La leptine, du métabolisme au cerveau

Nouvelles pistes pour le Syndrome de Rett

Jean-Luc Gaiarsa

Institut de Neurobiologie de la Méditerranée, INSERM, Aix-Marseille Université

LE MENU

ENTRÉE

Un peu d'histoire …

PLAT

Leptine et syndrome de Rett

DESSERT

Pertinences cliniques
&
Perspectives thérapeutiques ?

SUGGESTION

N'hésitez pas à poser
des questions !!!

La leptine : Hormone de satiété

1950

OBESE, A NEW MUTATION IN THE HOUSE MOUSE*

ANN M. INGALLS, MARGARET M. DICKIE AND G. D. SNELL
Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine



1994



Positional cloning of the mouse *obese* gene and its human homologue

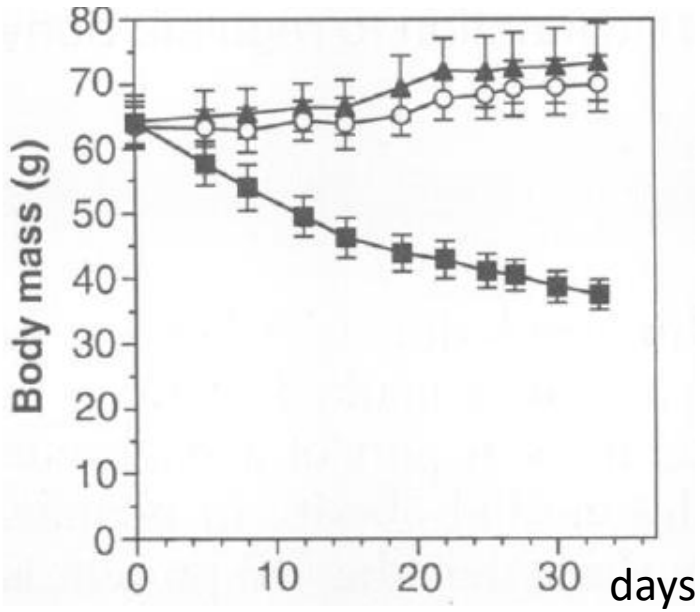
Yiying Zhang, Ricardo Proenca, Margherita Maffei, Marisa Barone, Lori Leopold & Jeffrey M. Friedman

Leptine du grec l*eptos*: mince

1995

Weight-Reducing Effects of the Plasma Protein Encoded by the *obese* Gene

Jeffrey L. Halaas, Ketan S. Gajiwala, Margherita Maffei, Steven L. Cohen, Brian T. Chait, Daniel Rabinowitz, Roger L. Lallone, Stephen K. Burley, Jeffrey M. Friedman*



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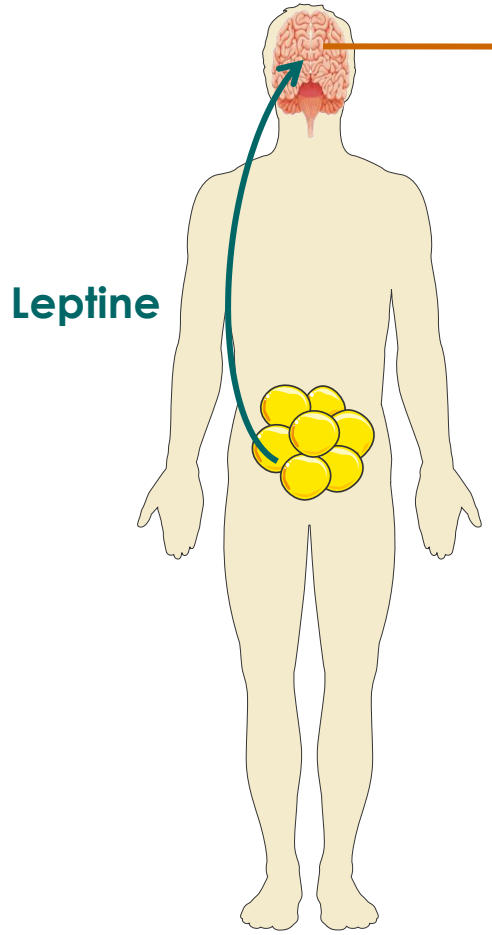
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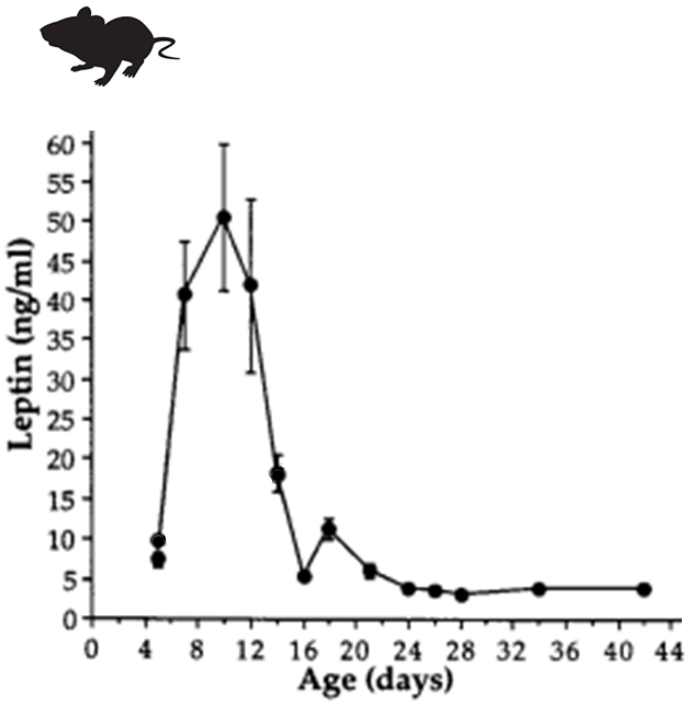
Hypothalamus

