Pharmacokinetic and Pharmacodynamic Interactions Between the P-glycoprotein Inhibitor Cyclosporin A and Escitalopram in Rodents

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Recent studies have revealed that the efflux transporter P-glycoprotein (P-gp) restricts brain levels of the antidepressant escitalopram. Moreover, pre-treatment with the P-gp inhibitor verapamil augments the antidepressant-like activity of escitalopram in mice, indicating that P-gp inhibition may represent a potential strategy to augment antidepressant treatment clinically. The present studies investigated pharmacokinetic and pharmacodynamic interactions between escitalopram and another P-gp inhibitor, cyclosporin A (CsA).

CsA (75 mg/kg i.p.) or vehicle was administered to C57BL/6j mice 1 h before escitalopram (0.1 or 1 mg/kg i.p.) or saline (n=9-14). Thirty min after the second injection, mice were subjected to the tail suspension test (TST), one of the most widely used models for assessing antidepressant activity in rodents. Brain tissue was subsequently harvested for analysis of hippocampal escitalopram levels, and prefrontal cortex (PFC) concentrations of serotonin (5-HT) and its metabolite 5-HIAA. Furthermore, the effect of pre-treatment with CsA in a mouse model of serotonin syndrome was investigated, in light of case studies which have reported incidences of this serious adverse drug reaction in patients treated with CsA and escitalopram. CsA (37.5, 75 or 150 mg/kg i.p.) or vehicle was administered one hour before treatment with both the 5-HT precursor 5-HTP (100 mg/kg i.p.) and escitalopram (2 mg/kg i.p.). Behaviours associated with serotonin syndrome were then scored by an observer blind to the treatment groups (n=7). Furthermore, microdialysis studies were undertaken in Sprague Dawley rats to investigate the effect of pre-treatment with CsA (25 mg/kg i.v.) on extracellular 5-HT concentrations in the PFC in response to administration of escitalopram (0.25 mg/kg i.v.) (n=4).

CsA pre-treatment resulted in a ~70-80% increase in hippocampal levels of escitalopram (p < 0.001; ANOVA). Escitalopram treatment reduced PFC 5-HT turnover in a dose-dependent manner, and this effect was augmented by pre-treatment with CsA (p < 0.01; ANOVA). There was no significant treatment effect on PFC levels of 5-HT. However, co-administration of CsA and escitalopram caused a significant reduction in PFC concentrations of the 5-HT metabolite, 5-HIAA (p<0.05; ANOVA). Pre-treatment with CsA did not enhance the antidepressant-like activity of escitalopram in the TST. CsA pre-treatment exacerbated the symptoms of serotonin syndrome in mice, with significantly greater behavioural scores recorded after pre-treatment with each of the doses of CsA tested (p<0.001). Intracerebral microdialysis revealed that pre-treatment with CsA attenuated the increase in extracellular 5-HT in the PFC evoked by escitalopram administration (p < 0.05; repeated measures ANOVA).

These results offer further evidence that escitalopram is a transported substrate of P-gp at the blood-brain barrier. Moreover, these studies reveal a novel pharmacodynamic interaction between CsA and escitalopram in relation to 5-HT turnover, and also highlight that co-administration of CsA and escitalopram may increase the risk and/or severity of serotonin syndrome. In contrast to previous findings involving another P-gp inhibitor (verapamil), pre-treatment with CsA did not augment the antidepressant-like activity of escitalopram in the TST. This may be related to CsA-mediated attenuation of escitalopram-evoked increases in extracellular 5-HT levels, as demonstrated by microdialysis studies.