Pharmacology Biochemistry & Behavior, Vol. 26, pp. 229–234. Copyright © Pergamon Journals Ltd., 1987. Printed in the U.S.A. 0091-3057/87 $3.00 + .00

Involvement of Brain Transmitters in the Modulation of Shock-Induced Aggression in Rats by Propranolol and Related Drugs

A. RAY,[1] M. ALKONDON AND P. SEN

Department of Pharmacology, University College of Medical Sciences, New Delhi 110029, India

Received 10 February 1986

RAY, A., M. ALKONDON AND P. SEN. *Involvement of brain transmitters in the modulation of shock-induced aggression in rats by propranolol and related drugs.* PHARMACOL BIOCHEM BEHAV **26**(2) 229–234, 1987.—(±)Propranolol (1, 3, 10 and 30 mg/kg) exhibited a differential effect on footshock aggression (FSA) in rats. Lower doses (1 and 3 mg/kg) of the drug facilitated FSA, whereas an inhibitory effect was observed with higher doses (10 and 30 mg/kg) of the same. (+)Propranolol (30 mg/kg) and UM-272 (1 and 10 mg/kg) as well as physostigmine (0.1 and 0.5 mg/kg) all produced inhibition of FSA. Similar FSA inhibitory effects were also observed with salbutamol (1 and 5 mg/kg). Pretreatment with atropine and not methylatropine attenuated the anti-aggressive effect of (±)propranolol (10 mg/kg) without appreciably altering the facilitatory effect (1 mg/kg) of the drug on FSA. In addition, at the anti-aggressive doses, (±)propranolol (10 mg/kg) and UM-272 (10 mg/kg), significantly inhibited brain cholinesterase enzyme activity when compared to saline controls. (±)Propranolol (10 mg/kg) also inhibited significantly the aggression induced by reserpine-apormorphine treatment. It is inferred that a central cholinergic and dopaminergic mechanism is involved in the anti-aggressive effect of (±)propranolol, whereas the low dose induced facilitation of affective aggression could be attributed to central β-adrenoceptor blockade.

Propranolol UM-272 Cholinesterase Aggression Dopamine

THE central effects of beta adrenergic blocking agents (β-blockers) have formed an important aspect of their pharmacological profile in recent years and the efficacy of these β-blockers in CNS disorders have been clearly demonstrated in both clinical [41] and experimental situations. Propranolol and some related drugs have been reported to modify amphetamine induced behavioural changes [22,26], oxotremorine tremor [4], electroshcok and metrazol convulsions [20,24], hexobarbitone narcosis [22] and spontaneous locomotor activity [11] in experimental animals. However, the mechanisms which regulate some of these central effects are not clearly defined and do not correlate well with their ability to block the β-adrenoceptors. Aggression, a centrally mediated behavioural paradigm, is accompanied by intense autonomic activation and complex neurochemical mechanisms have been suggested [30]. The brain biogenic amines are involved in its mediation [13, 27–29] and alterations in the levels of these amines and other transmitters are also known to modulate the above phenomenon. The noradrenergic system, in particular, contributes significantly [38] and the involvement of β-adrenoceptors has been strongly advocated. In different experimental situations, β-blockers have been shown to attenuate, facilitate or have no effect on aggressive behaviour in rats [1, 19, 34, 42] and various mechanisms (including those involving β-adrenoceptors) have been speculated for these effects. In addition to their primary ability of β-blockade, drugs like propranolol are also known to possess ancillary properties like anti-dopaminergic [37], anti-serotonergic [44] and cholinomimetic effects [2–4]. In light of the equivocally complex nature of observations, we critically evaluated the influence of propranolol and some related drugs on shock-induced aggression in rats with a view to elucidate the possible mechanisms involved in the modulation of the same by these drugs.

METHOD

Male albino rats (150–180 g) of Wistar strain were used for the study. They were maintained in the 12 hr light-12 hr dark cycle (lights on at 8 a.m.) and had free access to food and water till the morning of the day of the experiment. All experiments were performed, under blind conditions, at a room temperature of 22±2°C, during evening hours of the day. Aggression was induced by the methods described below.

