance in female mice. This reduction in female sexual behavior was associated with a reduced expression and activation of a population of nitric oxide producing neurons in the ventromedial hypothalamus, a brain region critical for the expression of female sexual behavior. This reduced neural activation was particularly observed when females were exposed to male odors, suggesting that the integration of sexually important cues into the brain was affected by exposure to pubertal stress. In sum, adverse effects such as stress, during puberty might lead to long-lasting negative effects on sexual functioning in females.



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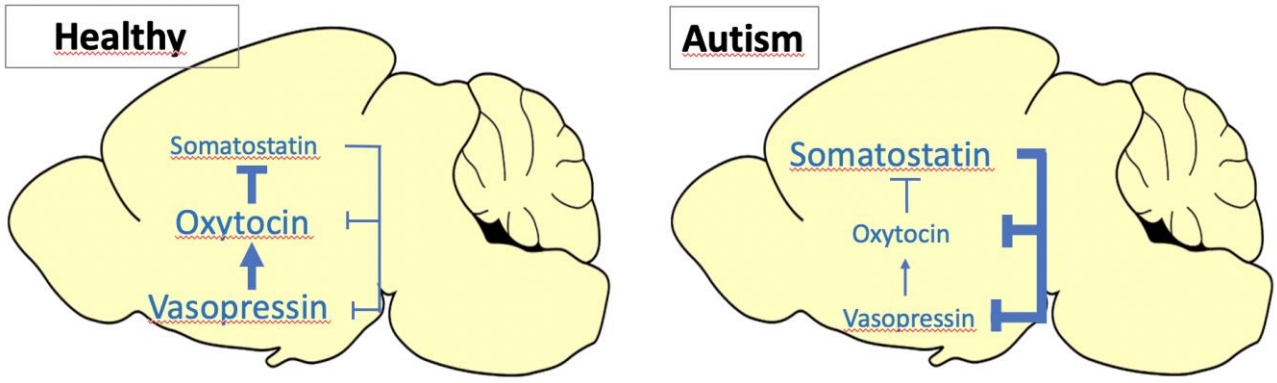
Towards more effective therapies against autism

Treatment of autism spectrum disorders is insufficient. The results of recent clinical trials involving the use of oxytocin or vasopressin are mixed. Scientists hypothesized that mixed clinical effects might arise from interrelated actions on prosocial and antisocial responses.
Using mice as model, scientists identified somatostatin inhibitory neurons in the lateral septum that respond to oxytocin and vasopressin, depending on the degree of peer affiliation. Oxytocin receptors inhibit these neurons via the GABA-B receptor, while vasopressin acts via GABA-A neurotransmission on presynaptic connections. Together, these neuropeptides prolonged social contacts by inhibiting intraseptal somatostatinergic activity according to the degree of affiliation between individuals.
When somatostatin is injected into the lateral septum, social contacts are shortened, while a somatostatin antagonist prolongs their duration. However, in animals carrying a mutation in the autism gene MAGEL2, treatment resistance resulted in a hypersomatostatinergic state with premature termination of social contacts.
The results suggest that co-therapy with oxytocin and vasopressin could reduce the hypersomatostatinergic state observed in autism. Furthermore, the use of somatostatinergic antagonists appears to be an alternative to oxytocin and vasopressin notably in subjects featuring endocrine resistance.



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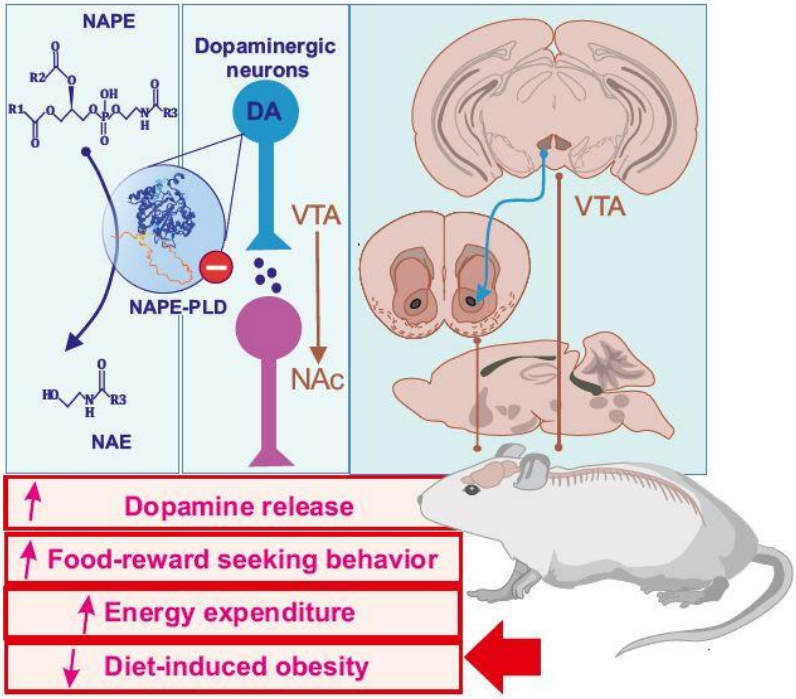
NAPE-PLD in the ventral tegmental area regulates reward events, feeding and energy homeostasis

