Clozapine as the most efficacious antipsychotic for activating ERK 1/2 kinases: role of 5-HT2A receptor agonism

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Antipsychotics (APDs) are divided into first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs) based on the concept that SGAs have reduced motor side effects. With this premise, this study examined in HeLa and other cell lines the effects of different APDs on the activation of ERK1/2 (Extracellular signal-regulated kinases) and AKT (Protein Kinase B) kinases, which may be affected in schizophrenia and bipolar disorder. Among the SGAs, Clozapine clearly resulted as the most effective drug inducing ERK1/2 phosphorylation with potency in the low micromolar range. Quetiapine and Olanzapine showed a maximal response of about 50% compared to Clozapine, while FGAs such as Haloperidol and Sulpiride did not have any relevant effect. Among FGAs, Chlorpromazine was able to partially activate ERK1/2 at 30% compared to Clozapine. Referring to AKT activation, Clozapine, Quetiapine and Olanzapine demonstrated a similar efficacy, while FGAs, besides Chlorpromazine, were incapable to obtain any particular biological response. In relation to ERK1/2 activation, we found that 5-HT2A serotonin receptor antagonists Ketanserin and M100907, both partially reduced Clozapine effect. In addition, we also observed an increase of potency of Clozapine effect in HeLa transfected cells with recombinant 5-HT2A receptor and in rat glioma C6 cells that express a higher amount of this receptor. This indicates that ERK1/2 stimulation induced by Clozapine could be to some extent mediated by 5-HT2A receptor, through a novel mechanism that is called “biased agonism”. This evidence may be relevant to explain the superiority of Clozapine among the APDs.

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