(-) Prise alimentaire

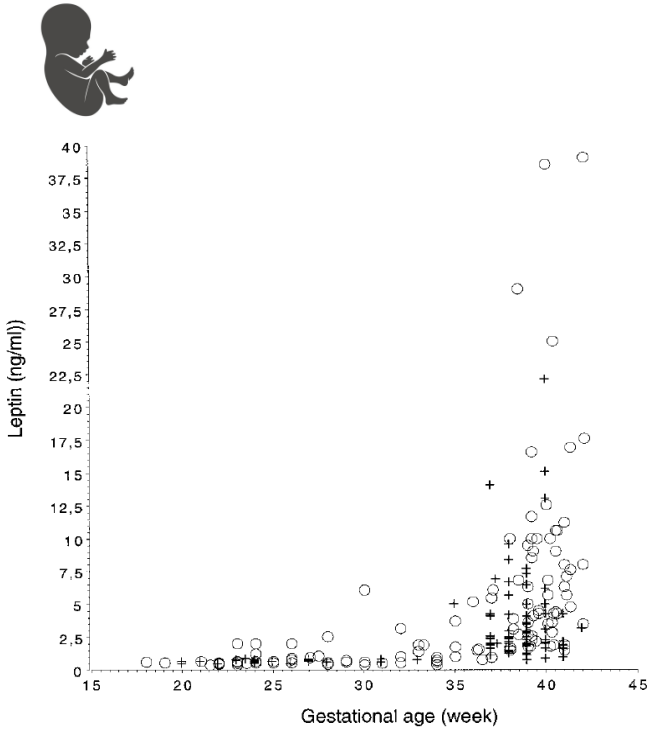
(+) Dépense énergétique



La leptine : Hormone de satiété. Oui mais pas uniquement

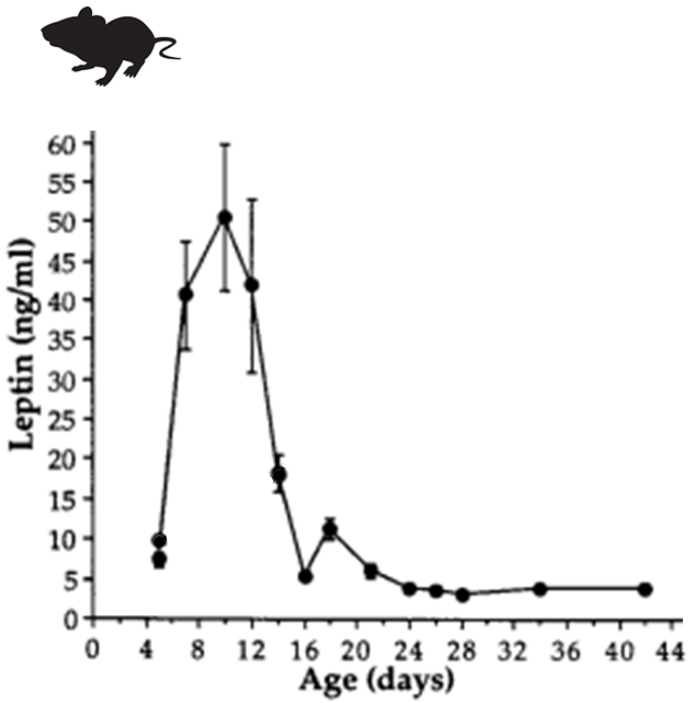


Devaskar et al., 1997



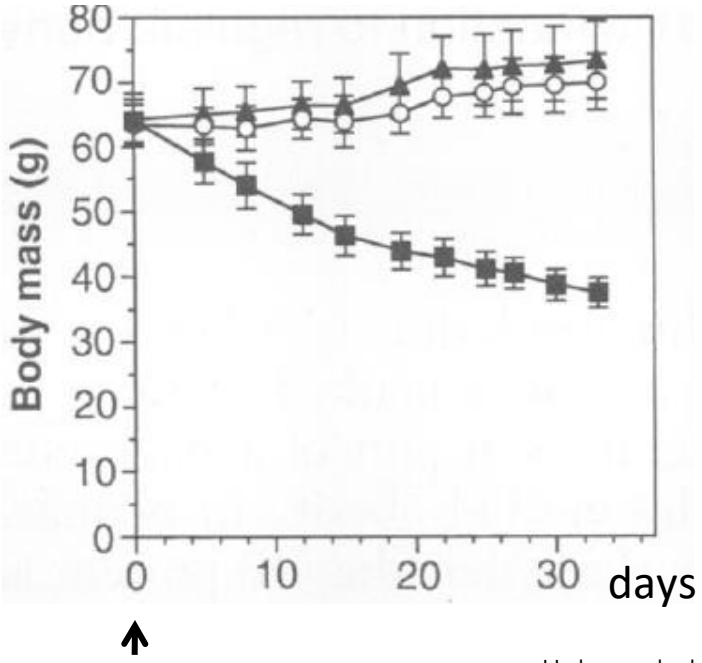
Jacquet et al., 1998

La leptine : Hormone de satiété. Oui mais pas uniquement



Devaskar et al., 1997

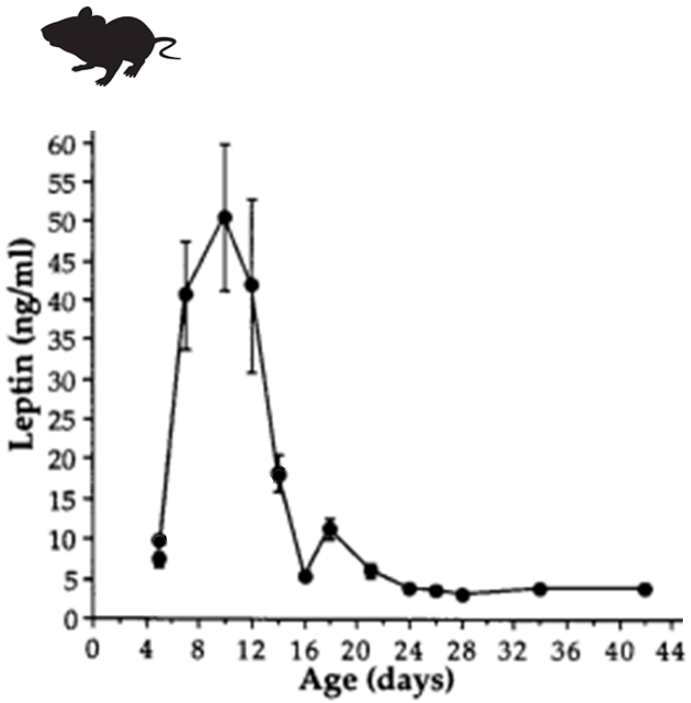
Souris adulte



Leptine

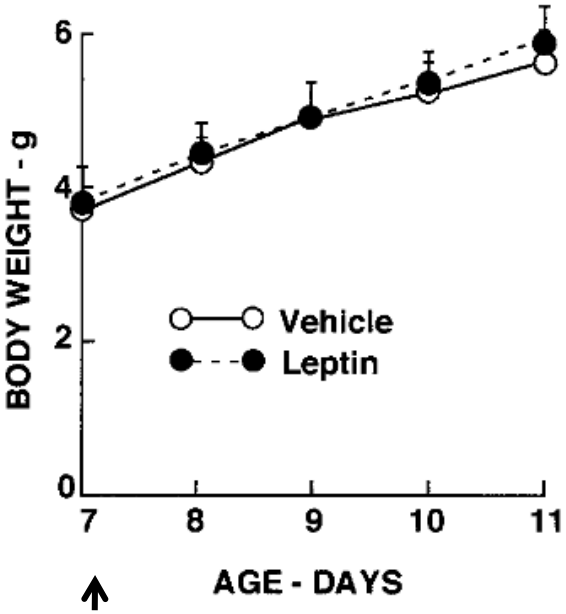
Halaas et al., 1995

La leptine : Hormone de satiété. Oui mais pas uniquement



Devaskar et al., 1997

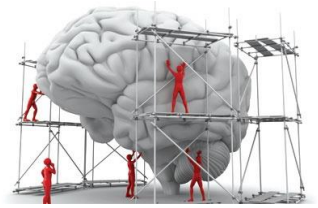
Souris jeune



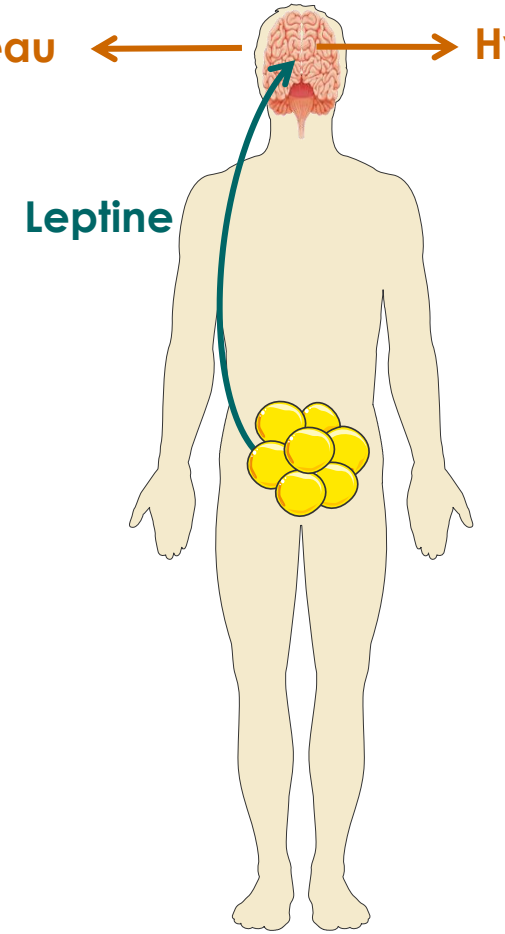
Mistry et al., 1999

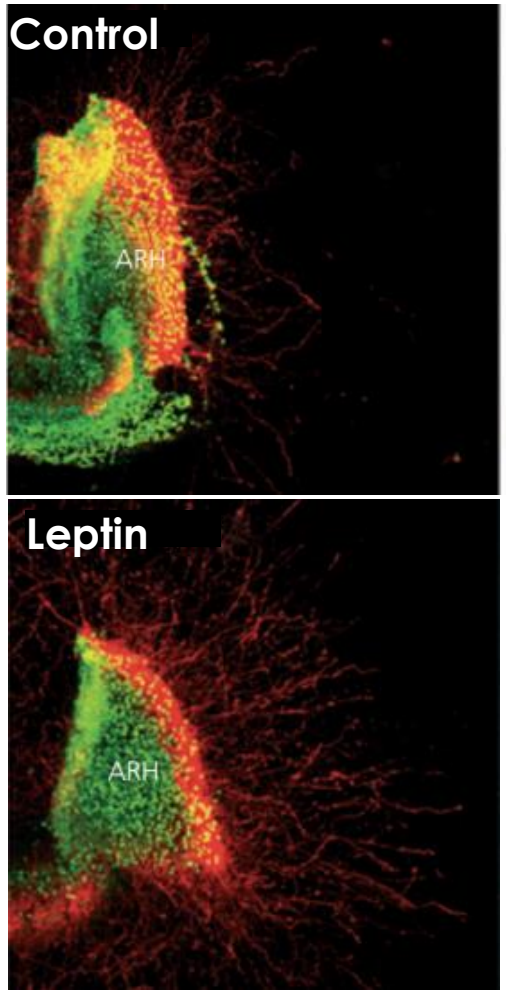
Leptine

La leptine : Un facteur neurotrophique



Développement du cerveau ← → Hypothalamus



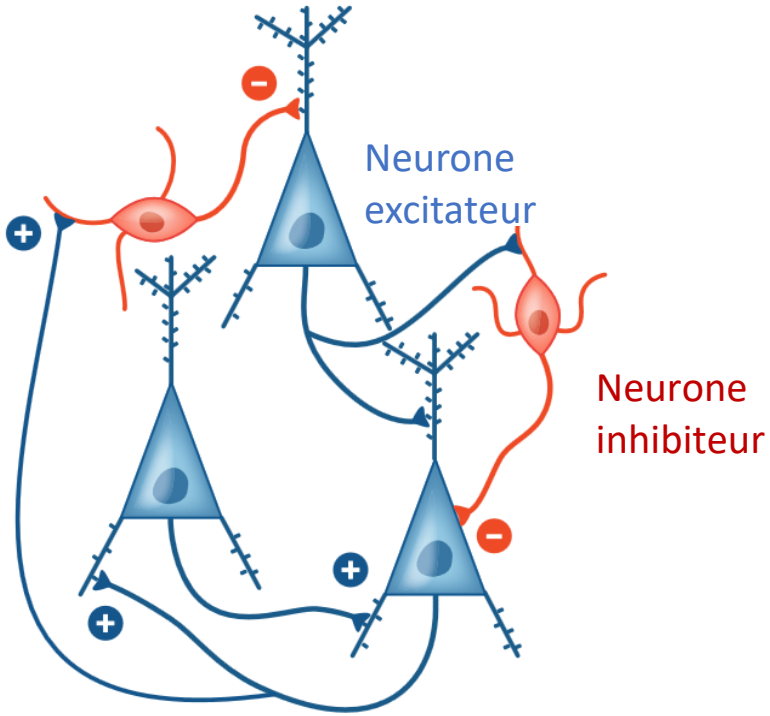


