Accelerated Synthesis of Dopamine in the Rat Brain after Methadone

Previous studies from our laboratory have shown that D,L-methadone increases brain homovanillic acid (HVA) levels in rats[1]. In the present study the effect of D,L-methadone on the in vivo conversion of H^3-tyrosine to Dopamine (DA) was measured in the rat basal ganglia.

Materials and methods. Experiments were carried out in male, Sprague-Dawley rats (180–210 g), caged in groups of 4 at an environmental temperature of about 20 °C. Animals were killed by decapitation and the brains rapidly removed, the corpus striatum dissected as described by GLOWINSKI and IVERSEN[2], and kept frozen at −20 °C until analyzed.

DA and HVA were assayed fluorometrically[3]. Endogenous and labelled tyrosine and DA were separated and assayed as described by COSTA and GROPPETTI[4].

Results. In agreement with previous results[1], we found that D,L-methadone significantly increased the HVA content in the basal ganglia but did not modify DA levels. In addition, Table I shows that the dextro isomer was ineffective.

Since these results suggest that D,L-methadone increased DA turnover, we studied the effect of the drug on the in vivo conversion of H^3-tyrosine to DA. In Table II are reported the specific activities (SA) of tyrosine and DA 20 min after the i.v. injection of a pulse dose of H^3-tyrosine in control rats and in rats treated with D,L-methadone 1 h previously. The SA of tyrosine in the basal ganglia was approximately 20% higher in the animals treated with methadone than in control rats. However, the SA of DA in the basal ganglia of animals treated with methadone was 230% higher than in control rats.

Discussion. These results indicate that methadone increases the synthesis of DA in the basal ganglia. This effect seems to be rather specific since methadone did not influence serotonin metabolism in the rat brain stem[1]. The fact that dextro-methadone is inactive both in raising HVA and in producing analgesia[5], suggests that the 2 effects might be strictly correlated.

The mechanism by which methadone stimulates DA synthesis is under investigation. The possibility that the therapeutic effect of methadone on heroin withdrawal syndrome originates from its effect on DA receptors should be considered.

Recently TAMARKIN, GOODWIN and AXELROD[6] and BOWERS, KLEBER and DAVIS[7] observed a decreased accumulation of HVA levels following probenecid in methadone addicts. Their data suggest a decrease in DA turnover in these subjects. It would be of interest to clarify whether the difference between our data and theirs depends on interspecies variations or a different experimental situation, i.e. methadone addiction and acute administration of the drug.

Table I. Effect of D,L-methadone on HVA levels in the rat basal ganglia

Treatment mg/kg i.p.	Basal ganglia HVA (μg/g)	DA (μg/g)
None	0.23±0.02	3.12±0.10
D,L-methadone 10	0.48±0.02[a]	3.27±0.15
D-methadone 20	0.21±0.01	3.10±0.20

[a] $P < 0.01$ in respect to control values (Student's *t*-test). Each value is the average ±S.E. of at least 20 determination. Drugs were given 2 h before sacrifice.

Table II. Effect of D,L-methadone on the conversion of H^3-tyrosine to H^3-dopamine (DA) in the basal ganglia

Treatment (No. of animals)	Specific activities[a] 20 min after the i.v. injection of H^3-tyrosine Basal ganglia Tyrosine	DA
None (14)	432±18	112±10
D,L-methadone (12)	503±21	255±15

[a] cpm/μg/g. Each value is the average ±S.E. of the number of experiments reported in parenthese. Methadone was given i.p. at the dose of 10 mg/kg 90 min before the injection of H^3-tyrosine (L-tyrosine-3,5-H^3; 500 μCi/kg, 25 Ci/mmoles).

Riassunto. Nei ratti, il D,L-metadone fa aumentare significativamente i livelli di acido omovanillico e stimola il turnover della dopamina nei gangli della base. Il destro isomero è inattivo.

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Nitroglycerin on the Carotid Artery and Femoral Artery of the Dog

In 1953 it was shown that the aorta strip of the rabbit can be contracted maximally by adrenaline, even when high concentrations of nitroglycerin are present in the organ bath: this phenomenon was called the 'break through' of the catecholamines through the nitroglycerin inhibition[1,2]. We previously described a similar 'break through' for strips of the femoral artery or femoral vein of the dog, and for the perfused hindleg of the dog[3].

The present report deals with results showing that this 'break through' is not present in the carotid artery strip of the dog, but that this difference between vessels cannot be demonstrated in vivo.

Materials and methods. Spirally cut strips of the femoral artery and the carotid artery of the dog are made to contract isotonically using a counterweight of 4 gm[1]. Increasing concentrations of the agonist, noradrenaline