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Effect of Morphine on Circling Behaviour in Rats with 6-Hydroxydopamine Striatal Lesions and Electrolesions of the Raphe Nucleus

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SLATER, P. *Effect of morphine on circling behaviour in rats with 6-hydroxydopamine striatal lesions and electrolesions of the raphe nucleus.* PHARMAC. BIOCHEM. BEHAV. **14**(5) 625–630, 1981.—Morphine antagonized d-amphetamine circling in rats which had received unilateral 6-OHDA lesions of the striatum but failed to reduce the circling in rats with both a unilateral 6-OHDA striatal lesion and a raphe (5-HT) lesion. Naloxone precipitated withdrawal of morphine tolerant rats greatly enhanced d-amphetamine circling when the rats had a 6-OHDA lesion but not when both 6-OHDA and raphe lesions were present. It is concluded that 5-HT is necessary for the morphine-induced inhibition of the circling. The effect of morphine tolerance and naloxone precipitated withdrawal on brain 5-HT function was investigated using a putative 5-HT rotation model in which both a dopamine and a 5-HT agonist were administered to rats with an asymmetrical medial raphe lesion. The findings suggest that chronic treatment with morphine increases striatal 5-HT function.

Acute and chronic morphine Circling behaviour 6-OHDA Raphe nucleus Dopamine 5-HT

MORPHINE affects brain transmitters, including acetylcholine, 5-hydroxytryptamine (5-HT) and dopamine [26]. In the case of dopamine, although morphine increases its synthesis in the striatum [24,42], it does not affect dopamine receptors [6, 9, 15]. One theory is that morphine stimulates opiate receptors on the presynaptic terminals of nigrostriatal dopamine neurones and thus reduces dopamine release [4]. This idea is supported by the finding that morphine inhibits amphetamine-induced circling behaviour [36] in the 6-hydroxydopamine (6-OHDA) circling model [25]. However, this circling model is more complex than first described, because 5-HT neurones that project to the striatum from the midbrain raphe nuclei [5] not only influence nigrostriatal dopamine neurones [10,29] but also modify circling behavior [29]. The raphe nuclei, which receive connections from the periaqueductal gray [30], a site that is particularly sensitive to opiates [19,20], can affect the actions of morphine. Lesions of the raphe nuclei and pharmacological procedures that deplete brain 5-HT reduce the antinociceptive action of morphine [12, 14, 17, 31].

Chronic morphine administration is known to be associated with increased behavioural responses to dopamine agonists [25,37]. Dopamine receptors may become more sensitive during chronic exposure to morphine, in a similar way to the disuse hypersensitivity which follows a period of interrupted dopaminergic transmission [34]. It is not known if chronic morphine treatment affects 5-HT receptors.

Unilateral lesions of the 5-HT axons which ascend in the brain from the raphe nuclei to the neostriatum, cause circling behaviour in rats which is modified by 5-HT agonists. This provides the basis for quantitative rotation models which have been used to examine striatal 5-HT function [21,35].

The present study, using rats with electrolytic medial raphe and striatal 6-OHDA lesions, aimed to determine if the effects of both acutely and chronically administered morphine on circling behaviour are mediated primarily by dopamine or 5-HT neurones.

METHOD

Female Sprague Dawley rats (150–160 g) were anaesthetized with methohexitone sodium (Brietal, 50 mg/kg IP) and positioned in a stereotaxic frame. Electrolytic lesions were made with an insulated tungsten electrode with a 0.5 mm exposed tip. A DC current (1 mA; 15 sec) was supplied from a Grass stimulator and constant current unit. The return current passed through the ear bars. Small asymmetric lesions of the medial raphe nucleus were made by lowering the electrode at a 20° angle from the vertical to the coordinates A 0.3 mm; L 0 mm; V −3.3 mm. Larger lesions, to destroy most of the medial raphe nucleus, were made by passing the lesioning current at 2 sites: A 0.3 mm; L 0 mm; V −3.3 mm and A 0.3 mm; L −0.3 mm; V −3.3 mm. The coordinates chosen were modified slightly from a stereotaxic atlas [23].

Some rats were given an intrastriatal injection of 6-OHDA 10 days after the raphe lesion. 6-OHDA hydrobromide (6 μg) was dissolved in 2 μl of sterile saline containing 0.2 mg/ml of ascorbic acid and injected stereotaxically at the coordinates A 8.5 mm; L 2.6 mm; V −1.0 mm.