Bouret et al., 2004

La leptine : Un facteur neurotrophique

G. Wayman D. Guimond C. Dumon S. Sahin





eLIFE
elifesciences.org

The adipocyte hormone leptin sets the emergence of hippocampal inhibition in mice

Camille Dumon[1†], Diabe Diabira[1], Ilona Chudotvorova[1], Francesca Bader[1,2], Semra Sahin[3], Jinwei Zhang[4], Christophe Porcher[1], Gary Wayman[3], Igor Medina[1], Jean-Luc Gaiarsa[1*]

SCIENCE SIGNALING | RESEARCH ARTICLE

NEUROSCIENCE

Leptin increases GABAergic synaptogenesis through the Rho guanine exchange factor β-PIX in developing hippocampal neurons

Gulcan Semra Sahin[1], Jose Luis Rodriguez-Llamas[1], Crystal Dillon[1], Igor Medina[2], Suzanne M. Appleyard[1], Jean-Luc Gaiarsa[2], Gary A. Wayman[1*]

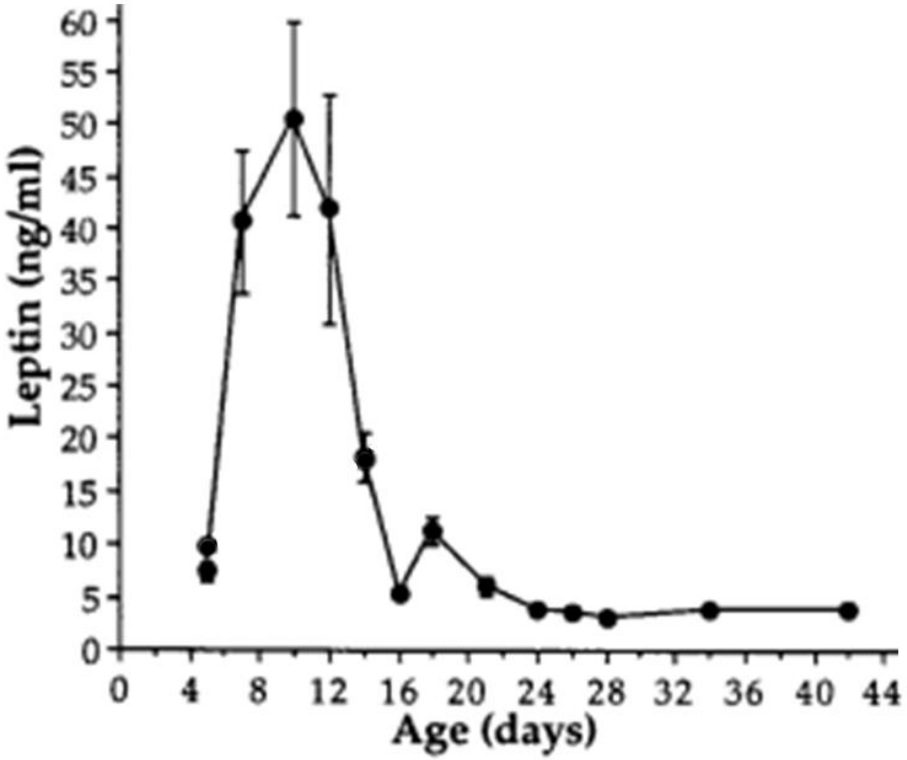
(Guimond et al. 2014; Dumon et al. 2018; 2019; 2020; Sahin et al. 2021)