The N-acyl phosphatidylethanolamine-specific phospholipase D (NAPE-PLD) catalyzes the production of N-acylethanolamines (NAEs), a family of endogenous bioactive lipids involved in various biological processes ranging from neuronal functions to energy homeostasis and feeding behaviors. Reward-dependent behaviors depend on dopamine (DA) transmission between the ventral tegmental area (VTA) and the nucleus accumbens (NAc), which conveys reward-values and scales reinforced behaviors. However, whether and how NAPE-PLD may contribute to the regulation of feeding and reward-dependent behaviors has not yet been investigated. This biological question is of paramount importance since NAEs are altered in obesity and metabolic disorders. Here, we show that transcriptomic meta-analysis highlights a potential role for NAPE-PLD within the VTA→NAc circuit. Using brain-specific invalidation approaches, we report that the integrity of NAPE-PLD is required for the proper homeostasis of NAEs within the midbrain VTA and it affects food-reward behaviors. Moreover, region-specific knock-down of NAPE-PLD in the VTA enhanced food-reward seeking and reinforced behaviors, which were associated with increased *in vivo* DA dynamics in response to both food- and non-food-related rewards together with heightened tropism towards food consumption. Furthermore, midbrain knock-down of NAPE-PLD, which increased energy expenditure and adapted nutrient partitioning, elicited a relative protection against high-fat diet-mediated body fat gain and obesity-associated metabolic features. In conclusion, these findings reveal a new key role of VTA NAPE-PLD in shaping DA-dependent events, feeding behaviors and energy homeostasis, thus providing new insights on the regulation of body metabolism.



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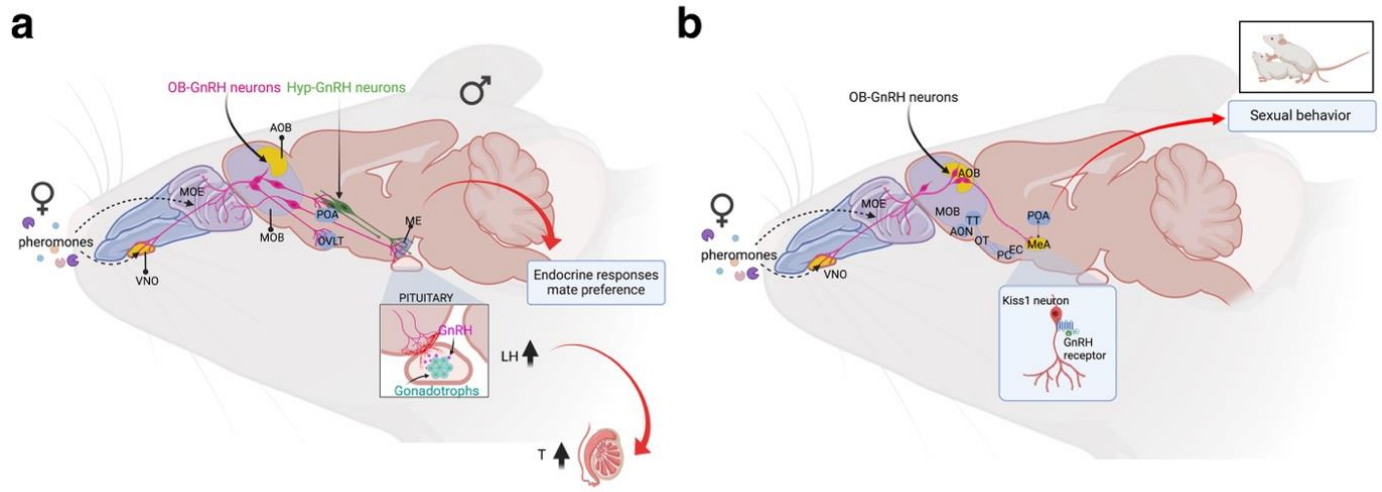
The Nose Knows: Neuroendocrine Cells That Turn Smells into Mating Cues

Scientists have made an intriguing discovery about how male mice recognize potential mates. They discovered that a group of brain cells, known as GnRH neurons, and which are known to control the development of sexual organs and reproduction, are located in the olfactory bulb, which processes odors. When a male mouse detects the scent of a female, these neurons become active, triggering a hormonal response that prepares the male for mating.

