Specific hypothalamic activation pattern by mGlu5 receptor blockade in vivo during pubertal development in female mice

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Background
Puberty is characterized by important changes in brain networks. The glutamate system plays a main role in modulating the onset of puberty as shown for NMDA receptor agonists and antagonists (Bettendorf, et al. 1999; Mejs-Rejeks, et al. 1991). However, the underlying mechanisms are poorly understood. Metabotropic mGlu5 receptors (mGlu5) are tightly linked to NMDA receptors (Perroy, et al. 2008). One subpopulation of GnRH-positive neurons is specifically activated by agonists of class I metabotropic receptors and are kispeptin-insensitive (Fig.1, Dumaisula, et al. 2008). The effect of mGlu5R5 blockade on neuroendormonal mechanisms controlling puberty initiation were not studied yet.

Figure 1

Objectives
To determine the effect of pharmacological blockade of mGlu5R on neuronal activation during puberty and changes associated with the initiation of puberty.

Methods
We used profiling of the expression of the immediate early gene c-fos, as marker of neuronal activity triggered by the selective mGlu5R antagonist 2-Methyl-6-(phenylthio)pyridine (mPDEP). Female mice at postnatal day (P) 16 to 40 (n=6) were treated intra peritoneal (i.p.) with 30 mg/kg MPEP. Coronal brain sections (50 μm) were obtained and DAB immunohistochemical analysis of c-Fos expression was performed using a rabbit anti-c-fos primary antibody (1:10,000, Calbiochem). Serum levels of LH and FSH were measured in P26 and P30 female mice (n=5) after 7 days of MPEP (Fig. 2) or normal saline treatment by non-magnetic bead immunoassay. Additionally body growth, weight and uterus weight were measured.

Conclusions
1. Our data provide new insights into the role of mGlu5R in pubertal development of female mice. Chronic MPEP treatment reduced LH and FSH levels at P26, suggesting a role of mGlu5R in the glutamatergic control of the hypothalamic-pituitary-gonadal (HPG) axis.
2. MPEP administration activated c-fos robustly in the PV/NH, a key regulator of the hypothalamic-pituitary-adrenal (HPA) axis. Future studies may further clarify the underlying neurobiological mechanisms and their functional consequences.

The authors declare no conflict of interests.

References

Results
1. MPEP activates paraventricular nucleus of the hypothalamus (PV/NH) We found a remarkably specific activation of the paraventricular nucleus of the hypothalamus (PV/NH) by MPEP, starting at P16 and continuing throughout puberty (P16 - P40), (Fig.3a-3e).

Figure 3

2. MPEP reduced LH and FSH levels at P26, but not at P30 MPEP reduced LH and FSH levels (pg/ml) as compared to normal saline (LH 38.43 +/- 7.65 to 28.68 +/- 4.18, for FSH 119.08 +/- 45.66 to 86.38 +/- 17.45, n.s.) at P26 (Fig. 4a). Absolute LH and FSH levels increased to P30 (LH 81.77 +/- 14.75, respective 91.46 +/- 7.89 saline/MPEP; FSH 163.46 +/- 52.95, respective 159.69 +/- 22.06 saline/MPEP n.s.) (Fig. 4b).

Figure 4

3. MPEP treatment does not affect growth, body weight or uterine development at P26 (Fig 5a) and P30 (Fig 5b)

Figure 5

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