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# EFFECT OF MECAMYLAMINE ON THE FATE OF DOPAMINE IN STRIATAL AND MESOLIMBIC AREAS OF RAT BRAIN; INTERACTION WITH MORPHINE AND HALOPERIDOL

LIISA AHTEE[1] & SEPPO KAAKKOLA

Department of Pharmacology, University of Helsinki, Siltavuorenpenger 10, SF-00170 Helsinki 17, Finland

**1** The effects of the nicotinic cholinoceptor blocking drug, mecamylamine (alone or in combination with morphine or haloperidol) were investigated on the striatal homovanillic acid (HVA) concentration and on the α-methyl-*p*-tyrosine (AMPT)-induced depletion of striatal or mesolimbic dopamine content in the brain of rats.

**2** Mecamylamine (2 mg/kg) alone did not alter the striatal HVA concentration, but it reduced the probenecid-induced accumulation of HVA. Mecamylamine pretreatment reduced the morphine- and haloperidol-induced elevation of striatal HVA concentration. Hexamethonium did not alter the striatal HVA concentration when given alone or in probenecid- or morphine-treated rats, whereas pempidine (8 mg/kg) clearly reduced the probenecid-induced accumulation of HVA in the striatum.

**3** Mecamylamine (2 and 8 mg/kg) slowed the rate of AMPT-induced depletion of dopamine from the striatum and mesolimbic area both in the brain of control rats and of rats treated with morphine or haloperidol.

**4** Mecamylamine slightly prolonged the cataleptic effect of morphine.

**5** The results indicate that mecamylamine inhibits the release of dopamine both from the striatal and mesolimbic dopaminergic neurones.

## Introduction

Nicotine induces catalepsy in mice (Zetler, 1968), in rats whose caudate-putamen or globus pallidus has been removed (Costall & Naylor, 1973), and after intraventricular administration in cats (Beleslin & Malobabić, 1972). There is also evidence that nicotinic cholinomimetic compounds enhance the release of dopamine from the corpus striatum of the rat *in vitro* and *in vivo* (Westfall, 1974; Giorguieff, Le Floc'h, Westfall, Glowinski & Besson, 1976). The cataleptic effect of neuroleptic compounds (Hornykiewicz, 1973) and that of narcotic analgesics (Kuschinsky, 1976; Ahtee, 1977) is accompanied by an increased concentration of striatal homovanillic acid (HVA) and an increased turnover of cerebral dopamine. The cataleptic effect and changes in cerebral dopamine metabolism produced by narcotic analgesics are prevented or abolished by nalorphine and naloxone and, therefore, seem to be specific effects of narcotic analgesics (Kuschinsky, 1976; Ahtee, 1977). In rats chronically treated with methadone, nicotine slightly potentiated and the nicotine-receptor blocking agent, mecamylamine, clearly blocked the cataleptic effect of methadone (Ahtee, 1976).

The present experiments were started to find out if mecamylamine would inhibit the effects of narcotic analgesics on the striatal HVA concentration and on the α-methyl-*p*-tyrosine (AMPT)-induced depletion of brain dopamine. As it soon became obvious that mecamylamine itself altered the metabolism of dopamine in the rat brain, we also studied the interaction between mecamylamine and the neuroleptic compound, haloperidol. The effects of drugs on the rate of disappearance of dopamine after inhibition of tyrosine hydroxylase by AMPT (Spector, Sjoerdsma & Udenfriend, 1965) were studied in striatal and mesolimbic areas, which are the main dopaminergically innervated areas connected with motor functions in the rat brain (Fuxe, Hökfelt & Ungerstedt, 1970).

## Methods

Male Wistar rats, weighing 220–300 g, or female Sprague-Dawley rats, weighing 190–240 g, kept on a standard diet and tap water *ad libitum*, were used. During the experiments the rats were individually

[1] Present address: School of Pharmacy, Department of Pharmacology, University of Helsinki, Kirkkokatu 20, SF-00170 Helsinki 17, Finland.

housed in plastic cages at 21–30°C in a noiseless room.

The drugs used were (±)-α-methyl-*p*-tyrosine methylester hydrochloride (AMPT; Labkemi AB, Gothenburg), haloperidol (a gift from Orion Oy, Helsinki), hexamethonium hydrochloride (Fluka AG, Buchs SG, Switzerland), mecamylamine hydrochloride (a gift from Merck Sharp & Dohme B.V. Haarlem, Netherlands), (−)-morphine hydrochloride (Pharmacopoeia Nordica), pempidine tartrate (a gift from May & Baker Ltd) and probenecid (a gift from Merck Sharp & Dohme). Probenecid was dissolved in a minimum volume of 0.1 N NaOH, an approximately 5% solution was made by adding 0.9% w/v NaCl solution (saline), and the pH was adjusted to 7–8 with 0.1 N HCl; the other drugs were dissolved in saline. Probenecid was injected in a volume of 0.5 ml/100 g, AMPT in a volume of 0.3 ml/100 g, and the other drugs in a volume of 0.1 ml/100 g. The drugs were injected intraperitoneally except for morphine and haloperidol which were given subcutaneously; the doses refer to the base.