Researchers have also showed that when the activity of these GnRH neurons was increased, male mice exhibited heightened interest in female scents. Conversely, reducing or removing the activity of these neurons led to diminished attraction to females. This indicates that these cells play a crucial role in helping male mice recognize potential mates and engage in mating behaviors.

This research underscores the complex interplay between chemical senses and reproductive behaviors, revealing how the brain orchestrates the intricate dance of attraction and mating.

Overall, these findings highlight the importance of GnRH neurons in regulating both fertility and social recognition in male mice, potentially offering clues about similar processes in other mammals.



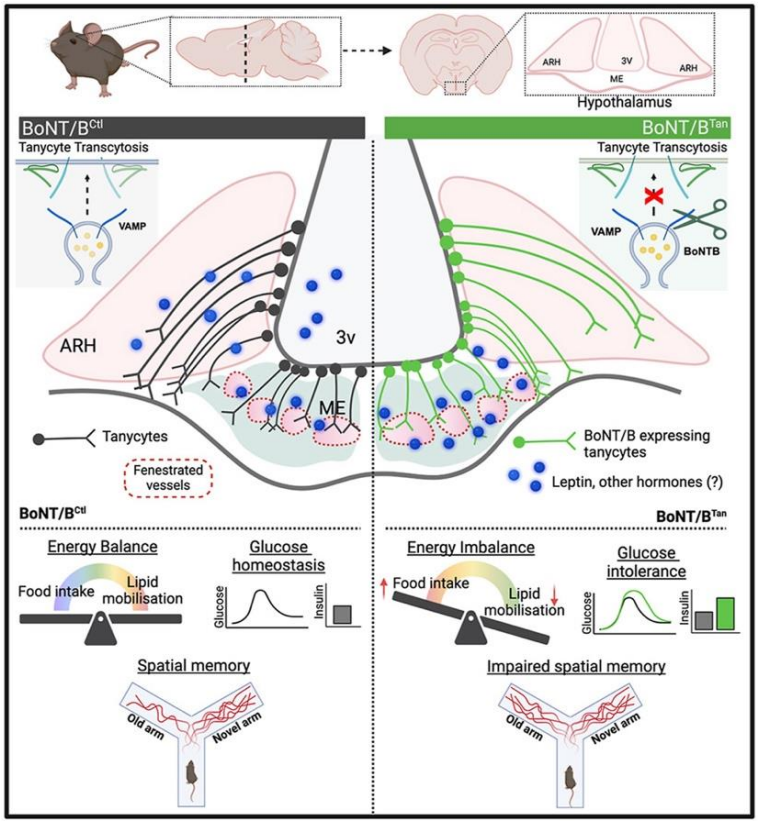
Decoster L, Trova S, Zucca S, Bulk J, Gouveia A, Ternier G, Lhomme T, Legrand A, Gallet S, Boehm U, Wyatt A, Wahl V, Wartenberg P, Hrabovszky E, Rácz G, Luzzati F, Nato G, Fogli M, Peretto P, Schriever SC, Bernecker M, Pfluger PT, Steculorum SM, Bovetti S, Rasika S, Prevot V, Silva MSB and Giacobini P. A GnRH neuronal population in the olfactory bulb translates socially relevant odors into reproductive behavior in male mice. ***Nat Neurosci.*** 2024 Sep;27(9):1758-1773. *doi:10.1038/s41593-024-01724-1.*

Tanycytic transcytosis inhibition disrupts energy balance, glucose homeostasis and cognitive function in male mice

High-caloric diets and genetic factors disrupt body-brain communication, fueling obesity and metabolic disorders. In this study we focus on the hypothalamic tanycytes role in energy balance regulation and cognition. We used a Cre-dependent approach to express botulinum neurotoxin type B (BoNT/B) in tanycytes of adult male mice, inhibiting vesicle-associated membrane protein (VAMP)-mediated release.

