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Propranolol-induced seizures in mice: the role of noradrenaline

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Abstract. The effects of some noradrenergic agents, phenobarbitone, diazepam and phenytoin on seizures produced by propranolol were investigated in mice. Isoprenaline and DL-threo-3,4-dihydroxyphenylserine (DOPS) effectively antagonized the seizures elicited by propranolol. Pargyline and imipramine significantly attenuated propranolol-induced seizures and also significantly potentiated the protecting effect of DOPS against the seizures. α-Methyl-p-tyrosine, disulfiram and reserpine significantly potentiated propranolol-elicited seizures. However, DOPS significantly antagonized the seizure-potentiating effects of α-methyl-p-tyrosine, disulfiram and reserpine. Phenylephrine, clonidine, prazosin, idazoxan, phenobarbitone, diazepam and phenytoin did not significantly alter propranolol-induced seizures. These results suggest that propranolol-induced seizures in mice may involve a noradrenergic mechanism mediated via central β-adrenoceptors.

Key words. Propranolol; seizures; noradrenergic mechanism; mice.

Propranolol is a nonselective β-adrenoceptor blocking drug which is commonly used to treat various cardiovascular diseases, notably essential hypertension, angina pectoris and cardiac arrhythmias. It is also useful in the treatment of anxiety and prophylaxis of migraine [1, 2]. Although propranolol and related drugs have been shown to reduce or completely suppress convulsions induced by electroshock, pentylenetetrazole and strychnine [3–5]; propranolol-induced convulsions in humans, especially in high doses and self-poisoning, have been reported [6–8]. However, it is unclear how propranolol produces convulsions. Buiumsohn et al. [9] reported that a nonspecific action on centrally located neurons related to propranolol's membrane stabilizing effects, as well as its high lipophilicity and ability to penetrate into cerebral tissues, is probably involved in the convulsions. Papanicolaou et al. [3], on the other hand, claimed that β-adrenoceptor antagonists exert an anticonvulsant effect through central β_2-adrenoceptors and that at high dose levels, additional anticonvulsant activity is associated with membrane stabilization in antagonists with this property. Propranolol is known to block the effects of noradrenaline at the β-adrenoceptors both centrally and peripherally [1, 2]. A large body of evidence implicates central noradrenaline in the mechanism controlling the seizure threshold, although the data available are conflicting. The stimulation or inhibition of the central noradrenergic system has been shown to have convulsant and anticonvulsant effects [10–13]. In view of these findings, this project was designed to investigate the role of noradrenergic mechanisms in seizures produced by propranolol in mice.

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Materials and methods

Animals. Male and female albino mice (bought from the Medical Research Council, Cape Town, South Africa) weighing 20–30 g were used throughout the experiment. They were housed in groups of eight per cage and allowed free access to both food and water. Each mouse was used for one experiment only.

Drugs. Propranolol hydrochloride (BE-TABS, South Africa), isoprenaline hydrochloride (Sterling Drug Ltd), phenylephrine hydrochloride (Sigma Chemical Co.), clonidine hydrochloride (Sigma Chemical Co.), DL-threo-3,4-dihydroxyphenylserine (DOPS, Sigma chemical Co.), pargyline hydrochloride (Sigma Chemical Co.), imipramine hydrochloride (Sigma Chemical Co.), α-methyl-DL-p-tyrosine methyl ester hydrochloride (AMPT, Sigma Chemical Co.), prazosin hydrochloride (Varichem Lab., Zimbabwe), tetraethylthiuram disulfide (Disulfiram, Sigma Chemical Co.), reserpine (Sigma Chemical Co.), phenobarbitone (Paris Chemical), idazoxan hydrochloride (Sigma Chemical Co.) and 5,5-diphenylhydantoin sodium salt (phenytoin, Sigma Chemical Co.) were all dissolved in physiological saline. Diazepam (Valium, Roche Products) was dissolved in a minimum amount of polyethylene glycol 400 (Fluka AG, Buchs) and adjusted to the appropriate volume with physiological saline. All drugs were injected intraperitoneally (i.p.), in a volume of 1 ml per 100 g of mouse. Control animals received equal volume injections of the appropriate vehicles which included saline and polyethylene glycol 400. The activity of any of the drugs used was not affected by vehicle treatment. Fresh drug solutions were prepared each day of the experiment. The drug pretreatment times prior to the injection of propranolol were 25 min (isoprenaline), 20 min (phenylephrine), 45 min (clonidine), 24 h (DOPS), 3 h (pargyline), 1 h 45 min (imipramine), 1 h (prazosin, idazoxan), 17 h (α-methyl-p-tyrosine), 6, 4 and 2 h (disulfiram), 21 h (reserpine), 10 min (phenobarbitone), 20 min (diazepam) and 30 min (phenytoin). The pretreatment times as well as the doses of some of the drugs used have been previously described [11, 14]. However, the pretreatment times and the doses of isoprenaline, imipramine, phenylephrine and phenytoin were established from preliminary studies in our laboratory.

