Table 1 Effect of morphine on agonist-stimulated cAMP production in rat neostriatal slices

	cAMP (pmol/mg protein)	*% Basal level*
Basal	3.08 ± 0.07	100
1 μM Morphine	2.18 ± 0.42	71
10 μM Isoprenaline	8.44 ± 0.30	274
10 μM Isoprenaline + 1 μM Morphine	8.50 ± 0.15	276
100 μM Adenosine	6.88 ± 0.61	223
100 μM Adenosine + 1 μM Morphine	7.12 ± 0.62	231
10 μM Prostaglandin E_1	9.26 ± 0.52	301
10 μM Prostaglandin E_1 × 1 μM Morphine	9.08 ± 0.31	295
100 μM Dopamine	6.32 ± 0.21	205
100 μM Dopamine × 1 μM Morphine	3.15 ± 0.12	102

cyclic AMP content of the supernatant determined as described previously.

In confirmation of the results of Forn, Krueger & Greengard, (1974) both dopamine and the β-adrenoceptor agonist isoprenaline caused increases in cyclic AMP formation in striatal slices (Table 1). Adenosine and prostaglandin E_1 (PGE_1) also both caused cyclic AMP increases (Table 1) and the latter two responses were not affected either by propranolol (10 μM) or by α-flupenthixol (1 μM), suggesting that there are several pharmacologically distinct receptors regulating cyclic AMP formation in rat neostriatum.

Morphine at concentrations from 10^{-7} to 10^{-4} M, caused a 30–50% decrease in cyclic AMP levels in striatal slices, however up to a concentration of 10^{-4} M, morphine did not affect basal adenylate cyclase activity in striatal homogenates.

Morphine (10^{-6} M) also caused a complete inhibition of the dopamine-stimulated cyclic AMP levels in striatal slices (Table 1). On the other hand, morphine up to a concentration of 10^{-3} M did not significantly affect the increases in cyclic AMP elicited by isoprenaline, adenosine, or PGE_1 (Table 1), suggesting that the opiate effect in the striatum is selective for dopamine. Morphine did not inhibit the dopamine-sensitive adenylate cyclase in striatal homogenates, except at very high concentrations (10^{-3}M). The effect of morphine, therefore, appears to require intact cells.

The effect of morphine on both basal and dopamine-stimulated cyclic AMP levels in striatal slices was blocked by naloxone (1 μM), suggesting that it is mediated through specific opiate receptors.

These results may provide a biochemical basis for the observed antagonistic effects of opiates on dopamine receptor-mediated behaviour *in vivo*.

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In vitro studies on the inhibition of monoamine uptake by Org 6582

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In vivo studies have revealed that Org 6582 (dl-8-chloro-11-antiamino-benzo-(b)-bicyclo[3.3.1] nona-3,6a (10a) diene hydrochloride) is a potent long acting inhibitor of rat brain 5-hydroxytryptamine (5-HT) uptake. In contrast to its effect on 5-HT uptake Org 6582 does not inhibit the *in vivo* central uptake of noradrenaline (NA) and dopamine (DA) (Goodlet, Mireylees & Sugrue, 1976; Sugrue, Goodlet & Mireylees, 1976). The objective of this study was to investigate the effects of Org 6582 on monoamine uptake *in vitro*. Drug effects on the uptake of [^{3}H]-NA and [^{3}H]-5-HT were studied using a crude synaptosomal fraction obtained from rat hypo-

thalamus (Horn & Snyder, 1972). Rat striatal synaptosomes were employed for [^{3}H]-DA studies. In all experiments the final concentration of monoamine in the incubating medium was 2.6×10^{-8} M. To investigate the effects of drug pretreatment on rat hypothalamic synaptosomal [^{3}H]-5-HT uptake, drugs were injected i.p. 1 h prior to sacrifice. Org 6582 and fluoxetine were equipotent in blocking [^{3}H]-5-HT uptake and both compounds were more potent than chlorimipramine. One and two days after pretreatment with Org 6582 (20 mg/kg, i.p.), [^{3}H]-5-HT uptake was inhibited 55% and 34% respectively. There was no inhibition of [^{3}H]-5-HT uptake one day after chlorimipramine (80 mg/kg, i.p.) pretreatment.

