Is the striato-nigral pathway responsible for 'feed-back' control of dopamine release?

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Blockade of post-synaptic dopamine (DA) receptors by haloperidol and similar neuroleptics is thought to increase DA turnover via a neuronal feedback pathway. The most obvious candidate for this function is the gabaminergic pathway from striatum to substantia nigra.

The pathway followed by the striato-nigral neurones was traced autoradiographically after [^{3}H]-leucine injection into striatum following the methods of Cowan, Gottlieb, Hendrickson, Price & Woolsey (1972). At the level of the mamillary bodies this pathway lies in the internal capsule more lateral than the ascending axons of the nigro-striatal system.

Electrolytic lesions of the striato-nigral pathway were made which completely spared the dopamine containing nigro-striatal projection. Rats with such lesions turned towards the lesioned side after i.p. apomorphine (0.5–5.0 mg/kg) and amphetamine (2 mg/kg). These animals behave like animals with large unilateral lesions of the striatum (Andén, Dahlström, Fuxe, Larsson, 1966) although they have normal levels of dopamine and its acid metabolites on both sides of the brain.

If the pathway from striatum to substantia nigra is involved in the response of the dopamine neurones to neuroleptics then the lesion should reduce the rise in homovanillic acid (HVA) 3,4,-dihydroxyphenylacetic acid (DOPAC) in the striatum after haloperidol administration. The level of DA was estimated by the methods of Coyle and Henry (1973), and HVA and DOPAC by a modification of the method of Pearson & Sharman (1975a), in single striata from rats injected with haloperidol (1 mg/kg i.p.) 30 min before they were killed. The concentration of HVA increased more than 500% on both sides in animals with unilateral lesions in the striato-nigral pathway. The increase in DOPAC (300%) and the decrease in DA (50%) were also similar in lesioned and unlesioned striata.

That the lesions were effective is indicated by a 60% fall in the levels of GABA in substantia nigra on the lesioned side estimated by a modification of the method of Pearson and Sharman (1975b) although the levels of DA were not different.

In conclusion it seems unlikely that a feed-back via the striato-nigral GABA containing neurones can be responsible for the effect of haloperidol on DA release.

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The effects of anorectic drugs on uptake and release of brain monoamines

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While it is generally agreed that the action of anorectic drugs in the CNS involves catecholamines and 5-hydroxytryptamine (5-HT), it is still not clearly established which neurochemical systems are affected by individual anorectic drugs. As many anorectic drugs have some indirect sympathomimetic activity it was decided to examine the ability of these compounds to block the uptake or to facilitate the release of dopamine, noradrenaline and 5-HT from brain tissues.

Uptake was measured by the method of Snyder & Coyle (1969), and release was measured by the method of Ferris, Tang & Maxwell (1972), using tritiated monoamines and synaptosomes prepared from rat brain regions rich in nerve terminals containing those monoamines.

Table 1 The effect of anorectic drugs on uptake and release of tritiated monoamines measured in synaptosomes prepared from the brain region indicated. The number of determinations made is indicated in the brackets.

	^{3}H-Dopamine (Striatum)		^{3}H-5-Hydroxytryptamine (Striatum)		^{3}H-Noradrenaline (Hypothalamus)
Compound	$IC_{50}(\mu M)$	$RC_{50}(\mu M)$	$IC_{50}(\mu M)$	$RC_{50}(\mu M)$	$IC_{50}(\mu M)$
D-Amphetamine	0.05 ± 0.007 (8)	0.25 ± 0.22 (6)	1.2 ± 0.3 (6)	3.0 ± 1.3 (5)	0.07 ± 0.006 (6)
Phenmetrazine	0.1 ± 0.04 (5)	10.0 ± 1.0 (4)	7.0 ± 1.0 (5)	80.0 ± 18.0 (5)	0.4 ± 0.06 (5)
Phentermine	0.23 ± 0.05 (4)	1.4 ± 1.3 (6)	1.4 ± 0.1 (4)	22.0 ± 13.0 (5)	0.4 ± 0.02 (5)
Mazindol	0.25 ± 0.04 (6)	44.0 ± 4.0 (6)	0.16 ± 0.06 (8)	90.0 ± 44.0 (5)	0.004 ± 0.004 (9)
Diethylpropion	120.0 ± 20.0 (4)	56.0 ± 3.0 (6)	($>10^{-4}$ M)	($>10^{-4}$ M)	16.0 ± 4.0 (4)
p-Chloramphetamine	0.16 ± 0.02 (5)	2.3 ± 0.1 (5)	0.02 ± 0.007 (5)	0.13 ± 0.04 (5)	0.5 ± 0.06 (6)
Norfenfluramine	1.7 ± 0.8 (3)	0.56 ± 0.17 (4)	0.24 ± 1.0 (5)	0.58 ± 0.05 (5)	0.5 ± 0.11 (5)
Chlorphentermine	6.0 ± 0.2 (4)	9.5 ± 1.0 (4)	0.085 ± 0.022 (5)	0.16 ± 0.07 (5)	0.9 ± 0.12 (5)
Fenfluramine	12.0 ± 3.0 (4)	34.0 ± 3.0 (4)	0.3 ± 0.13 (5)	0.65 ± 0.18 (5)	1.8 ± 0.8 (4)

IC_{50} and RC_{50} are the molar concentrations causing 50% inhibition of monoamine uptake and release respectively.

The results are expressed as IC_{50} and RC_{50} values, defined as the molar concentration of drug causing 50% inhibition of uptake, or 50% release of monoamine respectively. These values were derived from graphs in which % inhibition of uptake or % release was plotted against log molar concentration of anorectic drug.

The drugs examined were generally more potent as inhibitors of uptake than as releasers of monoamines. All the drugs examined were weak releasers of noradrenaline with $RC_{50} > 10^{-4}$ M.

Dexamphetamine, mazindol (5-hydroxy-5-(4′-chlorophenyl)-2,3-dihydro-5H-imidazo(2,1-a) isoindole), phentermine, phenmetrazine and diethylpropion were more potent in affecting uptake and release of dopamine than 5-HT. Fenfluramine, norfenfluramine, chlorphentermine and p-chloraphetamine were more potent in affecting release and uptake of 5-HT than dopamine. These results confirm that anorectic drugs act through either a dopaminergic or 5-HT mechanism in the brain (Kruk, 1973; Clineschmidt, McGuffin & Werner, 1974) and that noradrenergic mechanisms are unlikely to have a significant role in mediating anorectic responses.

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