Table 1. Convulsant effect of propranolol in mice.

Propranolol (mg/kg, i.p.)	No. convulsed/ No. used	Latency of tonic convulsion (min) mean ± SEM	
50	0/8	-	-
62.5	3/8	14.33	0.60
75	3/8	12.33	0.17
87.5	5/8	8.60	1.28
100	8/8	5.38	0.64
125	8/8	3.75	0.29

Convulsant activity assessment. A modified method of Vellucci and Webster [15] was used for the assessment of the convulsant activity of propranolol. Eight mice per dose of drug were used. Mice were placed singly in perspex cages (25 × 15 × 15 cm), for 30 min to acclimatize to their new environment before starting the experiment. The animals were observed for 30 min after the injection of propranolol. The time taken for the onset of tonic convulsions and the proportion of animals convulsing were noted. Animals that did not convulse within 30 min were recorded as not convulsing. Both the control and test experiments were carried out between 0800 h and 1700 h in a quiet laboratory with an ambient temperature of 20 ± 1 °C.

Statistical analysis. Data on the latency of tonic seizures were compared by the paired Student's *t*-test. Analysis of the proportion of animals convulsing was performed using the chi-squared test with Yate's correction for continuity.

Results

Convulsant effect of propranolol. Propranolol (50–125 mg/kg, i.p.) dose dependently elicited tonic seizures in mice (table 1), which manifested as extension of the hind limbs, sometimes with loss of the writhing reflex. The extension of the hind limbs was generally preceded by violent body movement. The convulsant effect of propranolol and the overall behaviour of the mice were not affected by the control vehicles.

Effects of isoprenaline, phenylephrine, prazosin, clonidine and idazoxan on propranolol seizures. Isoprenaline (5–20 mg/kg, i.p.) in a dose-related manner significantly delayed the latency of propranolol (100 mg/kg, i.p.)-elicited tonic seizures, and also significantly reduced the proportion of animals convulsing (table 2). Phenylephrine (2.5–10 mg/kg, i.p.) and clonidine (0.25–1 mg/kg, i.p.) did not not alter the seizures produced by propranolol (100 mg/kg, i.p.) to any significant extent. Similarly, prazosin (0.5–2 mg/kg, i.p.) and idazoxan (2–4 mg/kg, i.p.) did not affect either the onset or incidence of propranolol-induced seizures significantly

Table 2. Effect of isoprenaline on propranolol-induced seizures in mice.

Doses (mg/kg, i.p.)			Latency of tonic convulsion (min) mean ± SEM	
Propranolol	Isoprenaline	No. convulsed/ No. used		
100	0	8/8	5.25	0.42
100	5	7/8	8.71*	0.59
100	10	5/8	11.20*	0.85
100	20	3/8†	16.33*	0.44

*$p < 0.001$ vs. propranolol (100 mg/kg) control, Student's *t*-test.
†$p < 0.05$ vs. propranolol (100 mg/kg) control, chi-squared test.

Table 3. Effects of dihydroxyphenylserine (DOPS), pargyline and imipramine on propranolol-induced seizures in mice.

Doses (mg/kg, i.p.)					Latency of tonic convulsion (min) mean ± SEM	
Propranolol	DOPS	Pargyline	Imipramine	No. convulsed/ No. used		
100	-	-	-	8/8	5.17	0.44
100	2	-	-	8/8	7.25*	0.61
100	4	-	-	6/8	10.00***	0.71
100	8	-	-	3/8^{+}	12.67***	0.60
100	-	25	-	8/8	10.38***	0.50
100	-	50	-	8/8	13.00***	1.50
100	-	100	-	6/8	12.00**	1.63
100	2	100	-	3/8°	11.67$^{\blacktriangle}$	0.44
100	-	-	12.5	7/8	8.43**	0.84
100	-	-	25	7/8	11.00***	1.09
100	-	-	50	4/8	14.79***	0.72
100	2	-	25	3/8°	10.67$^{\blacksquare}$	0.33