Pretreatment with Org 6582 (80 mg/kg, i.p.) had no effect on [^{3}H]-NA uptake whereas desipramine (40 g/kg, i.p.) produced a 61% inhibition after 1 hour. [^{3}H]-DA uptake into striatal homogenates was unaffected by Org 6582 (80 mg/kg, i.p.) pretreatment whilst 1 h pretreatment with benztropine (40 mg/kg, i.p.), nomifensine (30 mg/kg, i.p.) or mazindol (40 mg/kg, i.p.) inhibited uptake by 25%, 38% and 46% respectively.

In other experiments drugs were added to the incubation medium at the commencement of the 10 min preincubation period prior to addition of ^{3}H-monoamine. Results are expressed as IC_{50} values, which is defined as the molar concentration of drug causing a 50% inhibition of uptake. IC_{50} values for blockade of [^{3}H]-5-HT, [^{3}H]-NA and [^{3}H]-DA uptake by Org 6582 were 1.8×10^{-7} M, 2.9×10^{-6} M and 1.3×10^{-5}M respectively. The corresponding values for chlorimipramine were 7.9×10^{-9} M, 1.1×10^{-7} M and 2.2×10^{-6} M. Kinetic analysis of the inhibition of [^{3}H]-5-HT uptake by rat hypothalamic synaptosomes showed that Org 6582 was a competitive inhibitor of 5-HT uptake with a K_i value of 8.9×10^{-8} M.

These observations reveal that Org 6582 is a competitive inhibitor of 5-HT uptake and confirm those previously found *in vivo* which demonstrated that Org 6582 is a potent, long acting, selective inhibitor of 5-HT uptake.

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Effects of intrahypothalamic injections of noradrenaline and carbachol on core temperature of unrestrained rats

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Amines (e.g. noradrenaline and acetylcholine) acting on the preoptic/anterior hypothalamic area play an important role in thermoregulation. Thus in rats, their injection into this site produces marked changes in body temperature. However, whereas some authors report hypothermia after noradrenaline, acetylcholine and their congeners, others obtain hyperthermia (e.g. Avery, 1971; Beckman, 1970; Kirkpatrick, Lomax & Jenden, 1967). These opposite effects may in part be attributed to differences in injected volume, ambient temperature and the site from which temperature is recorded (e.g. brain, rectal and liver temperatures may vary independently of each other). Since restraint, necessary for rectal temperature measurements, alone elevates body temperature, the effects of intrahypothalamic injections of the above amines were investigated in unrestrained rats in which body temperature was continuously measured from a thermistor implanted into the thoracic cavity (Poole & Stephenson, 1977a); in some rats, electrodes for recording electromyographic activity were placed in the neck muscles and an arterial cannula, for monitoring blood pressure and heart rate, in a carotid artery. Experiments were performed at 23 ± 1°C, the mid-point of their thermoneutral range (Poole & Stephenson, 1977b).

(–)-Noradrenaline hydrochloride (0.2 to 20 μg base in 1 μl of pyrogen-free 0.9% w/v NaCl solution) lowered core temperature. Latency to onset (0.8 ± 0.2 to 1.1 ± 0.1 min, mean ± s.d.) and the maximum fall (0.4 ± 0.1 to 3.1 ± 0.3°C) were dose-related, the larger doses producing correspondingly greater effects of shorter latency. Recovery occurred 18.7 ± 1.6 to 94.8 ± 13.9 min later, depending on dose, and after doses of 10 μg or less, this was followed by a 'rebound' hyperthermia of between 0.2 and 0.8°C. After small doses of noradrenaline (0.5 μg or less), this 'rebound' hyperthermia was sometimes greater than