The methylation level of the *Eap1* promoter is different during pubertal development in normal weight and obese female rats

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Background

Today it is clear that the transcription factor Enhanced at puberty (Eap) 1 is an important regulator of gonadotropin-releasing hormone (GnRH) neuronal function, which are the key-neurons for the pubertal process. Timely initiation of puberty is not only the result of neuronal and astroglial interaction within the GnRH neuronal network but also of the integration of various exogenous and endogenous signals reaching the hypothalamus. These signals might exert their influence by utilizing epigenetic modifications. This study investigates if weight influences epigenetic marks on the *Eap1* promoter resulting in an altered transcriptional function.

Study Design

Female rats [Crl:CD(SD)] grew up in litters of 12 or 3 pups. *Eap1* mRNA expression and the promoter methylation level were detected at different developmental phases (juvenil PND7-27, prepubertal (PND30/32) and pubertal (VO) by qPCR and bisulfite sequencing.

Results

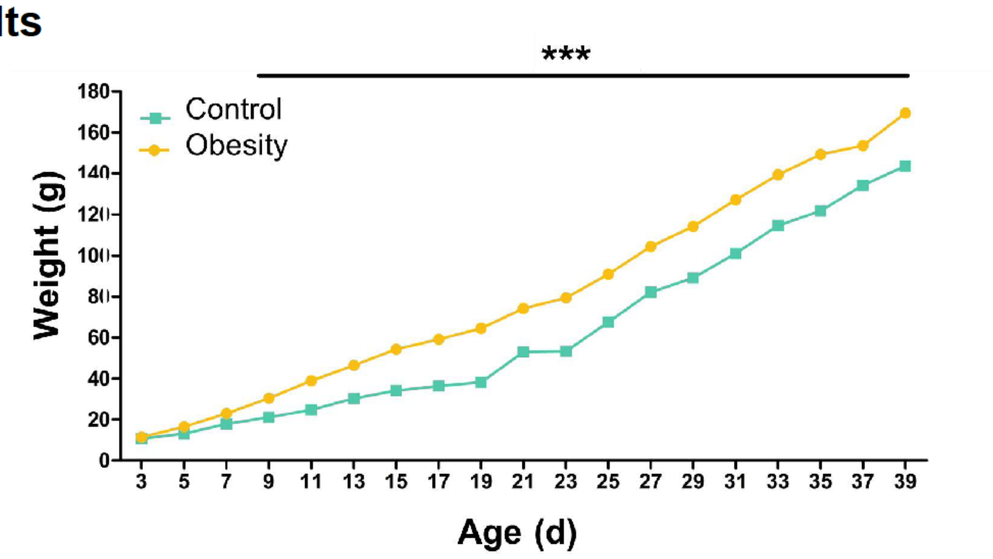

Fig. 1: Development of body weight in control and obese female rats
Body weight differs significantly between control (n=52) and obese rats (n=42) ****p<0.001 vs control*

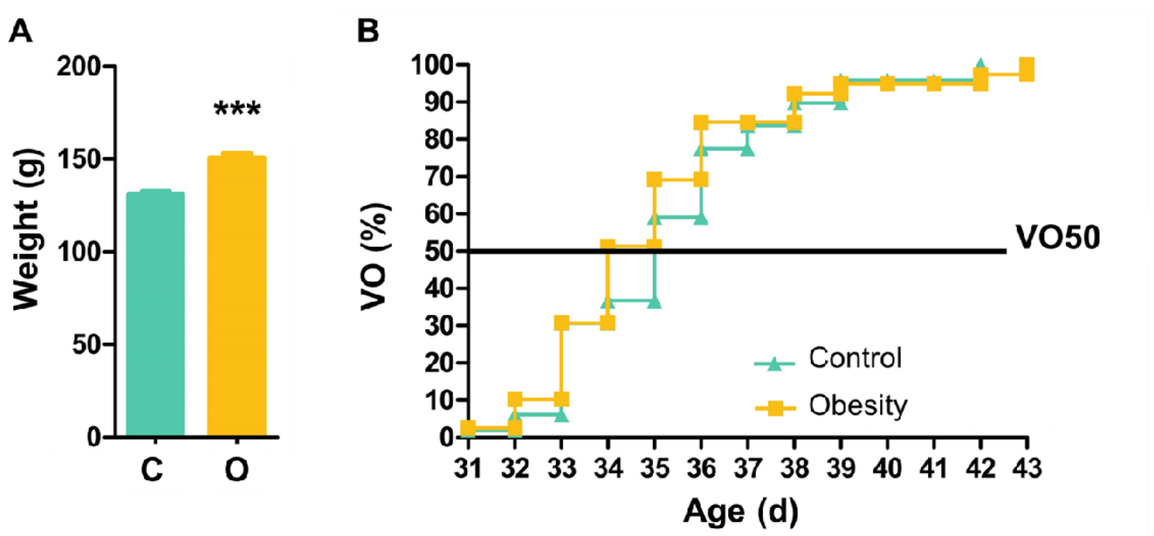

Fig. 2: Age of vaginal opening in control and obese female rats
A Obese rats (O, n=39) are heavier than control rats (C, n=48) at VO; ****p<0.001*
B Obese rats show an earlier VO compared to control rats.

