OPPOSITE EFFECTS OF CLOZAPINE AND SULPIRIDE ON THE LIPOPOLYSACCHARIDE-INDUCED INHIBITION OF THE GR-MEDIATED GENE TRANSCRIPTION IN FIBROBLAST CELLS

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Previously, we have found that some antipsychotic drugs are able to inhibit glucocorticoid receptor (GR)-mediated gene transcription. Since these drugs are known not only to inhibit hypothalamic-pituitary-adrenal (HPA) axis activity, but also to modulate the immunological system, the aim of the present study was to compare the effect of sulpiride and clozapine on GR function under basal culture conditions and during activation by lipopolysaccharide (LPS). The effect of clozapine and sulpiride alone and with LPS, the immune system activator, on glucocorticoid-mediated gene transcription was investigated in fibroblast cells, stably transfected with a mouse mammary tumor virus – chloramphenicol acetyltransferase plasmid (LMCAT cells).

Treatment of the cells with clozapine (3–10 µM) for 2 days significantly and in concentration-dependent manner decreased the chloramphenicol acetyltransferase (CAT) activity, while sulpiride (1, 3, 5 and 10 µM) was without any effect. LPS (1 µg/ml) given alone inhibited the corticosterone-induced gene transcription by ca. 35%. Clozapine (3, 5 and 10 µM) inhibited the effect of LPS (1 µM), while sulpiride, which alone had no effect on GR function, enhanced LPS (1 µM) action. The obtained results indicate that inhibition of GR-mediated gene transcription by LPS and clozapine can be a mechanism by which these compounds blocked some effects induced by glucocorticoids. Opposite effect of clozapine and sulpiride on LPS action may result from their distinct effect on activity of some kinases involved in regulation of GR transcriptional function and may determine their utility in the treatment of schizophrenia with or without immune system activation.

Key words: lipopolysaccharide, clozapine, sulpiride, GR-mediated gene transcription