P.4.03 Effect of the combinations of weak-opiate analgesics with antidepressants in the tail suspension test

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Purpose of the study: Depression is a serious and burdensome illness. Although selective serotonin reuptake inhibitors (SSRIs) have improve safety and tolerability on antidepressant treatment efficacy, the delay in the onset of action and the lack of therapeutic effect in some clinical cases claim for the search of new antidepressant drugs or combination strategies.

The present study, using the tail suspension test, has investigated a possible new antidepressant augmentation strategy. Taken into account that several preclinical and clinical evidences exist involving the antidepressant effect of opioid drugs, we propose to study the effect of the combination between the opioid drug, codeine, and classical antidepressant drugs. The antidepressant drugs chosen are, the selective noradrenaline reuptake inhibitor, desipramine, the SSRIs, fluoxetine, and the mixed reuptake inhibitor, duloxetine. The atypical analgesic with antidepressant-like properties, tramadol, and its enantiomers have been also included in the study.

Methods: The Tail Suspension Test in mice (CD1, 23–27 g) was performed as a model of antidepressant activity. Mice are individually suspended by the tail to a horizontal ring-stand bar. It is measured the time that the animal remains immobile during the 6 minutes test duration. Typically, mice demonstrated several escape-oriented behaviours interspersed with temporally increasing bouts of immobility.

Firstly, dose–response curves were performed with the following drugs: codeine (10–40 mg/kg), desipramine (5–20 mg/kg), fluoxetine (10–40 mg/kg), duloxetine (1.25–5 mg/kg), (±)-tramadol (16–64 mg/kg), (+)-tramadol (16–64 mg/kg), (–)-tramadol (16–64 mg/kg). Secondly, sub-effective doses of each drug where chosen for the combination study (opioid + monoamines). All drugs were intraperitoneally administered 30 min before test.

Results were analyzed by one-way ANOVA. Dose-response studies were conducted using the Dunnett's test and the Student Newman-Keuls test for the combination study, $p<0.05$ were considered to be significant.

Results: The combination of sub-active doses of codeine (20 mg/kg) plus the SSRIs, fluoxetine (40 mg/kg) significantly achieved decrease the immobility time compared with control animals ($p<0.05$). Similarly, the co-administration of codeine plus the opioid and selective serotonin re-uptake inhibitor, (+)-tramadol (16 mg/kg), reduced the immobility time compare with saline ($p<0.05$). However, the combination of sub-effective dose of codeine plus sub-effective dose of desipramine (5 mg/kg), duloxetine (1.25 mg/kg), (±)-tramadol (16 mg/kg) or (–)-tramadol (32 mg/kg) failed to reach statistical significance compared to control.

Conclusions: The co-administration of codeine, a weak-opiate analgesic plus a serotoninergic compound significantly decreased the immobility time in the tail suspension test. However, the combination of codeine plus a selective noradrenaline reuptake inhibitor or a mixed inhibitor failed to modify the immobility time. We further hypothesize that combination of opioid and serotoninergic mechanisms could be a new strategy for the development of more potent antidepressant drugs. Moreover, considering the analgesic properties of opioid drugs they could act on the physical dimension of depression.

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P.4.04 Substitution of venlafaxine by fluoxetine and tianeptine in a conditioned taste aversion paradigm

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Rationale: In vitro, venlafaxine blocks the synaptosomal uptake of serotonin and noradrenaline, and accordingly it has been described as an "SNRI" (serotonin/noradrenaline reuptake inhibitor [1]. Various animal models of depression have already confirmed, as venlafaxine was found to be active, its antidepressant effect [2]. However, the discriminative stimulus effect of this antidepressant has not been investigated yet, except in one study where it was used as a testing drug and substituted for both reboxetine, a NARI, and citalopram, a SSRI [3]. A conditioned taste aversion (CTA) procedure in mice was used to investigate the discriminative stimulus effect of venlafaxine, and whether this effect would be substituted by other antidepressants: fluoxetine, a SSRI, and tianeptine, serotonin reuptake enhancer.

Methods: Male Swiss-Webster mice (25–32 g) were used (n=8). Following a day of water deprivation, during