In mice fed standard diets, BoNT/B expression in tanycytes blocked leptin transport into the mediobasal hypothalamus, leading to central obesity marked by increased food intake, abdominal fat, and elevated leptin levels without significant weight changes. This manipulation promoted fatty acid accumulation, causing glucose intolerance and insulin resistance, together with compensatory insulin secretion. Additionally, impaired spatial memory was observed in BoNT/B-expressing mice, associating the tanycytic function to both metabolism and cognitive regulation.

These findings highlight tanycytes crucial role in brain-periphery communication, linking their function to type 2 diabetes and cognitive decline. The tanycytic BoNT/B mouse model offers insights into disease progression from prediabetes to advanced metabolic and cognitive disorders. Recognizing tanycytic transcytosis role in hormone transport could guide novel therapies addressing metabolic and cognitive comorbidities, particularly those worsening with age.



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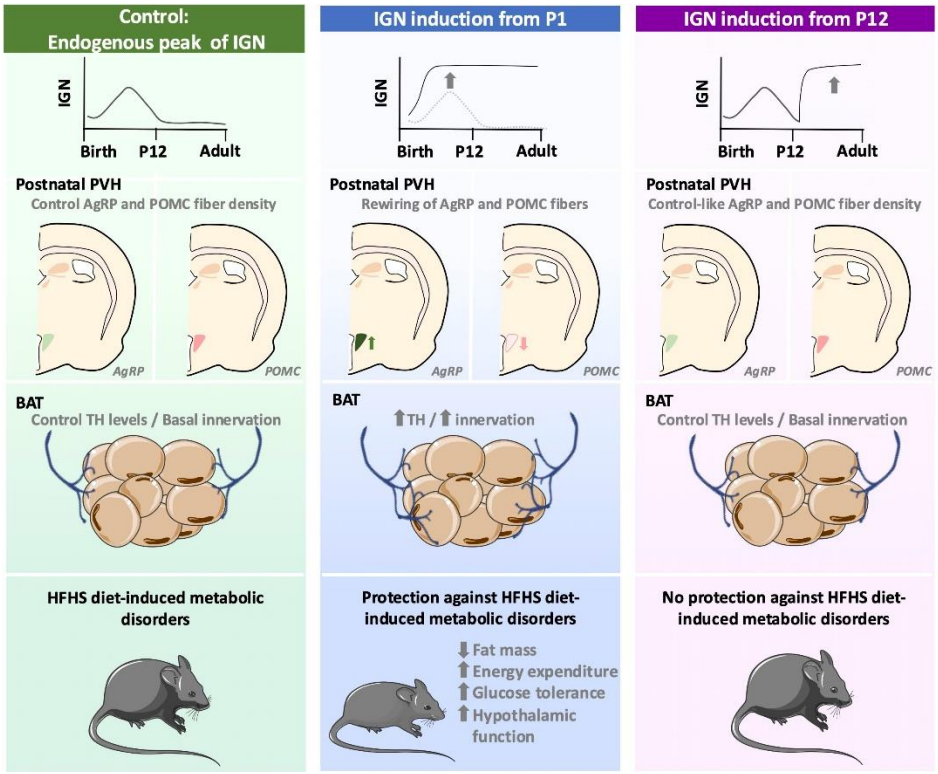
Intestinal gluconeogenesis controls the neonatal development of hypothalamic feeding circuits

Intestinal gluconeogenesis (IGN) is crucial for energy homeostasis through its signaling effects on the hypothalamus. During the neonatal period, IGN peaks alongside a leptin surge that regulates hypothalamic axonal outgrowth and peripheral autonomic innervation. This study explored the impact of the neonatal peak of IGN on the development of hypothalamic feeding circuits, adipose tissue innervation, and long-term metabolic health.

Using mice genetically engineered to overexpress *G6pc1*, the catalytic subunit of glucose-6-phosphatase, in the intestine, we induced neonatal IGN either from birth (P1) or after the endogenous peak (12 days later (P12)). In 20-day-old pups, IGN induction from P1 reorganized Agouti-related protein (AgRP) and Pro-opiomelanocortin (POMC) axonal projections to the paraventricular nucleus of the hypothalamus. It also increased tyrosine hydroxylase levels in brown adipose tissue, indicating enhanced sympathetic innervation. In adulthood, mice with IGN induction from P1 exhibited reduced fat mass, and resistance to high-fat/high-sucrose diet-induced metabolic disorders. However, none of these effects occurred when IGN was induced from P12.