*$p < 0.02$, **$p < 0.005$, ***$p < 0.001$ vs. propranolol (100 mg/kg) control, Student's t-test.
$^{+}p < 0.05$ vs. propranolol (100 mg/kg) control, chi-squared test.
$^{\blacksquare}p < 0.02$, $^{\blacktriangle}p < 0.005$ vs. DOPS (2 mg/kg) plus propranolol (100 mg/kg), Student's t-test.
°$p < 0.05$ vs. DOPS (2 mg/kg) plus propranolol (100 mg/kg), chi-squared test.

(results not shown). Isoprenaline in the doses used caused a slight but brief increase in the motility of the animals, clonidine (0.25–1 mg/kg, i.p.) sedated them, and phenylephrine, prazosin and idazoxan did not affect the behaviour of the animals prior to the administration of propranolol.

Effects of dihydroxyphenylserine (DOPS), pargyline and imipramine on propranolol seizures. DOPS (2–8 mg/kg, i.p.) dose dependently and significantly prolonged the latency of propranolol (100 mg/kg, i.p.)-induced seizures. The incidence of the seizures was also significantly reduced by DOPS (8 mg/kg, i.p.). Pargyline (25–100 mg/kg, i.p.) and imipramine (12.5–50 mg/kg, i.p.) significantly delayed the latency of tonic seizures produced by propranolol. Pargyline (100 mg/kg, i.p.) caused a 25% reduction in the number of animals convulsing, whereas imipramine (50 mg/kg, i.p.) reduced the incidence of the seizures by 50%. Pargyline (100 mg/kg, i.p.) and imipramine (25 mg/kg, i.p.) potentiated the seizure-protecting effect of a low dose of DOPS (2 mg/kg, i.p.) by significantly prolonging the latency of propranolol-induced seizures and also significantly reducing the number of animals convulsing (table 3). DOPS (2–8 mg/kg, i.p.), pargyline (25–100 mg/kg, i.p.) and imipramine (12.5–50 mg/kg, i.p.) did not alter the overall behaviour of the mice before the injection of propranolol.

Effects of α-methyl-p-tyrosine (AMPT), disulfiram and reserpine on propranolol seizures. AMPT (100 mg/kg, i.p.) effectively shortened the onset of propranolol (100 mg/kg, i.p.)-induced seizures. AMPT (50 mg/kg, i.p.) did not affect propranolol seizures. Similarly, disulfiram (3×50–3×100 mg/kg, i.p.) and reserpine (20 mg/kg, i.p.) significantly shortened the latency of propranolol-elicited seizures. Reserpine (10 mg/kg, i.p.) did not significantly affect the seizures. A low dose (62.5 mg/kg, i.p.) of propranolol produced tonic seizures in 37.5% of the animals. AMPT (100 mg/kg, i.p.), disulfiram (3×50 mg/kg, i.p.) and reserpine (20 mg/kg, i.p.) potentiated the seizure-producing effect of low dose (62.5 mg/kg, i.p.) of propranolol by profoundly shortening the onset and increasing the incidence of the seizures by 87.5%, 100% and 100% respectively. On the other hand, DOPS (8 mg/kg, i.p.) significantly antagonized the potentiating effects of AMPT (100 mg/kg, i.p.), disulfiram (3×50 mg/kg, i.p.) and reserpine (20 mg/kg, i.p.) on propranolol-induced seizures by significantly prolonging the latency of seizures and also reducing the number of animals convulsing by 50%, 62.5% and 50% respectively (table 4). AMPT (50–100 mg/kg, i.p.) and reserpine (10–20 mg/kg, i.p.) decreased the motility whereas disulfiram (3×50–3×100 mg/kg, i.p.) did not affect the behaviour of the animals prior to the injection of propranolol.

Effects of phenobarbitone, diazepam and phenytoin on propranolol seizures. Phenobarbitone (7.5–12.5 mg/kg, i.p.) did not significantly affect the latency and/or the incidence of seizures induced by propranolol (100 mg/kg, i.p.). Similarly, diazepam (0.25–1 mg/kg, i.p.) and phenytoin (8–32 mg/kg, i.p.) did not significantly alter the seizures produced by propranolol (100 mg/kg, i.p., results not shown). Phenobarbitone (7.5–12.5 mg/kg, i.p.) and diazepam (0.25–1 mg/kg, i.p.) sedated the animals, whereas phenytoin (7.5–12.5 mg/kg, i.p.) did not affect their behaviour prior to the administration of propranolol.

