

Neurochemical basis for combination effects of SSRI and antipsychotic drug

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Selective serotonin reuptake inhibitors (SSRIs) are widely used for the treatment for depression, but about 30-50% of patients do not initially respond to SSRIs. Some clinical studies show that antipsychotics are effective when added to an SSRI in the case of depression in which treatment with an SSRI alone is not effective (called treatment-resistant depression). In Japan, combination therapy of the typical antipsychotic sulpiride and the SSRI fluvoxamine is applied on treatment of treatment-resistant depression. However, the neurochemical mechanism for the combination effect is not fully understood. We examined the effect of coadministration of sulpiride and fluvoxamine in an animal model of depression and studied the effect of the combination on the release of neurotransmitters (serotonin, dopamine, noradrenaline, and acetylcholine) in the brain. In this symposium, we first demonstrate that coadministration of sulpiride and fluvoxamine has an antidepressant-like effect in mice. Then, we present the results of a microdialysis analysis showing that this combination selectively activates dopaminergic neurons in the prefrontal cortex, but not in the striatum. These findings suggest that cortical dopamine system may play a key role in the antidepressant-like effect of the combination. The experimental details of this presentation are published in the following papers. *Neuropsychopharmacology* 30, 43-51 (2005); *Eur. J. Pharmacol.* 520, 86-90 (2005); *J. Pharmacol. Sci.* 102, 419-422 (2006).