La leptine : Hormone de satiété. Oui mais pas uniquement





Développement du cerveau **Fonctionnement du cerveau**

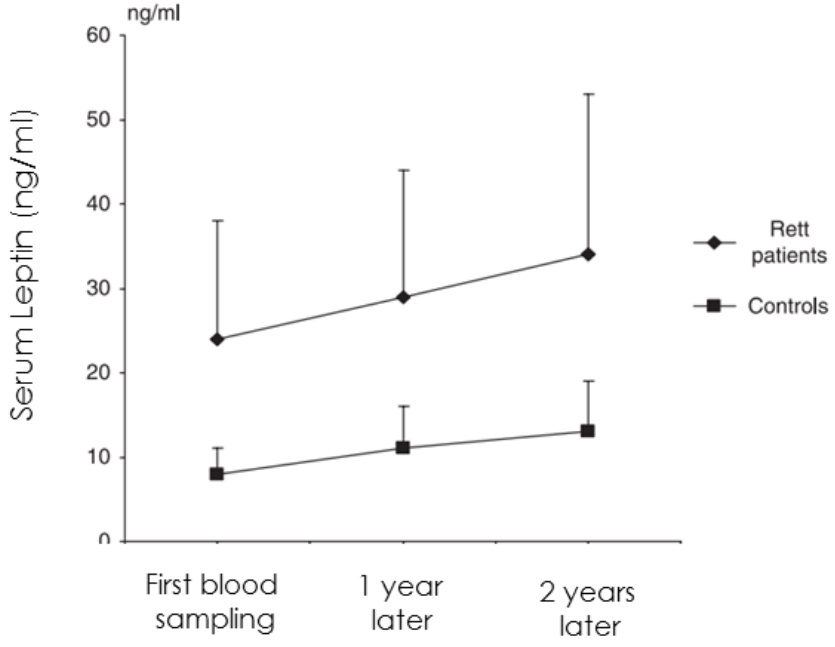


Devaskar et al., 1997

Les taux de leptine sont anormalement élevés dans le RTT



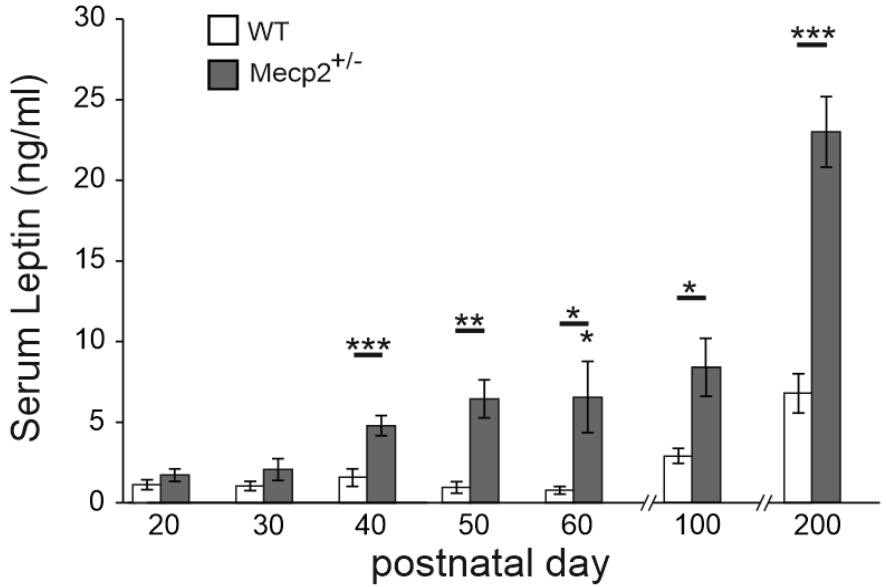
Âge moyen 9±3 ans



Acampa et al., 2008; Blardi et al., 2007; 2009.

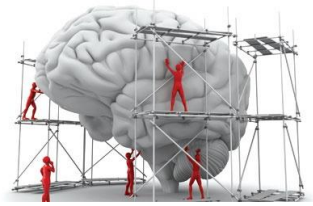


Mecp2^{tm1-1} bird



Park et al., 2014; Torres-Andrade et al., 2014; Fukuda et al., 2019.

La leptine: Une hormone aux multiples fonctions



Développement du cerveau

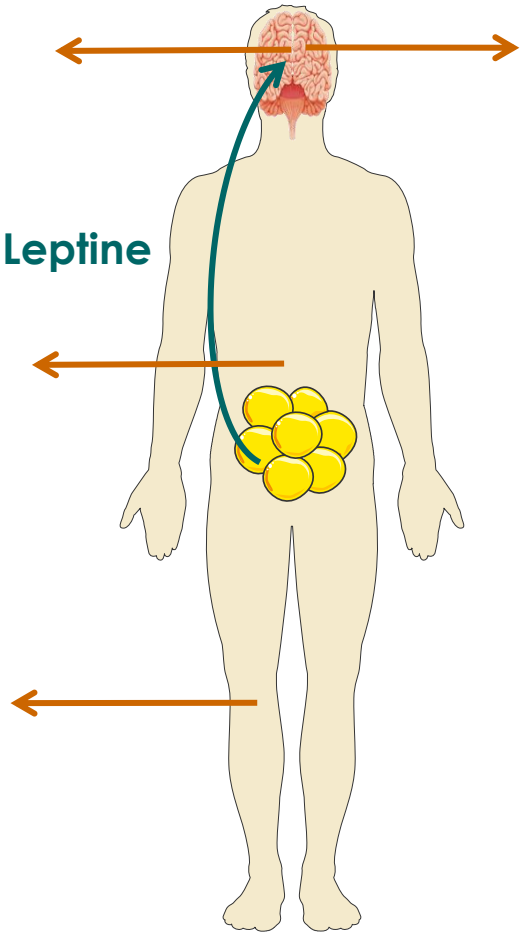


Développement des organes



Minéralisation osseuse

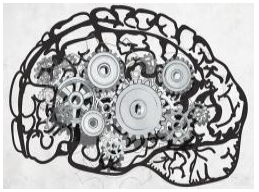
Masse musculaire



Fonctionnement du cerveau



- Satiété/Métabolisme
- Puberté



- Motricité
- Mémoire
- Emotions



- Respiration
- Rythme cardiaque
- Pression artérielle



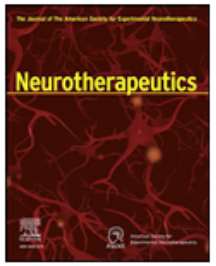
Y. Belaïdouni

Neurotherapeutics 23 (2026) e00910

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Original Article

Leptin antagonism improves Rett syndrome phenotype in symptomatic *Mecp2*-deficient mice

Yasmine Belaïdouni [a,*], Diabe Diabira [a], Pascal Salin [b], Mélanie Brosset-Heckel [a], Victoria Valsamides [a], Jean-Charles Graziano [a,1], Catarina Santos [d], Clément Menuet [a], Gary A. Wayman [c], Jean-Luc Gaiarsa [a,*]

