FC14.1

Abstract ID: 158

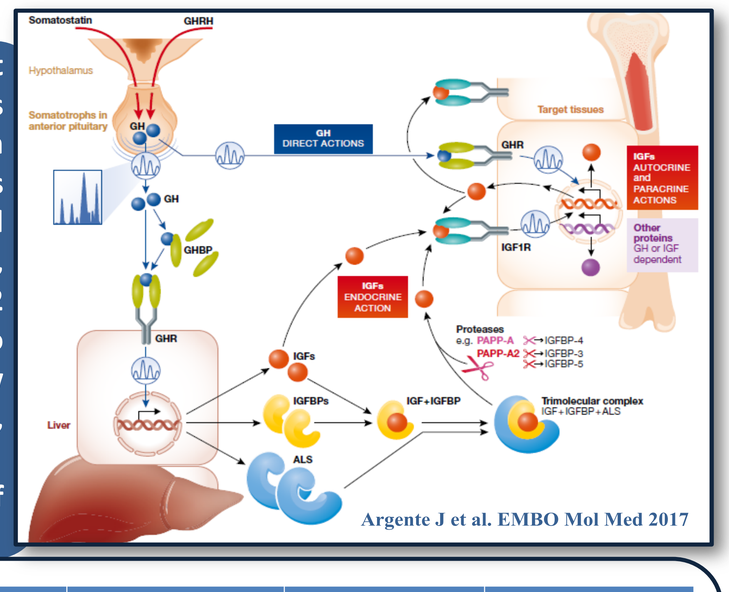
PAPP-A2 DEFICIENCY RESULTS IN SEX-DEPENDENT MODIFICATIONS IN HYPOTHALAMIC REGULATION OF ENERGY HOMEOSTASIS

Patricia Rivera[1] (riveragonzalez183@gmail.com), Antonio Vargas[2] (antonio.vargas@ibima.eu), Javier Bonsón[2] (javibonson@gmail.com), Julian K. Christians[3] (julian_christians@sfu.ca), Fernando Rodríguez de Fonseca[2] (fernando.rodriguez@ibima.eu), Julie A. Chowen[1,4,5] (julieann.chowen@salud.madrid.org), Juan Suárez[2] (juan.suarez@ibima.eu), Jesús Argente[1,4,5] (jesus.argente@uam.es)

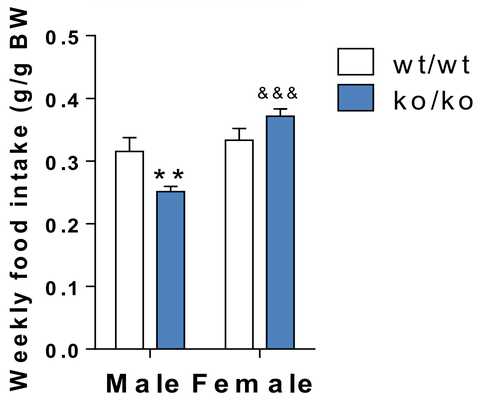
[1]Department of Pediatrics & Pediatric Endocrinology, Hospital Infantil Universitario Niño Jesús, Universidad Autónoma de Madrid, Madrid, Spain. [2]Instituto de Investigación Biomédica de Málaga (IBIMA), UGC Salud Mental, Hospital Universitario Regional de Málaga, Málaga, Spain. [3]Department of Biological Sciences, Simon Fraser University, Burnaby, Canada. [4]Hospital de la Princesa Research Institute, Madrid, Spain. [5]Centro de Investigación Biomédica en Red de Fisiopatologia de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, Madrid, Spain.

