

THE EFFECT OF ACUTE ANTIDEPRESSANT TREATMENT ON AMPHETAMINE-INDUCED STRIATAL DOPAMINE AND SEROTONIN RELEASE IN LOW AND HIGH EXPLORING RATS



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PURPOSE OF THE STUDY

Although the monoamine hypothesis of depression has mainly focused on noradrenaline (NA) and serotonin (5-HT) as substrates of depression and antidepressant drug action, a role for the involvement of the mesotelencephalic dopamine (DA) system in the action of antidepressants has also been suggested [1]. Two of the core symptoms in depression, persistently reduced motivation and increased anxiety, co-occur in low exploring vs. high exploring rats (LE- and HE-rats, respectively). LE and HE animals display their characteristic behavioural profile persistently over time, the 'depressed' LE phenotype also being more anxious in the plus-maze and displaying more passive coping strategies in the forced swimming test [2]. LE- and HE-rats have a number of neurochemical differences in several brain regions, e.g., striatum, and a genome-wide expression analysis using the Illumina platform has revealed ample of differentially expressed genes [2, 3, 4]. In order to find out whether LE- and HE- rats would differ in sensitivity to an antidepressant treatment with regard to its ability to potentiate dopaminergic and serotonergic neurotransmission, in the present study we investigated the potency of a tricyclic antidepressant, a selective 5-HT reuptake inhibitor (SSRI) and a selective noradrenaline reuptake inhibitor (NARI) to alter amphetamine-stimulated dopamine and serotonin release in striatum in low and high exploring rats.

METHODS

Male Wistar rats (Scanbur BK AB, Sweden; Harlan Laboratories, the Netherlands) were classified as low or high explorers on the basis of their spontaneous exploratory activity in the exploration box as described previously [2]. Rats belonging into the lower (LE) or upper quartile (HE) of the initial distribution of exploratory activity were used. A self-made concentric Y-shaped microdialysis probe (7 mm shaft length, 3 mm active tip) was implanted in the striatum (AP: +0.7; ML: +3.0; DV: -7.0) according to the rat brain atlas [5]. Microdialysis procedure was conducted in freely moving animals. The probes were perfused with Ringer solution at a constant flow rate of 1.5 µl/min. Five baseline samples were collected in 15-min periods, followed by administration of either imipramine (10 mg/kg, i.p.) or vehicle (Experiment 1); or fluoxetine, reboxetine (both 10 mg/kg, i.p.) or vehicle (Experiment 2). D-Amphetamine (0.5 mg/kg i.p.) was administered immediately after the collection of the 13th sample (two hours after the antidepressant/vehicle treatment), after which another eleven samples were collected. The quantity of DA and 5-HT in the samples was measured by high-performance liquid chromatography with electrochemical detection (Antec Leyden BV, the Netherlands).

RESULTS

In both Experiments (Figure 1), no differences between LE- and HE-groups in baseline conditions (samples 1-5) in either DA or 5-HT levels in striatum were observed.

In Experiment 1, imipramine administration alone (samples 6-13) did not modify the extracellular DA levels, but increased the 5-HT levels in both LE and HE animals to a similar extent. While amphetamine-stimulated 5-HT release (samples 14-24) was potentiated to a similar extent in LE- and HE-rats, acute imipramine pretreatment produced a more robust increase in the amphetamine-stimulated DA release in striatum of HE-rats as compared to LE-rats.

In Experiment 2, neither reboxetine nor fluoxetine administration alone (samples 6-13) modified extracellular DA levels and reboxetine also had no effect on extracellular 5-HT levels. Fluoxetine increased extracellular 5-HT in LE and HE animals to a similar extent. After amphetamine administration (samples 14-24), HE-rats showed greater DA-levels irrespective of the preceding treatment with either SSRI, NARI or vehicle. Amphetamine-stimulated 5-HT release was more potent in fluoxetine-pretreated HE-rats than in respective LE-rats, and reboxetine-pretreatment was without an effect.

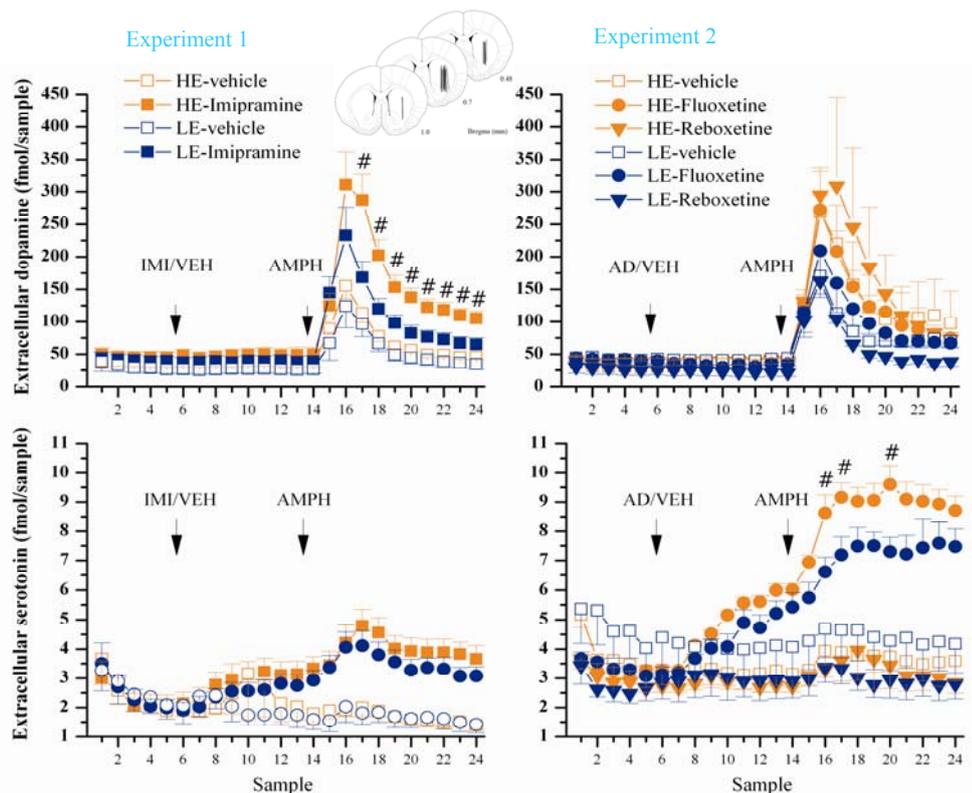


Figure 1. # - $p < 0.05$ vs corresponding LE-group. $N = 3-7$ per group.

CONCLUSIONS

Acute imipramine but not fluoxetine or reboxetine potentiated amphetamine-induced dopamine release in striatum significantly more in HE-rats as compared to LE-rats, suggesting a mechanism independent of direct 5-HT and NA reuptake blockade. 5-HT reuptake blockade with fluoxetine had a more robust effect on amphetamine-stimulated serotonin overflow in HE-rats.

While the mechanisms remain to be elucidated, these differences in sensitivity to imipramine and fluoxetine in LE- and HE-rats may model the individual differences in response to antidepressant treatment.

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DISCLOSURE

The authors report no conflict of interest.