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Serotonin-Norepinephrine Interactions in the Tremorolytic Actions of Phenoxybenzamine and Trazodone[1]

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HWANG, C. E. AND M. H. VAN WOERT. *Serotonin-norepinephrine interactions in the tremorolytic actions of phenoxybenzamine and trazodone.* PHARMAC. BIOCHEM. BEHAV. 10(1) 27–29, 1979.—Phenoxybenzamine (5 mg/kg IP) and trazodone (5 mg/kg IP) reduced tremors produced in mice by administration of oxotremorine (10 mg/kg), harmaline (80 mg/kg), catechol (60 mg/kg), kepone (200 mg/kg) and clonidine (100 mg/kg). Azapetine (10 mg/kg IP) in combination with L-5-hydroxytryptophan (50 mg/kg IP) reduced the tremor induced by oxotremorine, catechol, kepone and clonidine. In mice with lower thoracic spinal cord transection, phenoxybenzamine and trazodone reduced catechol-induced tremor above and below the site of transection. These findings suggest that an alpha noradrenergic-serotonergic neuronal balance in the spinal cord may modulate tremors of different etiologies.

Drug-induced tremor Serotonin Norepinephrine Phenoxybenzamine Trazodone

TREMORS are associated with pathological processes at different levels of the neuraxis. This study was undertaken to determine if there are any neurotransmitter abnormalities which are common to tremors originating from different foci. We have examined the effects of various pharmacologic agents, which are known to modify different central nervous system (CNS) neurotransmitter actions, on tremors in mice induced by the tremorogenic compounds oxotremorine, harmaline, catechol, kepone and clonidine. Two drugs, phenoxybenzamine (dibenzyline) and trazodone reduced tremor produced by all of these agents despite heterogenicity of their etiologies. Oxotremorine-induced tremor is associated with an increase in basal ganglia acetylcholine; the tremor and cholinergic dysfunction are alleviated by antimuscarinic drugs [4,6]. The tremor produced by oxotremorine in rodents has been considered to be an animal model of parkinsonism. Harmaline, a monoamine oxidase inhibitor, has been postulated to produce tremors by stimulating cerebellar climbing fibers in the olivo-cerebellar pathway which in turn activates purkinje cell firing in the cerebellum [7, 14, 17]. The pathophysiology of catechol-induced tremor is thought to be activation of the gamma system in the spinal cord and the brain stem reticulo-spinal pathway [1,2]. Kepone is an organochlorine insecticide which produces a reversible chronic tremor by an unknown mechanism [9]. The antihypertensive drug, clonidine, stimulates central alpha-adrenergic receptors and at high doses produces tremors in animals [11,16].

METHOD

Tremor was induced in male Swiss-Webster mice (25–30 g) by intraperitoneal injection of oxotremorine (10 mg/kg), harmaline (80 mg/kg), catechol (60 mg/kg) and clonidine (100 mg/kg). Kepone (200 mg/kg) was administered intragastrically. The intensity of tremor was measured using an electronic activity meter (Columbus Instruments, Columbus, Ohio), which was tuned at 40 μA. None of the tremorogens produced hyperactivity and the activity counts due to tremor were 12 to 20 times the counts of naive animals. Kepone produced tremor approximately 2 hr after administration and the intensity of tremor persisted unchanged for 4 to 5 hr, subsequently diminishing gradually over a 24 hr period. Six 5 min activity counts were recorded at 2.5 to 3 hr after kepone administration, a pharmacologic agent was injected, and six 5 min counts were again recorded at 3.5 to 4 hr after kepone. The tremor activity of the other, shorter acting, tremorogens was counted for a single 5 min period, and the effect of pharmacologic agents on tremor was compared with saline injected controls. Pharmacologic agents and saline were injected intraperitoneally 30 min prior to injection of tremorogens. Statistical evaluation of drug treatment was made

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TABLE 1

EFFECTS OF PHENOXYBENZAMINE, TRAZODONE, AZAPETINE, L-5HTP AND COMBINATION OF AZAPETINE AND L-5HTP ON TREMOR

	Oxotremorine (10 mg/kg)	Harmaline (80 mg/kg)	Counts/5 min Catechol (60 mg/kg)	Kepone (200 mg/kg)	Clonidine (100 mg/kg)
Control	340 ± 12	312 ± 12	480 ± 45	417 ± 18	424 ± 6
Phenoxybenzamine (5 mg/kg)	184 ± 29† (46%)	175 ± 23* (44%)	242 ± 24† (50%)	88 ± 18† (80%)	252 ± 37† (41%)
Trazodone (5 mg/kg)	275 ± 27	210 ± 38	295 ± 36† (39%)	137±31† (66%)	220 ± 38† (48%)
Azapetine (10 mg/kg)	313 ± 22	314 ± 23	420 ± 22	465 ± 77	414 ± 11
L-5HTP (50 mg/kg)	342 ± 31	370 ± 16	523 ± 32	476 ± 29	228 ± 40† (46%)
Azapetine + L-5HTP (10 + 50)	234 ± 38* (32%)	371 ± 73	252 ± 33† (47%)	200 ± 17† (53%)	294 ± 21† (31%)
F Value	4.32 $p<0.01$	6.41 $p<0.005$	13.66 $p<0.005$	21.77 $p<0.005$	11.82 $p<0.005$
Allowances for					
* = $p<0.05$	94	118	119	131	100
† - $p<0.01$	117	148	149	164	124
by Dunnett's test					

The values are the mean ± SEM of activity counts from 6–8 mice. Naive mice have activity counts of 25 to 30 per 5 min. The numbers in parentheses are the % reduction in tremor.

by one-way analysis of variance followed by Dunnett's test.

