Br. J. Pharmac. (1979), **65**, 573–578

SHORT AND LONG-TERM EFFECTS OF RESERPINE ON THE CONCENTRATION OF 1-(4-HYDROXY-3-METHOXYPHENYL)-ETHANE-1,2-DIOL (MOPEG-SO_4) IN THE BRAIN OF THE RAT

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1 Reserpine (1.25 mg/kg i.p.) induced an increase (172% of controls) in the concentration of 1-(4-hydroxy-3-methoxyphenyl)-ethane-1,2-diol sulphate (MOPEG-SO_4) in rat brain and a decrease in the noradrenaline (NA) concentration to 50% of controls 2 h after injection. At this time the MOPEG-SO_4/NA ratio was 0.28. Thereafter the MOPEG-SO_4 concentration declined and the NA concentration decreased further to 28% of control.

2 Higher doses of reserpine (2.5 and 5 mg/kg i.p.) did not induce a larger increase in the concentration of MOPEG-SO_4.

3 While a second dose of reserpine (1.25 mg/kg i.p.) given 24 h after the first did not increase the MOPEG-SO_4 concentration, amphetamine (5.0 mg/kg i.p.) administration or electrical stimulation significantly increased the concentration of MOPEG-SO_4.

4 NA and MOPEG-SO_4 concentrations were examined during 5 days after a single dose of reserpine (1.25 mg/kg i.p.). While the concentration of NA started to return towards normal after 24 h, that of MOPEG-SO_4 remained at approximately 70% of controls during the entire period.

5 The probenecid-induced accumulation rate of MOPEG-SO_4 was significantly lower 3 and 4 days after reserpine and returned to the control value on the fifth day. At this time the concentration of NA had reached 50% of the control value.

6 These experiments indicate that MOPEG-SO_4 is not the major metabolite of NA during the initial phase of reserpine-induced NA release. Reserpine acts on the storage pool while amphetamine (like electrical stimulation) acts on the functional pool. During the first phase of post-drug recovery, there is a clear decrease in NA output which appears to be regulated by the concentration of NA in the storage pool.

Introduction

1-(4-Hydroxy-3-methoxyphenyl)-ethane-1,2-diol sulphate (MOPEG-SO_4) is one of the major metabolic end-products of noradrenaline (NA) in rat brain (Schanberg, Breese, Schildkraut, Gordon & Kopin, 1968a; Schanberg, Schildkraut, Brees & Kopin, 1968b) and it has been proposed that the concentration of this metabolite may be considered as an index of neuronal activity (Meek & Neff, 1973; Korf, Aghajanian & Roth, 1973a, b; Kostowski, Samanin, Bareggi, Marc, Garattini & Valzelli, 1974).

Both the mechanism and the site of action of reserpine on brain NA storage have been clarified (Carlsson, 1965) but the effect of this drug on the formation of NA metabolites in rat brain has not been described.

Many experiments have shown that the recovery of neuronal function after reserpine administration is a complex phenomenon. The onset of recovery of the neuronal capacity to retain [^{3}H]-NA after reserpine administration occurs when the endogenous NA concentration is still low (Andèn, Magnusson & Waldeck, 1964; Andèn & Henning, 1966). The supply of newly transported NA granules by axonal flow appears necessary for the recovery of the monoamine reuptake mechanism (Andèn & Lundborg, 1970; Häggendal & Dahlstrom, 1970; Häggendal & Dahlstrom, 1971).

Whether the recovery of nerve function after reserpine parallels the recovery of the reuptake mechanism or requires complete re-establishment of NA in the storage pool is uncertain. The aim of the present experiments was to correlate the time course of the impairment in NA storage induced by reserpine with changes in neuronal function as evaluated by the endogenous brain MOPEG-SO_4 concentration.