[1]Requests for reprints should be addressed to Dr. A. Ray at his present address: Department of Psychology, Division of Behavioral Neuroscience, P.O. Box 20, St. Francis Xavier University, Antigonish, Nova Scotia, Canada B2G 1C0.

TABLE 1

EFFECTS OF (±)PROPRANOLOL, SOME RELATED DRUGS, ATROPINE AND PHYSOSTIGMINE ON FOOTSHOCK AGGRESSION IN RATS

Treatment (mg/kg)	n*	Aggressive Score (Mean ± S.E.) Before Drug	After Drug	Difference†
Saline (5 ml)	14	60.6 ± 9.24	65.0 ± 8.98	(+) 4.4 ± 2.72
(±)Propranolol (P, 1)	10	82.4 ± 16.10	129.6 ± 17.52	(+)47.2 ± 6.95[a]
P(3)	8	63.6 ± 7.84	77.8 ± 7.92	(+)14.2 ± 3.71
P(10)	10	89.6 ± 9.31	28.3 ± 6.55	(−)61.3 ± 6.67[a]
P(30)	8	69.3 ± 7.96	20.6 ± 2.49	(−)48.7 ± 8.29[a]
(+)Propranolol (10)	9	72.1 ± 11.92	85.6 ± 13.09	(+)13.5 ± 6.87
(+)Propranolol (30)	8	75.8 ± 17.37	28.3 ± 7.12	(−)47.5 ± 12.65[a]
UM-272 (1)	9	61.8 ± 6.54	40.5 ± 8.32	(−)21.3 ± 8.44
UM-272(10)	8	80.0 ± 5.91	38.1 ± 4.70	(−)41.9 ± 4.27[a]
Salbutamol (1)	7	85.2 ± 7.99	66.5 ± 5.33	(−)18.7 ± 3.18
Salbutamol (5)	7	92.6 ± 9.06	62.0 ± 6.18	(−)30.6 ± 4.07[b]
Atropine (A, 1)	8	79.8 ± 7.69	72.1 ± 6.61	(−) 7.8 ± 4.62
AMN(1)	8	56.5 ± 7.96	65.6 ± 12.87	(+) 9.1 ± 5.57
A + P(1)	8	90.6 ± 10.17	131.1 ± 11.74	(+)40.5 ± 6.98
A + P(10)	9	83.0 ± 7.61	66.0 ± 9.21	(−)17.0 ± 6.84[c]
AMN + P(10)	8	76.6 ± 8.42	30.8 ± 9.08	(−)45.8 ± 7.41
Physostigmine (0.1)	8	59.6 ± 9.85	44.0 ± 8.71	(−)15.6 ± 3.05
Physostigmine (0.5)	8	65.7 ± 8.86	40.5 ± 2.19	(−)25.2 ± 4.89[b]

*Pairs of rats.
†(+) and (−) prefixes indicate an increase or decrease in the score.
AMN=atropine methyl nitrate.
Overall, $F(17,137)=7.95$, $p<0.01$.
[a]$p<0.005$; compared to saline control group.
[b]$p<0.05$; compared to saline control group.
[c]$p<0.005$; compared to P(10) alone—Dunnett's t-test.

Footshock Technique

In this method [27], pairs of rats were footshocked at a time in an aggressometer (Techno), which was a perspex chamber (21×17×15 cm) with parallel grid floor through which alternate current could be passed by an inbuilt shock generator. The stimulation parameters were 100 V, 0.5 mA, 5 shocks/sec and 5 msec pulse duration. On footshock, the rats stood up on their hindlimbs, apposed each other and either struck at (with forepaws), wrestled with or bit at (with or without bleeding) each other. One strike was scored as 1, one wrestling bout as 2, one bite without bleeding as 3 and one bite with bleeding as 4. Rats which exhibited more than one such score during one minute exposure to footshock were screened as aggressive and selected for the study. A pair of rats were footshocked at a time for 3 min each, before and 1 hr after saline or drug administration and the total score during each electroshock exposure was counted with the help of a digital counter. The differences in the scores (before treatment − after treatment) were calculated for each treatment group and compared with the same of the respective controls. Rats once exposed to a particular treatment schedule were not used again during the entire study. The scoring method adopted here was more objective in that it gave a better idea of the intensity of aggression. It has also been used effectively in our earlier studies [27–29]. Analgesia was tested by the classical method of tail-flick to heated resistance wire (0.5 ohm/cm at 6.5 A) with the help of an analgesimoter (Techno) and the tail withdrawal latencies were noted after saline or drug administration.

