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INTRANASAL EFFECTS OF AN ANALOGUE OF THE GLIOPEPTIDE ODN ON ENERGY HOMEOSTASIS

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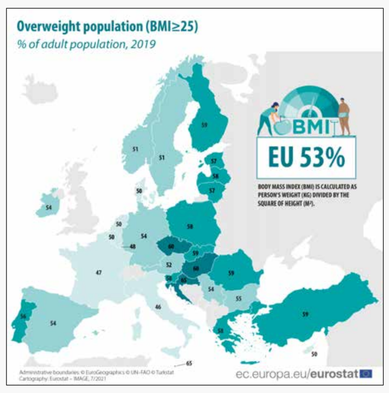
OBESITY MAJOR PUBLIC HEALTH PROBLEM IN INDUSTRIALIZED COUNTRIES



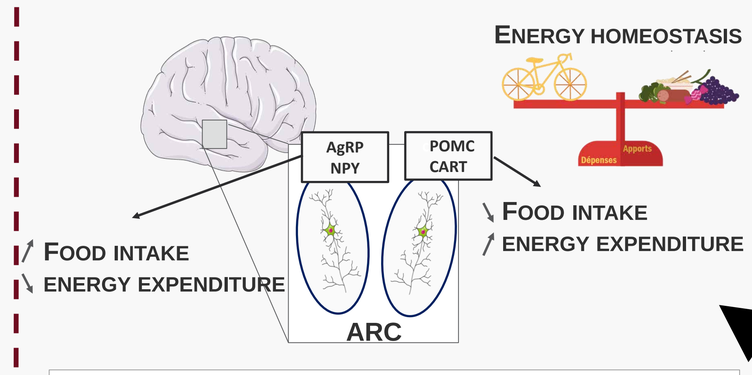
Overweight and obesity - BMI statistics

RISK FACTORS:

→ TYPE 2 DIABETES
→ CARDIOVASCULAR DISEASE
→ CANCERS

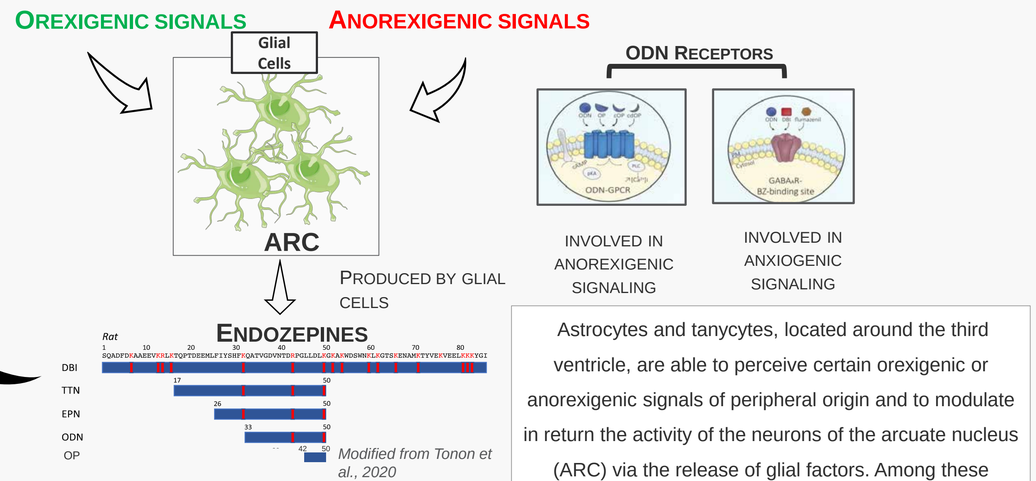
Levian et al.,2014

HYPOTHALAMIC REGULATION OF FOOD INTAKE
▪ NEURONAL COMPONENT



The hypothalamus strongly contributes to the homeostatic control of energy balance by integrating information linked to the nutritional status and arising from peripheral organs

HYPOTHALAMIC REGULATION OF FOOD INTAKE
▪ GLIAL COMPONENT



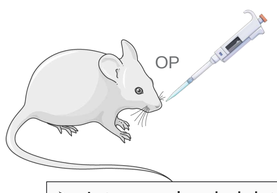
Modified from Tonon et al., 2020

Astrocytes and tanycytes, located around the third ventricle, are able to perceive certain orexigenic or anorexigenic signals of peripheral origin and to modulate in return the activity of the neurons of the arcuate nucleus (ARC) via the release of glial factors. Among these different molecules, the endozepines and particularly ODN are a family of gliopeptides of interest.