[a] *INMED, INSERM, Aix Marseille University, Marseille, France*
[b] *IBDM, CNRS, Aix-Marseille University, Marseille, France*
[c] *Program in Neuroscience, Department of Integrative Physiology and Neuroscience, Washington State University, Pullman, WA, United States*
[d] *Phenotype Expertise, Marseille, France*

ARTICLE INFO

Keywords:
Leptin
Mecp2
Rett syndrome
Breathing
Mice

ABSTRACT

Rett syndrome (RTT) is a severe X-linked neurodevelopmental disorder caused by mutations in *MECP2*. Elevated circulating levels of the adipocyte hormone leptin are consistently observed in patients and in mouse models, yet their contribution to disease progression has remained unclear. Here, we show that reducing leptin signaling—either pharmacologically or genetically—significantly alleviates RTT-like phenotypes in *Mecp2*-deficient mice. In males, these interventions preserved general health, prevented weight loss, and improved breathing and locomotor functions. At the neuronal level, they restored excitatory/inhibitory balance in the hippocampus and somatosensory cortex and rescued hippocampal synaptic plasticity. In females, delaying the pathological rise of leptin levels postponed symptom progression. These findings uncover leptin as a key contributor to RTT pathophysiology and position leptin-targeted interventions as a promising therapeutic strategy for this currently untreatable disorder.

Contribution de la leptine au syndrome de Rett : Protocole



Mecp2$^{tm1\text{-}1}$ bird
(Guy et *al.*, 2001)



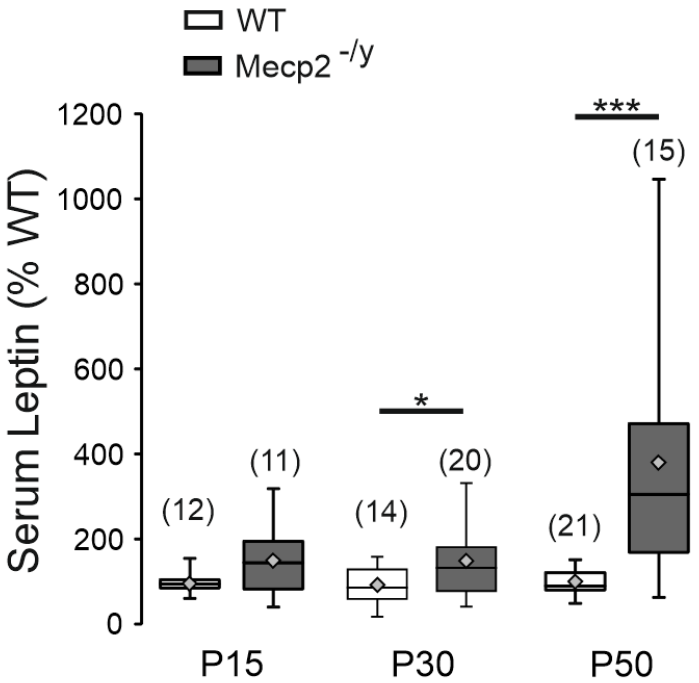
- **Symptômes**
  - Motricité réduite
  - Difficultés respiratoires
  - Anxiété
  - Troubles cognitifs
  - Epilepsie

  - Système gastro-intestinale (mobilité, microbiote)
  - Métabolisme
  - Système osseux
  - Atrophie musculaire

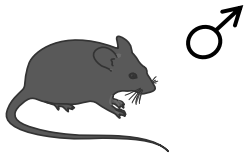
  - Perte de poids (mâle)

  - Mort prématurée (mâle)

- **Au niveau neuronal :**
  - Atteintes morphologiques
  - Altération balance excitation/inhibition
  - Diminution plasticité synaptique



Contribution de la leptine au syndrome de Rett : Protocole



Mecp2^{tm1-1} bird
(Guy et *al.*, 2001)



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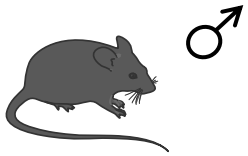
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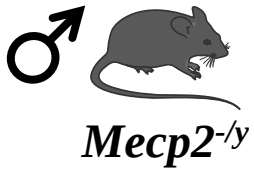
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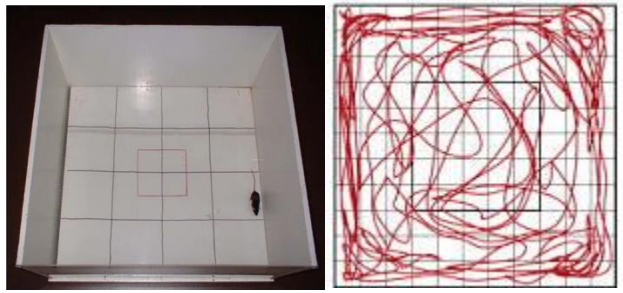
Leptine