Reserpine-Apomorphine Technique

In this model of aggression [6] reserpine (5.0 mg/kg) was administered 4 hr prior to apomorphine (1.5 mg/kg), both intraperitoneally (IP). Groups of three rats were used at a time and placed under an inverted bell-jar (diameter 19 cm, height 34 cm) with holes at the sides and top to allow ventilation. Immediately after apormorphine injection the rats became aggressive and fought vigorously with each other. The total fighting score for each group was quantified for a period of 15 min after apomorphine treatment in a manner similar to that adopted in the footshock technique and the aggressive scores of the drug treated groups were compared to the same of saline controls for statistical significance.

Brain Cholinesterase Estimation

For determination of rat brain ChE activity, the animals were killed by cervical dislocation 1 hr after administration of either saline or drug and the brains were removed immediately. Each rat brain was homogenized in 7 ml of ice cold phosphate buffer separately at pH 8.0 and centrifuged at 10,000 rpm at 0°C for 10 min. The supernatant homogenate was tested for ChE enzyme activity colorimetrically by the method of de la Huerga *et al.* [16] by using acetylcholine (ACh) as substrate. The protein content of the supernatant homogenate was determined by the method of Lowry *et al.* [25] and the ChE enzyme activity was expressed as the number of μmols of ACh hydrolysed per mg of protein per hr.

TABLE 2

EFFECT OF PROPRANOLOL ON TAIL-WITHDRAWAL LATENCIES IN RATS

Treatment (mg/kg)	Tail-Withdrawal Latencies (sec) (mean ± S.E.)*
Saline (5 ml)	6.4 ± 0.43
(±) Propranolol (P, 1)	5.7 ± 0.35 (N.S.)
P(3)	6.6 ± 0.20 (N.S.)
P(10)	6.1 ± 0.81 (N.S.)
P(30)	7.7 ± 0.66 (N.S.)

*n=7 per group.
N.S.: Not significant compared to saline control (Dunnett's *t*-test).

TABLE 3

EFFECT OF (±)PROPRANOLOL ON RESERPINE-APOMORPHINE AGGRESSION IN RATS

Treatment (mg/kg)	n*	Aggressive Score (Mean ± S.E.)
Saline (5 ml)	9	329.7 ± 87.10
(±Propranolol (1)	8	303.8 ± 75.10
(±)Propranolol (10)	8	26.3 ± 18.10[a]

*Number of groups with 3 rats per group (see the Method section).
Overall, H(2)=19.2, $p<0.001$ (Kruskall-Wallis test).
[a]$p<0.05$ (compared to saline control, Mann-Whitney U-test, two-tailed).

Drugs

The drugs used in the study were: (±)Propranolol HCl and (+)propranolol HCl (both from ICI), UM-272 (G. D. Searle and Co.), physostigmine salicylate, atropine salicylate and reserpine (all from Boehringer-Ingelheim) and apomorphine HCl, atropine methyl nitrate and 5-hydroxytryptophan (all from Sigma). All drugs (doses calculated as free bases) were dissolved in physiological saline except reserpine, which was dissolved in minimal quantity of glacial acetic acid and diluted to appropriate volume after neutralising with 0.1 N NaOH to achieve a pH of 6.0 and apomorphine, which was dissolved in 1% ascorbic acid and diluted with saline for volume. The drugs were administered IP in a volume of 5 ml/kg except atropine and atropine methyl nitrate (AMN) which were given subcutaneously. The pretreatment time for the drugs under investigation was 1 hr except for 5-hydroxytryptophan (5-HTP), where it was 2 hr.

The statistical analysis was done by one way ANOVA followed by Dunnett's *t*-test for post-hoc comparisons for the data of the footshock method. The results of reserpine-apomorphine method and brain cholinesterase estimation were analysed by Kruskal-Wallis one way ANOVA for non-parametric data followed by Mann-Whitney U-test (two-tailed) for comparison between means. A p value of 0.05 or less was considered to represent a significant difference within and between treatment groups in all experiments.

