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Antidepressants differentially affect striatal amphetamine-stimulated dopamine and serotonin release in rats with high and low novelty-oriented behaviour

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ABSTRACT

In the studies of depression pathogenesis and antidepressant action, the monoaminergic hypothesis of depression has mainly focused on the serotonergic and noradrenergic mechanisms. However, dopaminergic neurotransmission is also linked to both depressive symptomatology as well as antidepressant effects. We have previously shown that persistent inter-individual differences in the rat behavioural activity in novel environments is associated with differences in the striatal extracellular levels of dopamine and serotonin, depressive-like behaviour and the expression of several depression-related genes. The aim of the current study was to investigate the relative potency of the tricyclic antidepressant imipramine, the selective serotonin re-uptake inhibitor fluoxetine, and the selective noradrenaline re-uptake inhibitor reboxetine (all drugs administered in the dose of 10 mg/kg, i.p.) to enhance amphetamine-stimulated dopamine and serotonin release in the striatum using *in vivo* microdialysis in awake, freely-moving rats, categorized into high explorers (HE) and low explorers (LE) based on their spontaneous novelty-oriented behaviour. The basal extracellular dopamine and serotonin concentration in the striatum did not differ between the LE- and HE-rats. None of the antidepressants alone were able to modify baseline striatal dopamine levels, but the amphetamine-stimulated dopamine release was significantly higher in the HE-rats after acute and chronic imipramine (but not fluoxetine or reboxetine). Acute imipramine and fluoxetine, but not reboxetine, increased both the basal and amphetamine-stimulated levels of serotonin in the striatum. Again, the HE-rats had higher amphetamine-stimulated serotonin release after fluoxetine administration. These findings suggest that rats with depressive-like phenotype are less sensitive to the neurochemical effects of antidepressants in the striatum. These results may have relevance in understanding the neurobiological bases for inter-individual differences in antidepressant treatment response in humans and development of novel medicines.

1. Introduction

The monoaminergic hypothesis of depression has been predominant for the past 60 years, mainly focusing on serotonin and noradrenaline [1] but with recently substantially increased interest in the role of dopamine, particularly owing to the association of low dopaminergic state with the loss of interest and inability to feel pleasure as core symptoms of depression [2–4]. Apparently, primary dysfunction in any of the monoaminergic systems can spread to others in order to bring about the complex and obviously heterogeneous condition that we recognize as major depression [5]. Also, while the primary effect of many types of antidepressant drugs is to enhance serotonergic and/or noradrenergic neurotransmission [6], antidepressants can also, probably indirectly, modify the activity of the midbrain dopamine system. For example, both acute and chronic administration of the tricyclic antidepressants has been shown to increase basal extracellular dopamine levels and/or potentiate cocaine- and amphetamine-stimulated dopamine release in the rat nucleus accumbens and striatum [7–10]. Nevertheless, findings in the studies investigating the effects of antidepressants with more selective mechanisms of action are much less consistent and likely region-specific: selective serotonin reuptake inhibitors (*e.g.* fluoxetine, citalopram) have been shown to decrease, have no effect, or increase basal and stimulated dopamine release in the nucleus accumbens and striatum [7,8,11–17], and increase it in the frontal cortex [11,18,19]. Similarly, antidepressants with selectivity at the noradrenaline

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transporter preferentially increase extracellular dopamine levels in the frontal cortex, but not the striatum and the nucleus accumbens, and have been shown to not modify serotonin levels in the brain [20–26].

These variable results may be related to differential regulation of mesotelencephalic dopaminergic mechanisms, well captured in studies on inter-individual differences. For example, dopamine release in the nucleus accumbens is lower in the Flinders Sensitive Line rats as compared to control Sprague-Dawley rats after cocaine administration, but this difference is eliminated by pre-treatment with desipramine [27]. This may be important for modelling antidepressive drug action: as antidepressants fail to elicit a clinically significant effect in a large proportion of patients, a neurochemical model that indicated an atypically high antidepressant activity in subjects with less sensitivity to known drugs could inform development of drugs selectively active on neural pathways not sufficiently affected by treatment with the available medicines.

Two of the core symptoms of depression: heightened anxiety and reduced motivation, can be studied as a cluster in rats using a paradigm based on novelty-oriented, exploratory behaviour: We have developed and pharmacologically characterized a test of spontaneous exploratory activity [28,29] which combines aspects of forced and free exploration and is able to separate rats into groups with low motivation to explore/high anxiety, and high motivation to explore/low anxiety (low explorers—LE, and high explorers—HE, respectively) enabling highly reliable prediction of further novelty-, anxiety-, and depression-related behaviours [30]. The 'depressive-like' LE-rats display more anxious behaviour in the elevated plus-maze, and increased immobility in the forced swimming test [30]. Cerebral metabolic activity differs between the two groups in brain regions implicated in defensive behaviours and cognitive processing of sensory stimuli [31,32]. A genome-wide microarray expression analysis revealed several differentially expressed genes in the LE- and HE-rats, suggesting that the ratio of the excitatory and inhibitory neurotransmission is higher in the LE-rats [33].

