LETTER TO THE EDITOR

EFFECT OF BETA-ADRENOCEPTOR BLOCKING AGENTS ON ISOLATION AND APOMORPHINE-INDUCED AGGRESSION IN RODENTS

Sir,

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Neurotransmitters like noradrenaline (NA), dopamine (DA) and 5-hydroxytryptamine (5-HT) play an important role in isolation and apomorphine-induced aggression (7,8,13,15). Fighting attacks induced by isolation result from an increased 5-HT release and action of 5-HT on postsynaptic receptors (6,9,14,17,19). Weinstock *et al.* (16) have reported that propranolol, pindolol and metoprolol are potent 5-HT antagonists (3).

Apomorphine has been reported to produce "bizzare" social behaviour consisting of "wrestling" postures and vigorous fighting in rats (7,13). It acts directly upon DA receptors to induce fighting (13). Combination of clonidine and apomorphine induces intense fighting and appears to involve the central NA, DA and 5-HT neurones (5,18). We made an attempt to elicit the effect of propranolol, sotalol and practolol on aggression induced by isolation and apomorphine.

Albino mice (20-30 *g*) and albino rats (100-280 *g*) of Haffkine strain and of either sex were used. The method of Dunham and Miya (4) was employed to determine the relatively nontoxic dose and the peak activity time for propranolol, sotalol and practolol. The median effective dose (ED_{50}) in mice was determined by the method Miller and Tainter (10). For isolation-induced aggression the method of Yen *et al.* (20) was used. Male albino mice were isolated for a period of 3 weeks. The animals were not allowed to see each other or to have any physical contact. Fighting occurred when a non-isolated mouse was placed in the home cage of the isolated mouse. The fighting response was recorded for 5 min. Fighting was also induced by administration of apomorphine (5 *mg/kg*, ip) in pairs of rats covered by a glass bell jar (13). Fighting started within 5 minutes of apomorphine administration, and lasted up to 45 min)

Statistical analysis of data was done by the Student's t-test for independent means.

Propranolol HCl, sotalol HCl, practolol HCl and apomorphine HCl (all from ICI Pharmaceuticals, Bombay) were dissolved in normal saline (0.9% NaCl) and injected ip. The beta-blockers were administered in accord with their pre-treatment time (see below). The control groups received normal saline (1.0 *ml/kg*, ip).

In rotarod test, propranolol, sotalol and practolol had an $ED_{50} \pm$ SEM of 28.30± 3 39, 374.0±61.09 and 370.9±102.3 *mg/kg*, ip respectively. The peak activity time for propranolol, sotalol and practolol was 10, 20 and 10 min, respectively. Use of beta-blockers in further tests depended on this information.

Propranolol (14 *mg/kg*, ip) had no major effect, but in higher doses (21, 28 *mg/kg*, ip) it inhibited fighting attacks significantly (Table I). Propranolol (14 *mg/kg*, ip) had little effect on apomorphine-induced fighting, but with 21 *mg/kg*, ip fighting attacks were inhibited significantly (Table I).

Sotalol (94 and 187 *mg/kg*, ip) significantly reduced the number of isolation-induced fighting attacks, but in higher of the two doses the effect on apomorphine-induced fighting was insignificant (Table I). Practolol (278 *mg/kg*, ip) had little effect on isolation-induced or on apomorphine-induced fighting attacks (Table I).

Higher doses of propranolol and sotalol caused reduction in isolation-induced fighting attacks. Practolol even in a high dose was ineffective. Isolation-induced aggression results from an increased 5-HT release acting on postsynaptic 5-HT receptors (3,5,9,16,19). Propranolol perhaps antagonizes this action at the postsynaptic receptor sites, whereas practolol has an insignificant effect.

Propranolol alone reduced apomorphine-induced fighting attacks. Apomorphine possibly acts by stimulation of both pre-and postsynaptic DA receptors leading to aggression (11,14). Propranolol in high doses has known antidopamine effect. In addition, propranolol and some other beta-adrenoceptor blockers have been reported to possess central nervous system depressant (1, 12), and peripheral neuromyoplegic (2) activity. It is suggestible that these activities may in part account towards the antiaggression action of beta-blockers.

TABLE I : Effects of propranolol, sotalol and practolol on isolation and apomorphine-induced aggression in rodents.

Group	Drug	Toral pairs of mice/ rats	Pretreat-ment time (min)	Dose (mg/kg, ip)	Isolation-induced aggression (IIA) in mice		Apomorphine-induced aggression (AIA) in rats	
					Fighting attacks observed in 5 min (Mean±S.E.M.)	P	Fighting attacks observed in 45 min (Mean±S.E.M.)	P
I	(Saline)	6		1	18±1.04	—	244.16±9.48	—
II	Propranolol	6	10	14**	17±0.58	NS	227.83±8.22	NS
				21***	14 66±0.87	<0.05	202.83±9.24	<0.02
				28****	12.0 ±0.58	<0.001	—	—
III	Sotalol	6	20	94*	8.0 ±0.68	<0.001	—	—
				187**	5.0 ±0.58	<0.001	239.66±3.96	NS
				281***	—	—	229.33±7.51	NS
IV	Practolol	6	10	278***	15.66±0.73	NS	234.5 ±8.04	NS

* 1/4 ED_{50} *** 3/4 ED_{50} NS=Not significant
** 1/2 ED_{50} **** ED_{50}
in rotarod test with mice

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