Pharmacological evaluation of selected atypical antipsychotics in an experimental model of Post-Traumatic Stress Disorder (PTSD)

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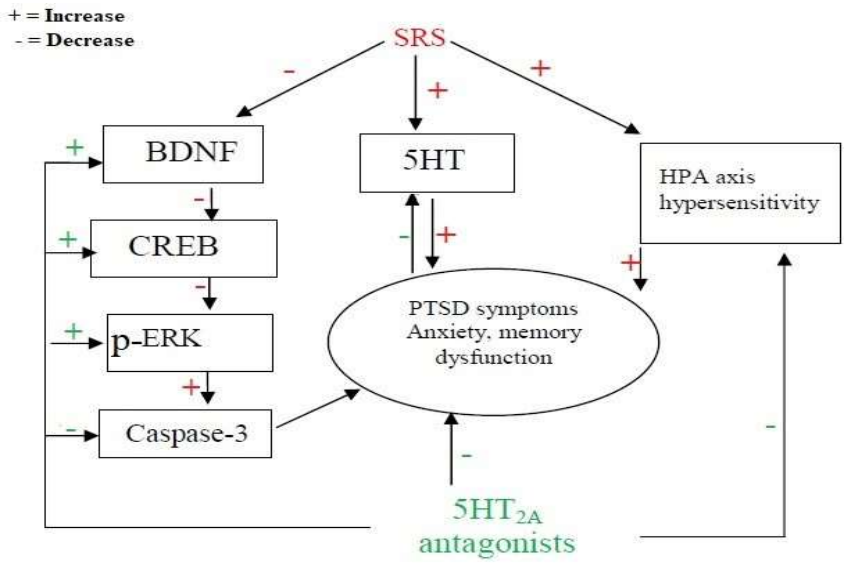
From the study, it appears that the selected atypical antipsychotics have significant anti-stress effects. The drugs showed significant anti-stress effects in terms of gastric ulcer, plasma corticosterone and also plasma norepinephrine. The drugs also had a mitigating effect on the monoamines like 5HT and DA in the stressed brain. Further, none of the drugs had significant extrapyramidal side effects. The anti-stress experimentation confirmed the anti-stress properties of OLZ, APZ and RIS and also indicated a lack of EPS effects at the doses selected. These studies also indicated the tolerability of long-term administration of the selected drugs for further experimentation in the PTSD model.

The stress re-stress model of PTSD showed to enhance anxiety-like behaviours and also cognitive deficits. Administration of these drugs alleviated the anxiety-like behaviour as seen in the enhancement of open arm entries and time spent in EPM. Further, the cognitive deficits were mitigated, as seen by the improvement in novel arm entries and also enhancement of spatial memories in the Y-maze. The drug OLZ showed improvement in the behavioural parameters in terms of anxiety-like and cognitive improvements at a dose of 1 and 10mg/kg doses.



APZ showed similar effects at a single dose of 10mg/kg, while the RIS showed behavioural improvements at a single dose of 0.1mg/kg. The corticosterone levels were reduced by the SRS procedure in rats. This indicates severe disruption of the HPA axis, which controls mood and other emotional behaviours. All the selected drugs showed to enhance the plasma corticosterone levels, which were decreased by the SRS. This indicates the restoration of HPA axis function to a significant extent which could further enhance the mood-related behaviours in PTSD. The SRS procedure enhanced the serotonin levels in the AMY region of the brain but not in PFC. The drugs OLZ, APZ and RIS significantly mitigated the PTSD-induced 5HT levels in the AMY. SRS showed to inhibit the expression of BDNF and CREB, whereas it enhanced the p-ERK and caspase-3 in both PFC and AMY regions of the brain. BDNF and CREB modulate the memory dysfunction in the AMY and PFC. They also mitigate anxiety-like symptoms of PTSD. This indicates that these selected drugs bring about positive modulation in the brain. They tend to enhance the extinction of fear memories which could relieve persistent symptoms of PTSD. The expression of p-ERK and caspase-3 was enhanced by SRS in the PFC and AMY. The drugs OLZ, AMY and RIS, showed to decrease the expression of these proteins. The decreased expression of p-ERK and caspase-3 would lead to inhibition of apoptotic pathways and enhance cell survival. In addition, the enhanced levels of BDNF and CREB levels could promote nerve growth and plasticity. Since these atypical antipsychotics have anti-serotonergic effects and their effect on the serotonergic system could play a key role in the therapeutic effects of PTSD. However, the effect of these drugs on cell growth factors indicate there is an enhancement in the neuroadaptive mechanism, which could bring about long-lasting changes in the brain, leading to the complete remission of PTSD symptoms. However, further mechanistic studies interlinking the monoamines, cell growth factors and HPA axis could provide further insights in to their pharmacological actions in the treatment of PTSD.