The impact of clozapine on the dopamine D₂ receptor binding in ketamine induced attentional set shift task model

Marta Dubiel*, Agata Faron-Górecka, Paulina Pabian, Maciej Kusmider, Magdalena Kolasa, Joanna Solich, Dariusz ŻuraweK and Marta Dziedzicka-Wasylewska

Department of Pharmacology, Institute of Pharmacology, Polish Academy of Sciences, Krakow, Poland

Deficits in cognitive abilities are widely recognized as a core feature of schizophrenia. One of the cognitive deficits model in rodent is the attentional set-shifting task (ASST). In this test, the mouse has to learn to pay attention and respond to the relevant cue (i.e. digging medium) and ignore an irrelevant cue (i.e. odor), and pairing a food reward with the medium. In the crucial phase (extra dimension shift, EDS) leading dimension (i.e. digging medium) is changed and then the odor becomes a new leading dimension. Ketamine (KET) evokes cognitive impairments, observed in the ASST as selective deficits of mice EDS performance. Therefore, modulation of the behavioral effects induced by KET in ASST provides good animal model to study the mechanism of action of antipsychotic agents.

First aim of our study was to investigate if clozapine (CLO), an atypical antipsychotic, could reverse ketamine-induced impairments and improve cognitive function. KET in a dose of 20 mg/kg was administered repeatedly i.p. for 7 consecutive days, then exchanged for CLO in two doses (0.3 and 1 mg/kg, i.p.) for the next 7 days. ASST was performed following 14 days of drug administration. Since the dopamine D₂ receptor (D₂R) is one of main targets of antipsychotic pharmacotherapy for the treatment of schizophrenia, the second goal was to examine the effect of KET and CLO to the D₂R binding. In this part of study we used the same paradigm of drug treatment as in the behavioral study. For the autoradiography study on the mouse brain section the [³H]domperidone was used as radioligand.

The biochemical results indicate that KET administered repeatedly affects the level of D₂ receptors in the lateral striatum. Decrease of D₂R after administration of CLO at 0.3 mg was observed in the cortex and lateral striatum. On the other hand, CLO at 1 mg induced the increase of D₂R in lateral striatum. Repeated administration of KET and CLO (0.3 or 1 mg) induced increase of D₂R in lateral striatum. In other brain regions an increase of D₂R was observed following KET and CLO (1 mg) administration. The biochemical results seem to confirm the results observed in the ASST test, where CLO (1 mg) after ketamine administration potentiated cognitive impairments observed in the EDS phase. It seems that the observed effects may be related to the phenomenon of dopamine supersensitivity, which can lead to cognitive difficulties.

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*Submitting author e-mail: dubmar@if-pan.krakow.pl