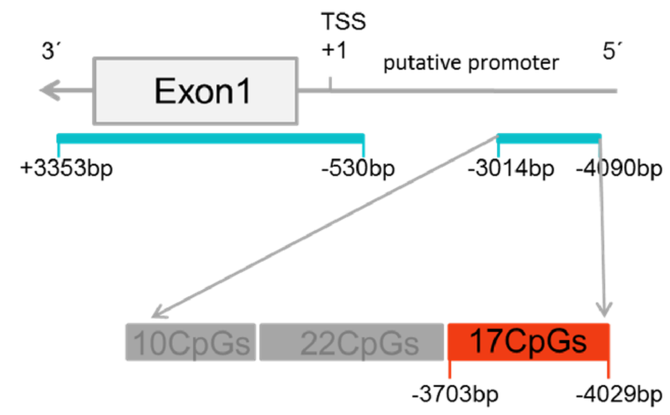

Fig. 3: CpG islands of *Eap1* gene/promoter
In silico analysis of *Eap1* (NC_005105.3) shows two CpG islands (blue). The following methylation results refer to CpG island 1, which encompasses 17 CpG motifs (red box).

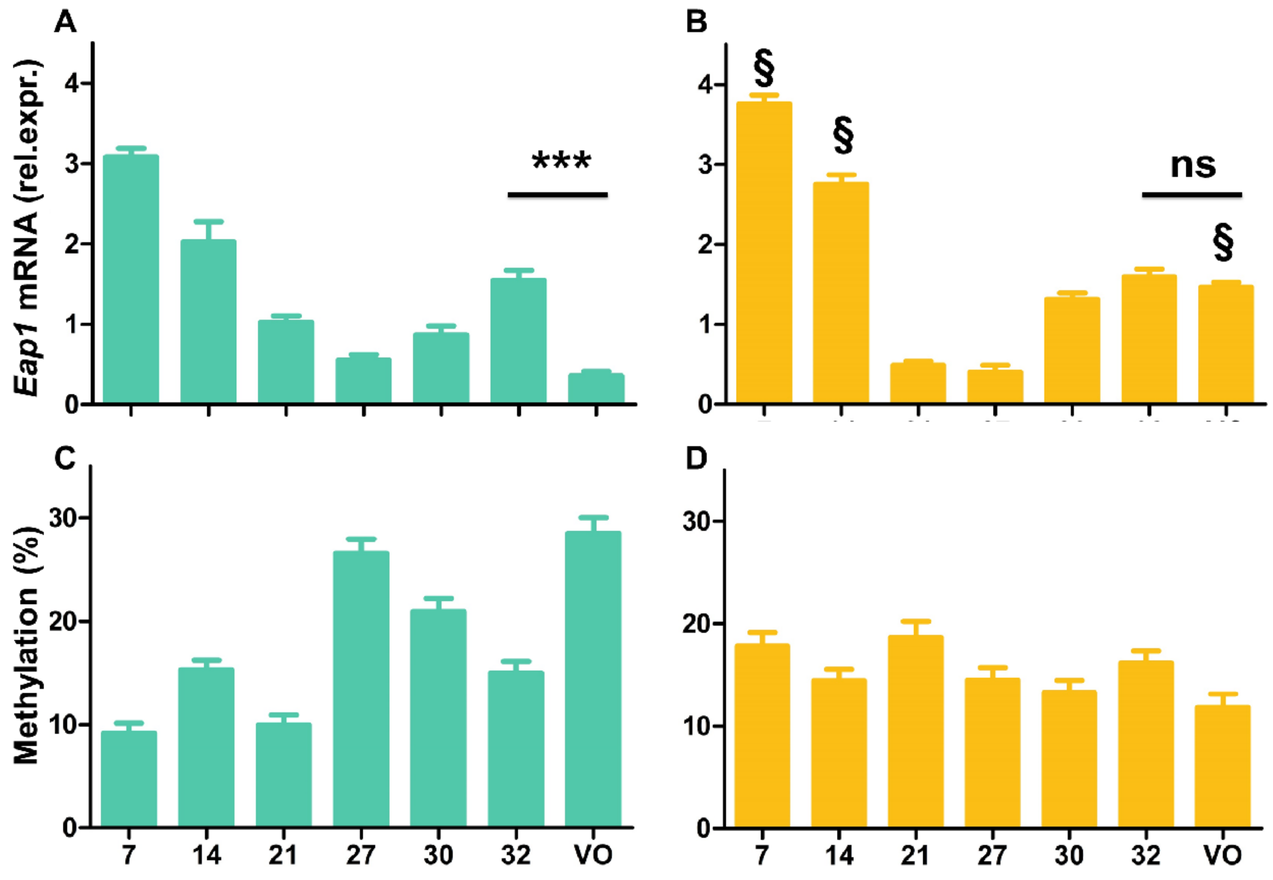

Fig. 4: Hypothalamic expression of *Eap1* mRNA and methylation of CpG island 1
A/B The expression of *Eap1* mRNA is higher in obese (**B**) vs control (**A**) animals (§ p<0.05 control vs obese; ***p >0.001 in control rats)
C In normal weight conditions, total methylation level is lower in the prepubertal phase and increases dynamically in the pubertal phase.
D Obesity results in constant blunted methylation profile in the first CpG island of the *Eap1* promoter.

Summary

1. Obese rats show an advanced pubertal onset and are significantly heavier at the day of vaginal opening.
2. The hypothalamic expression level of *Eap1* mRNA is increased in obese rats.
3. In normal weight conditions the expression of *Eap1* mRNA and the methylation level of the *Eap1* promoter seems to be negatively correlated.
4. Contrary, in obese animals the differential methylation profile is abrogated.

Conclusion

Endogenous factors (weight) seem to be able to modify the methylation level of the puberty regulating transcription factor *Eap1.*

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