Previously we have reported that the LE- and HE-rats have marked differences in the striatal dopaminergic neurotransmission: LE-rats have lower basal and amphetamine-stimulated dopamine release and a lower proportion of high-affinity D_2-receptors in the striatum (but not nucleus accumbens) [30,34]. The aim of the present study was to find out whether the LE- and HE-rats would differ in the sensitivity to antidepressant treatment with regard to its ability to potentiate the psychostimulant effect on dopaminergic and serotonergic neurotransmission. Thus, we investigated the potency of a three antidepressants with a different mechanism of action: the tricyclic antidepressant imipramine, the selective serotonin reuptake inhibitor fluoxetine, and the selective noradrenaline reuptake inhibitor reboxetine to alter basal and amphetamine-stimulated dopamine and serotonin release in the striatum of LE- and HE-rats.

2. Materials and methods

2.1. Animals

Male Wistar rats (in Experiment 1 and 3: Scanbur BK AB, Sweden; in Experiment 2: Harlan Laboratories, the Netherlands) were housed four per cage in standard transparent polypropylene cages under controlled light cycle (lights on from 08:00 h to 20:00 h) and temperature (19–21 °C), with free access to tap water and food pellets (diet R70, Lactamin, Sweden). The experiments were in accordance with EU legislation (directive 2010/63/EU) and the experimental protocol was approved by the Animal Experimentation Committee at the Estonian Ministry of Agriculture.

2.2. Drugs

The tricyclic antidepressant imipramine, administered in the dose of 10 mg/kg, was dissolved in the sterile saline solution and administered as an intraperitoneal (i.p.) injection in Experiments 1 and 3. In Experiment 2, the selective serotonin re-uptake inhibitor fluoxetine and the selective noradrenaline re-uptake inhibitor reboxetine, both administered in the dose of 10 mg/kg, were also dissolved in saline, and administered as an i.p. injection. All control animals received a saline injection. D-Amphetamine sulphate was dissolved in saline and administered i.p. in the dose of 0.5 mg/kg.

2.3. General procedure

Two-month-old rats were first tested for their exploratory behaviour in the exploration box test, followed by the *in vivo* microdialysis experiment that included administration of amphetamine (0.5 mg/kg, i.p.). In Experiment 3, after classification as HE or LE, all animals received one imipramine (10 mg/kg, i.p.) or vehicle injection per day for two consecutive weeks, followed by the *in vivo* microdialysis experiment (the general procedure is presented schematically in Fig. 1). Immediately following the completion of the microdialysis experiment, all animals were deeply anaesthetized with chloral hydrate (350 mg/kg, i.p.) and decapitated. The brain was kept at −80 °C until determination of the probe locations. Only data from the animals with correct probe locations was included in the statistical analysis.

2.4. Exploration box test

The exploration box test was carried out as described in Ref. [30]. The exploration box was made of metal and comprised a 0.5 m × 1 m open area (the height of side walls 0.4 m) and a 20 cm × 20 cm × 20 cm compartment attached to one of the shorter sides of the open area. The open area was divided into eight equal-sized squares, and four objects, three unfamiliar (a glass jar, a cardboard box, and a wooden handle) and one familiar (a food pellet), were placed onto certain squares (the locations of the objects remained the same throughout the experiment). The floor of the small compartment was covered with wood shavings. The open area was directly accessible from the small chamber through an opening (20 cm × 20 cm). The exploration box test was initiated by placing the rat into the small compartment which was then covered with a lid for the duration of the test. The following parameters were recorded by an observer: (a) latency of entering the open area with all four paws; (b) entries into the open area; (c) line crossings, (d) rearing; (e) exploration of the three unfamiliar objects in the open area; (f) the time spent exploring the open area. To provide an index of exploration considering the elements of both inquisitive and inspective exploration, the scores of line crossings, rearing and object investigations were summed for each animal. After each animal, the exploration box was wiped clean with a wet tissue. A single test session lasted 15 min and the experiments were carried out under dim light conditions (3–7 lx in the open area). All animals were exposed to the exploration box on two consecutive days. The classification of rats into groups of high or low explorers (HE or LE, respectively) was based on the sum of the exploratory events on the second exposure to the exploration box test. Only animals that did not emerge from the small compartment of the exploration box were categorized as LE, while rats belonging to the upper quartile were classified as HE. The mean (±standard error of mean) exploratory activity levels of the HE-animals in Experiments 1–3 were as follows. In Experiment 1, for saline-treated HE-rats ($n = 5$): 156 ± 19; imipramine-treated HE-rats ($n = 7$): 183 ± 18; in Experiment 2, for saline-treated HE-rats ($n = 4$): 173 ± 19; fluoxetine-treated HE-rats ($n = 4$): 216 ± 15;