Release of dopamine in the nucleus accumbens of rats by thyrotropin releasing hormone (TRH)

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In a previous paper we demonstrated that TRH enhanced various dopamine-mediated behaviours. Biochemical and behavioural data suggested that TRH may enhance dopamine release (Green, Heal, Grahame-Smith & Kelly, 1976). The effects of TRH in the nigrostriatal and mesolimbic systems have now been investigated.

Injection of dopamine into the nucleus accumbens of rats increases locomotor activity and this effect is enhanced by monoamine oxidase inhibitor pretreatment (Costall & Naylor, 1976). We now find that injection of TRH (10 μg in 1 μl saline bilaterally) into the n. accumbens increases locomotor activity and produces behavioural changes similar to those produced by dopamine (Table 1). Pretreatment with tranylcypromine (5 mg/kg i.p.) 30 min before TRH potentiated these responses (Table 1). Injection of haloperidol (2.5 μg bilaterally) into the n. accumbens of tranylcypromine pretreated rats blocked the effects of TRH (10 μg bilaterally) injected 15 min later. Furthermore, destruction of the presynaptic dopaminergic terminals with 6-hydroxydopamine (8 μg bilaterally) abolished the effects of intra-accumbens injection of TRH (10 μg bilaterally) alone or 30 min after tranylcypromine (5 mg/kg i.p.) (Table 1). These rats demonstrated normal responses to intra-accumbens injection of dopamine (5 μg bilaterally) 30 min after tranylcypromine (5 mg/kg i.p.) (Table 1). All these results suggest TRH may be acting in the n. accumbens by releasing dopamine.

Peripheral injection of TRH (20 mg/kg i.p.) produced a short-lasting increase in locomotion and behavioural changes similar to those produced by injection of TRH into the n. accumbens. These effects were blocked by haloperidol (1 mg/kg i.p.) and were not mimicked by injection of thyroid stimulating hormone (TSH; 20 mg/kg i.p.) suggesting that the changes are probably dopamine-mediated and independent of the hypothalamus–pituitary–thyroid axis.

Table 1 Effect of bilateral 6-hydroxydopamine lesioning of the nucleus accumbens on TRH and dopamine-induced locomotor activity

Injection into n. accumbens	*Control rats*		*6-Hydroxydopamine-lesioned rats*
Saline (1 μl bilaterally)*	330 ± 71 (4)	N.S.	384 ± 61 (4)
	$P < 0.01$		N.S.
TRH (10 μg bilaterally)*	956 ± 131 (4)	$P < 0.01$	421 ± 57 (4)
Saline (1 μl bilaterally, 30 min after tranylcypromine 5 mg/kg i.p.)*	1150 ± 155 (4)	N.S.	1305 ± 228 (4)
	$P < 0.01$		N.S.
TRH (10 μg bilaterally, 30 min after tranylcypromine 5 mg/kg i.p.)*	4422 ± 841 (4)	$P < 0.05$	1696 ± 208 (4)
Saline (1 μl bilaterally, 30 min after tranylcypromine 5 mg/kg i.p.)†	745 ± 85 (5)	N.S.	930 ± 149 (4)
	$P < 0.01$		$P < 0.02$
Dopamine (5 μg bilaterally, 30 min after tranylcypromine 5 mg/kg i.p.)†	2269 ± 304 (5)	N.S.	2591 ± 438 (4)

The results are the mean ± s.e.mean of the total number of movements in: *90 min period following injection of TRH or †60 min period following injection of dopamine after discounting the first 5 min period. The number of observations are shown in brackets.
N.S., not significant.
Results were analysed using the Student's paired *t* test except for lines marked † which were analysed with a Student's unpaired *t* test.

Injection of TRH (20 mg/kg i.p.) either alone or 30 min after tranylcypromine (5 mg/kg i.p.) failed to produce turning in unilateral nigrostriatal lesioned rats and pretreatment with TRH (2 mg/kg i.p.) did not potentiate turning produced by methamphetamine (0.5 mg/kg) in tranylcypromine pretreated animals.

These results suggest TRH can release dopamine in the nucleus accumbens but not the caudate nucleus, and are consistent with the recent observations of Miyamoto & Nagawa (1977).

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Effects of morphine on uptake and release of dopamine in mouse and rat striatal synaptosomes

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There is a large species variation in locomotor responses following morphine. In the mouse, Rethby, Smith & Villareal (1971), Villareal, Guzman & Smith (1973), and Kuschinsky & Hornykiewicz (1974) report that morphine causes increase in locomotor activity, an effect which the latter authors found could be prevented by pretreatment with α-methyl-*p*-tyrosine, and which could be restored by treatment with L-DOPA. Kuschinsky & Hornykiewicz (1974) suggested therefore that the increase in locomotor activity in the mouse following morphine could be due to dopamine release. In the rat, Babbini & Davis (1972) and Smee & Overstreet (1976) found that morphine caused an initial decrease in locomotor activity, followed by hyperactivity, while Kuschinsky & Hornykiewicz (1974) only reported a catalepsy response. They suggested that in the rat, morphine causes decrease of dopamine release, and consistent with such a hypothesis, was the finding of Blundell, Crossman & Slater (1976), who found that morphine reduced the circling response to (+)-amphetamine in rats with unilateral 6-hydroxydopamine lesions in the striatum.

We have investigated the ability of morphine to inhibit uptake, or cause the release of [^{3}H]-dopamine ([^{3}H]-DA), in synaptosomes prepared from rat or mouse striatum, and also the ability of morphine to affect inhibition of uptake, or release of [^{3}H]-DA caused by (+)-amphetamine in similar synaptosomal preparations.

Uptake inhibition and release experiments were made as previously described (Kruk & Zarrindast, 1976).

In experiments to study the effects of morphine on inhibition of uptake or release of [^{3}H]-DA, 8 determinations were made at each of 6 concentrations in the range 10^{-9} M to 10^{-4} M. In neither mouse nor rat synaptosomes was there any evidence for either facilitation or inhibition of uptake or release of [^{3}H]-DA in the dose range of morphine examined.

(+)-Amphetamine was found to block [^{3}H]-DA uptake with IC_{50} values of 2×10^{-7}M (rat) and 3×10^{-8} M (mouse). Morphine, in the concentration range 10^{-9} M to 10^{-4} M, did not significantly affect the (+)-amphetamine induced inhibition of [^{3}H]-DA uptake.

(+)-Amphetamine caused release of [^{3}H]-DA with RC_{50} values of 7×10^{-7} M (rat) and 4×10^{-7} M (mouse). Morphine, in the range 10^{-7} M to 10^{-4} M did not significantly affect the (+)-amphetamine induced release of [^{3}H]-DA. Our results do not support the hypothesis of Kuschinsky & Hornykiewicz (1974) that morphine has a direct presynaptic action at dopamine nerve terminals in mouse and rat striatum.

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