0007-1188/79/040573-06 $01.00

Table 1 Short term effect of reserpine on the concentrations of noradrenaline (NA) and MOPEG-SO_4 in the whole brain of rat

Treatment	*Dose*	*Hours after injection*	*NA* (nmol/g)	*% control*	*MOPEG-SO_4* (nmol/g)	*% control*	*MOPEG-SO_4 NA*
Solvent	—	—	2.80 ± 0.10 (14)	100	0.57 ± 0.02 (15)	100	
Reserpine	1.25	1	1.99 ± 0.13* (4)	71	0.76 ± 0.08* (5)	135	
Reserpine	1.25	2	1.36 ± 0.09* (4)	57	0.98 ± 0.02* (8)	172	0.28
	1.25	4	0.93 ± 0.15* (4)	33	0.74 ± 0.04* (4)	132	
	1.25	24	0.77 ± 0.01* (4)	28	0.46 ± 0.06 (5)	82	
Reserpine	2.5	1	1.90 ± 0.20* (4)	68	0.78 ± 0.05* (6)	136	
Reserpine	2.5	2	1.30 ± 0.10* (4)	46	0.99 ± 0.03* (6)	173	0.28
Reserpine	5.0	1	—	—	0.85 ± 0.10* (5)	149	
Reserpine	5.0	2	1.29 ± 0.10 (4)	46	0.96 ± 0.06 (5)	174	0.26

Mean values ± s.e. mean are shown.
* $P < 0.01$ compared to solvent group, Dunnet's test (Dunnet, 1955)

Table 2 Effects of reserpine, amphetamine and electrical stimulation on MOPEG-SO_4 concentrations in cortex-hippocampus.

First treatment	*Dose (mg/kg i.p.)*	*Second treatment*	*Dose (mg/kg i.p.)*	*No of Animals*	*MOPEG-SO_4 (ng/g)*	*% saline*	*% reserpine*
Solvent	—	Saline	—	5	0.54 ± 0.03	100	—
Reserpine	1.25	Saline	—	5	0.43 ± 0.03	80	100
Solvent	—	Reserpine	1.25 mg/kg	5	0.93 ± 0.04*	172	—
Reserpine	1.25	Reserpine	1.25 mg/kg	5	0.47 ± 0.04	—	102
Solvent	—	Amphetamine	5.0 mg/kg	5	0.78 ± 0.03*	145	—
Reserpine	1.25	Amphetamine	5.0 mg/kg	5	0.63 ± 0.02†	—	146
Solvent	—	Elec. stimulation[3]	—	6	0.88 ± 0.04*	163	—
Reserpine	1.25	Elec. stimulation[3]	—	6	0.69 ± 0.03†	—	160

Mean values ± s.e. mean are shown.
[1] The first treatment was given 22 h before the second treatment; [2] animals were killed 2 h after reserpine and amphetamine, 20 min after electrical stimulation; [3] see methods.
Dunnet's test (Dunnet, 1955): * $P < 0.01$ vs saline pretreated animals; † $P < 0.01$ vs reserpine pretreated animals.

Methods

Male Charles-River rats, weighing 150 to 200 g were kept in Makrolon (polycarbonate) cages at constant room temperature (21 to 22°C) and relative humidity (60%) with a 12 h dark-light cycle. The animals had free access to water and food. Rats were treated with reserpine (Serpasil, Ciba) dissolved in a vehicle consisting of 5 ml of polyethyleneglycol 300, 1 ml of benzyl alcohol, 50 mg of ascorbic acid and water to 100 ml) or amphetamine sulphate (dissolved in 0.9% w/v NaCl solution (saline)) or with the appropriate drug solvent as specified in Tables 1–3.

Rats were killed by decapitation, the brains were removed and brain regions (whole brain without cerebellum, cortex-hippocampus) dissected and frozen on dry ice. Brain tissues were kept at −80°C overnight and, on the morning following dissection, were homogenized in 4 to 7 ml of 0.2 N $ZnSO_4$ solution and an equivalent amount of 0.2 N $Ba(OH)_2$ solution was added. After centrifugation at 30,000 *g* the supernatant was filtered and either directly passed through Sephadex DEAE A-25 columns or stored frozen at −80°C until assay. Internal standards of authentic MOPEG-SO_4 were added to supernatants of brains of untreated rats and analysed in parallel with the brain samples. MOPEG-SO_4 was isolated and assayed as previously described (Bareggi, Marc & Morselli, 1974) by a modification of the method of Meek & Neff (1972). In parallel experiments, NA was assayed by the method of Chang (1964). Brain tissue was homogenized in 9.7 ml of 0.4 N $HClO_4$, 0.2 ml of 10% disodium edetate (EDTA) and 0.1 ml of 6% cysteine. After centrifugation the clear supernatant was adjusted to pH 8.0 with 1 M Tris buffer, pH 9.0. Following adsorbtion on alumina, NA was eluted with 0.1 N HCl and oxidized with iodine to yield a fluorescent trihydroxyindole. The fluorescence was measured with an Aminco-Bowman Spectrophotofluorimeter.