Lebrun et al., 2021

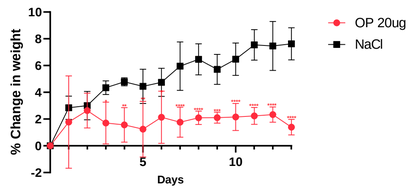
THERAPEUTIC ROLE OF THE ODNERGIC SYSTEM IN THE TREATMENT OF OBESITY?

1 The i.n. administration of OP as an alternative to i.c.v. route



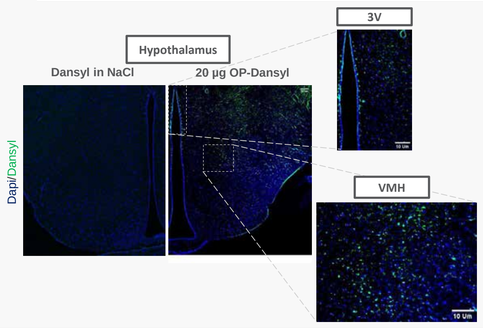
OP:

- C-terminal part of ODN
- Bioactive analog of ODN
- As potent as ODN *in vitro* $[Ca^{2+}]_i$ mobilization in astrocytes



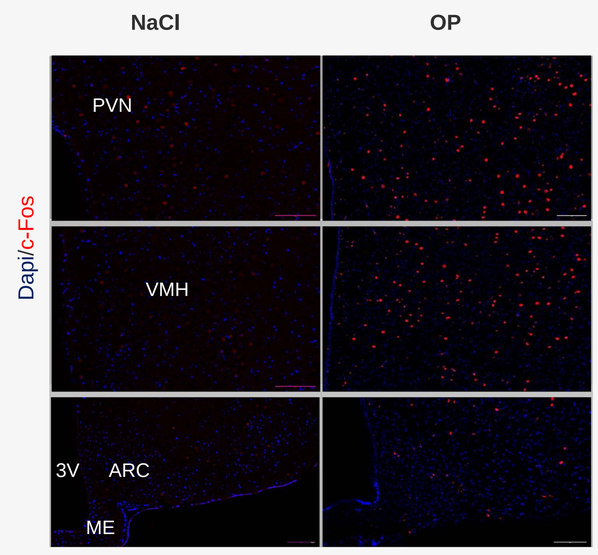
- Intranasal administration of OP (20 µg/day/mice), an ODN-derived analog, results in the cessation of body weight gain in adult normally fed mice starting from the 3rd day of treatment.

2 Cerebral biodistribution of dansyl-OP



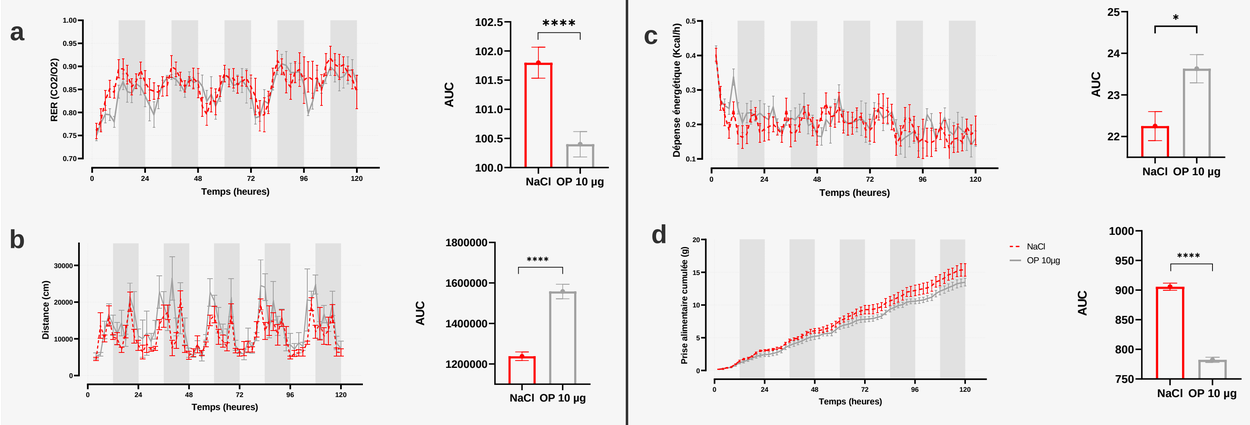
- To monitor the delivery of our peptide to the target brain regions through the intranasal route, we conjugated the OP sequence with dansyl. These preliminary results allow for the visualization of the peptide at the brain level, primarily in the cortex, hippocampus, around the third ventricle, and the VMH.

