Pharmacology Biochemistry & Behavior, Vol 22, pp 153–155, 1985 © Ankho International Inc Printed in the U S A 0091-3057/85 $3 00 + 00

BRIEF COMMUNICATION

Enhancement of Phenol-Induced Tremor Caused by Central Monoamine Depletion

TAKAHIKO SUZUKI[1] AND KENSUKE KISARA

Department of Pharmacology, Tohoku College of Pharmacy, Sendai, Miyagi 983, Japan

Received 19 September 1983

SUZUKI, T AND K KISARA *Enhancement of phenol-induced tremor caused by central monoamine depletion* PHARMACOL BIOCHEM BEHAV 22(1) 153–155, 1985 —The effects of monoamine depletors and monoamine denervators on phenol-induced tremor were studied in mice. The tremor induced by phenol was enhanced by pretreatment with reserpine or tetrabenazine, but not with syrosingopine However, α-methyl-p-tyrosine, p-chlorophenylalanine or 6-hydroxydopamine did not affect the tremor These results suggest that the depletion of central monoamines as a whole contribute to the enhancement of the tremor induced by phenol

Phenol Tremor Monoamine Depletion

IN order to relieve man from the pain caused by carcinoma, various phenol solutions have been used as the neuron blocking agents [10]. Following intravenous use of phenol solution for relieving the pain, the induction of convulsion in man has been reported by Benson [3] It is well known that phenol and its derivatives are capable of inducing tremor or convulsions. However, there is little evidence concerning the mechanism or characteristics of phenol-induced tremor. In the present paper, a study was carried out to determine if the administration of monoaminergic agents influenced the tremor induced by phenol.

METHOD

Male dd-Y strain mice weighing 20–25 g were used. For behavioral observation, mice were placed in individual stainless cages, and the length of time to occurrence of tremor from phenol injection (latency) and duration of the tremor were measured. The tremor was graded on a 4 point scale according to the magnitude as follows; −: normal, +· slight, ++: moderate and +++· severe. Drugs used were as follows; phenol (Kanto Chemical Co , Japan), reserpine (Sigma), tetrabenazine (TBZ, ICN Pharmaceuticals, Inc), D,L-α-methyl-p-tyrosine (α-MPT, Sigma), D,L-parachlorophenylalanine (PCPA, Sigma), syrosingopine (Sigma), 6-hydroxydopamine hydrochloride (6-OHDA, Sigma) and 5,6-dihydroxytryptamine hydrochloride (5,6-DHT, Sigma) Phenol was diluted to 1 v/v% and injected by subcutaneous route. 6-OHDA and 5,6-DHT were administered intracerebroventricularly after being dissolved into 0.5% ascorbic acid-Ringer's solution, and the others were suspended in 0.5% Tween 80 and injected by the intraperitoneal route.

RESULTS

Pretreatment with reserpine at the doses ranging from 1 to 5 mg/kg produced a marked enhancement of intensity and duration of the phenol-induced tremor in a dose dependent manner. The duration was extended to about 270% of the control group by 5 mg/kg of reserpine. At this dose, the lack of righting reflex was observed in all mice, but latency was not changed significantly by any doses of reserpine. Following pretreatment with 100 mg/kg of TBZ, the duration of phenol-induced tremor was extended to 330%, and latency was shortened to 65% of the control group. The lack of righting reflex was also observed in all mice, and 20% of the mice were dead with tonic convulsion at the 100 mg/kg dose of TBZ. Syrosingopine, on the contrary, had no effect on latency, duration and intensity of the tremor at a dose of 10 mg/kg Both of αMPT and PCPA did not change experimental measurements of phenol-induced tremor. The tremor was not altered by any doses of 6-OHDA. 5,6-DHT slightly enhanced the intensity of the tremor, but did not affect to the duration and latency

DISCUSSION

The main finding of the present study shows that phenol-induced tremore is affected by monoaminergic agents. In the present study, phenol-induced tremor was enhanced markedly by pretreatment with reserpine and TBZ. But the

[1]Requests for reprints should be addressed to T Suzuki, Department of Pharmacology, Tohoku College of Pharmacy, 4-4-1, Komatsushima, Sendai, Miyagi 983, Japan

TABLE 1

THE EFFECT OF DRUGS WHICH AFFECT TO THE MONOAMINERGIC SYSTEM ON 1% PHENOL-INDUCED TREMOR

Drugs	Dose and injection time before phenol	Tremor Latency (sec)	Tremor Max Intensity	Tremor Duration (min)
Control(1)	0 5% Tween 80	106 9 ± 8 4	+	26 97 ± 1 56
Reserpine	1 mg/kg, 24 hr	96 7 ± 6 9	+	30 0 ± 1 76
	2 5	102 5 ± 6 9	++	36 6 ± 6 67
	5	99 4 ± 5 2	+++	72 2 ± 8 84†
Tetrabenazine	50 mg/kg, 3 hr	124 2 ± 8 3	++	34 6 ± 2 00*
	100	79 2 ± 7 6*	+++	89 6 ± 16 17†
Syrosingopine	10 mg/kg, 24 hr	107 9 ± 6 5	+	25 4 ± 1 86
αMPT	50 mg/kg × 3 days	110 0 ± 6 4	+	26 8 ± 1 28
	100 × 3 days	117 5 ± 6 7	+	27 2 ± 2 40
PCPA	300 mg/kg, 24 hr	108 3 ± 7 6	+	26 5 ± 1 20
Control(2)	Ringer's solution	94 6 ± 6 2	+	34 1 ± 2 57
6-OHDA	10 μg/mouse, 1 week	110 0 ± 7 0	+	33 2 ± 2 42
	20	109 3 ± 12 2	+	36 0 ± 2 11
	40	117 9 ± 9 6	+	32 2 ± 2 10
5,6-DHT	50 μg/mouse, 1 week	104 3 ± 6 4	++	34 7 ± 2 10