The rats were killed by decapitation and the brain was rapidly removed and dissected on ice (Zeman & Innes, 1963). The striata from two brains were pooled for estimation of HVA. The striata from one brain and mesolimbic areas (consisting of tuberculum olfactorium, nucleus amygdaloideus centralis and medialis, and parts of nucleus accumbens) from two brains were used for the estimation of dopamine. Dopamine was estimated spectrophotofluorimetrically as described by Shellenberger & Gordon (1971). HVA was estimated by the method of Portig, Sharman & Vogt (1968). The recovery for added dopamine was 89 ± 1.5% (mean ± s.e. mean from 4 estimations) and for HVA 77 ± 1.5% ($n$ = 17). Results have been corrected for losses.

Catalepsy was scored as described by Simon, Malatray & Boissier (1970) and by Cashin & Sutton (1973). Four tests were employed: a 3 cm high bar, a 9 cm high bar, parallel bars and a vertical grid. Each test was scored from 0 to 2. The scores of the four tests were added so that the maximum score was 8.

## Results

### *Effect of mecamylamine on striatal homovanillic acid concentration*

Table 1 shows that mecamylamine in a dose of 2 mg/kg did not alter the concentration of HVA in rat striatum at 80, 140 or 380 min after administration. However, this dose of mecamylamine reduced the probenecid-induced accumulation of HVA by 18% at 1 h and by 40% at 2 h after probenecid administration (Table 2).

Mecamylamine pretreatment reduced the morphine-induced elevation of striatal HVA concentration by about 60% at 1 h and by 40% at 2 h but no longer had an effect at 4 h after the administration of morphine (30 mg/kg). Mecamylamine also did not significantly reduce the increase in striatal HVA concentration in rats treated with 10 mg/kg of morphine (Table 1) except when probenecid was used to block the transport of HVA from brain (Sharman, 1967) (Table 2). At 1 h after the administration of the drugs, mecamylamine reduced the morphine-induced elevation of striatal HVA concentration in rats treated with morphine plus probenecid by 45% (10 mg/kg of morphine) and by 66% (30 mg/kg of morphine), respectively. However, at 2 h after the administration of the drugs mecamylamine did not alter the striatal HVA concentration in rats treated with morphine plus probenecid (Table 2).

Mecamylamine (2 mg/kg), given 5 min before haloperidol, did not alter the haloperidol-induced elevation of striatal HVA concentration. The striatal HVA

**Table 1** Effect of mecamylamine and hexamethonium on the morphine-induced increase in striatal homovanillic acid (HVA) concentration.

| Pre-treatment[1] | $h$[2] | HVA (μg/g) Saline | Morphine 10 | Morphine 30 |
|---|---|---|---|---|
| Saline | 1 | 0.67 ± 0.02 (5) | 1.13 ± 0.07 (6) | 1.22 ± 0.05 (9) |
| Mecamylamine | 1 | 0.61 ± 0.007 (5) | 0.86 ± 0.30 (6) | 0.84 ± 0.05 (5)** |
| Hexamethonium | 1 | 0.61 ± 0.03 (3) | — | 1.14 ± 0.05 (4) |
| Saline | 2 | 0.60 ± 0.03 (5) | 1.55 ± 0.06 (8) | 1.62 ± 0.11 (6) |
| Mecamylamine | 2 | 0.57 ± 0.03 (4) | 1.33 ± 0.17 (7) | 1.15 ± 0.11 (6)* |
| Saline | 4 | 0.60 ± 0.04 (6) | 1.46 ± 0.14 (3) | 1.96 ± 0.42 (3) |
| Mecamylamine | 4 | 0.66 ± 0.06 (3) | 1.70 ± 0.11 (4) | 1.89 ± 0.41 (3) |

Values are given ± s.e. mean; $n$ in parentheses.
[1] Mecamylamine (2 mg/kg) and hexamethonium (10 mg/kg) were given to female Sprague-Dawley rats 20 min before saline or morphine (10 or 30 mg/kg). [2] Time after injection of morphine.
Compared to saline pretreated group: *$P < 0.05$; **$P < 0.001$.

