IN VIVO STUDY OF MECHANISM OF PROPRANOLOL-INDUCED BLOCKADE OF NEUROMUSCULAR TRANSMISSION*

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Summary: *In vivo* experiments with propranolol on neuromuscular transmission in cat sciatic gastrocnemius nerve muscle preparation have shown curare-type competitive block. In addition, there appears to be a beta-adrenoceptor component of this blockade.

Key words: propranolol neuromuscular blockade *in vivo* experiments

INTRODUCTION

The effects of the *beta*-adrenoceptor blocker, propranolol, on neuromuscular transmission and skeletal muscle have been studied by several investigators (2,6,7). Although the involvement of *beta*-adrenoceptors in mediating the direct actions of adrenaline on the mammalian skeletal muscle is well documented (1), the effects of *beta*-adrenoceptor blocking agents on neuromuscular system in "*in vitro*" and "*in vivo*" experiments are not consistent (4,6,7). Recently it has been reported that the neuromuscular blocking effect of sotalol in "*in vitro*" experiments has a two-fold mode of action: tubocurarine-like action and *beta*-adrenoceptor blockade (5). We have now investigated the effect of propranolol on neuro-muscular system in "*in vivo*" experiments.

MATERIALS AND METHODS

Cats (either sex, 2-4 *kg*) were anaesthetized with chloralose, (80 *mg*/*kg*, i v) and artificially ventilated. The sciatic gastrocnemius nerve muscle preparation was set up. Stimulation was carried out alternately every 10 sec by supramaximal pulses applied directly to the muscle (pulse width 5 msec.) or to the nerve (pulse width 0.2 msec). Retrograde intra-arterial drug injections were made through the cannulated ipsilateral femoral artery.

RESULTS AND DISCUSSION

Propranolol (1-4 *mg*) reduced indirectly-evoked twitches of the gastrocnemius muscle; the reduction of direct twitches was moderate and was observed only with higher concentrations (Table I). The regression of mean maximal blockade of indirect twitches against the log doses of propranolol was linear and highly significant ($P < 0.001$). With each concentration of propranolol, the decline of twitch height was exponential. Propranolol (4 *mg*) produced a mean blockade of 90%; the mean latency period and the time to half decay of twitch tension were 0.8

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and 1.9 min respectively (Table I). The blocking activity of propranolol like that of tubocurarine (40 μg) was antagonized by neostigmine, KCl, succinylcholine, choline and tetraethylammonium (Table II). Propranolol and tubocurarine had an additive action (the mean block due to propranolol 0.5 *mg* along with tubocurarine, 10 μg was 66%; while that due to propranolol and tubocurarine given separately in the same doses was 40% and 25%, respectively; n=4). Tubocurarine blockade was antagonized by adrenaline and noradrenaline; isoprenaline was ineffective (Table II). Furthermore, the anticurare action of adrenaline was blocked completely by tolazoline (10 μg) injected 1-2 min before adrenaline (n=4). On the other hand, propranolol blockade was antagonized by adrenaline as well as by isoprenaline; noradrenaline was partly effective (Table II). The antagonism of adrenaline and isoprenaline to propranolol was not significantly ($P>0.05$) affected by tolazoline (n=4). Finally, tolazoline produced a quick and complete reversal of propranolol-blockade, whereas it had no effect on the blockade produced by tubocurarine (Table II). This is in agreement with the reported ability of tolazoline to antagonise *in vitro* the neuromuscular blocking action of sotalol but not of tubocurarine(3).

The block of indirect twitches by propranolol does not appear to be due to diminished synthesis of acetylcholine since choline was only partly effective in antagonizing the blockade

TABLE I: Cat sciatic gastrocnemius nerve muscle preparation. Effect of propranolol on electrical stimulation.

Propranolol (*mg*)	*n*=	*Indirect twitches*			*Direct twitches, mean % blockade ± S.E.*
		latency period (*min*)	*mean % blockade ± S.E.*	*time to half-decay* (*min*)	
0.5	5	1.5 ± 0.3	26.0 ± 1.9	—	5.0 ± 2.0
1	5	1.1 ± 0.2	56.2 ± 3.0	—	13.5 ± 2.9
2	5	1.0 ± 0.2	78.0 ± 3.1	2.1 ± 0.3	15.4 ± 3.8
4	10	0.8 ± 0.1	90.0 ± 3.3	1.9 ± 0.2	—18.0 ± 2.3

TABLE II : Antagosnism of propranolol and tubocurarine-induced blockade of indirectly-induced contractions of cat sciatic gastrocnemius nerve muscle preparation by various drugs. The test dose of propranolol (4 *mg*) and tubocurarine (40 μg) were that they produced over 90% blockade of indirect twitches. Values are means from a minimum of 4 experiments. (Doses of adrenaline, noradrenaline and isoprenaline refer to the base and of the other compounds to the salts).

Drug	(*mg*)	*Mean % antagonism of blockade*	
		propranolol	*tubocurarine*
Neostigmine	0.025	60	70
KCl	0. 20	40	55
Succinylcholine	0.020	45	32
Choline	0.1	52	60
Tetraethylammonium	0.2	70	72
Isoprenaline	0.005	86	0
Adrenaline	0.005	80	60
Noradrenaline	0.005	15	27
Tolazoline	4.0	100	0

produced by propranolol. The nature of the blocking activity as well as the antagonistic effect of various drugs which either increase the release (tetraethylammonium) or increase the efficiency of the released transmittor (neostigmine, succinylcholine) suggest that propranolol has a tubocurarine-like mode of action. This is also in agreement with the neuromuscular blockade demonstrated with propranolol *in vitro* (4). Isoprenaline and adrenaline antagonised the blocking effect of propranolol almost completely (Table II). This suggests that propranolol also possesses *beta*-adrenoceptor component of action as described earlier *in "vitro"* with sotalol on skeletal muscle. Lastly, the local anaesthetic activity of propranolol (2,3) may also contribute to the neuromuscular blockade produced by this drug.

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