Pregnancy associated plasma protein (PAPP)-A2 is an insulin-like growth factor (IGF) binding protein (BP) protease that regulates IGF-1 availability affecting postnatal growth. A new syndrome characterized by short stature, skeletal abnormalities and reduced bone density caused by the absence of PAPP-A2 proteolytic activity resulted from loss-of-function mutations in the human PAPP-A2 gene was discovered by Argente and Dauber in 2016. As a consequence, PAPP-A2-deficient patients exhibit high circulating levels of IGF-1 bound to its ternary complex (IGFBP-3 or IGFBP-5 and IGF-ALS) resulting in decreased concentrations of free IGF-1. Because these patients do not exhibit GH deficiency and PAPP-A2 is unavailable for human use, they were treated with recombinant human IGF-1 (rhIGF-1). Short-term therapy with rhIGF-1 in children with PAPP-A2 deficiency increased growth velocity and height. Although IGF-1 was first discovered due to the observation that it was able to stimulate longitudinal growth, the list of physiological and pathophysiological processes involving this growth factor is now extensive and includes metabolism, development of specific neurosensory systems, neuroprotection, longevity, cancer, obesity, eating disorders, and neurodegenerative diseases .

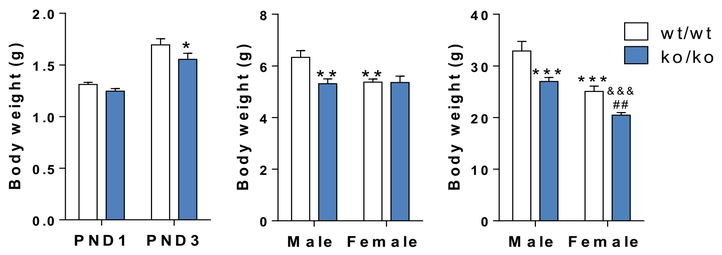
The present study aimed to characterize the effects of constitutive *Pappa2* gene deletion on hypothalamic regulation of energy homeostasis in adult male and female mice.