TABLE 4

EFFECT OF (±)PROPRANOLOL AND UM-272 ON RAT BRAIN CHOLINESTERASE (ChE) ENZYME

Treatment (mg/kg)	n	ChE Enzyme Activity (μmols of ACh Hydrolysed/mg protein/hr) (Mean ± S.E.)
Saline (5 ml)	8	2.3626 ± 0.1711
(±)Propranolol (1)	7	2.2940 ± 0.1264
(±)Propranolol (10)	8	1.8446 ± 0.0805[a]
UM-272 (10)	8	1.8410 ± 0.1495[a]

Overall, H(3)=7.99, $p<0.05$ (Kruskall-Wallis test).
[a]$p<0.05$ (compared to saline control, Mann-Whitney U-test, two-tailed).

RESULTS

(±)Propranolol produced a dose related effect on footshock aggression (FSA) in rats. In lower doses (1 and 3 mg/kg) there was an enhancement in the FSA score when compared to the saline control values, the effect of 1 mg/kg being statistically significant ($p<0.005$), Dunnett's *t*-test), (Table 1). On the other hand, in higher doses (10 and 30 mg/kg) there was an appreciable reduction ($p<0.005$) in the fighting score when compared to the controls. However, at the dose of 30 mg/kg, (±)propranolol treated rats showed clear signs of motor incoordination and were unable to maintain their normal posture prompting us thereby to exclude this dose for further studies with the drug. The dextro isomer of propranolol (10 mg/kg) did not produce any significant effect on FSA but (+)propranolol (30 mg/kg) effectively inhibited FSA ($p<0.005$) and no signs of motor incoordination, described earlier, were observed. UM-272 (1 and 10 mg/kg), an analog of propranolol, also reduced FSA at both dose levels, the results with 10 mg/kg being statistically significant ($p<0.005$). The β-adrenergic agonist, salbutamol (1 and 5 mg/kg) also inhibited FSA, but the effect of the latter dose being significant ($p<0.05$) when compared to saline controls (Table 1). In the subsequent interaction studies with (±)propranolol, doses of 1 and 10 mg/kg of the drug were selected.

Pretreatment with atropine (1 mg/kg) significantly antagonized the inhibitory effect of (±)propranolol (10 mg/kg) on FSA without altering appreciably the facilitatory effect observed with 1 mg/kg of the beta blocker (Table 1). Atropine methyl nitrate (MAN), however, failed to alter the FSA attenuating ability of (±)propranolol (10 mg/kg). Both atropine and AMN, per se, had no significant effect on FSA when compared to saline controls ($p>0.05$). In addition, physostigmine (0.1 and 0.5 mg/kg) also lowered FSA scores, the effect with 0.5 mg/kg being statistically significant ($p<0.05$, Dunnett's *t*-test). At these dose levels, however, no exaggerated cholinergic signs like hypersecretion or tremor were observed. (±)Propranolol (10 mg/kg) also could not antagonize significantly the facilitation of FSA induced by 5-HTP (10 mg/kg, IP) when compared to the appropriate saline controls (the differences in FSA being: saline + 5-HTP, 46.4±13.82 vs. propranolol + 5-HTP, 41.7±7.08, n=8 in each case, $p>0.05$, Student's *t*-test). At the doses used in this study, (±)propranolol did not modify significantly

($p>0.05$, N.S.), the nociceptive responses as measured by the classical tail withdrawal latency, when compared to saline controls (Tabie 2).

In the aggression induced by combination of reserpine-apomorphine treatment (RAA), (±)propranolol (10 mg/kg) pretreatment significantly inhibited the RAA score when compared to saline controls ($p<0.05$; Mann-Whitney U-test, two-tailed) (Table 3). The lower dose of 1 mg/kg of this drug however, had no appreciable influence on this model of experimental aggression.

(±)Propranolol (10 mg/kg) pretreatment significantly inhibited ChE enzyme activity of rat brain homogenates in vivo ($p<0.05$) (Table 4) whereas a dose of 1 mg/kg was ineffective in this regard. Similar inhibition of rat brain ChE activity was also observed with UM-272 (10 mg/kg) treatment, when compared to saline controls ($p<0.05$).