The circling experiments began after a 14 day post opera-

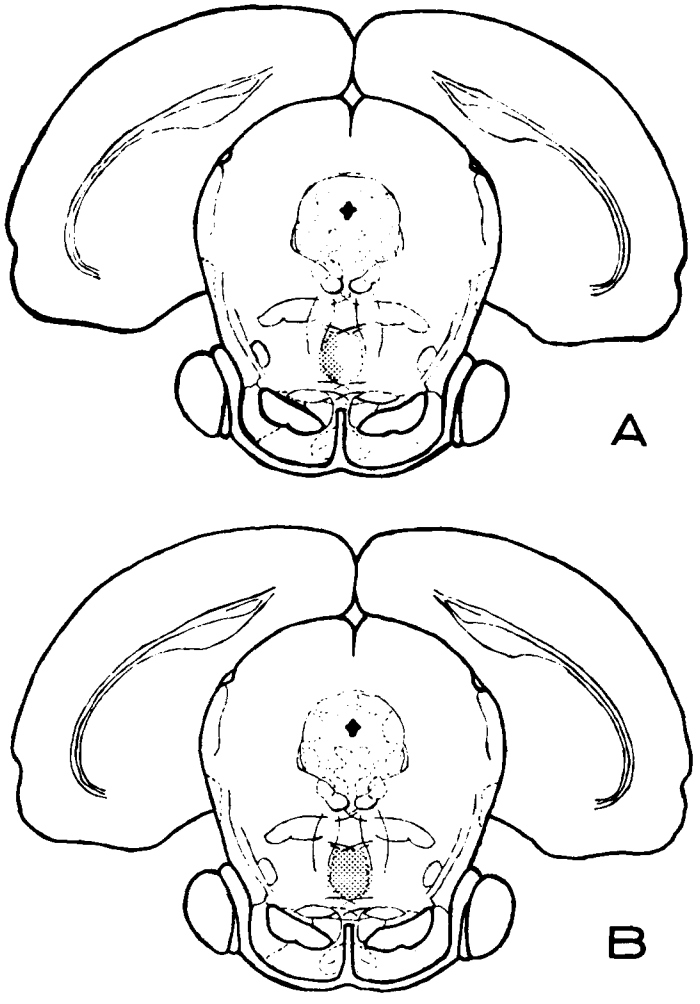

FIG. 1. Diagrams to illustrate the location and extent of (A) asymmetric and (B) total electrolesions of the medial raphe nucleus made in the rat hindbrain. Shaded areas represent the lesion.

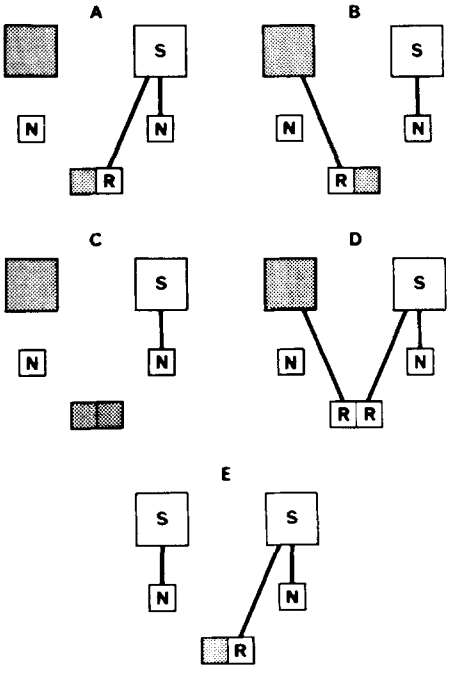

FIG. 2. Diagrams (A–E) showing the electrolytic medial raphe lesions and the 6-OHDA striatal lesions performed on groups of rats. Shaded areas represent the lesion locations and the 5-HT (raphe-striatal) and dopamine (nigro-striatal) pathways reminaing intact are shown. Abbreviations: S, striatum; N, substantia nigra; R, medial raphe nucleus.

tive interval. Rats were placed individually on a flat surface using an area 75×75 cm in quiet evenly lit room. Spontaneously circling was counted after 20 min. The number of full 360° turns made in both directions were recorded. Drug-induced circling was initiated by IP administration of dopamine and 5-HT agonists to rats randomly assigned to groups. The rats were returned to the recording area immediately after the injection and the number and direction of complete turns were recorded by an observer who was unaware of the treatment schedule. Time-response curves were obtained for each dopamine agonist. Mean circling rates were calculated from 10 min sample periods that included the peak effects. The circling rates of 2 groups were compared using the non-parametric Mann-Whitney U test.