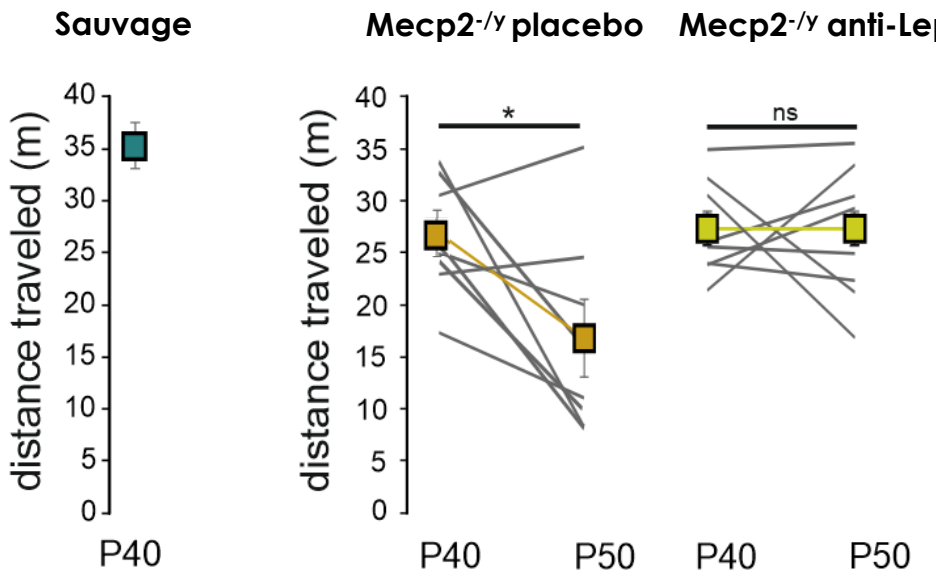


Contribution de la leptine au syndrome de Rett

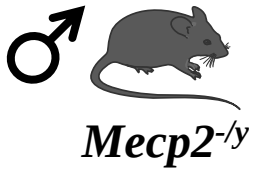


Activité locomotrice

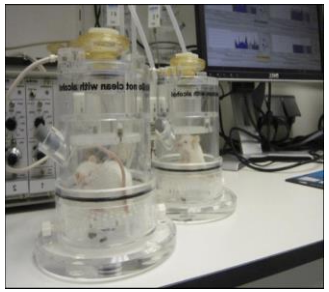


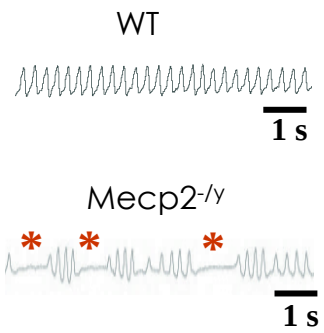


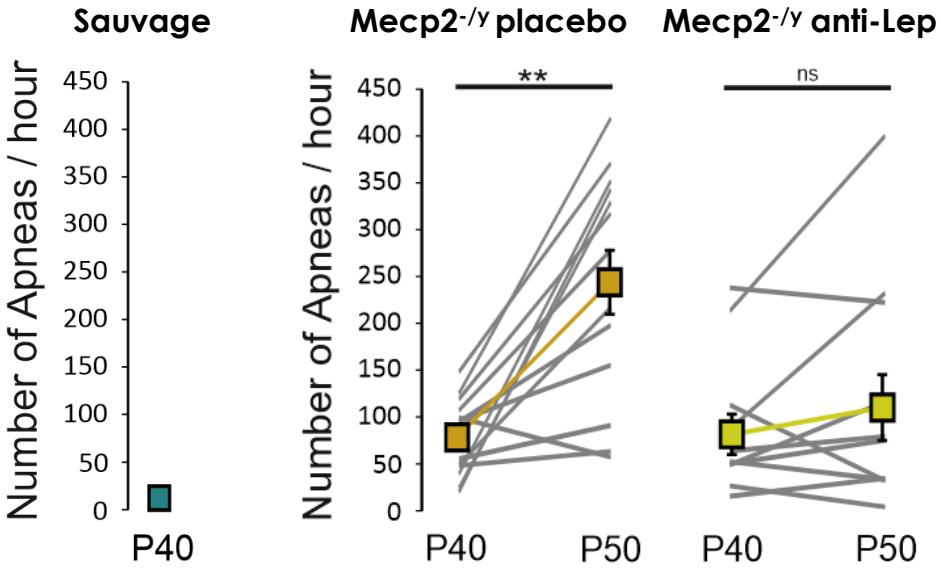
Contribution de la leptine au syndrome de Rett