DISCUSSION

The results of the present study clearly indicate a dose related effect of (±)propranolol on footshock aggression (FSA) in rats. An anti-aggressive effect was observed with higher doses (10 and 30 mg/kg) of this drug and was evident in both footshock and reserpine-apomorphine (RAA) models of aggression (Tables 1 and 3). The most logical assumption would be that this anti-aggressive effect was a result of propranolol's ability to block the central β-adrenoceptors (the primary property of the drug) as this drug readily crossed the blood brain barrier and this has been suggested by earlier investigators [19, 34, 42]. But the observation that (+)propranolol (30 mg/kg) (50 times less potent as a β-blocker) [12] also antagonized FSA significantly (Table 1) suggests that β-blockade was possibly not the only prerequisite for this effect. This contention was reaffirmed when UM-272 (1 and 10 mg/kg), an analog of propranolol with no β-blocking ability [33] also inhibited FSA. The fact that a higher dose of (+)propranolol (30 mg/kg) was required to antagonize FSA, could possibly be attributed to lesser penetrability of the drug into the CNS [23].

Cholinergic involvement in neuropsychiatric disorders has been suggested [14,40] and cholinomimetic drugs have been found to be effective in antagonizing experimental models of such states [9,15]. In view of the intricate balance existing between the sympathetic and parasympathetic divisions of the autonomic nervous system, suppression or blockade of one could result in increased activity of the other and such a possibility could not be ruled out in the case of adrenergic blocking agents like propranolol. In fact, the role of cholinergic system in the pharmacological actions of propranolol has been well documented in our laboratory [3–5] and it has been shown that (±)propranolol and related drugs inhibit the cholinesterase enzyme [2,36]. On the basis of the above observations the involvement of a cholinergic modulation in the effect of propranolol could well be speculated. The fact that atropine and not AMN (a quaternary analogue of atropine, with poor CNS access), in the present study, significantly antagonized the FSA reducing effect of (±)propranolol (10 mg/kg) (Table 1), suggested a central cholinergic involvement in the anti-aggressive effect of the drug. This was further supported by the observation that physostigmine, a centrally acting cholinesterase enzyme inhibitor, also inhibited FSA significantly. Finally, our in vivo studies with (±)propranolol and UM-272 (10 mg/kg) on rat brain homogenates, clearly showed the ability of both these drugs to inhibit rat brain ChE enzyme significantly (Table 4), thereby strongly indicating a cholinergic link in this anti-aggressive effect of (±)propranolol. Earlier studies have indicated a facilitatory cholinergic mechanism in the modulation of shock-induced aggression [32]. However, our results were not in agreement with the above contention. In fact, in the present study, atropine pretreatment failed to alter the FSA potentiating effect of (±)propranolol (1 mg/kg) (Table 1). In addition, at this dose level, the β-blocker could not significantly enhance brain ACh activity by way of ChE enzyme inhibition (Table 4).

The role of pain sensitivity in the modulation of shock-induced aggression by drugs has been reported [18,31] and this could well have contributed to the effect of (±)propranolol on FSA. But the observation that (±)propranolol, at the doses used, did not alter the tail withdrawal latencies significantly when compared to saline controls (Table 2) ruled out the involvement of any possible nociceptive component in the propranolol effect.

Dopamine (DA) and serotonin (5-HT) have been implicated as modulatory neurotransmitters in footshock aggression [29]. Though the facilitatory role of DA in the modulation of FSA has been widely acclaimed, the reports with 5-HT, however, are equivocal. Some investigators have suggested an inhibitory role of this amine [35], whereas others have found no appreciable modulatory role for the same [43]. In contrast to these findings, reports from our studies [29] as well as others [7] have suggested a clearcut facilitatory role of 5-HT is this model of aggression. The ambiguity in the findings could be explained, at least in part, by the wide variation in experimental situations in which these effects were assessed by several workers. However, propranolol has been reported to possess both anti-DA [37] and anti-5-HT [44] effects. In fact, (±)propranolol (10 mg/kg) significantly antagonized the aggression induced by reserpine-apomorphine treatment. A dopaminergic mechanism is known to mediate this model of drug-induced aggression (as DA blockade nullified it) [6] and an anti-aggressive effect produced by (±)propranolol suggested that an anti-DA effect could also be involved in this effect of the drug. This contention is supported by the fact that β-blockers like propranolol have been reported to modulate other central effects mediated via dopaminergic mechanisms in the brain [22,26]. On the other hand, inability of (±)propranolol (10 mg/kg) to alter significantly the facilitation of FSA induced by 5-HTP (which is blocked by anti-5-HT agents [29]), ruled out the involvement of 5-HT receptor blockade in this aggression inhibiting effect of propranolol.