**Table 2** Effect of mecamylamine and hexamethonium on the morphine-induced increase in striatal homovanillic acid (HVA) concentration in probenecid-treated rats

| *Pretreatment*[1] | *h*[2] | *HVA (μg/g) Probenecid only* | *Probenecid + morphine 10* | *Probenecid + morphine 30* |
|---|---|---|---|---|
| Saline | 1 | 1.19 ± 0.03 (3) | 1.91 ± 0.05 (5) | 2.07 ± 0.11 (6) |
| Mecamylamine | 1 | 0.98 ± 0.07 (3)* | 1.35 ± 0.16 (5)** | 1.28 ± 0.17 (3)** |
| Hexamethonium | 1 | 1.29 ± 0.20 (3) | — | 2.26 ± 0.08 (4) |
| Saline | 2 | 1.55 ± 0.10 (5) | 2.46 ± 0.32 (3) | 2.34 ± 0.23 (3) |
| Mecamylamine | 2 | 0.93 ± 0.13 (3)* | 2.45 ± 0.27 (3) | 2.34 ± 0.10 (3) |

Values are mean ± s.e. mean; *n* in parentheses.
[1] Mecamylamine (2 mg/kg) or hexamethonium (10 mg/kg) were given 25 min and morphine (10 or 30 mg/kg) 5 min before probenecid (200 mg/kg) to female Sprague-Dawley rats. [2] Time after injection of morphine.
The striatal HVA concentration of control rats in this experiment was 0.66 ± 0.02 μg/g ($n = 6$). Compared to saline pretreated group: $^*P < 0.05$, $^{**}P < 0.01$.

concentration was 2.15 ± 0.45 μg/g (mean ± s.e. mean; $n = 3$) at 2 h and 3.02 ± 0.38 μg/g ($n = 3$) at 4 h after haloperidol 0.1 mg/kg; the corresponding concentrations in mecamylamine pretreated rats were 2.61 ± 0.19 μg ($n = 3$) and 2.81 ± 0.26 ($n = 3$), respectively. However, Table 3 shows that in probenecid-treated rats, mecamylamine clearly decreased the haloperidol-induced elevation of striatal HVA concentration.

Hexamethonium neither reduced the concentration of striatal HVA (Table 1) nor the probenecid-induced accumulation of HVA (Table 2). It did not affect the elevation of striatal HVA caused by morphine (Tables 1 and 2). Pempidine did not alter the concentration of HVA in the striatum, but it reduced the probenecid-induced accumulation of HVA (Table 4).

**Table 3** Effect of mecamylamine on the haloperidol-induced increase of striatal homovanillic acid (HVA) concentration in probenecid-treated rats

| *Treatment*[1] | *HVA (μg/g)* |
|---|---|
| Saline | 0.62 ± 0.02 (3) |
| Probenecid | 1.09 ± 0.02 (3) |
| Haloperidol + probenecid | 3.79 ± 0.05 (3)* |
| Mecamylamine + haloperidol + probenecid | 2.66 ± 0.22 (3)** |

Values are mean ± s.e. mean; *n* in parentheses.
[1] Mecamylamine (2 mg/kg) was given 25 min and haloperidol (0.1 mg/kg) 5 min before probenecid (200 mg/kg) to female Sprague-Dawley rats, which were killed 1 h after probenecid.
Compared to probenecid group: $^*P < 0.001$; $^{**}P < 0.01$. Compared to haloperidol + probenecid group: $^{**}P < 0.01$.

*Effect of mecamylamine on the α-methyl-p-tyrosine-induced decrease of striatal or mesolimbic dopamine content*

Treatment of rats with α-methyl-*p*-tyrosine (AMPT, 200 mg/kg) 3 h before they were killed decreased the striatal dopamine concentration by 54% and the mesolimbic dopamine concentration by 68%. Morphine and haloperidol accelerated the AMPT-induced depletion of dopamine content so that, in morphine-pretreated rats, the dopamine concentration decreased by 64% (striatum) and by 80% (mesolimbic area) and, in haloperidol-pretreated rats, the decrease was 73% in the striatum and 82% in the mesolimbic area (Figure 1).

Mecamylamine slowed the rate of AMPT-induced dopamine depletion. The striatal dopamine concentration decreased in 3 h in mecamylamine-pretreated rats by 37% (mecamylamine-dose: 2 mg/kg) or 45% (8 mg/kg) and the mesolimbic concentration by 53% (2 mg/kg) or 55% (8 mg/kg), respectively. Mecamyl-

**Table 4** Effect of pempidine alone or in combination with probenecid on the striatal homovanillic acid (HVA) concentration

| *Treatment*[1] | *HVA (μg/g)* |
|---|---|
| Saline | 0.57 ± 0.03 (4) |
| Pempidine | 0.57 ± 0.05 (4) |
| Probenecid | 1.44 ± 0.07 (5) |
| Pempidine + probenecid | 0.78 ± 0.06 (4)* |

[1] Pempidine (8 mg/kg) was given 25 min before probenecid (200 mg/kg). Male Wistar rats were killed 2 h after probenecid.
Compared to probenecid group: $^*P < 0.001$.

