Role of the metabotropic mGlu5 glutamate receptor in the initiation of puberty and reproduction in female mice

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OBJECTIVES

The neuroendocrine mechanisms of the initiation of puberty are still incompletely deciphered. Accumulating data indicate a main role of the glutamate system in regulating hypothalamic GnRH (*Dumalska I, et al. 2008; Iremonger KJ, et al. 2010)*. Mice lacking metabotropic mGlu5 receptors (mGluR5) show sever unexplained infertility (*Lu YM, et al. 1997)*. We aimed in the present study to analyze the specific role of mGluR5 in the initiation of puberty and reproduction in mice.

CONCLUSIONS

- Our results suggest an important role of mGluR5 in the modulation of puberty onset and fertility.
- In addition to the well described Kisspeptin and MKRN3 others factors as for example specific glutamate activation of mGluR5 may trigger the biological clock of puberty onset (Fig.3).
- Future research on the role of mGlu5 receptor in the GnRH-mediated gonadotropin secretion will address this issue.

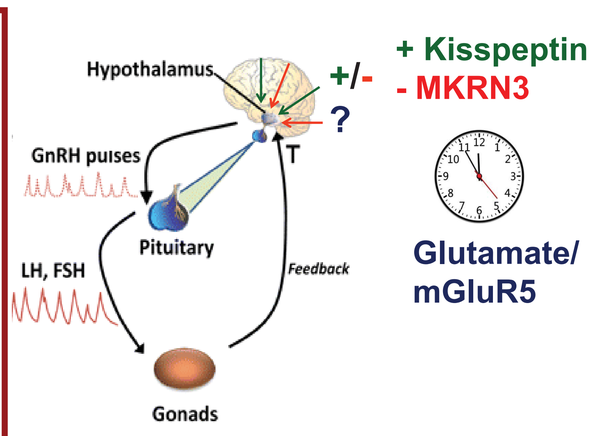

Fig. 3. Possible mechanism of Glutamate signals on mGluR5 *(adapted after Jameson, J.L. Rites of passage through puberty: A complex genetic ensemble. PNAS. 2007)*

METHODS

Sexual maturation of mGluR5 knockout (KO) and wildtype littermates was investigated by recording in vivo vaginal opening (VO); estrous cycles (using vaginal smears) and uterine weight after sacrifice. Further we investigated the reproductive performance by quantifying the latency to the first litter and total number of pups born per female. Serum gonadotropins were measured by magnetic bead immunoassay in mGluR5 KO and wildtype females. All experiments were approved by the German Committee on Animal Care. Statistical analysis was performed by survival curve analysis and Log-rank (Mantel-Cox) test for Fig. 1(A-D), Student's *t* test or a two-way ANOVA test followed by Bonferroni post hoc tests, respectively. Analysis were made using the Prism GraphPad Software and reported as mean +/- SEM, $p<0.05$ was considered significant.

RESULTS

Figure 1.