The observation that lower doses (1 and 3 mg/kg) of (±)propranolol facilitated FSA (Table 1) was interesting. Noradrenaline (NA) has been reported to be the tonic inhibitory transmitter in this form of aggression [13, 28, 29] though there are reports to the contrary [19]. The central β-adrenoceptor population is also known to be altered by modulating the NA levels in the brain [10,45], suggesting that NA could be the transmitter at these (β) receptor sites. Also lesions of locus coeruleus (an area rich in NA neuronal cells) [21] and intracerebroventricular administration of 6-hydroxydopamine [17,39] have been shown to faciliate FSA. The inhibitory role of NA was further supported by the observation, in the present study, that the β-adrenergic agonist, salbutamol (1 and 5 mg/kg) inhibited FSA (Table 1) and could indicate the possible involvement of β_2-adrenoceptors in this effect, though further studies would be needed to substantiate this. In view of the above, it is likely that the blockade of central β-adrenoceptors by the lower

doses of (±)propranolol (1 and 3 mg/kg), would result in an enhancement of FSA (through disinhibition) by producing a functional deficiency of NA at these receptor sites. The fact that this effect was not observed with higher doses of (±)propranolol could be attributed to the predominance of other mechanisms, viz. cholinomimetic and anti-DA, involved at these dose levels. Also, the failure to get a similar enhancement of RAA with (±)propranolol (Table 3) is not unexpected, since the noradrenergic tone could already be at a low ebb as a result of reserpine pretreatment.

ACKNOWLEDGEMENTS

The generous gifts of UM-272 iodide by G. D. Searle and Co. (IL) and (+)propranolol HCl by ICI (London) are gratefully acknowledged. The authors are also thankful to Professor Peter Henke for his kind cooperation and Ms. Jane Aker for secretarial assistance during the preparation of this manuscript.