The effect of acute morphine on drug-induced circling was determined by pretreating groups of lesioned rats for 30 min with 5 mg/kg IP morphine sulphate. Chronic morphine administration consisted of implanting lesioned rats with 2 subcutaneous morphine tablets. Each tablet contained 75 mg of morphine base and the tablets remained in place for 5 days. Naloxone (1 mg/kg IP) was administered to produce a precipitated withdrawal. The severity of the withdrawal signs was assessed by counting the number of wet-dog shakes. Drugs that initiated circling were given 45 min after naloxone.

At the completion of the experiments, 10% of the rats with lesions were anesthetized with pentobarbitone sodium and perfused with heparinized saline followed by buffered formol-saline. After post-fixation (1 week), serial 15 μm sections were cut and stained with luxol fast blue-basic fuchsin. The raphe and striatal lesions were confirmed histologically. The remaining animals were used for the measurement of striatal dopamine and 5-HT [39].

RESULTS

Electrolesions of the medial raphe nucleus destroyed either one side of the nucleus, with very little of the adjacent reticular formation, or removed most of the median nucleus (Fig. 1). Rats with asymmetric raphe lesions turned spontaneously in wide circles towards the non-lesioned side during their normal exploratory activity. In contrast rats with a striatal 6-OHDA lesion turned occasionally towards the lesioned ride. Rats with both types of lesion turned only towards the side with the 6-OHDA lesion. In every case, the spontaneous turning was highly irregular and impossible to quantify on a flat surface. The pattern of the lesions in relation to the two sides of the brain is shown in Fig. 2.

Lesioned rats received 2.5 mg/kg IP of d-amphetamine sulphate. In every case, d-amphetamine produced vigorous rotation in close circles. The lesions, the direction of circling and the mean circling rates are shown in Table 1. D-amphetamine caused the rats to circle towards the side with the 6-OHDA lesion. In contrast, rats with a medial raphe lesion not only turned away from the lesioned side but also rotated more slowly and therefore made fewer turns per

TABLE 1

EFFECT OF MORPHINE ON THE CIRCLING PRODUCED BY d-AMPHETAMINE IN RATS WITH AN ASYMMETRIC MEDIAL RAPHE LESION AND A 6-OHDA STRIATAL LESION

Lesion and number of rats	Circling direction	Mean turns/min* Pre-morphine	Post-morphine†
Left striatum (7)	Left	16.7±0.5	3.9±0.4[1]
Left raphe (5)	Right	8.9±0.6[2]	7.4±0.7
Left raphe + left striatum (6)	Left	18.1±1.1	2.0±0.3[1]
Right raphe + left striatum (5)	Left	10.2±0.8[2]	9.7±0.6

*Each result is the mean±SE recorded 30–40 min after d-amphetamine (2.5 mg/kg IP). †Morphine was administered 30 min before d-amphetamine.

[1]Significance of difference between pre- and post-morphine turning $p<0.01$.

[2]Significance of difference between turning rates of striatal and raphe lesioned rats $p<0.05$.

TABLE 2

EFFECT OF CHRONIC MORPHINE TREATMENT/PRECIPITATED WITHDRAWAL ON d-AMPHETAMINE CIRCLING IN RATS WITH A MEDIAL RAPHE LESION AND A 6-OHDA STRIATAL LESION

Lesion and number of rats	Circling direction	Mean turns/min* Pre-morphine	Morphine withdrawn†
Left striatum (7)	Left	14.3±0.7	39.2±2.2[1]
Left striatum + left raphe (6)	Left	8.1±0.2	7.9±0.3
Left striatum +right raphe (6)	Left	9.0±0.4	1.9±0.3[1]
Left striatum + left and right raphe (5)	Left	25.6±2.7	20.4±3.1

*Each result is the mean±SE recorded 30–40 min after d-amphetamine (2.5 mg/kg IP). †Naloxone (1 mg/kg IP) was administered 45 min before d-amphetamine.

[1]Significance of difference between pre- and post-morphine turning $p<0.01$.

TABLE 3

EFFECTS OF CHRONIC MORPHINE TREATMENT/PRECIPITATED WITHDRAWAL ON CIRCLING PRODUCED BY QUIPAZINE, APOMORPHINE AND d-AMPHETAMINE IN RATS WITH AN ASYMMETRIC MEDIAL RAPHE LESION

Drugs	Dose	Mean turns/min* Pre-morphine	Morphine withdrawn†
Apomorphine	1 mg/kg	5.5±0.3	2.9±0.9[1]
Apomorphine + quipazine	1 mg/kg	8.1±0.4	12.3±0.2[1]
d-Amphetamine	2.5 mg/kg	9.1±0.3	3.2±0.2[2]
d-Amphetamine + quipazine	2.5 mg/kg 1 mg/kg	11.1±1.2	18.4±1.8[2]