Activité respiratoire







Contribution de la leptine au syndrome de Rett

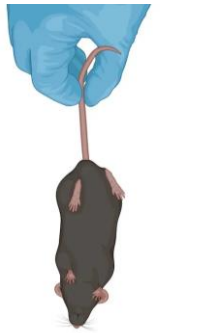
Etat de santé

Posture Aspect Activité Tremblement Stéréotypies











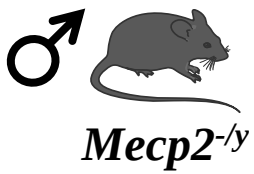


4 3 2 1 0

Absence de phénotype

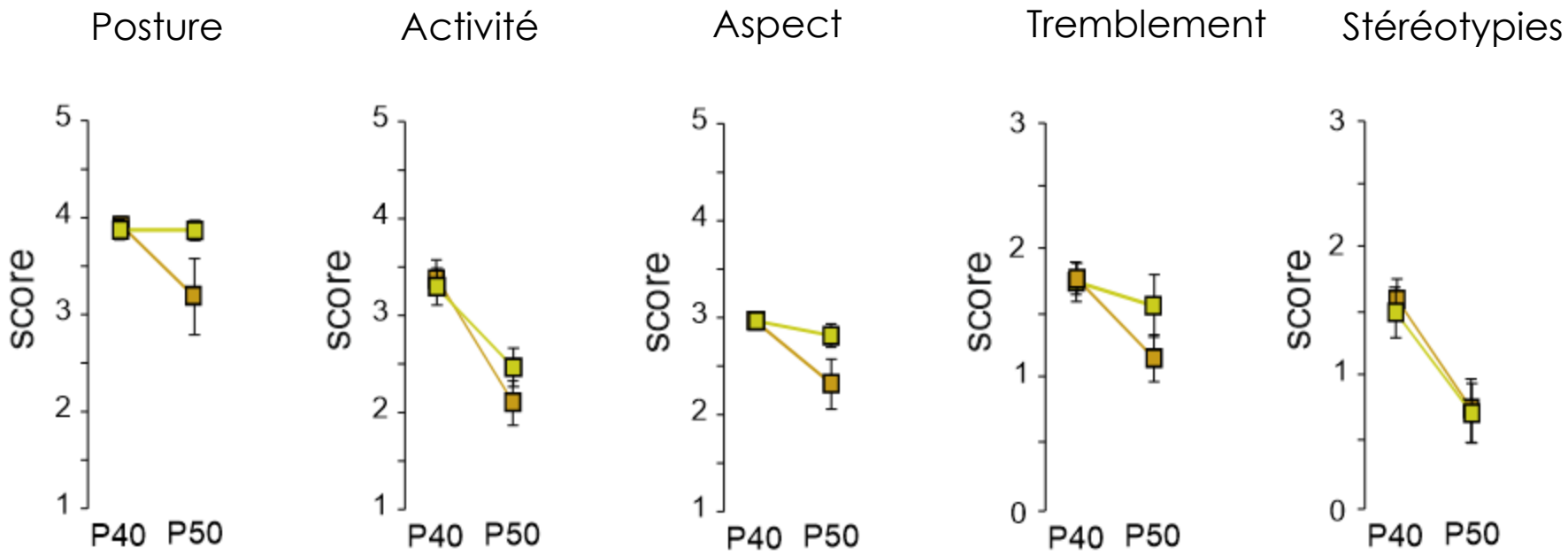
Phénotype sévère

Contribution de la leptine au syndrome de Rett

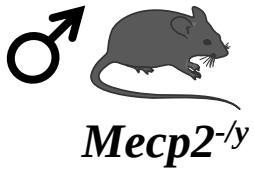


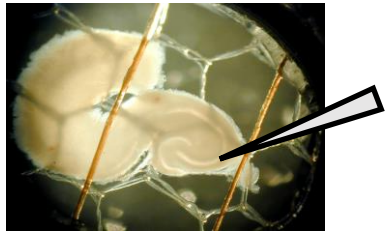
Etat de santé

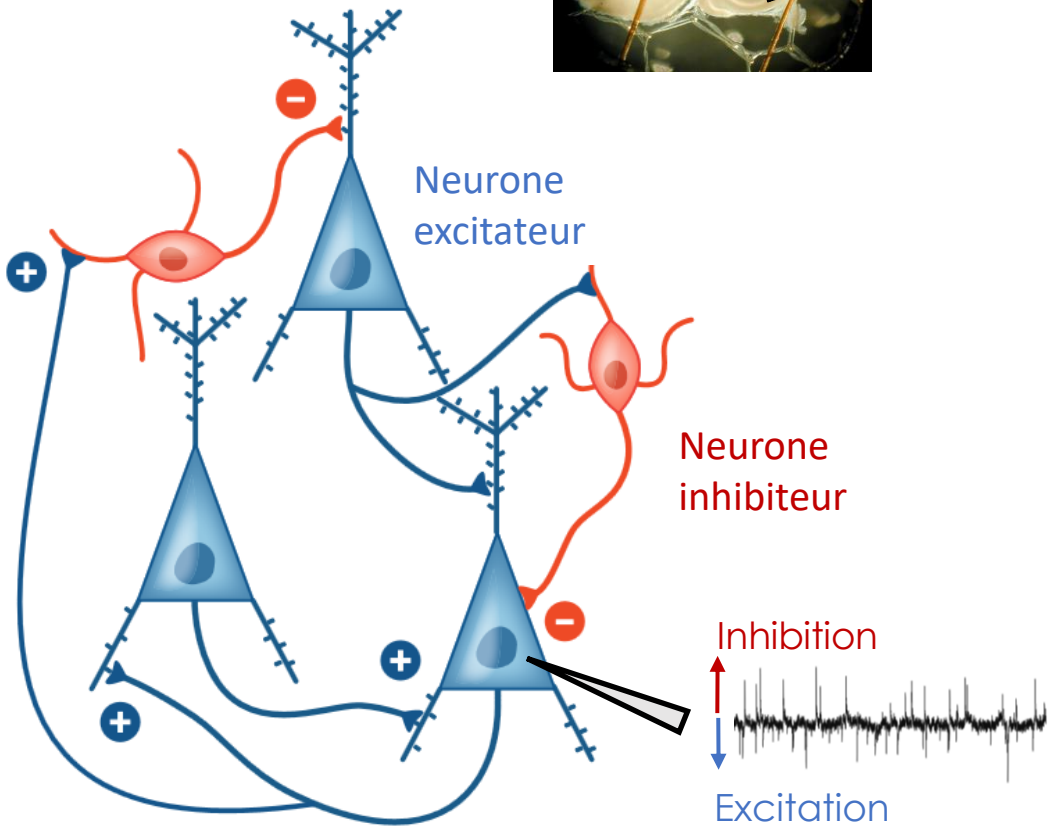
Mecp2$^{-/y}$ placebo

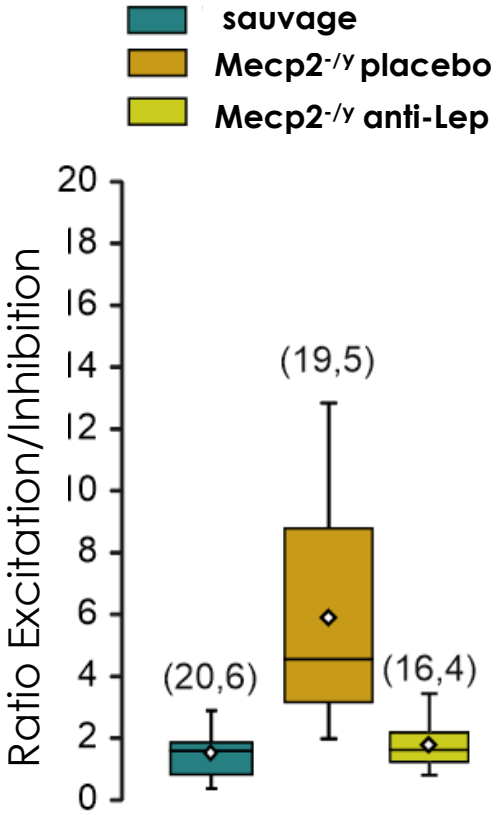


Contribution de la leptine au syndrome de Rett









Conclusion

Le blocage du transport de la leptine vers le cerveau prévient l'aggravation de certains symptômes

chez les souris Rett mâles.

Blocage du transport de la leptine vers le cerveau



Réduction de la production de leptine



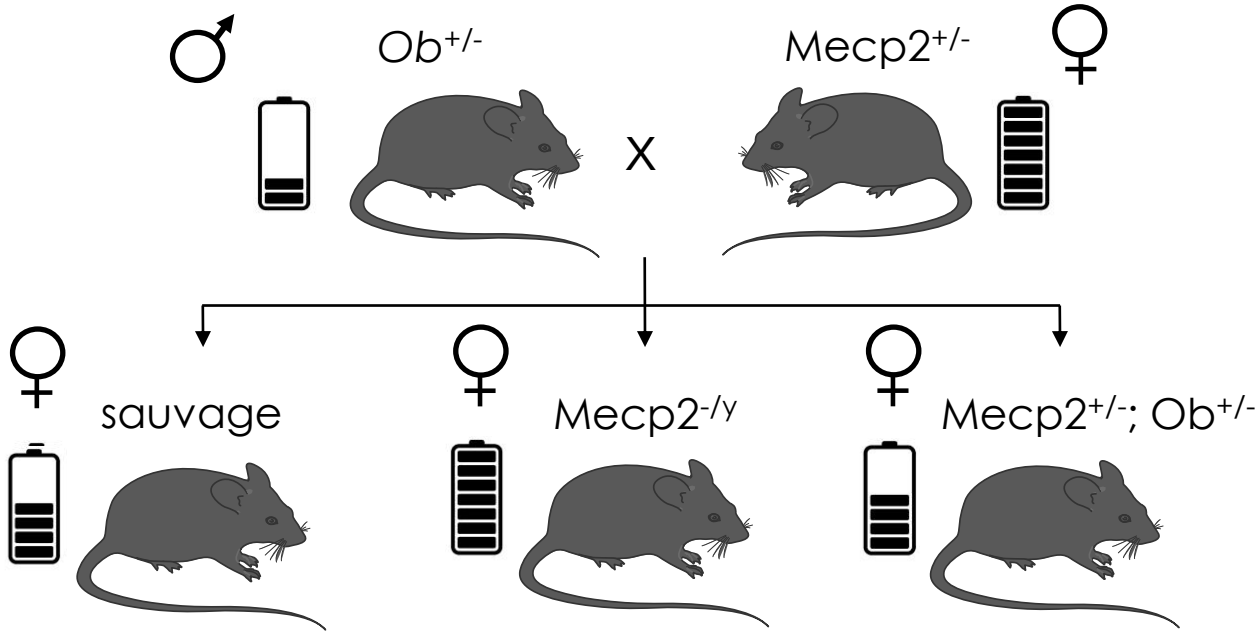
Contribution de la leptine au syndrome de Rett

OBESE, A NEW MUTATION IN THE HOUSE MOUSE*

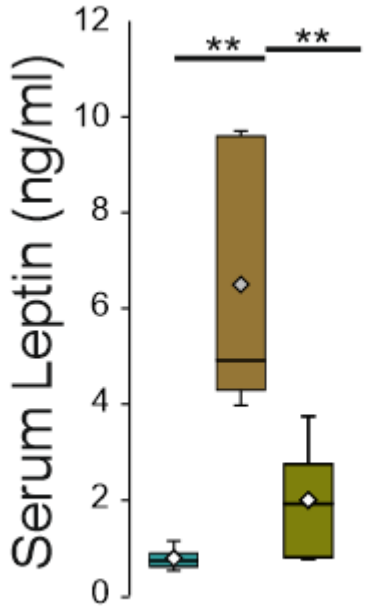
ANN M. INGALLS, MARGARET M. DICKIE AND G. D. SNELL
Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine



$ob^{-/-}$



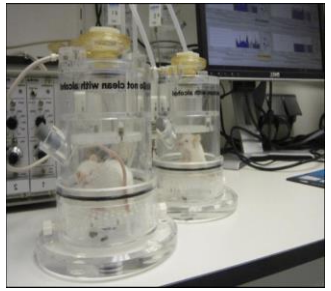


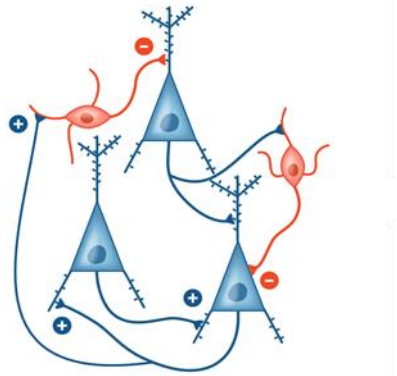


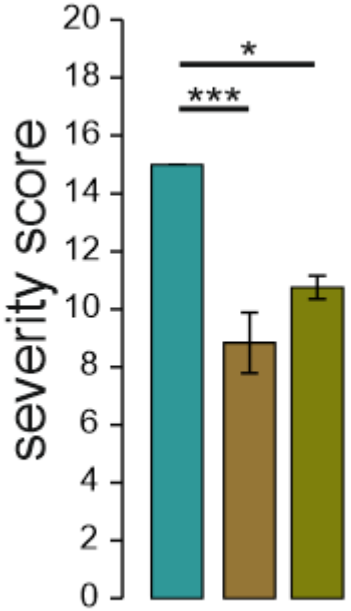
Contribution de la leptine au syndrome de Rett