REFERENCES

1. Albert, D. J., R. C. K. Wong, K. N. Brayley and H. C. Fibiger. Evaluation of adrenergic, cholinergic and dopaminergic involvement in the inhibition of hyperreactivity and interanimal aggression by the medial hypothalamus in the rat. *Pharmacol Biochem Bheav* **11**: 1–10, 1979.
2. Alkondon, M., A. Ray and P. Sen. Effect of beta adrenergic blocking agents and some related drugs on plasma and RBC cholinesterase enzyme in vitro. *Ind J Exp Biol* **21**: 519–521, 1983.
3. Alkondon, M., A. Ray and P. Sen. Role of vagus in the antagonism of ouabain induced arrhythmias in dogs by beta adrenoceptor antagonists and related drugs. *J Pharm Pharmacol* **36**: 702–704, 1984.
4. Alkondon, M., A. Ray and P. Sen. Cholinergic involvement in the modulation of oxotremorine tremor in mice by propranolol. *Arch Int Pharmacodyn Ther* **277**: 161–167, 1985.
5. Alkondon, M., A. Ray and P. Sen. Autonomic regulation in the ocular hypotensive action of β-adrenergic blocking agents. *J Pharm Pharmacol* **38**: 319–322, 1986.
6. Ammiraju, C. H., G. P. Gupta and K. P. Bhargava. Pharmacological characterization of central receptors in aggressive behavior. In: *Drugs and Central Synaptic Transmission*, edited by P. B. Bradley and B. N. Dhawan. London: Macmillan Press, 1976, pp. 283–290.
7. Anand, M., G. P. Gupta and K. P. Bhargava. Effect of tryptaminergic drugs on electroshock fighting behaviour in rats. *Eur J Pharmacol* **39**: 389–391, 1976.
8. Anand, M., G. P. Gupta and K. P. Bhargava. Modification of electroshock fighting by drugs known to interact with dopaminergic and noradrenergic neurons in normal and brain lesioned rats. *J Pharm Pharmacol* **29**: 437–439, 1977.
9. Arnfed, T. and A. Randrup. Cholinergic mechanisms in the brain inhibiting amphetamine-induced stereotyped behaviour. *Acta Pharmacol Toxicol (Copenh)* **26**: 384–394, 1968.
10. Bannerjee, S. P., L. S. King, S. J. Riggi and S. K. Chanda. Development of β-adrenergic receptor subsensitivity by antidepressants. *Nature* **268**: 455–456, 1977.
11. Barar, F. S. K. and B. R. Madan. Effect of ten beta adrenoceptor blocking agents on spontaneous motility and pentobarbital induced anaesthesia in mice. *Ind J Med Res* **61**: 1054–1061, 1973.
12. Barrett, A. M. and V. A. Cullum. The biological properties of the optical isomers of propranolol and their effects on cardiac arrhythmias. *Br J Pharmacol* **34**: 43–55, 1968.
13. Daruna, J. H. Patterns of brain monoamine activity and aggressive behaviour. *Neurosci Biobehav Rev* **2**: 101–113, 1978.
14. Davis, K. L., L. E. Hollister, P. A. Berger and J. D. Barchas. Cholinergic imbalance hypothesis of psychoses and movement disorders: Strategies for evaluation. *Psychopharmacol Commun* **1**: 533–543, 1975.
15. Davis, K. L., L. E. Hollister and J. Tepper. Cholinergic inhibition of methylphenidate induced stereotypy: Oxotremorine. *Psychopharmacology (Berlin)* **56**: 1–4, 1978.
16. de la Huerga, J., C. Yesinick and H. Popper. Colorimetric method for determination of serum cholinesterase. *Am J Clin Pathol* **22**: 1126–1133, 1952.
17. Eichelman, B., N. B. Thoa and K. Y. Ng. Facilitated aggression in the rat following 6-hydroxydopamine administration. *Physiol Behav* **8**: 1–3, 1972.
18. Fanselow, M. S., R. A. Sigmundi and R. C. Bolles. Naloxone pretreatment enhances shock-elicited aggression. *Physiol Psychol* **8**: 369–371, 1980.
19. Hegstrand, L. R. and B. Eichelman. Increased shock-induced fighting with supersensitive β-adrenergic receptors. *Pharmacol Biochem Bheav* **19**: 313–320, 1983.
20. Jaeger, V., B. Esplin and R. Capek. The anti-convulsant effects of propranolol and β-adrenergic blockade. *Experientia* **35**: 80–81, 1979.
21. Kostowski, W., A. Czlonkowski, M. Jerlicz, A. Bidzinski and M. Hauptmann. Effects of lesions on the locus coeruleus on aggressive behaviour in rats. *Physiol Behav* **21**: 695–699, 1978.
22. Leszkovszky, G. and L. Tardos. Some effects of propranolol on the central nervous system. *J Pharm Pharmacol* **17**: 518–520, 1965.
23. Levy, A., S. H. Ngai, A. D. Finck, K. Kawashima and S. Spector. Disposition of propranolol isomers in mice. *Eur J Pharmacol* **40**: 93–100, 1976.
24. Louis, W. J., J. Papanicolaou, R. J. Summers and F. J. E. Vajda. Role of central β-adrenoceptors in the control of pentylenetetrazole induced convulsions in rats. *Br J Pharmacol* **75**: 441–446, 1982.
25. Lowry, O. H., N. J. Rosebrough, A. L. Faar and R. J. Randall. Protein measurement with folin phenol reagent. *J Biol Chem* **193**: 265–275, 1951.
26. Mantagazza, P., K. Naimzada and M. Riva. Effects of propranolol on some activities of amphetamine. *Eur J Pharmacol* **4**: 25–30, 1968.
27. Ray, A., K. K. Sharma and P. Sen. Effect of histaminergic drugs on footshock induced aggressive behaviour in rats. *Eur J Pharmacol* **73**: 217–219, 1981.
28. Ray, A., K. K. Sharma, M. Alkondon and P. Sen. Modulation of footshock aggression in rats by clonidine: Involvement of both α_1 and α_2 adrenoceptors. *J Pharm Pharmacol* **35**: 595–596, 1983.
29. Ray, A., K. K. Sharma, M. Alkondon and P. Sen. Possible interrelationship between the biogenic amines involved in the modulation of footshock aggression in rats. *Arch Int Pharmacodyn Ther* **265**: 36–41, 1983.
30. Reis, D. J. Central neurotransmitters and aggression. In: *Research Publications of the Associations for Research in Nervous and Mental Disease*, Vol 52, edited by S. H. Frazier. New York: Raven Press, 1974, pp. 119–148.
31. Rodgers, R. J. The medial amygdala: serotonergic inhibition of shock-induced aggression and pain sensitivity in rats. *Aggress Behav* **3**: 277–288, 1977.

