Asymmetry of turning behaviour of rats induced by amphetamine and apomorphine[1]

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Summary. Turning behaviour of rats following injection of amphetamine is in the same direction as following apomorphine. Unilateral common carotid artery ligation does not affect this asymmetry. Thus the reason for the asymmetry in turning behaviour following injection of amphetamine is probably due to postsynaptic dopaminergic asymmetry within the corpus striatum.

When placed in a round bowl rats injected with amphetamine manifest their hyperactivity by a turning behaviour. Peculiarly, most animals rotate preferentially either right or left[2]. This turning behaviour is probably related to dopamine-mediated circling[3,4]. Glick et al.[5] have demonstrated an imbalance between the concentrations of dopamine in the corpus striatum on each side. In rats turning right the concentration of dopamine is higher in the left corpus striatum, and vice versa[5]. Based on these findings Glick et al.[5] suggested that the turning behaviour produced by amphetamine is due to an increased amount of dopamine released from one corpus striatum as compared to the other. In other words, the reason for the asymmetry is presynaptic. In order to examine this hypothesis, we have injected rats with amphetamine and apomorphine, and recorded their rotating behaviour. Furthermore, we have tested the effect of unilateral changes in cerebral blood flow on the responses to amphetamine and apomorphine.

Materials and methods. 20 Charles River albino rats of either sex, weighing 200–300 g, were placed individually in a rotometer. The rotometer was a round glass cylinder measuring 25 cm in diameter. The animals were held around the chest by a harness which allowed them free movements and which was connected to an overhead measuring device in which full circles as well as $\frac{1}{8}$ of each rotation performed by the animal in each direction were recorded. Rotations were recorded 10 min before and 30–60 min after injection. Drugs used were dl-amphetamine, 5 mg/kg, and apomorphine hydrochloride 0.5–1.0 mg/kg (plus ascorbic acid 0.2 mg/ml), injected i.p. Only animals in which rotation was consistent in direction in 2 experiments (or more) with each drug were considered.

After the direction of rotation induced by these 2 drugs was determined for each rat, an unilateral ligation of the common carotid artery was performed in the neck, either contra-lateral (n=7) or ipsi-lateral (n=3) to the direction of rotation. On subsequent days, the rats were injected again with amphetamine, and the direction of rotation was determined.

Results and discussion. 17 animals rotated consistently in 1 direction following both dl-amphetamine and apomorphine. In 3 animals the direction of rotation following 1 drug (or both) was not consistent and these were discarded.

According to these results, rats injected with either amphetamine or apomorphine rotate in the same direction, rather than in opposite ones as reported by Glick et al.[6]. Both drugs activate postsynaptic dopaminergic receptors, but through different mechanisms. While apomorphine is a direct receptor agonist, the action of amphetamine is dependent upon catecholamines released from presynaptic terminals. At much lower dosage than used in the present experiments, apomorphine acts on presynaptic receptors, and inhibits spontaneous dopamine release. Because of the massive postsynaptic stimulation caused by apomorphine, the change of spontaneous release is of no practical consequence. This implies that the mechanism responsible for the asymmetry of the response to amphetamine (or apomorphine) is postsynaptic rather than presynaptic as previously suggested[5]. Glick et al.[5] have found that dopamine levels in the corpus striatum have an asymmetrical distribution, being higher on the side contralateral to the direction of circling. According to our results, the interpretation of these results is probably that on that side where postsynaptic receptors are more sensitive (or more numerous), the spontaneous release of dopamine is decreased. Feedback loops inhibit dopamine release on that side, causing accumulation of transmitter.

Another possible explanation of our results may be unequal blood supply to the 2 hemispheres. According to this explanation the corpus striatum on one side receives more blood - and therefore more drug - than the contralateral organ. We have tested this possibility by ligating the common carotid artery on the side on which the blood flow was supposed to be higher. Although this procedure does not eliminate all blood supply to the brain on that side, it probably reduces and slows the flow. Unilateral ligation of the common carotid artery in rats either ipsi- or contralateral to the circling direction did not change the direction of rotation induced by amphetamine (10 rats). Thus asymmetry of blood flow is not likely to be the cause of the direction preference.

It has recently been demonstrated that unilateral lesions of midbrain raphe nuclei induce contraversive turning which is augmented by dopaminergic agonists[7]. Unilateral locus coeruleus lesions induce ipsiversive turning[8]. Thus, dopamine-mediated circling seems to be modulated by serotoninergic as well as noradrenergic influences. If, due to imbalance of modulating influences, one corpus striatum is more sensitive to dopamine, this could hamper the animal's ability to progress forward. Moreover, any effect which causes asymmetry of motor performance through other mechanisms could also be manifested as rotation in a circular cage. For example, hemiparesis would be expected to result in ipsiversive turning, which would be particularly obvious when motor activity is high. Both amphetamine and apomorphine are stimulant drugs, and they may therefore unveil latent motor asymmetries between the 2 sides which may not be directly related to the dopaminergic system.

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