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# THE ROLE OF GABA-A RECEPTOR IN THE SYNERGISM BETWEEN SSRI AND ANTIPSYCHOTICS IN SCHIZOPHRENIA

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Currently available antipsychotics are often effective against positive symptoms of schizophrenia but have limited effect in treating core features such as negative or cognitive symptoms. New drugs developed on the basis of current dogmas have shown no breakthroughs in effectiveness and novel understandings of the mechanisms responsible for symptom productions and treatment response are needed.

Clinical studies have shown that resistant negative symptoms may improve when antipsychotics are augmented with selective serotonin reuptake inhibitor (SSRI). This augmenting effect cannot be explained by summating pharmacological effects of the individual drugs. We reasoned that study of this synergism may reveal novel mechanisms relevant to the core features of schizophrenia and their treatment.

Here we present results of in vitro and in vivo laboratory studies showing that the SSRI-Antipsychotic combination, produces unique changes in gamma-aminobutyric acid (GABA)-A receptor and its regulating system which are different from each individual drug . The changes include GABAA receptor phosphorylation, and cellular compartment distribution and changes in proteins modulating GABAA activity including PKC, GSK, ERK and BDNF.

Results are also presented from clinical studies showing that SSRI augmentation in schizophrenia patients results in changes in blood mononuclear cell mRNA encoding for GABAA receptor and related proteins which are similar to those observed in the laboratory and associated with clinical improvement. Taken together these findings support the view that GABA A receptor modulation may be part of the mechanism mediating SSRI-antipsychotic synergistic effect ameliorating some core features of schizophrenia.

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