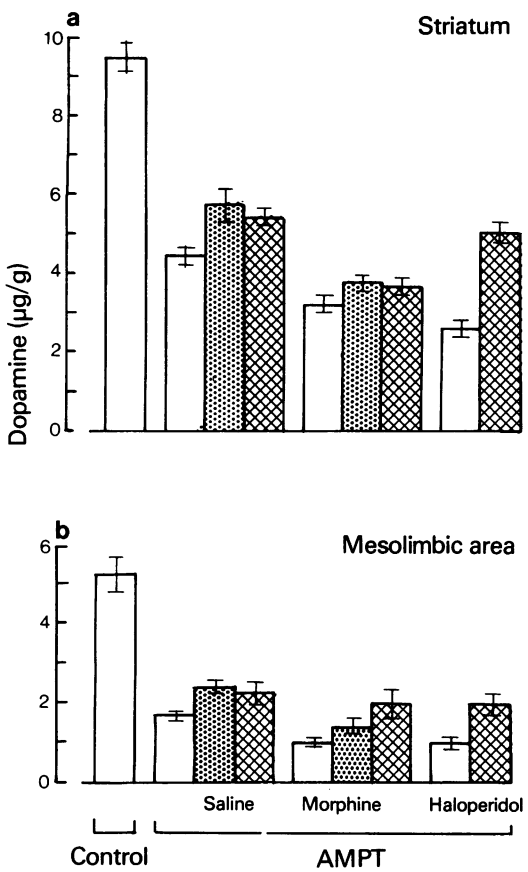


**Figure 1** The effect of mecamylamine on the α-methyl-*p*-tyrosine (AMPT, 200 mg/kg, 3 h before decapitation)-induced decrease of (a) striatal and (b) mesolimbic dopamine concentration in Wistar male rats treated with saline, morphine (10 mg/kg) or haloperidol (0.1 mg/kg) 5 min before AMPT. Mecamylamine (2 mg/kg: dotted columns; 8 mg/kg: cross-hatched columns) was given 25 min before AMPT. Each column represents a mean of 6 to 8 (striatum) or 3 to 4 (mesolimbic area) estimations; vertical bars show s.e. mean.

Significance of differences between groups:

| | Striatum | Mesolimbic area |
|---|---|---|
| AMPT *vs* AMPT + morphine: | $P < 0.001$ | $P < 0.01$ |
| AMPT *vs* AMPT + haloperidol: | $P < 0.001$ | $P < 0.01$ |
| AMPT *vs* AMPT + mecamylamine 2: | $P < 0.01$ | $P < 0.01$ |
| AMPT *vs* AMPT + mecamylamine 8: | $P < 0.01$ | $P < 0.01$ |
| AMPT + morphine *vs* AMPT + mecamylamine 2 + morphine: | NS | NS |
| AMPT + morphine *vs* AMPT + mecamylamine 8 + morphine: | NS | $P < 0.05$ |
| AMPT + haloperidol *vs* AMPT + mecamylamine 8 + haloperidol: | $P < 0.001$ | $P < 0.05$ |

amine also slightly reduced the depletion of dopamine in the striata of rats treated with morphine plus AMPT and clearly reduced the depletion of striatal dopamine in those treated with haloperidol plus AMPT. The dose of 8 mg/kg of mecamylamine significantly decreased the depletion of mesolimbic dopamine in morphine or haloperidol plus AMPT-treated rats (Figure 1).

*Effect of mecamylamine on the cataleptic effect of morphine or haloperidol*

Mecamylamine prolonged the cataleptic effect of morphine. The cataleptic score of Sprague-Dawley female rats at 3 h after 10 mg/kg of morphine was 0.6 ± 0.2 (mean ± s.e. mean; $n = 6$). In rats pretreated with mecamylamine 2 mg/kg this score was 2.3 ± 0.6 ($n = 6$; $P < 0.05$). The corresponding scores in rats treated with 30 mg/kg of morphine were 4.3 ± 0.9 (saline pretreatment, $n = 6$) and 7.0 ± 0.5 (mecamylamine; $n = 6$; $P < 0.05$). Mecamylamine pretreatment did not alter the cataleptic scores of rats treated with 0.1 or 1 mg/kg of haloperidol during a 4 h experiment.