Discussion

The involvement of noradrenergic system in propranolol-induced seizures was investigated in mice. The

Table 4. Effects of α-methyl-p-tyrosine (AMPT), disulfiram and reserpine on propranolol-induced seizures in mice.

Doses (mg/kg, i.p.)						Latency of tonic convulsion (min) mean ± SEM	
Propranolol	AMPT	Disulfiram	Reserpine	DOPS	No. convulsed/ No. used		
100	-	-	-	-	8/8	5.17	0.45
62.5	-	-	-	-	3/8	14.67	0.93
100	-	-	-	8	3/8$^{\square}$	14.33***	0.44
100	50	-	-	-	8/8	4.88	0.65
100	100	-	-	-	8/8	2.88**	0.41
62.5	100	-	-	-	7/8$^{\bullet}$	8.29^{++}	0.98
100	100	-	-	8	4/8	7.25$^{\triangle}$	0.58
100	-	3 × 50	-	-	8/8	3.13*	0.57
100	-	3 × 100	-	-	8/8	3.00*	0.61
62.5	-	3 × 50	-	-	8/8$^{\blacksquare}$	9.00^{+}	1.02
100	-	3 × 50	-	8	3/8$^{\phi}$	8.67°	0.44
100	-	-	10	-	8/8	4.00	0.59
100	-	-	20	-	8/8	3.38*	0.50
62.5	-	-	20	-	8/8$^{\blacksquare}$	9.13^{+++}	0.69
100	-	-	20	8	4/8	8.25$^{\blacktriangledown}$	0.52

*$p < 0.02$, **$p < 0.005$, ***$p < 0.001$ vs. propranolol (100 mg/kg) control, Student's t-test.
$^{+}p < 0.02$, $^{++}p < 0.01$, $^{+++}p < 0.005$ vs. propranolol (62.5 mg/kg), Student's t-test.
$^{\triangle}p < 0.001$ vs. AMPT (100 mg/kg) plus propranolol (100 mg/kg), Student's t-test.
°$p < 0.001$ vs. disulfiram (3 × 50 mg/kg) plus propranolol (100 mg/kg), Student's t-test.
$^{\blacktriangledown}p < 0.001$ vs. reserpine (20 mg/kg) plus propranolol (100 mg/kg), Student's t-test.
$^{\square}p < 0.05$ vs. propranolol (100 mg/kg) control, chi-squared test.
$^{\bullet}p < 0.01$, $^{\blacksquare}p < 0.005$ vs. propranolol (62.5 mg/kg), chi-squared test.
$^{\phi}p < 0.05$ vs. disulfiram (3 × 50 mg/kg) plus propranolol (100 mg/kg), chi-squared test.

data obtained show that isoprenaline and other nor adrenergic drugs such as DOPS, pargyline, imipramine, AMPT, disulfiram and reserpine altered the seizures elicited by propranolol.

The present findings show that propranolol produced dose-dependent tonic seizures in mice. Isoprenaline is a nonselective β-adrenoceptor agonist which mimics the activity of noradrenaline at the β-adrenoceptors [1, 2]. It is not surprising, therefore, that isoprenaline (5–20 mg/kg, i.p.) antagonized the seizures elicited by propranolol. This result is consistent with the findings of Ivnan et al. [8] which showed that the convulsion produced by propranolol during self-poisoning was antagonized with a massive dosage of isoprenaline. Phenylephrine is a potent and selective α_1-adrenoceptor agonist which acts by mimicking the effect of noradrenaline at the α_1-adrenoceptors [1, 2]. Clonidine, on the other hand, is a selective α_2-adrenoceptor agonist which lowers the levels of noradrenaline peripherally and centrally by inhibiting its release and hence, reducing the activity [1, 2]. Clonidine has also been widely reported to possess anticonvulsant properties [16]. According to Forster [1] and Rang et al. [2], prazosin is a selective α_1-adrenoceptor antagonist which acts by blocking the effects of noradrenaline at the α_1-adrenoceptors. Prazosin has also been shown to exert some anticonvulsant effect [11]. Idazoxan, a selective α_2-adrenoceptor antagonist, raises noradrenaline levels by enhancing its release and has also been shown to have proconvulsant activity [16, 17]. The present data show that phenylephrine (2.5–10 mg/kg, i.p.), clonidine (0.25–1 mg/kg, i.p.), prazosin (0.5–2 mg/kg, i.p.) and idazoxan (2–4 mg/kg, i.p.) did not significantly alter propranolol seizures. These data support the involvement of central β-adrenoceptors in propranolol seizures.