This study highlights the critical role of neonatal IGN in shaping hypothalamic feeding circuits and adipose tissue innervation during a limited perinatal window. Early-life IGN induction could be a novel approach to improving metabolic resilience and preventing obesity-related disorders in adulthood.



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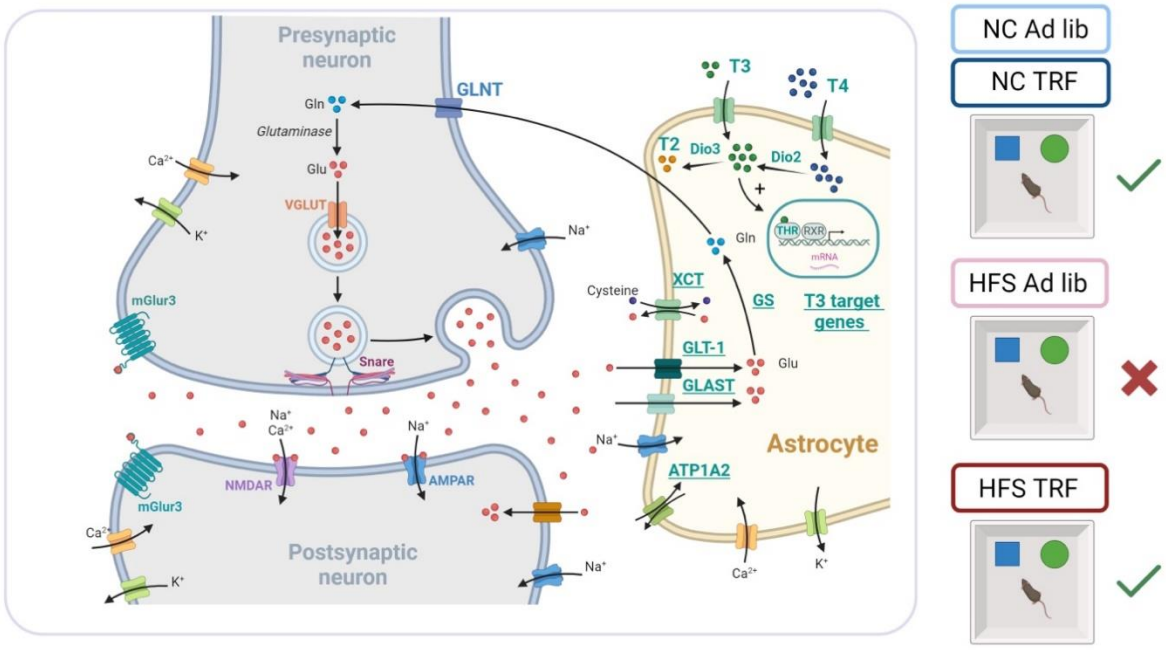
Time-restricted feeding prevents memory impairments induced by obesogenic diet consumption, via hippocampal thyroid hormone signaling.

Obese subjects show alterations in memory processes as well as in circadian biological rhythms. This is particularly worrisome in adolescents whose brains are still maturing. The objectives of this project were at understanding the cellular and molecular mechanisms underlying the therapeutic effect of time-restricted feeding (TRF) on obesity associated memory impairments. TRF is a nutritional intervention where food intake is re-aligned to circadian rhythms without calorie restriction. We identified behavioral and hippocampal molecular circadian disruptions in our model of juvenile consumption of obesogenic (HFS) diet A 4-week TRF protocol was sufficient to prevent the alteration of circadian rhythms of food intake, respiratory exchange ratio and energy expenditure observed in mice consuming HFS diet *ad libitum* since weaning. This TRF protocol also displayed beneficial effects on hippocampal-dependent memory deficits observed in mice with unlimited access to HFS diet, independently of body fat levels. Finally, TRF also normalized part of the hippocampal translatome altered by *ad libitum* HFS diet consumption and restored the diurnal expression of genes that displayed blunted expression under *ad libitum* HFS diet. In particular, *ad libitum* HFS diet led to a reduced response of the thyroid hormone signaling pathway during memory formation that was rescued by TRF.



