Karolinska Institutet

Institutionen för Fysiologi och Farmakologi

Utility of Combined Treatment with Antipsychotic and Antidepressant Drugs: Scientific Rationales and Clinical Implications

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Farmakologens föreläsningssal, Nanna Svartz väg 2, Karolinska Institutet

Torsdagen den 10 oktober, 2013, kl 09.00

av
Carl Björkholm
Leg. Apotekare

Huvudhandledare:
Professor Torgny H Svensson
Karolinska Institutet
Institutionen för Fysiologi och Farmakologi

Bihandledare:
Docent Kent Jardemark
Karolinska Institutet
Institutionen för Fysiologi och Farmakologi

Docent Björn Schilström
Karolinska Institutet
Institutionen för Fysiologi och Farmakologi

Fakultetsopponent:
Professor John H Krystal
Yale University, USA
Department of Psychiatry

Betygsnämnd:
Professor Lars Oreland
Uppsala Universitet
Institutionen för neurovetenskap

Professor Tomas Hökfelt
Karolinska Institutet
Institutionen för Neurovetenskap

Professor Jörgen Engel
Göteborgs Universitet
Institutionen för Neurovetenskap och Fysiologi

Stockholm 2013

ABSTRACT

The atypical antipsychotic drug (APD) clozapine is the most efficacious APD in treatment-resistant schizophrenia including negative symptoms and cognitive impairment, and still lacks extrapyramidal side effects (EPS). Clozapine, which also possesses an antidepressant effect and can be used as monotherapy in bipolar disorder, has a broad receptor binding profile with higher affinity for the α_2-adrenoceptor and several serotonergic receptors than D_2 receptor, enhances dopamine output in the medial prefrontal cortex (mPFC) and facilitates glutamatergic NMDA receptor-mediated transmission in pyramidal cells in the same brain region. These effects may clearly contribute to its superior clinical efficacy, although haematological side effects limit its use. The atypical APD olanzapine lacks e.g. the high affinity to the α_2-adrenoceptor, as well as the high efficacy of clozapine, and generates dose dependent EPS. Previous studies show that addition of the selective α_2-adrenoceptor antagonist idazoxan to olanzapine may enhance its antipsychotic-like effect and increase dopamine output in the mPFC, effects that might also be achieved by inhibition of the norepinephrine transporter (NET).

In the present study we investigated whether adjunct treatment with reboxetine, a selective NET inhibitor used for the treatment of depression, might generate another means to augment the antipsychotic-like effect of olanzapine and, in principle, provide a somewhat more clozapine-like effect. Addition of reboxetine potentiated the antipsychotic-like effect of low doses of olanzapine, without increasing EPS liability. This combined treatment also preferentially enhanced cortical dopamine output and NMDA receptor-mediated currents in pyramidal cells of the mPFC in slice preparations. The results propose that adjunct NET inhibition by reboxetine may be used to augment the antipsychotic effect of low doses of olanzapine in schizophrenia and improve the effect on negative symptoms and cognitive impairments. We continued to experimentally investigate whether NET inhibition by norquetiapine, an active metabolite of quetiapine in humans but not in rodents, and a potent NET inhibitor, may contribute to the overall effects of quetiapine in patients. To this end we studied the effects of reboxetine added to quetiapine in rodents and found an augmented antipsychotic-like effect and a selectively enhanced dopamine output in the mPFC. As the increased extracellular dopamine levels in the mPFC were accompanied by a decrease in DOPAC levels, the enhanced extracellular dopamine levels should represent a consequence of NET inhibition. Although high concentrations of quetiapine alone facilitated NMDA-induced currents in the mPFC, concomitant NET inhibition was found to generate the same effect at a low, subeffective concentration of quetiapine, being mediated via the dopamine D_1 receptor. Consequently, NET inhibition generated by the active metabolite norquetiapine in patients should, in principle, contribute to the clinical antipsychotic effect of quetiapine, which is obtained at low D_2 receptor occupancy, and furthermore serve to improve depressive symptoms as well as cognitive impairments.

Low to moderate doses of atypical APDs added to selective serotonin reuptake inhibitors (SSRIs) have been found to augment the antidepressant effect with a rapid onset compared to SSRIs alone. Our data show that addition of low doses of the novel atypical APD asenapine to the SSRI escitalopram enhances the output of monoamines in the mPFC and also facilitates not only NMDA, but also AMPA receptor-mediated transmission in pyramidal cells of the mPFC, both effects being mediated via activation of the dopamine D_1 receptor. A similar effect was also obtained by a combination of low concentrations of olanzapine and the SSRI fluoxetine. Significantly, a systemic ketamine injection 24 hours prior to the electrophysiological experiments, which previously has been found to produce a rapid and potent antidepressant-like effect in rodents, significantly potentiated AMPA receptor-mediated transmission in the mPFC in our study. Consequently, our data propose that asenapine may be clinically used as adjunct to SSRIs in treatment-resistant depression to augment and hasten the clinical response. Overall our data thus propose that the relatively rapid onset of the augmented antidepressant effect of combined antipsychotic and antidepressant drug treatments may be related to an enhanced AMPA receptor-mediated transmission in the PFC, in analogy with the effects of ketamine.

In summary, our experimental results suggest that an enhanced efficacy in both schizophrenia and depression may be achieved by combined administration of atypical APDs and antidepressant drugs.

ISBN: 978-91-7549-312-1