MODULATION OF PRE-SYNAPTIC AND POST-SYNAPTIC PROTEINS AFTER PROLONGED TREATMENT WITH ANTIPSYCHOTIC DRUGS

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Antipsychotics represent the mainstay of schizophrenia pharmacotherapy. It is well known that first (FGA) and second (SGA) generation antipsychotics have distinct effects on disease symptoms, which may reflect the different modulation of proteins important for signaling and cell-cell communication. To this end, we have recently demonstrated that SGA, but not FGA, drugs increase the phosphorylation of ERK1/2 in prefrontal cortex. As follow-up of this work, we decided to investigate other players of pre-synaptic (synapsin 1A, syntaxin 1A and synaptotagmin 1) and post-synaptic (NMDA receptors, the scaffolding protein PSD95 and α-CaMKII) cellular compartments. Analyses were performed in cytosolic (S2), membrane-enriched (P2) and triton X100-insoluble fractions (TIF) of prefrontal cortex of rats injected for 2 weeks with saline, olanzapine (2mg/Kg, twice daily) or haloperidol (1mg/Kg, once daily). Animals were sacrificed 24 hours after the last injection. Olanzapine as well as haloperidol increased synapsin 1A (haloperidol: +49%; olanzapine: +49%), syntaxin 1A (haloperidol: +77%; olanzapine: +63%) and synaptotagmin 1 (haloperidol: +30%; olanzapine: +25%) in the cytosol of prefrontal cortex suggesting that both drugs display enhancing effects on presynaptic proteins. In the TIF fraction, enriched in post-synaptic densities and NMDA receptors, treatment with haloperidol, but not olanzapine, reduced the levels of NMDA subunits NR1 (-19%) and NR2A (-25%) without changing NR2B levels, yielding to a decreased NR2A/NR2B ratio, upon which NMDA receptor function depends. In addition, PSD95 and α-CaMKII levels were significantly reduced in the TIF fraction after haloperidol (-23% and -25%, respectively), but not olanzapine treatment. In line with these results, we were able to show, through immunoprecipitation experiments, that the interaction between phospho-α-CaMKII and NR2A/2B was reduced in prefrontal cortex by haloperidol (-33%), further pointing to an altered function of NMDA receptors in this brain region. Collectively, our date define a two step action of antipsychotic drugs, which involve a potentiation of presynaptic functions, common to FGA and SGA, as well as a different impact on post-synaptic glutamatergic neurotransmission. Based on these findings, we suggest that chronic administration of FGAs may uncouple presynaptic and postsynaptic compartments leading to an exacerbation of the glutamatergic deficits reported in schizophrenia. Conversely, the putative increase of presynaptic activity elicited by olanzapine might, at least in part, improve functions that are defective at the level of prefrontal cortex.