In order to gain further information about the fate of NA released by drugs or other stimuli, we have calculated an arbitrary index from the decrease in the concentration of NA and the increase in the concentration of MOPEG-SO_4 when new steady levels have been reached. The index is the ratio of MOPEG-SO_4 (nmol accumulated − nmol control) divided by NA (nmol control − nmol released). This arbitrary index serves only as an approximate estimation of the NA metabolism and it is used here to compare the activities of different drugs or stimuli (such as electrical stimulation) on NA disposition.

Electrical stimulation of locus coeruleus NA cells was carried out as described by Korf *et al.* (1973a), as modified by Kostowski *et al.* (1974). Rats were anaesthetized with chloral hydrate (400 mg/kg) and placed in a Stoelting stereotaxic instrument. A 3 mm hole was made in the skull and coaxial electrodes (NE − 100, Kopf instruments) were implanted according to the following coordinates: P = 1.6 − 1.7 mm. L = 1 mm, H = 2.5–2.6 mm above the interaural line.

The stimulus was provided by a Grass Stimulator (Mod.S4) and was a monophasic pulse of 2 ms duration and a current of 400 μA. Stimulation time was 20 min. Frequencies varied from 5 to 30 Hz in order to find a stimulation level at which the increase in MOPEG-SO_4 was not maximal. The increase in concentration of MOPEG-SO_4 was found to be linear with frequency between 5 and 20 Hz. A frequency of 15 Hz which gave reproducible increases in MOPEG-SO_4 of about 50% to 60% over the con-

Table 3 Long-term effect of reserpine (1.25 mg/kg i.p.) on noradrenaline (NA) and MOPEG-SO_4 concentrations in rat brain

Time (days)	*Noradrenaline* (nmol/g)	% *control*[a]	*MOPEG-SO_4* (nmol/g)	% *control*[b]
1	0.77 ± 0.01* (4)	26	0.46 ± 0.06 (5)	82
2	0.81 ± 0.02* (4)	29	0.40 ± 0.02† (5)	72
3	0.94 ± 0.04* (5)	34	0.37 ± 0.02† (5)	66
4	1.39 ± 0.15* (5)	50	0.40 ± 0.04 (5)	72
5	1.49 ± 0.15* (5)	54	0.36 ± 0.02† (5)	64

Mean values ± s.e. mean are shown.
[a] Control value: 2.78 ± 0.10 nmol/g (18); [b] control value: 0.58 ± 0.02 nmol/g (16).
* $P < 0.01$ compared to controls; † $P < 0.05$ (Dunnet's test, Dunnet, 1955).