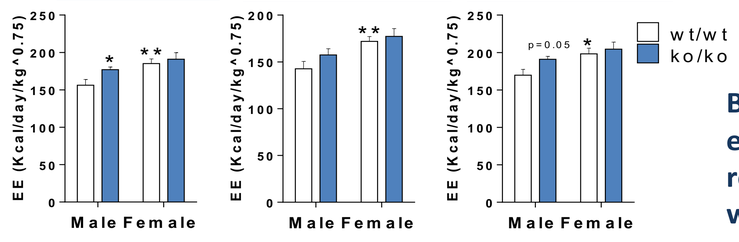
Adulthood



Newborn · Weaning · Adulthood



48 hours · Light phase · Dark phase

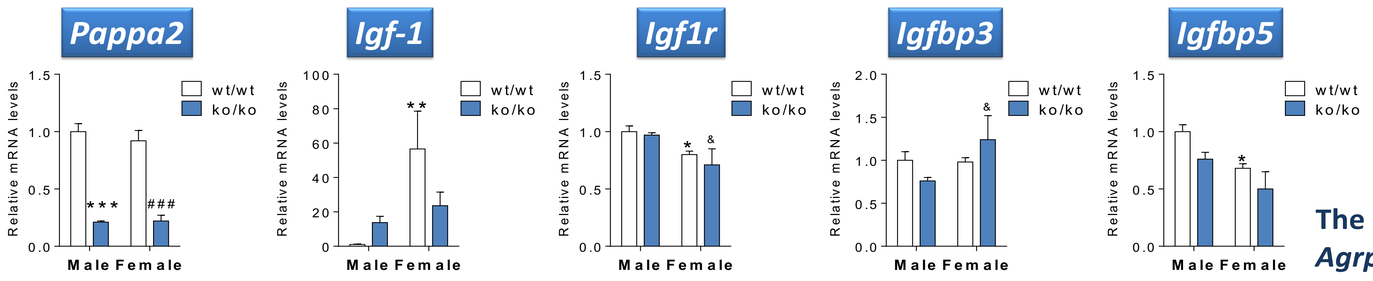


***Pappa2* deficiency affects food intake in a sex-dependent manner.**

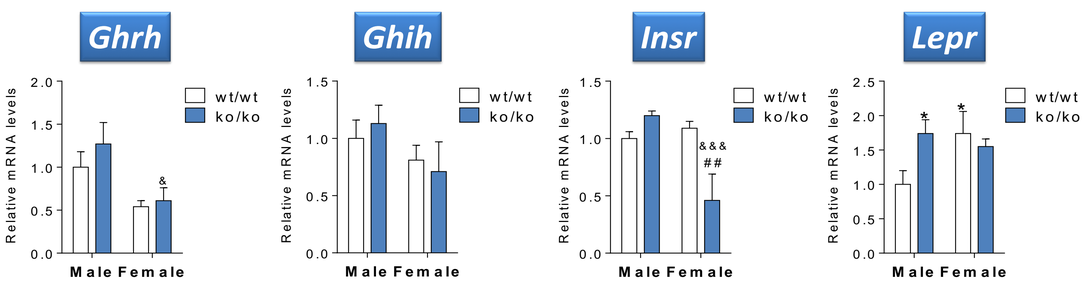
TABLE 1	Interaction	Genotype	Sex
BW (g) at weaning (PND20)	$F_{1, 34} = 6.613$ **P = 0.0147**	$F_{1, 34} = 6.998$ **P = 0.0123**	$F_{1, 34} = 5.496$ **P = 0.0250**
BW (g) at adulthood (8 months of age)	ns	$F_{1, 40} = 20.39$ **P < 0.0001**	$F_{1, 40} = 38.27$ **P < 0.0001**
EE (48 hours)	ns	ns	$F_{1, 28} = 9.891$ **P = 0.0039**
EE (Light phase)	ns	ns	$F_{1, 28} = 12.01$ **P = 0.0017**
EE (Dark phase)	ns	ns	$F_{1, 28} = 8.032$ **P = 0.0084**
Food intake (g/g BW) at adulthood (8 months of age)	$F_{1, 24} = 10.24$ **P = 0.0038**	ns	$F_{1, 24} = 18.55$ **P = 0.0002**

Body weight (BW) in newborn, weaning and adulthood and food intake and energy expenditure (EE) in adulthood of *Pappa2*$^{wt/wt}$ and *Pappa2*$^{ko/ko}$ mice. Data are represented as mean ± S.E.M. Tuckey-corrected tests: *vs wt/wt or wt/wt male, #vs wt/wt female; &vs ko/ko male. Table 1 shows two-way ANOVA statistical values.

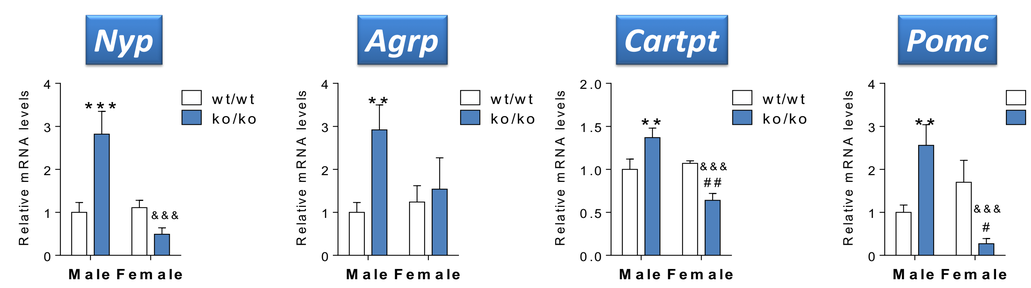
Pappa2 · *Igf-1* · *Igf1r* · *Igfbp3* · *Igfbp5*



Ghrh · *Ghih* · *Insr* · *Lepr*



Nyp · *Agrp* · *Cartpt* · *Pomc*

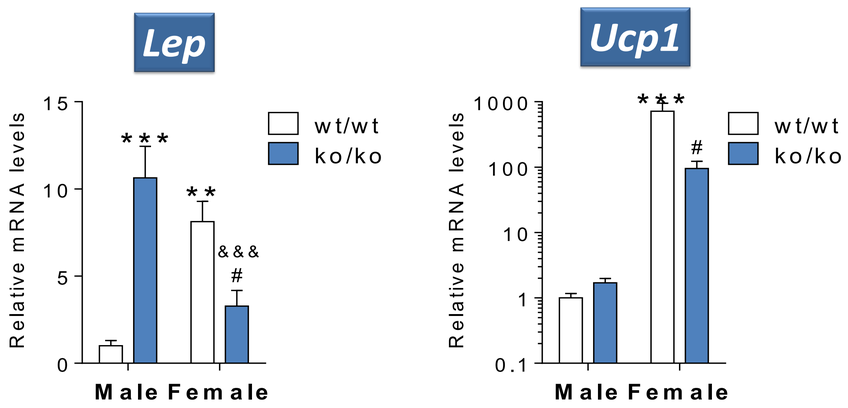


***Pappa2* deficiency affects the hypothalamic gene expression of appetite (*Npy*) and satiety (*Cartpt*, *Pomc*) regulation-related hypothalamic neuropeptides, as well as insulin receptor (*Insr*), in a sex-dependent manner.**