3 Hypothalamic areas activated by i.n. administration of OP



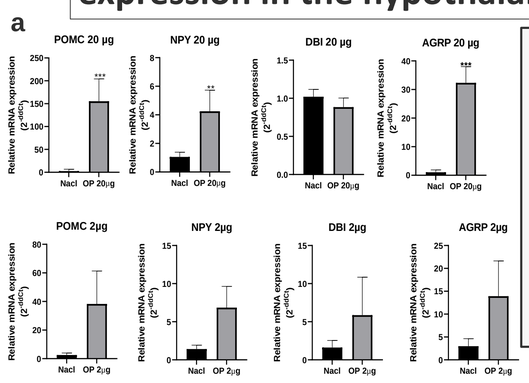
- Fluorescence microscopy allowed visualization of doubly labeled neuronal populations (c-Fos, Dapi) within the mice hypothalamus. The immunohistochemistry images obtained show specific c-Fos labeling limited to 3 main regions, namely the paraventricular (PVN), arcuate (ARC) and ventromedial nuclei (VMH) .

4 The intranasal administration of OP affects metabolic parameters

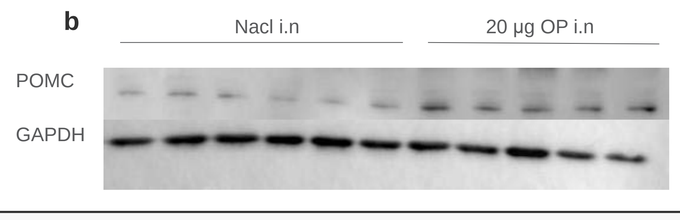


The results show that the intranasal administration of OP in obese mice has significant effects on energy metabolism and appetite regulation. A dose of 10 µg of OP leads to a notable decrease in the respiratory exchange ratio (RER) (a), indicating an increase in the use of lipids as an energy source from body reserves. OP also increases motor activity (b) and energy expenditure in the mice (c), while reducing their food intake (d).

5 The effect of i.n. administration of OP on mRNA expression in the hypothalamus



- The representative Western blot revealed a significant increase in POMC protein levels in hypothalamic extracts following i.n. administration of 20 µg OP, in contrast to treatment with NaCl (fig b). This finding was corroborated by real-time RT-PCR, which demonstrated elevated expression levels of the POMC, NPY, and AGRP genes in the hypothalamus following the same 20 µg OP administration, indicating a potential shift toward anorexigenic neuropeptide activity (POMC) from orexigenic neuropeptides (NPY and AGRP) (panel a).

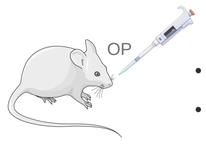


Conclusions and perspectives

In summary, our findings demonstrate the efficacy of the i.n. route for delivering OP to the brain, resulting in activation of identical hypothalamic regions as observed with i.c.v. injection. **These data affirm the therapeutic promise of the ODN/GPCR system in addressing human conditions linked to energy metabolism.**

➢ THE IMPACT OF I.N. ADMINISTRATION OF OP ON ENERGY METABOLISM IN WT MICE

i.c.v. injection of ***Cyclo$_{(1-8)}$ [$_D$Leu^5] OP*** *an* ***ODN-GPCR antagonist***



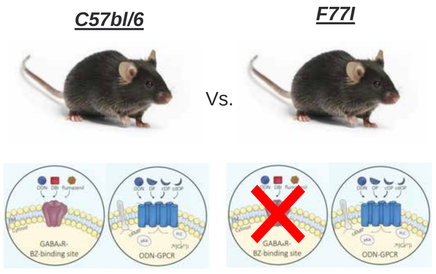
i.n. administration of OP

Evaluation of:

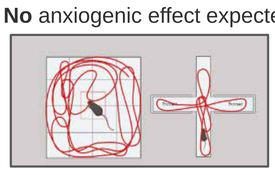
- **Food intake**
- **Body weight**

➢ ANOREXIGENIC EFFECT OF OP IN F77I MICE

C57bl/6 Vs. ***F77I***



1. i.c.v. injection of **ODN**
   → **No** anxiogenic effect expected



2. **c-Fos** immunohistochemistry
3. OP instilation in normally fed and diet-induced obesity mice

➢ NEUROANATOMICAL PATHWAYS AND HYPOTHALAMIC TARGETS OF THE OP

Monitor the mode of OP penetration in the nasal epithelium and then its central and peripheral biodistributions by β-imaging of a radioactive analogue of OP ([^{3}H]OP) in collaboration with the CEA.

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