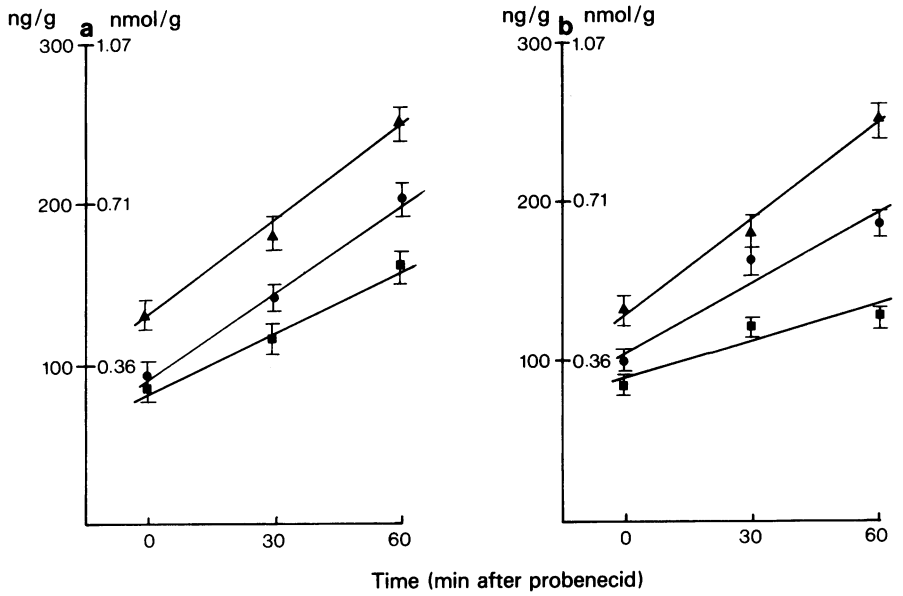

Figure 1 Probenecid-induced accumulation of MOPEG-SO_4 at various times after reserpine (1.25 mg/kg i.p.). (a) (▲) Solvent, b = 2.01, (●) reserpine 2 days, b = 1.65, not significantly different from solvent; (■) reserpine 3 days, b = 0.83, $P < 0.01$ vs. solvent. (b) (▲) Solvent, b = 2.01; (■) reserpine 4 days, b = 1.24, $P < 0.01$ vs. solvent; (●) reserpine 5 days, b = 1.79, not significantly different from solvent. Vertical lines show s.e. mean.

trol values, was used in the experiments shown in Table 2.

Results

Reserpine (1.25 mg/kg i.p.) increased the concentration of MOPEG-SO_4 in whole brain. The highest concentration was reached 2 h after injection, thereafter MOPEG-SO_4 concentrations returned towards control values (Table 1) being only slightly below (83%) the control value 24 h after drug administration (Table 1). NA concentration showed a sharp decrease in the first 2 h, falling to 50% of the control concentration. The concentration thereafter slowly decreased to 28% of control values 24 h after reserpine (Table 1).

When MOPEG-SO_4 reached the highest concentration, the MOPEG-SO_4/NA ratio was 0.28 (Table 1). Higher doses of reserpine did not produce a larger increase in MOPEG-SO_4 concentration, even though a slightly larger decrease in NA concentration was obtained (Table 1).

A second dose of reserpine (1.25 mg/kg i.p.) given 24 h after the first did not induce a second increase in MOPEG-SO_4 concentration (Table 2). On the other hand, amphetamine (5.0 mg/kg i.p.) and electrical stimulation (see methods) were still able to induce a significant increase in the concentration of MOPEG-SO_4 after reserpine pretreatment (Table 2). Furthermore the proportional increase was similar in both reserpine-treated and untreated animals (Table 2).

The long-term effect of reserpine was studied by following NA and MOPEG-SO_4 concentrations for 5 days after a single injection of reserpine (1.25 mg/kg i.p.). While NA concentrations showed a clear trend toward recovery, beginning 48 h after injection, MOPEG-SO_4 concentrations did not show any change and remained around 65 to 72% of the control value (Table 3).

In order to investigate further this apparent discrepancy between NA and MOPEG-SO_4 concentrations during post-drug recovery, and to obtain information on the dynamics of NA release, the rate of the probenecid-induced accumulation of MOPEG-SO_4 was evaluated 2, 3, 4 and 5 days after injection of reserpine (Figure 1a and b). While the rate of MOPEG-SO_4 accumulation cannot give a measure of NA turnover (Meek & Neff, 1973) it may be useful as an indication of NA output under various experimental conditions. On these days, at 09 h 00 min probenecid or saline was injected into reserpine or saline pretreated rats. Animals were killed 30 min and 60 min after probenecid. Saline-treated animals, killed at the same intervals, served as zero values. The rate of probenecid-induced accumulation of MOPEG-SO_4 was significantly lower (Figure 1a and b) 3 and 4 days after

reserpine, whereas it was not significantly decreased 2 and 5 days after drug administration.

Discussion

The experiments have shown that, in contrast to previous results in mice (Caesar, Hague, Sharman & Werdinius, 1974), reserpine induces a significant increase of MOPEG-SO_4, which parallels the initial depletion of NA. However, the low value of MOPEG-SO_4/NA ratio suggests that a large proportion of the NA liberated is not converted to MOPEG-SO_4, which does not appear to be the major metabolite of NA in this case. Indeed the MOPEG-SO_4/NA ratio is much lower shortly after reserpine administration than in other experimental conditions in which the neurotransmitter is liberated into the synaptic cleft such as electrical stimulation, stress, amphetamine or piribedil treatment (Bareggi *et al.*, 1978a, b). Thus MOPEG-SO_4 appears to be the major metabolite of NA only when the neurotransmitter is released from the functional pool into the synaptic cleft and reaches the postsynaptic receptors (Korf *et al.*, 1973a; Bareggi *et al.*, 1978a, b). MOPEG-SO_4 therefore reflects the release of the transmitter from the presynaptic neurone and provides a useful measure of the functional activity of noradrenergic neurones (Meek & Neff, 1973; Bareggi *et al.*, 1978a; Bareggi, Genovese & Markey, 1978c).