*Each result is the mean contraversive circling rate±SE recorded 20–30 min after apomorphine and 30–40 min after d-amphetamine. †Naloxone (1 mg/kg IP) was administered 45 min before apomorphine/d-amphetamine. Significance of difference between pre- and post-morphine turning: [1]$p<0.05$, [2]$p<0.01$.

minute than 6-OHDA lesioned rats. Morphine (5 mg/kg IP, 30 min) antagonized d-amphetamine circling in 6-OHDA lesioned rats but had no effect in rats with an asymmetric raphe lesion (Table 1). Some rats received two lesions: a raphe lesion and a striatal lesion. d-Amphetamine circling rates were determined (Table 1). A raphe lesion on the opposite (right) side of the brain to the striatal lesion caused the rats to make slower revolutions, and therefore fewer turns per minute, compared to rats with the striatal lesion alone. Morphine antagonized circling in rats with both lesions on the same side (Fig. 1A) but had no effect when the lesions were on opposite sides (Fig. 1B and Table 1). It is concluded that morphine strongly antagonizes d-amphetamine only when the striatum in which d-amphetamine releases most dopamine has an intact 5-HT innervation.

The experiments were repeated using rats which had received chronic treatment with morphine for 5 days followed by 1 mg/kg of naloxone IP. Naloxone caused an immediate morphine withdrawal syndrome which included jumping, teeth chattering episodes and wet-dog shakes. The lesions had no effect on the mean number of wet dog shakes. Naloxone precipitated withdrawal led to a substantial increase in the mean d-amphetamine circling rate recorded in rats with a 6-OHDA striatal lesion (Table 2). In contrast, sudden withdrawal had no effect on the circling rate of a group of rats with a striatal 6-OHDA lesion and a lesion of the entire medial raphe. Groups of rats with a 6-OHDA striatal lesion and an asymmetric raphe lesion on either the same side of the brain or on the opposite side were withdrawn following chronic morphine treatment. In the case of the group of rats with the two lesions on the same side, the mean circling rate was unaffected by chronic morphine, whereas the group with the lesions on opposite sides recorded a depressed circling rate followed morphine withdrawal. It is concluded that striatal 5-HT has an important influence on the changes in the d-amphetamine circling associated with morphine withdrawal.

A 5-HT rotation model has been described [35] in which the contralateral circling induced by either apomorphine or d-amphetamine in rats with an asymmetric medial raphe lesion is increased by the 5-HT receptor agonist quipazine. This rotation model was used to investigate the effect of chronic morphine treatment on striatal 5-HT function. The circling rate of rats with a raphe lesion was established (Table 3). A standard, submaximal dose of quipazine (1 mg/kg IP) caused statistically significant increases in the apomorphine/d-amphetamine circling rates. Morphine was then administered chronically for 5 days and, following naloxone precipitated withdrawal, the circling determinations were repeated. There were highly significant reductions in the apomorphine/d-amphetamine circling rates of the lesioned, withdrawn rats. However, in contrast, morphine withdrawn rats which were given quipazine together with apomorphine/d-amphetamine displayed highly significant increases in the mean circling rates (Table 3). It is concluded that morphine tolerance and withdrawal is associated with an increased circling response to the 5-HT receptor agonist quipazine.

TABLE 4

STRIATAL 5-HT AND DOPAMINE IN BRAINS FROM RATS WITH MEDIAL RAPHE AND STRIATAL 6-OHDA LESIONS

Lesion	Left striatum*		Right striatum*	
	5-HT	Dopamine	5-HT	Dopamine
None (control)	1.39±0.1	6.43±0.21	1.27±0.02	6.67±0.33
Left raphe	0.80±0.10[1]	6.29±0.20	1.40±0.02	6.35±0.09
Left striatum	—	2.97±0.31[2]	—	6.40±0.11
Left raphe + left striatum	0.62±0.04[1]	1.98±0.44[2]	1.41±0.03	7.00±0.09
Right raphe + left striatum	1.40±0.02	2.20±0.30[1]	0.77±0.03[1]	6.62±0.30
Entire raphe + left striatum	0.62±0.04[1]	2.12±0.20[1]	0.69±0.05[1]	6.44±0.40

*Each result is the mean±SE (μg/g) obtained with 8 rats. Significance of difference between lesioned and non-lesioned results: [1]$p<0.01$, [2]$p<0.001$.