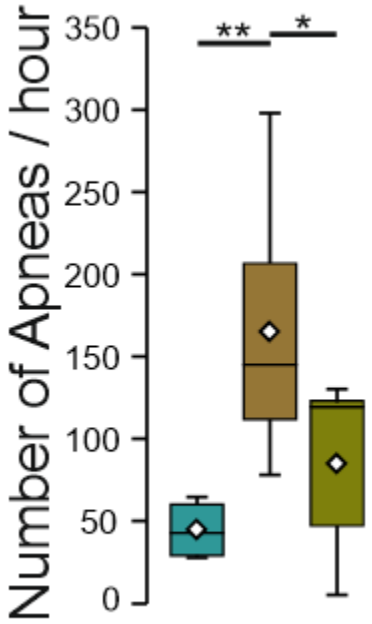
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Mecp2$^{+/-}$; ob$^{+/-}$

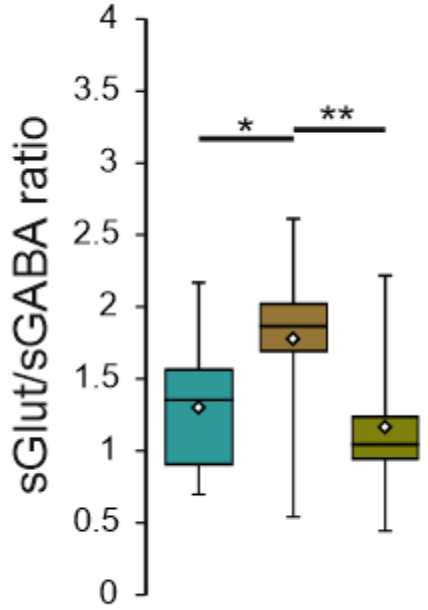












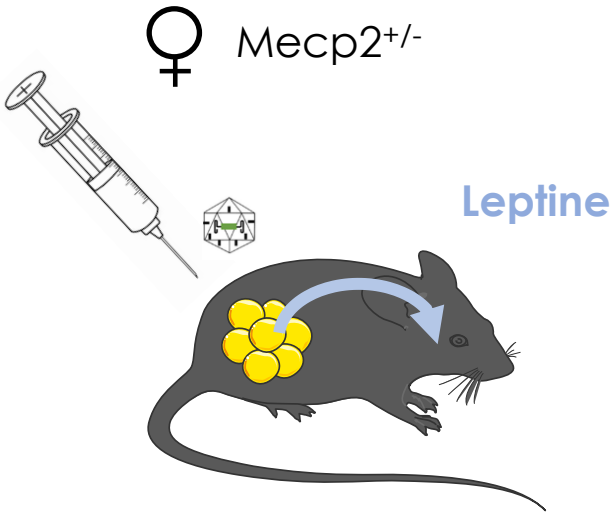
Contribution de la leptine au syndrome de Rett

1. **Perspective thérapeutique** - Développer une stratégie visant à normaliser la production de leptine.

2. **Validation clinique** - Les taux de leptine peuvent servir de biomarqueurs dans le syndrome de Rett ?

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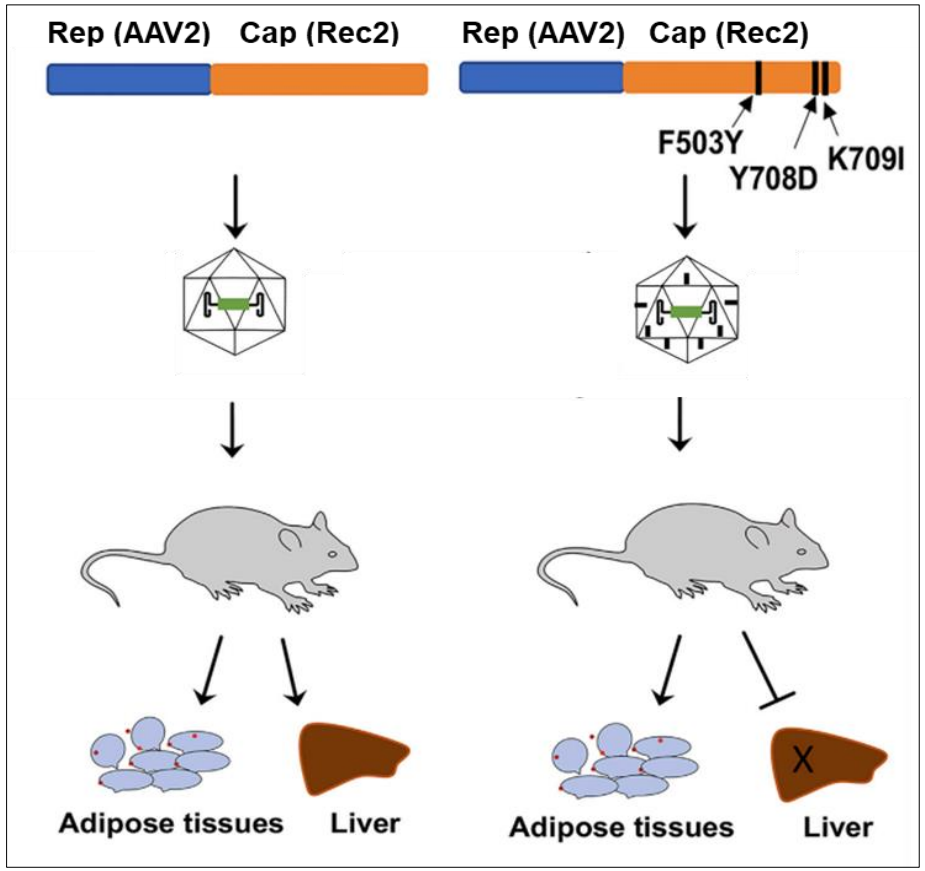
Développer une stratégie de thérapie génique visant à réduire la production de leptine

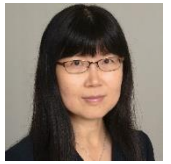


Article

Development of an adipose-tropic AAV capsid ablating liver tropism

Wei Huang,[1,2] Rhiannon Bates,[1,2] Bhavya Appana,[1,2] Tawfiq Mohammed,[1,2] and Lei Cao[1,2,3,*]





Cao Lei
Ohio State University

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THE OHIO STATE UNIVERSITY

La leptine : un biomarqueur diagnostique et pronostique du Rett ?



Pr. M. Milh, la Timone

Taux sanguin de leptine



⇦ ? ⇨



- Sévérité
- Progression
- Mutation

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Inmed Institut de neurobiologie de la méditerranée
Inserm La science pour la santé From science to health
amU Aix Marseille Université

AFSR Association Française du Syndrome de Rett
NIH National Institutes of Health
Fondation Jérôme Lejeune chercher, soigner, défendre
Institut Marseille Maladies rares Aix+Marseille Université
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