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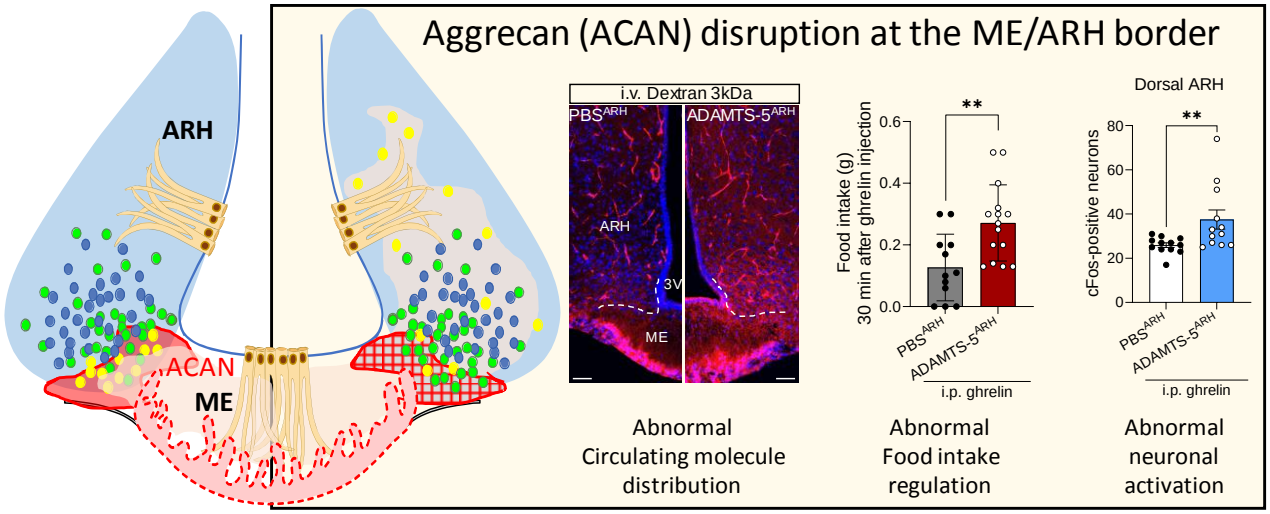
A plastic aggrecan barrier modulated by peripheral energy state gates metabolic signal access to arcuate neurons.

The arcuate nucleus of the hypothalamus (ARH) contains neurons vital to the maintenance of energy homeostasis that sense blood-borne metabolic hormones, signal changes in metabolic state and orchestrate the appropriate adaptive response. Despite the juxtaposition of the ARH with the median eminence (ME), a circumventricular organ devoid of a typical blood-brain-barrier, only a few ventral ARH neurons have direct access to blood-borne molecules extravasating into the ME parenchyma due to the existence of a dorsolateral diffusion barrier of unknown nature. Here, Laura Kuczynski-Noyau, Sixtine Karmann, and colleagues show that the deposition of aggrecan, a perineural net proteoglycan, by ARH neuropeptide Y (NPY) neurons create a peculiar ventrodorsal diffusion gradient. Fasting triggers additional aggrecan deposition more dorsally, reinforcing the diffusion barrier, particularly around NPY neurons adjacent to ME capillary loops that enter the ARH and become fenestrated under food deprivation. Genetic or aggrecanase-mediated disruption of aggrecan deposits results in the unregulated diffusion of blood-borne molecules, including ghrelin, into the ARH and impairs the physiological response to refeeding. Our findings reveal the molecular nature and plasticity of the previously unexplained ME/ARH diffusion barrier, and indicate a novel physiological role for this perineural net in hypothalamic metabolic hormone sensing and, thus, energy homeostasis.



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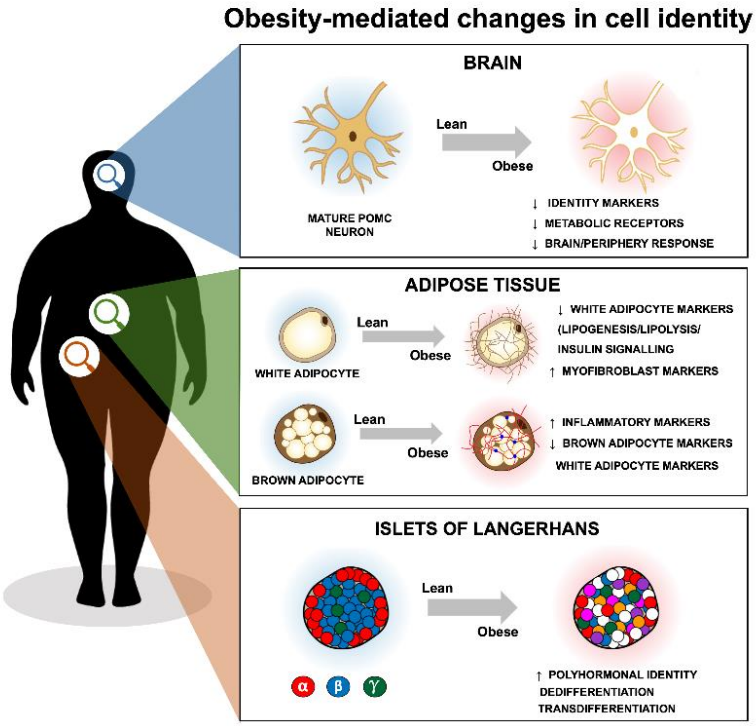
Single cell tracing of Pomc neurons reveals recruitment of 'Ghost' subtypes with atypical identity in a mouse model of obesity