Tremorogens were also studied in mice 7 days after lower thoracic spinal cord transection under ether anesthesia.

The drugs used in this study were: oxotremorine sesquifumarate (Aldrich), harmaline HCl (Sigma), catechol (Sigma), clonidine HCl (Boehringer Ingelheim), kepone (decachlorooctahydro-1, 3, 4-metheno-2H-cyclobuta(cd)-pentalen-2-one) (Allied Chemical), phenoxybenzamine HCl (Dibenzyline®, Smith Kline and French), trazodone HCl (2-{3-[4(m-chlorophenyl)1-piperazinyl]-propyl}-S-triazolo (4,3-α)-pyridin-3-(2H) one,(Mead Johnson), azapetine phosphate (Hoffmann La Roche), and L-5-hydroxytryptophan (Calbiochem). All doses indicated in the text refer to the salt.

RESULTS

Phenoxybenzamine and trazodone reduced tremor produced by all tremorogens in mice (Table 1). Neither drug had any sedative action at the doses used and did not change the activity counts of naive mice. Trazodone inhibits the reuptake of serotonin thus potentiating endogenous brain serotonin activity [8]. Trazodone, like phenoxybenzamine, also blocks alpha-adrenergic receptors [13]. Therefore, the effect of another alpha-adrenergic receptor blocker azapetine was measured in the 5 tremor models. Azapetine had no significant effect on any of the 5 forms of tremor. Increasing brain serotonin by administration of its precursor L-5-hydroxytryptophan (L-5HTP) enhanced harmaline tremor and only reduced the tremor produced by kepone. However, pretreatment with the combination of azapetine and L-5HTP reduced the tremors produced by oxotremorine, kepone, catechol and clonidine but not harmaline-induced tremor (Table 1).

Under ether anesthesia the spinal cord was transected at the lower thoracic region in mice. Seven days after spinal cord transection the same doses of tremorogens, as listed in Table 1 were administered to groups of 6–8 post-operated mice. Only catechol produced tremors in skeletal muscles both below as well as above the level of transection. The remainder of the tremorogens induced tremors only above the level of spinal cord transection. Intraperitoneal injections of trazodone (5 mg/kg) and phenoxybenzamine (5 mg/kg) reduced catechol-induced tremor equally well in the fore and hind limbs of mice with spinal cord transections. The effect of L-5HTP (50 mg/kg) and azapetine (10 mg/kg) on tremor could not be evaluated since this drug combination produced death 10 to 15 min after injection in mice with spinal cord transections.

DISCUSSION

Trazodone is an investigational drug which has been shown to be an effective antidepressant [3]. In patients with mental depression associated with Parkinson disease, trazodone was noted to reduce tremor as well as depression [12]. The major pharmacologic action of trazodone is the potentiation of CNS serotonin by blockade of its reuptake [8]. However, trazodone also has been demonstrated to block alpha-adrenergic receptors as phenoxybenzamine does [13]. In a recent study, phenoxybenzamine was reported to increase brain serotonin turnover [15]. We suspected that the

tremorolytic properties of trazodone and phenoxybenzamine might be due to the combined effects of blockade of alpha-adrenergic receptors and potentiation of CNS serotonin. Neither the specific alpha receptor blocker, azapetine, nor the serotonin precursor, L-5HTP, alone had any significant general anti-tremor action although, in combination, their tremorolytic effect was comparable to trazodone and phenoxybenzamine. Only harmaline tremor did not respond to azapetine in combination with L-5HTP. Harmaline is a monoamine oxidase inhibitor and enhances L-5HTP-induced increase in brain serotonin by blocking its catabolism. Toxic levels of brain serotonin also produce tremor [10], which could explain the failure of harmaline tremor to respond to L-5HTP in combination with azapetine. Harmaline tremor is not due to monoamine oxidase inhibition alone since other monoamine oxidase inhibitors do not produce tremor.

The neurochemistry and pathophysiology of each of the five tremor models are presumably different [1, 2, 4, 6, 7, 11, 14, 16, 17]. Trazodone, phenoxybenzamine, and L-5HTP with azapetine may reduce tremor in all of these animal models by modulating some final common pathway. Unlike the other tremorogens in this study catechol may act directly on the spinal cord since this chemical produces tremor both above and below the level of spinal cord transection. Since trazodone and phenoxybenzamine reduced catechol tremor above and below the level of transection, one possible site of action may be in the spinal cord or even more peripherally. Nerve terminals containing serotonin and norepinephrine have been demonstrated in the spinal cord [5]. A balance of serotonergic and noradrenergic input to alpha motor neurons, the gamma system or spinal interneurons may modulate tremor impulses of different origins in the CNS.

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