The mRNA levels of *Pappa2, Igf-1, Igf1r, Igfbp3, Igfbp5, Ghrh, Ghih, Insr, Lepr, Nyp, Agrp, Cartpt* and *Pomc* in the hypothalamus of *Pappa2*$^{wt/wt}$ and *Pappa2*$^{ko/ko}$ mice. Data are represented as mean ± S.E.M. Tukey-corrected tests: *vs wt/wt or wt/wt male, #vs wt/wt female; &vs ko/ko male. Table 2 shows two-way ANOVA statistical values.

TABLE 2	Interaction	Genotype	Sex
Pappa2	ns	$F_{1, 22} = 113.9$, **P < 0.0001**	ns
Igf-1	ns	ns	$F_{1, 24} = 7.640$, **P = 0.0108**
Igf1r	ns	ns	$F_{1, 25} = 12.00$, **P = 0.0019**
Igfbp3	ns	ns	ns
Igfbp5	ns	$F_{1, 22} = 5.636$, **P = 0.0277**	$F_{1, 22} = 10.75$, **P = 0.0038**
Ghrh	ns	ns	$F_{1, 26} = 10.31$, **P = 0.0035**
Ghih	ns	ns	ns
Insr	$F_{1, 26} = 9.885$, **P = 0.0041**	ns	$F_{1, 26} = 6.062$, **P = 0.0208**
Lepr	ns	ns	ns
Npy	$F_{1, 26} = 13.62$, **P = 0.0010**	ns	$F_{1, 26} = 11.27$, **P = 0.0024**
Agrp	ns	$F_{1, 25} = 5.021$, **P = 0.0342**	ns
Cartpt	$F_{1, 25} = 16.74$, **P = 0.0004**	ns	$F_{1, 25} = 11.39$, **P = 0.0024**
Pomc	$F_{1, 24} = 16.41$, **P = 0.0005**	ns	$F_{1, 24} = 4.639$, **P = 0.0415**

Lep · *Ucp1*



mRNA levels of *Lepr and Ucp1 in epididymal white adipose tissue* (eWAT) of *Pappa2*$^{wt/wt}$ and *Pappa2*$^{ko/ko}$ mice. Data are represented as mean ± S.E.M. Tukey-corrected tests: *vs wt/wt or wt/wt male, #vs wt/wt female; &vs ko/ko male

1. **Among the effects of Pappa2 deficiency on energy metabolism, we highlight that male mice with Pappa2 deletion eat less, weigh less and exhibit higher energy expenditure than WT males in adulthood. This effect was not found in adult females.**
2. **The higher mRNA levels of leptin receptor (Lepr), Cartpt and Pomc (satiety), as well as Npy and Agrp (appetite), in the hypothalamus of male mice with Pappa2 deletion differs from those of the same-genotype females compared with the respective same-sex controls.**
3. **The higher mRNA levels of leptin (satiety) in eWAT of Pappa2 KO males contrast with the lower mRNA levels of leptin and the thermogenic factor Ucp1 (Uncoupling protein 1) in the eWAT of Pappa2 deletion females compared with the respective same-sex controls.**

In conclusion, central and peripheral mechanisms regulating energy homeostasis are affected in *Pappa2*$^{ko/ko}$ mice in a sex-specific manner. However, how a reduction in IGF availability due to *PAPP-A2* deficiency modulates the development and functioning of hypothalamic metabolic circuits remains to be determined.

58ESPE RFC14-001

GH and IGFs

Jesús Argente

Poster presented at: ESPE 2019 VIENNA

PosterSessionOnline.com