## Discussion

The findings that mecamylamine decreased the accumulation of striatal HVA in probenecid-treated rats and reduced the rate of disappearance of striatal and mesolimbic dopamine after blockade of catecholamine synthesis by AMPT, suggest that mecamylamine reduces the output of dopamine. Peripheral nicotinic mechanisms do not seem to be involved in these effects of mecamylamine, because hexamethonium which blocks nicotine receptors but only poorly reaches the brain (Volle & Koelle, 1975) did not alter the probenecid-induced accumulation of HVA whereas the tertiary amine, pempidine, clearly reduced it. Thus, the action of mecamylamine is most probably the opposite of that of nicotine, which has

been shown to increase the release of dopamine from rat striatum both *in vitro* and *in vivo* (Westfall, 1974; Giorguieff *et al.*, 1976). Furthermore, our results fit well with the hypothesis of Giorguieff *et al.* (1976) that on dopaminergic terminals there are nicotinic presynaptic receptors which are involved in the regulation of the release of dopamine.

The observations that mecamylamine slightly prolonged the cataleptic effect of morphine in rats and did not reduce the cataleptic effect of haloperidol in rats (present experiments) or in mice (Zetler, 1971), are easily explained on the assumption that mecamylamine decreases the output of dopamine. It is noteworthy that the effect of mecamylamine on the methadone-induced catalepsy is opposite to its effect on morphine-induced catalepsy. In rats treated acutely with methadone (10 mg/kg), mecamylamine (2, 4 or 8 mg/kg) slightly but statistically significantly reduced the catalepsy (Ahtee and Ylikylä, unpublished observations). In rats treated chronically with methadone this effect of mecamylamine was more obvious (Ahtee, 1976). Furthermore, in rats, which had been treated chronically with morphine twice daily for 30 days by increasing the daily dose of morphine from 20 to 50 mg/kg, mecamylamine clearly antagonized the cataleptic effect of methadone but did not alter that of morphine. In these rats 200 mg/kg of morphine caused less catalepsy than 15 mg/kg of methadone, although, in untreated rats, 30 mg/kg of morphine and 10 mg/kg of methadone are about equally cataleptic (Ahtee and Ylikylä, unpublished observations). Thus, it is possible that methadone possesses some nicotinic agonistic activity which can be best observed in animals which are tolerant to narcotic analgesics.

The reduction of striatal HVA concentration by mecamylamine could only be demonstrated when the transport of HVA from brain was blocked or when the formation of dopamine (and HVA) was increased by morphine. Even in a dose of 15 mg/kg, mecamylamine did not alter the striatal HVA concentration in rats treated only with mecamylamine (Haubrich & Goldberg, 1975). In contrast, the muscarinic antagonist drugs (O'Keeffe, Sharman & Vogt, 1970; Bartholini & Pletscher, 1971) and especially the dopamine receptor stimulating drugs (Roos, 1969) decrease the striatal and brain HVA concentration by 30 to 40% (atropine) and by 80 to 90% (apomorphine). Therefore it is probable that the nicotinic mechanisms play a smaller role in the regulation of dopamine synthesis and release than the muscarinic or dopaminergic mechanisms do. The presynaptically located dopaminergic receptors (Carlsson, 1975; Carlsson, Kehr & Lindqvist, 1977) seem to be especially important regulators of dopamine synthesis and release.

Mecamylamine decreased the rate of disappearance of dopamine after synthesis was blocked to a similar degree in the striatum and in the mesolimbic area. This suggests that the nicotinic mechanisms operate both in the striatal and mesolimbic dopaminergic synapses and that the relative importance of the nicotinic mechanisms in these synapses is similar. The doses of 2 and 8 mg/kg of mecamylamine decreased the rate of disappearance of dopamine to about the same degree in the striata of AMPT-treated and morphine plus AMPT-treated rats as well as in the mesolimbic area of AMPT-treated rats. However, in the mesolimbic area of morphine plus AMPT-treated rats, in which the disappearance rate of dopamine was faster than in the above-mentioned tissues, the dose of 8 mg/kg of mecamylamine was certainly more effective than the dose of 2 mg/kg in preventing the disappearance of dopamine. Most clearly, mecamylamine (8 mg/kg) decreased the AMPT-induced disappearance of dopamine in the brain of haloperidol-treated rats, the tissue in which this rate was fastest of all those studied. Thus, it is likely that the nicotinic mechanisms which regulate the release of dopamine either become activated or their relative importance is simply increased when the turnover and/or the rate of release of dopamine increases.

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