32. Rodgers, R. J. and K. Brown. Amygdaloid function in central cholinergic mediation of shock induced aggression in the rat. *Aggress Behav* **2:** 131–152, 1976.
33. Schuster, D. P., B. R. Lucchesi, N. L. Nobel, M. N. Mimnaugh, R. E. Counsell and F. J. Kniffen. the anti-arrhythmic properties of UM-272, a dimethyl quaternary derivative of propranolol. *J Pharmacol Exp Ther* **184:** 213–227, 1973.
34. Sheard, M. The role of drugs affecting catecholamines on shock elicited fighting in rats. In: *Catecholamines Basic and Clinical Frontiers*, edited by E. Usdin, I. Kopin and J. Barchas. New York: Pergamon Press, 1979, pp. 1690–1692.
35. Sheard, M. H. and M. Davis. Shock elicited fighting in rats: The importance of intershock interval upon the effect of p-chlorophenylalanine (PCPA). *Brain Res* **111:** 433–437, 1976.
36. Simon, G. and M. Winter. The effect of sympatholytic and sympathomimetic agents on acetylcholinesterase and cholinesterase activity. *Biochem Pharmacol* **25:** 881–882, 1976.
37. Simon, P., R. Chermat, M. Th. Fosset and J. R. Boissier. Inhibiteurs beta adrenergiques et stereotypies provoqe par l'amphetamine on l'apomorphine chez le rat. *Psychopharmacologia* **23:** 357–364, 1972.
38. Stolk, J. M., R. L. Conner, S. Levine and J. D. Barchas. Brain norepinephrine metabolism and shock induced fighting behavior in rats: Differential effects of shock and fighting on the neurochemical response to a common footshock stimulus. *J Pharmacol Exp Ther* **190:** 193–209, 1974.
39. Thoa, N. B., B. Eichelman and L. K. Ng. Shock induced aggression-effect of 6-hydroxydopamine and other pharmacological agents. *Brain Res* **43:** 467–475, 1972.
40. Tod, H. and M. S. Jones. A study of cholinesterase activity in nervous and mental disorders. *Q J Med* **6:** 1–3, 1937.
41. Tyrer, P. J. Use of β-blocking drugs in psychiatry and neurology. *Drugs* **20:** 300–308, 1980.
42. Vassout, A. and A. Delini-Stula. Effets de β-bloquers (propranolol et oxprenolol) et du diazepam sur differents modeles d'aggressivite chez le rat. *J Pharmacol* **8:** 5–14, 1977.
43. Vergnes, M., A. Depaulis and A. Boehrer. Parachlorophenylalacine-induced serotonin depletion increases offensive but not defensive aggression in male rats. *Physiol Behav* **36:** 653–658, 1986.
44. Weinstock, M., C. Weiss and S. Gitter. Blockade of 5-hydroxy-tryptamine receptors in the central nervous system by β-adrenoceptor antagonists. *Neuropharmacology* **16:** 273–276, 1977.
45. Wolfe, B., T. K. Harden, J. R. Sporn and P. B. Molinoff. Presynaptic modulation of beta adrenergic receptors in rat cerebral cortex after treatment with antidepressants. *J Pharmacol Exp Ther* **207:** 446–457, 1978.