The paper explores the complex relationship between obesity and the hypothalamus, a region rich in diverse neurons that regulate behaviour and metabolism. These neurons play a critical role in monitoring the body's energy needs through crosstalk with peripheral signals. Contrary to the traditional view that neural diversity in the hypothalamus is fixed after development, the evidence presented challenges this idea.

Using state-of-the-art lineage tracing and single cell profiling of hypothalamic pre-opiomelanocortin (Pomc) expressing neurons in adult mice, we have uncovered 'ghost' neurons characterised by minimal expression of both the key identity marker Pomc and several other markers that define this neuronal population.

Unlike classical Pomc neurons, 'ghost' neurons have unique molecular properties that make them undetectable by standard neuroanatomical techniques and promoter-based reporter mice used in Pomc research. These atypical neurons also display different functional properties. Notably, the number of 'ghost' neurons increases in diet-induced obese mice without the involvement of neurogenesis or cell death, suggesting a potential adaptability of neuronal identities in response to obesity-related stimuli.

This study highlights how changes in adult neuronal identity maintenance may be closely linked to maladaptive hypothalamic functions in obesity. It also suggests the potential for identifying molecular targets that modulate neuronal identity as a treatment for obesity and metabolic disorders.



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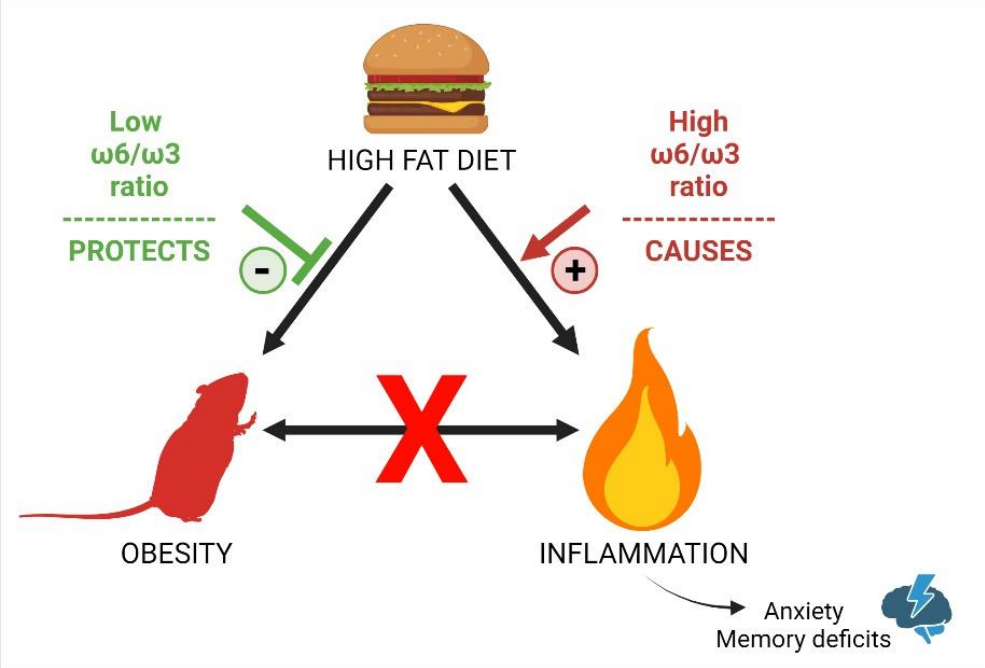
Dietary fatty acid composition drives neuroinflammation and impaired behavior in obesity