The values for latency and duration of the tremor are the mean ± SEM of 8–15 mice 6-OHDA and 5,6-DHT were compared to control(2), and the others were compared to control(1) Statistical significance, *$p<0.05$ and †$p<0.001$

tremor was not affected by pretreatment with syrosingopine, a peripheral monoamine depletor [6, 8, 9]. From these results, it is inferred that the depletion of central monoamines contribute to the enhancement of the tremor induced by phenol, and depletion of peripheral monoamines is not involved in the enhancement of the tremor However, chemical lesions of catecholaminergic and serotonergic neurons caused by 6-OHDA [4,12] and 5,6-DHT [12], respectively, hardly affected to the tremor. Furthermore, αMPT [11] and PCPA [5], catecholamines and serotonin synthesis inhibitor, respectively, also caused no enhancement of the tremor induced by phenol. Therefore, severe depletion of monoamines as a whole may induce the hypersensitivity of neurons, and central monoamines as a whole, not individually, may possibly play a role as the stabilizer against the hyperexcitation caused by phenol in the brain

Otsuka and Nonomura [7] have reported that phenolic substances act on motor nerve endings so that a large quantity of acetylcholine is released by a single nerve impulse, and they have proposed the hypothesis that phenolic substances might act on central synapses by the presynaptic mechanism, increasing the release of transmitters Banna and Jabbur [1] have also reported that phenol has facilitatory effect on central synaptic transmission, and this facilitation is decreased after repetitive administration of phenol Therefore, they have suggested that phenol-induced facilitatory effect on the central synaptic transmission is due to the increase of transmitter release. But the results obtained from present study suggest that phenol-induced tremor is not caused by releasing monoamines, because the monoamine depletors or monoamine denervators did not inhibit the occurrence of phenol-induced tremor

Although the present preliminary investigation gives no information about the mechanism of phenol-induced tremor, it suggests that clearing the action of reserpine to the phenol-induced tremor may be a key to understand the central action of phenol

ACKNOWLEDGEMENTS

We gratefully acknowledge Dr Y Ogura, professor at Tohoku University, for his thoughtful comments and suggestions on this manuscript, and also acknowledge Dr T Sakurada's help with the preparation of this paper

REFERENCES

1 Banna, N R and S J Jabbur Increased transmitter release induced by convulsant phenols *Brain Res* **20:** 471–473, 1970

2 Baumgarten, H C , A Bjorklund, L Lachenmayer, A Nobin and U Stenevi Long-lasting selective depletion of brain serotonin by 5,6-dihydroxytryptamine *Acta Physiol Scand (Suppl)* **373:** 1–15, 1971

3 Benson, H T Convulsions secondary to intravascular phenol A hazard of celiac plexus block *Anesth Analg (Cleve)* **58:** 150–151, 1979

4 Breese, G R and T D Traylor Effect of 6-hydroxydopamine on brain norepinephrine and dopamine Evidence for selective degeneration of catecholamine neurons *J Pharmacol Exp Ther* **174:** 413–420, 1970

5 Koe, B. K. and A Weissman p-Chlorophenylalanine A specific depletor of brain serotonin *J Pharmacol Exp Ther* **154:** 499–516, 1966
6 Leroy, J G and A F De Schaepdryver Catecholamine levels of brain and heart in mice after iproniazid syrosingopine and 10-methoxydeserpidine *Arch Int Pharmacodyn Ther* **130:** 231–234, 1961
7 Otsuka, M and Y Nonomura The action of phenolic substances on motor nerve endings *J Pharmacol Exp Ther* **140:** 41–45, 1963
8 Pham-Huu-Chanh and A F De Schaepdryver On the pharmacology of syrosingopine and reserpine *Arch Int Pharmacodyn Ther* **157:** 207–213, 1965
9 Quinton, R M The increase in the toxicity of yohimbin induced by imipramine and other drugs in mice. *Br J Pharmacol* **21:** 51–66, 1963
10 Smith, M. C Histological findings following intrathecal injections of phenol solutions for relief of pain *Br J Anaesth* **36:** 387–406, 1984
11 Spector, S , A. Sjoerdsma and S Udenfriend Blockade of endogeneous norepinephrine synthesis by α-methyl-p-tyrosine, an inhibitor of tyrosine hydroxylase *J Pharmacol Exp Ther* **147:** 86–95, 1965
12 Ungerstedt, U 6-Hydroxydopamine induced degeneration of central monoamine neurons *Eur J Pharmacol* **5:** 107–110, 1968