A different metabolic end-product, possibly DOPEG-SO_4, appears to be the major metabolite when NA is liberated intraneuronally from the storage pool after reserpine (Stone, 1973). Data about metabolites of exogenous NA obtained by Stone (1973) showed that following intraventricular injection of [^{3}H]-NA, reserpine administration induced a greater formation of [^{3}H]-DOPEG-SO_4 than of [^{3}H]-MOPEG-SO_4. Therefore it may be suggested that the increase in MOPEG-SO_4 early after reserpine administration is due to that fraction of neurotransmitter which escapes intraneuronal destruction and reaches the postsynaptic receptors. Reserpine may initially induce sympathomimetic effects such as hyperthermia which is prolonged by imipramine-like agents (Jori & Garattini, 1965).

Data showing that in reserpinized animals, a further dose of reserpine cannot further increase the concentration of MOPEG-SO_4 while amphetamine or electrical stimulation are still capable of increasing it further support the view that amphetamine and reserpine act by different mechanisms in releasing NA. The data confirm the current view that amphetamine and electrical stimulation act on a functional pool not sensitive to reserpine, while reserpine acts on the storage pool (Bareggi *et al.*, 1978a).

It has already been shown that reserpine impairs the storage mechanism and, in an initial phase, releases the neurotransmitter by impairing its storage in the intraneuronal granules (Iversen, 1967). Newly synthesized neurotransmitter, not in granules, is destroyed by intraneuronal monoamine oxidase (MAO) and this leads to impairment of noradrenergic transmission (Burnstock & Holman, 1962; Anden & Henning, 1966). Recovery of nerve function after reserpine is slow and has a multiphase time course which differs according to the parameter studied (Häggendal & Dahlstrom, 1970; 1971).

The time course of the recovery of neuronal activity after reserpine has still not been completely determined. It has been recently shown that a supersensitivity is developed by the postsynaptic receptor 24 h after reserpine (Williams & Pirch, 1974). This suggests that there is a decrease in NA output following the initial phase of neurotransmitter release. Our data showing a lower concentration and a decreased rate of probenecid-induced accumulation of MOPEG-SO_4 during the post-drug recovery phase, confirm that reserpine induces a decrease in NA output.

The first neuronal function to be recovered is the ability to store the neurotransmitter in the new granules transmitted by axonal flow (Häggendal & Dajlstrom, 1970; Andèn & Lundborg, 1970). The neuronal ability to take up and to store [^{3}H]-NA has been shown to begin recovery 24 h after reserpine (Häggendal & Dahlstrom, 1970). Re-establishment of this function enables the intraneuronal NA pool to be reconstituted. From the functional point of view, our data seem to indicate that recovery of the ability to store NA does not lead to normal neurotransmitter output.

Output does seem to return to normal once the intraneuronal concentrations of NA have been rebuilt to about 50% of control. NA concentrations in the storage pool may therefore be the factor which regulates the neuronal output of the neurotransmitter. The output remains lower than normal until a threshold concentration of NA is reached.

In conclusion, our investigation has shown that reserpine effects on brain NA neurones have a multiphasic time-course. First, there is the releasing phase, when large amounts of NA are released from the storage pool. Data suggest that in this case MOPEG-SO_4 is not the major metabolite of NA formed. It appears reasonable to assume that the increase in MOPEG-SO_4 concentration seen in this phase is due to the metabolism of that fraction of NA which escapes intraneuronal destruction and reaches the synaptic cleft.

Second, there is a decreased NA output, as reflected by the decrease in the probenecid-induced MOPEG-SO_4 accumulation rate, which reaches its lowest value on the third day. At this time, the NA

concentrations have already begun to recover. Finally, there is a recovery of neuronal output which is almost normal on the fifth day, when the NA concentration is 50% or more of control values.

The authors wish to thank Dr M. Carruba for his stimulating contribution in reviewing the manuscript. This work has supported by grant No 5.172-36-00110-35-053 from the University of Connecticut Research Foundation.

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(Received January 24, 1978. Revised July 26, 1978.)