Blaschko et al. [18] and Thorn and Ludwig [19] showed that DOPS is directly converted to noradrenaline in vivo. In the present study, DOPS (2–8 mg/kg, i.p.) attenuated the seizures produced by propranolol. It is possible that the antagonism of propranolol seizures by DOPS might be due to the noradrenaline formed from it in vivo which activated central β-adrenoceptors. According to Forster [20], imipramine elevates noradrenaline levels in the brain by blocking its neuronal reuptake. Our data show that imipramine (12.5–50 mg/kg, i.p.) protected the animals against propranolol seizures. The elevated levels of noradrenaline at the synapse due to the action of imipramine probably antagonize the seizures produced by propranolol. This result is in agreement with the observation of Chermat et al. [21] who reported the anticonvulsant effects of imipramine against convulsions in quaking mouse. Pargyline is thought to act by inhibiting monoamine oxidase enzymes thereby elevating endogenous levels of all the monoamines [22]. In this study, pargyline (25–100 mg/kg, i.p.) markedly delayed the seizures elicited by propranolol. It is possible that the delay in propranolol seizures might be due to the raised endogenous levels of noradrenaline following the inhibition of monoamine oxidase enzymes by pargyline. This result agrees with that of Lehmann [23] who reported that monoamine oxidase inhibitors protected mice against audiogenic seizures. Our data show that pargyline (100 mg/kg, i.p.) and imipramine (25 mg/kg, i.p.) significantly potenti-

ated the seizure-protecting effect of DOPS. These data implicate noradrenaline in propranolol seizures.

The present data show that α-methyl-p-tyrosine (100 mg/kg, i.p.), disulfiram ($3 \times 50 - 3 \times 100$ mg/kg, i.p.) and reserpine (20 mg/kg, i.p.) significantly potentiated seizures elicited by a low dose (62.5 mg/kg, i.p.) of propranolol. According to Spector et al. [24] and Svensson and Waldech [25], α-methyl-p-tyrosine specifically depletes brain catecholamines by inhibiting the enzyme tyrosine hydroxylase, which catalyses the rate-limiting step in the catecholamine synthetic pathway. Disulfiram is known to deplete brain noradrenaline stores by inhibiting the enzyme dopamine-β-hydroxylase, which normally converts dopamine to noradrenaline [2, 26]. Forster [1] and Rang et al. [2] reported that reserpine depletes monoamine stores by interfering with their uptake and storage in the vesicles. It is possible therefore that α-methyl-p-tyrosine, disulfiram and reserpine potentiate propranolol seizures because they all deplete brain noradrenaline. It is significant that DOPS, which is directly converted to noradrenaline in vivo, effectively attenuated the seizure-enhancing effects of α-methyl-p-tyrosine, disulfiram and reserpine. These data further implicate noradrenaline in propranolol-induced seizures.

In our studies, propranolol seizures were found to be resistant to potent standard antiepileptic drugs such as phenobarbitone (7.5–12.5 mg/kg, i.p.) and diazepam (0.25–1 mg/kg, i.p.), both of which are thought to exert their antiepileptic effects by enhancing the effect of γ-aminobutyric acid, the major inhibitory neurotransmitter in the brain, and phenytoin (8–32 mg/kg, i.p.), which is thought to produce its antiepileptic effect by blocking the influx of sodium ions into the cerebral neurons and hence, inhibiting the generation of repetitive action potentials [27]. It is also significant to note that seizures produced by propranolol have been shown not to be related to depression of blood pressure or hypoglycaemia [28].

The data obtained in the present study suggest that noradrenergic mechanisms may be involved in propranolol seizures and that since isoprenaline (a nonselective β-adrenoceptor agonist) effectively attenuated the seizures, whereas phenylephrine (an α_1-adrenoceptor agonist), clonidine (an α_2-adrenoceptor agonist), prazosin (an α_1-adrenoceptor antagonist) and idazoxan (an α_2-adrenoceptor antagonist) did not alter the seizure to any significant extent, central β-adrenoceptors may be mediating the seizures in mice.

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