The levels of 5-HT and dopamine measured in striata removed from normal and lesioned rats are shown in Table 4. Asymmetric raphe lesions caused a statistically significant reduction in the 5-HT content of the ipsilateral striatum. The 5-HT content of the contralateral striatum was unchanged. Large medial raphe lesions depleted 5-HT in both striata. Medial raphe lesions had no effect on striatal dopamine content. Intrastriatal injection of 6-OHDA caused a statistically significant loss of dopamine but had no effect on 5-HT.

DISCUSSION

A previous study has shown that morphine antagonizes d-amphetamine circling in nigro-striatal lesioned rats [36]. d-Amphetamine causes ipsiversive circling in 6-OHDA lesioned rats by releasing dopamine predominantly in the non-lesioned striatum [16]. In the present study, a raphe lesion that destroyed part of the 5-HT innervation of the striatum that had intact dopamine neurones prevented the morphine-induced inhibition of d-amphetamine circling. Although electrolesions of the raphe may produce nonspecific damage, this did not involve any detectable loss of striatal dopamine. The findings strongly suggest that normal 5-HT function is required for morphine to alter striatal dopamine release. This hypothesis is consistent with the findings that morphine alters the firing rate of 5-HT-containing raphe neurones [18] as well as affecting 5-HT and dopamine synthesis [13]. 5-HT is frequently implicated in the pharmacological actions of morphine. Lesions of the raphe nuclei which reduce brain 5-HT also antagonize morphine's antinociceptive action [1, 12, 27, 31, 43]. However, the action of morphine on raphe neurones is not mediated by specific opiate receptors [27], unlike the effect of morphine on 5-HT synthesis [13]. This suggests that morphine has dual actions on 5-HT neurones and that 5-HT nerve terminals, like dopamine nerve terminals [4], may have prejunctional opiate receptors that can modify 5-HT synthesis and release. The relationship between 5-HT and dopamine in the striatum is uncertain. One theory is that 5-HT neurones tonically inhibit the nigro-striatal dopamine neurones [2, 3, 10, 29]. Another hypothesis is that 5-HT and dopamine have a cooperative function in the striatum [39]. Whatever the nature of the 5-HT-dopamine connection, a close functional relationship between the two transmitters in the striatum is established and is emphasized by the fact that dopamine agonists greatly intensify the spontaneous circling which results from an asymmetric medial raphe lesion [7,8].

An earlier study has shown that chronic morphine treatment leads to an increase in the circling response to d-amphetamine in 6-OHDA lesioned rats [37]. The present results show that a medial raphe lesion prevents the increase in the d-amphetamine circling in withdrawn rats. Furthermore, when the raphe lesion and the 6-OHDA lesion affected the same striatum, there was a strong antagonism of d-amphetamine circling in withdrawn rats. These findings suggest that 5-HT mechanisms are closely involved in the adaptation of striatal transmitter function that accompanies chronic morphine treatment. It is not clear why the loss of 5-HT in the 6-OHDA treated striatum should also profoundly affect d-amphetamine circling in withdrawn rats. However, neither the dopamine nor the 5-HT lesions were complete, and significant amounts of both transmitters remained in the lesioned striata. The changes in striatal neurotransmitter metabolism and receptor function that accompany chronic morphine treatment probably develop to some extent in the lesioned striata.

The present findings suggest that chronic morphine administration might increase 5-HT receptor sensitivity. Naloxone-precipitated withdrawal is known to be associated with increased behavioural responses to dopamine and 5-HT agonists [33]. It is established that 5-HT receptors can become supersensitive when denervated, although a short-lasting pharmacological reduction in 5-HT release appears to have no effect on receptors [22, 28, 38, 40]. A rat circling model suitable for studying 5-HT function in vivo has recently been described [35]. The model relies on the finding that 5-HT agonists alter the rate of circling produced by d-amphetamine in rats with an asymmetric medial raphe lesion [7,8]. This putative 5-HT circling model was used in the present study to investigate the effect of morphine tolerance and naloxone precipitated withdrawal on the stimulation of apomorphine and d-amphetamine induced circling produced by the 5-HT agonist quipazine. Quipazine had markedly different effects on dopamine-induced circling in naive and morphine withdrawn rats. These preliminary findings suggest that chronic exposure of rats to morphine leads to an

increased sensitivity of striatal 5-HT receptors which, in turn, enhances the release of striatal dopamine. Chronic morphine administration might influence some other striatal transmitters. There are reports that quipazine increases striatal acetylcholine [11,32], although the doses of quipazine required were greatly in excess of that employed in the present study. Nevertheless, the possibility that morphine alters a serotonergic cholinergic interaction [11] in the striatum has to be remembered in the interpretation of the present data.

In conclusion, these results suggest that both the acute and chronic actions of morphine on striatal dopamine function rely upon 5-HT neurones.

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