Prenatal immune activation induces maturation-dependent alterations in the prefrontal GABAergic transcriptome, cognitive impairments and dopaminergic hyperfunction: modulation by the benzodiazepine-positive allosteric modulator SH-053-2′F-S-CH3

J. Richetto1, U. Meyer2, M. A. Riva1,3

1Dept. of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy.
2Laboratory of Physiology and Behavior, Swiss Federal Institute of Technology (ETH) Zurich, Switzerland.
3Center of Excellence on Neurodegenerative Diseases, University of Milan, Milan, Italy

Cortical GABAergic abnormalities have been widely documented in neuropsychiatric disorders with prenatal infectious etiologies, including schizophrenia and autism. However, the extent to which prenatal exposure to immune challenge can induce long-term alterations in GABAergic gene transcription remains largely elusive. Thus, we used a well established mouse model of prenatal immune activation induced by maternal gestational administration of the viral mimetic poly(I:C) (= polyriboinosinic-polyriboctydilic acid) to demonstrate that prenatal immune activation causes maturation-dependent alterations in GABAergic gene expression within prefrontal cortex and hippocampus. Moreover, we investigated whether the GABAergic abnormalities observed were associated with cognitive impairments and dopaminergic hyperfunction, which are among the cardinal symptoms of schizophrenia.

The spectrum of GABAergic abnormalities induced by prenatal immune activation included altered mRNA expression levels of various pre- and post-synaptic GABAergic markers, which were associated with impairments in spatial matching-to-position working memory, spatial novelty preference and increased sensitivity to systemic amphetamine. On these bases, we investigated whether pharmacological treatment with the novel benzodiazepine-positive allosteric modulator SH-053-2′F-S-CH3 (the (S) stereoisomer of 8-ethynyl-6-(2-fluorophenyl)-4-methyl-4H-2,5,10b-triaza-benzo[e]azulene-3-carboxylic acid ethyl ester) could rescue the cognitive and behavioral abnormalities observed in these animals. This drug is selective for the α2, α3 and α5 subunits of the GABA (A) receptor, whose expression is altered in animals prenatally exposed to poly(I:C). In particular, we tested SH-053-2′F-S-CH3 for its effects on spatial novelty preference and hyperactive locomotor response to amphetamine in control and poly(I:C) exposed animals. While confirming that prenatal immune challenge induces cognitive and behavioral abnormalities in the form of spatial novelty preference and locomotor response to amphetamine, our study demonstrated that SH-053-2′F-S-CH3 does not rescue the cognitive impairments of poly(I:C) treated animals. In particular, the drug worsened the cognitive performance of both control and prenatally immune challenged animals. On the other hand, treatment with SH-053-2′F-S-CH3 was capable of reducing the increased locomotor response to amphetamine observed in prenatally immune challenged mice. These results suggest that benzodiazepine-positive allosteric modulators may be useful for treating schizophrenia-related dopaminergic hyperfunction, whereas their impact on cognitive dysfunction remains to be established.