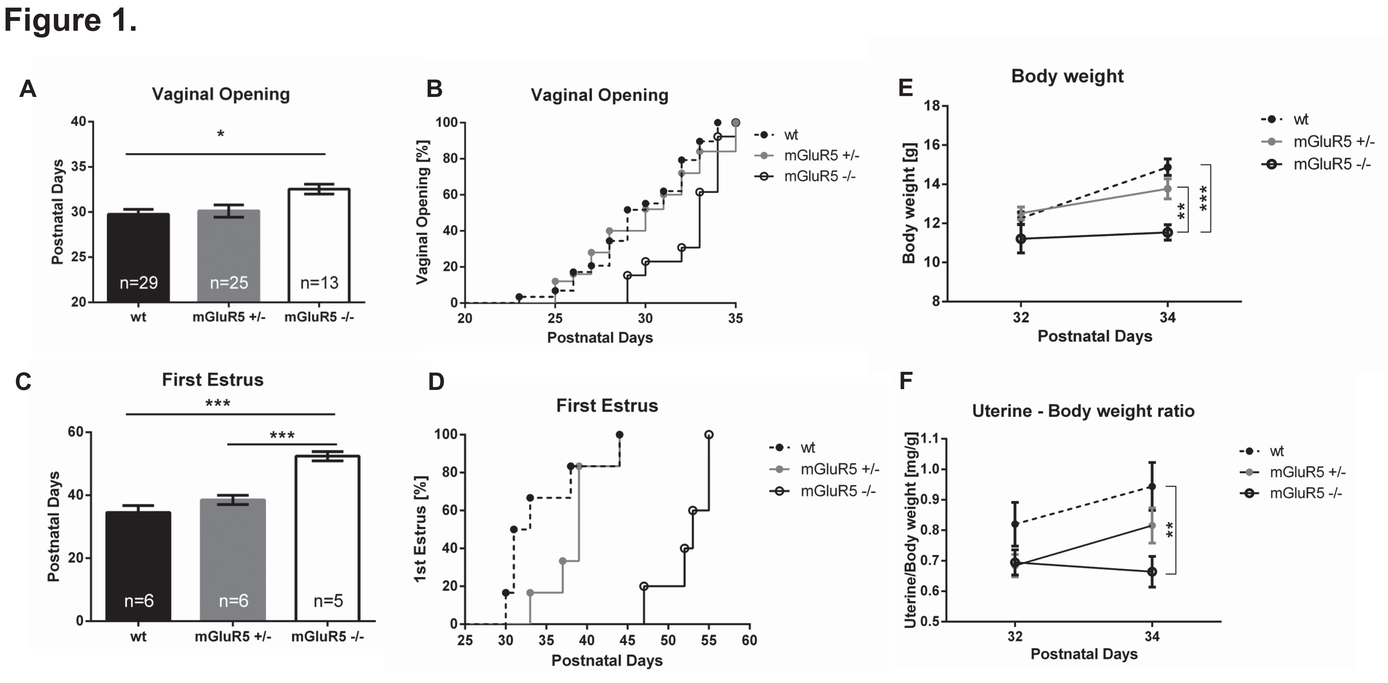

Figure 1. Delayed sexual maturation in mGluR5 -/- female mice. Significant delay in the time till VO was noticed in mGluR5 -/- female mice (32.54 +/- 0.57 days, white columns, respectively open circles), compared to wildtype littermates (29.76 +/- 0.55 days, black columns, respectively filled circles) (**A** and **B**). Delayed first estrous cycle in mGluR5 -/- females (52.4 +/- 1.47 days) compared with wildtype animal (34.5 +/- 2.23 days) (**C and D**). Body weight (g) gain (**E**) in P32 and P34 wildtype, mGluR5 +/- and mGluR5 -/- mice. Ratio of uterine weight to body weight (mg/g) at P32 and P34 mice of the respective genotype (**F**). * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Figure 2.

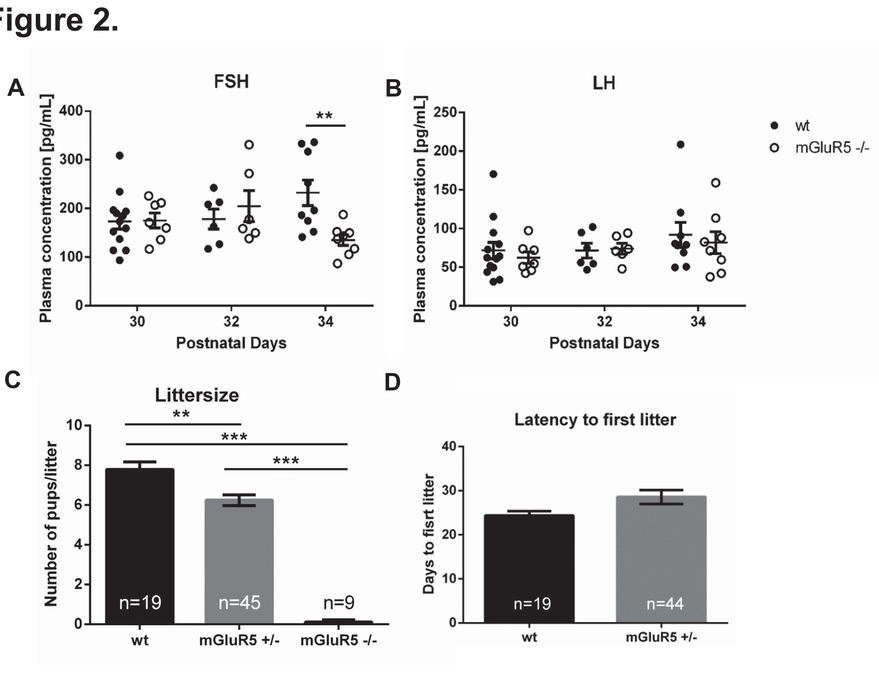

Figure 2. Changes in gonadotropin levels in mGluR5 -/- mice. Serum levels of FSH (**A**), and LH (**B**), of wildtype and mGluR5 -/- female during puberty (P30-P34). **Reduced fertility** quantified as the average number of pups/female in mGluR5 -/- (0.11 +/- 0.11), mGluR5 +/- and wildtype animals (7.79 +/- 0.38) (**C**) and latency to the first litters in mGluR5 +/- (28.57 +/- 1.52 days) and wildtype female mice (24.39 +/- 0.98) (**D**). ***$p < 0.001$ **$p<0.01$.

RESULTS

1. mGluR5 KO mice showed markedly delayed puberty, as determined by time of VO (Fig. 1A and 1B), first estrus (Fig. 1C and 1D) and uterus weight (Fig. 1F).
2. Significant decrease in serum levels of follicle-stimulating hormone (Fig. 2A), reduced reproductive performance (Fig. 2C), and delayed latency to the first litter (Fig. 2D) were recorded in mGluR5 KO females. LH levels were similar between the groups (Fig. 2B).

The authors declare no conflict of interests.

References

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