Nutrient composition in obesogenic diets may influence the severity of disorders associated with obesity such as insulin-resistance and chronic inflammation. Here we hypothesized that obesogenic diets rich in fat and varying in fatty acid composition, particularly in omega 6 (ω6) to omega 3 (ω3) ratio, have various effects on energy metabolism, neuroinflammation and behavior. Mice were fed either a control diet or a high fat diet (HFD) containing either low (LO), medium (ME) or high (HI) ω6/ω3 ratio. Mice from the HFD-LO group consumed less calories and exhibited less body weight gain compared to other HFD groups. Both HFD-ME and HFD-HI impaired glucose metabolism while HFD-LO partly prevented insulin intolerance and was associated with normal leptin levels despite higher subcutaneous and perigonadal adiposity. Only HFD-HI increased anxiety and impaired spatial memory, together with increased inflammation in the hypothalamus and hippocampus. Our results show that impaired glucose metabolism and neuroinflammation are uncoupled, and support that diets with a high ω6/ω3 ratio are associated with neuroinflammation and the behavioral deterioration coupled with the consumption of diets rich in fat.



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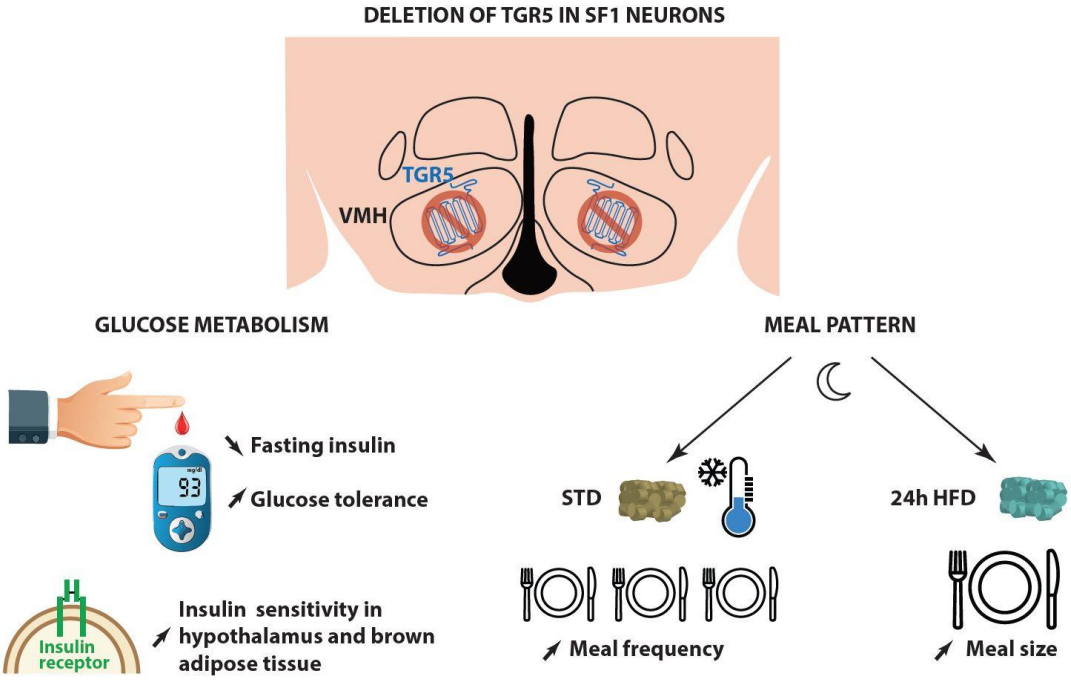
TGR5 receptors in SF1-expressing neurons of the ventromedial hypothalamus regulate glucose homeostasis

Steroidogenic factor-1 (SF1) neurons in the ventromedial hypothalamus play essential roles in regulating energy balance and glucose homeostasis. The bile acid receptor Takeda G protein-coupled receptor 5 (TGR5), which is expressed in the hypothalamus, controls some of the effects of bile acids on food intake and body weight through mechanisms that are not yet well understood. In this study, we utilized a genetic approach alongside metabolic phenotyping and molecular analyses to examine the impact of TGR5 deletion in SF1 neurons on energy balance and glucose metabolism.

Our findings indicate that TGR5 in SF1 neurons does not significantly affect food intake or body weight under standard chow conditions. However, it does play a role in the adaptive feeding response to acute exposure to cold or a high-fat diet without altering energy expenditure. Importantly, TGR5 in SF1 neurons appears to inhibit glucose metabolism, as the deletion of this receptor enhances whole-body glucose uptake and improves insulin signaling in both the hypothalamus and brown adipose tissue. These results provide new insights into the role of neuronal TGR5 in metabolic regulation, demonstrating that TGR5 in SF1 neurons promotes satiety by altering meal patterns in response to metabolic signals, while also influencing whole-body insulin sensitivity.



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