INTRODUCTION

Lisdexamfetamine dimesylate (LDX) is a pharmacologically inactive prodrug that is converted into d-amphetamine following contact with red blood cells. LDX is only approved for use in patients with attention-deficit/hyperactivity disorder (ADHD).

Major depressive disorder (MDD) and suicidality are well known comorbidities of ADHD [1,2]. ADHD increases the risk of developing MDD in adulthood [3] and pharmacotherapy of ADHD probably has a protective effect on this adverse outcome [4]. Therefore, we have explored the neurochemical interaction between the ADHD prodrug, LDX, and the serotonin and noradrenergic reuptake inhibitor antidepressant, duloxetine.

Intracerebral microdialysis has shown that therapeutically relevant doses of LDX produce substantial and prolonged increases in extracellular concentrations of noradrenaline and dopamine in the prefrontal cortex (PFC) and striatum [5]. We have performed dual probe, intracerebral microdialysis experiments to investigate the interactions between LDX and duloxetine on extracellular 5-HT (serotonin), noradrenaline and dopamine in hippocampus, nucleus accumbens, prefrontal cortex and striatum of freely-moving rats.

METHODS

Male Sprague-Dawley rats (250-350 g; Charles River UK) were maintained on a 12 h/12 h light/dark cycle, at 21±2 °C and 55±20% humidity with free access to food and water.

Under gaseous anesthesia, two concentric microdialysis probes (CMA, Sweden) were stereotaxically implanted into hippocampus (HIPP; 4 mm tip, AP: -4.8 mm; L: ±/4.8 mm relative to bregma; V: -7.8 mm relative to the skull surface) and nucleus accumbens (ACC; 2 mm tip, AP: +2.2 mm; L: ±/1.5 mm; V: -8.0 mm) or into PFC (2 mm tip, AP: +3.2 mm; L: ±/2.5 mm; V: -4.0 mm) and striatum (STR; 4 mm tip, AP: +0.2 mm; L: ±/3.0 mm; V: -7.8 mm according to the stereotaxic atlas of Paxinos and Watson (1986)).

The following day groups of rats (n = 7-8) were given vehicle (2 ml/kg, po) + vehicle (2 ml/kg, ip), LDX (1.5 mg/kg d-amphetamine base po) + vehicle (ip); vehicle (po) + duloxetine (5 mg/kg, ip) or LDX (1.5 mg/kg, po) + duloxetine (5 mg/kg, ip). Following collection of 3 basal samples, LDX was administered at 1 - 20 min following duloxetine at t = 0 min. Samples were collected for a further 3 hr.

Noradrenaline, dopamine and 5-HT in the dialysis samples were quantified by reverse-phase, ion-pair, HPLC coupled with electrochemical detection (ALEXXYS, Antec).

Results are reported as the average percentage of baseline in the 0-3h time-bin.

Table 1. Basal extracellular monoamine concentrations in the prefrontal cortex, hippocampus, nucleus accumbens and striatum

<table>
<thead>
<tr>
<th>Monoamine neurotransmitter</th>
<th>Prefrontal cortex</th>
<th>Hippocampus</th>
<th>Nucleus accumbens</th>
<th>Striatum</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT (serotonin)</td>
<td>0.068 ± 0.010</td>
<td>0.092 ± 0.009</td>
<td>0.066 ± 0.017</td>
<td>0.085 ± 0.011</td>
</tr>
<tr>
<td>Dopamine</td>
<td>0.77 ± 0.08</td>
<td>0.81 ± 0.10</td>
<td>6.6 ± 0.4</td>
<td>24.7 ± 0.9</td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>0.348 ± 0.036</td>
<td>0.319 ± 0.059</td>
<td>0.38 ± 0.104</td>
<td>0.370 ± 0.064</td>
</tr>
</tbody>
</table>

Baseline extracellular concentrations of monoamines (nmol/l) were calculated from the average of the AUC in the 0-3h time-bins for the vehicle control group (n = 8).

RESULTS

The basal concentrations of extracellular monoamines in brain regions from the vehicle controls are reported in Table 1.

- Duloxetine increased the efflux of noradrenaline and 5-HT in PFC (Figure 1A) and hippocampus (Figure 1B) and 5-HT in the striatum (Figure 1D).
- Duloxetine enhanced the extracellular concentrations of dopamine in PFC (Figure 1A) and hippocampus (Figure 1B).
- LDX increased extracellular noradrenaline and dopamine efflux in PFC (Figure 1A). It increased dopamine, but not noradrenaline, efflux in hippocampus (Figure 1B), nucleus accumbens (Figure 1C) and striatum (Figure 1D).
- Combining LDX with duloxetine increased extracellular noradrenaline and dopamine in PFC, all 3 monoamines in the hippocampus, dopamine and 5-HT in the striatum and dopamine in the nucleus accumbens (Table 2; Figures 1A-D).
- When administered in combination, the complementary actions of LDX and duloxetine on monoaminergic neurotransmission were present in all regions (Table 2; Figures 1A-D). The exception was the PFC where the findings were equivocal.

There was a synergistic augmentation of LDX-induced dopamine efflux in the nucleus accumbens (Table 2; Figure 1C) and striatum (Table 2; Figure 1D).

CONCLUSIONS

LDX increased dopamine neurotransmission in PFC, hippocampus, nucleus accumbens and striatum to complement the duloxetine-induced increases of noradrenaline and 5-HT in PFC and hippocampus, and 5-HT in striatum. LDX did not attenuate the neurochemical effects of duloxetine. On the contrary, combining duloxetine with LDX synergistically enhanced the effect of LDX on dopamine efflux in nucleus accumbens and striatum. Together, these findings suggest that the combination of duloxetine and LDX may enhance sub-cortical dopamine transmission more extensively than duloxetine alone.

REFERENCES: