Role of the metabotropic mGlu5 receptor in puberty: neuroendocrinological and psychiatric implications

I. Inta¹, R. De Angelis², E. Domonkos¹, U. Boehm², P. Gass¹, M. Bettendorf³

¹Central Institute of Mental Health, Psychiatry and Psychotherapy, Mannheim, Germany

²University of Saarland School of Medicine, Pharmacology and Toxicology, Homburg, Germany

³University Children's Hospital Heidelberg, Paediatric Endocrinology and Diabetes, Heidelberg, Germany

Objectives: We aimed in the present study to analyze the specific role of **mGlu5 receptor (mGluR5) dysfunction** in the initiation of puberty and behavioral changes associated with psychiatric disorders.

Background: The glutamate system plays a crucial role in the initiation of puberty and the onset of main neuropsychiatric disorders during this critical developmental period. Metabotropic mGluR5 were implicated in several psychiatric diseases, including schizophrenia and mood disorders. **mGluR5 antagonists like 2-Methyl-6-(phenylethynyl)pyridine (MPEP)** are among the most efficient **anxiolytic** agents in animal models; nevertheless, it is unknown, if age-specific differences exist. Interestingly, mice lacking metabotropic mGluR5 show severe, yet **unexplained infertility**. However, the underlying mechanisms are yet poorly investigated.

Materials and Methods: Behavioral alterations were analyzed using standard tests (Open Field Test, Dark-Light Box) upon treatment with MPEP at pre-, post-pubertal and adult stages. Animals performed the tests as follows: mice in pre-pubertal age on postnatal days (PND) 24-26, mice in post-pubertal age on PND 42-44 and adult mice on PND 84-86. Sexual maturation of mGluR5 knockout (KO) and wildtype littermates was investigated by recording the vaginal opening, estrous cycles and uterine weight. Further, we investigated the reproductive performance and serum gonadotropin hormone in female mice.

Results and Conclusions: We found specific differences between pre- and post-pubertal stages in the locomotor activity and the anxiolytic effect of MPEP. MPEP did not induce anxiolytic actions before puberty. mGluR5 KO mice showed markedly delayed puberty, as determined by time of VO, first estrus, uterus weight, decrease in serum levels of follicle-stimulating hormone (FSH), and reduced reproductive performance. These results are novel and suggest an important role of mGluR5 in peri-pubertal anxiety mechanisms, puberty onset and fertility. They may have implications regarding novel therapies during this developmental period.

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. 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.

Figure 3. Differential age-dependent anxiolytic effect of the mGluR5 antagonist MPEP pre- vs. post-puberty as assessed in the Dark-light box paradigm in mice treated at pre-, postpubertal and adult stages with saline vs. MPEP. Latency to first exit of the dark compartment (a) and latency to reach the opposing wall of the lit compartment (b) were reduced in adult mice treated with MPEP vs. controls. The number of exits in mice treated with MPEP was significantly higher in adult vs. pre-pubertal mice and vs. adult controls (c), indicating an anxiolytic effect of MPEP only at adult stages. The time spent in the lit compartment (d) was similar in all experimental groups. ***p < 0.001 **p<0.01.