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Synergistic Effect of Propranolol and Quipazine on Desipramine Enhanced Shock-Elicited Fighting in Rats

VINEETA PRASAD AND MICHAEL H. SHEARD

Department of Psychiatry, Yale University School of Medicine and Connecticut Mental Health Center, 34 Park Street, New Haven, CT 06519

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PRASAD, V. AND M. H. SHEARD. *Synergistic effect of propranolol and quipazine on desipramine enhanced shock-elicited fighting in rats.* PHARMACOL BIOCHEM BEHAV 19(3) 419–421, 1983.—Changes in shock-elicited fighting (SEF) were measured following single or repeated injections (IP) of dl-propranolol (5 mg/kg, 20 mg/kg) or quipazine (1.25 mg/kg, 2.5 mg/kg) given either alone or in combination to saline or desipramine (DMI) (10 mg/kg) treated rats. DMI + propranolol (20 mg/kg) caused a greater increase in fighting than DMI + saline 18 hours after last dose. Propranolol (20 mg/kg) produced an equal inhibition in both of these groups at 15 min. Propranolol (5 mg/kg) had no effect. Quipazine (2.5 mg/kg) failed to alter DMI induced increase in SEF. The combination of propranolol (5 mg/kg) + quipazine (1.25 mg/kg) blocked the enhanced SEF significantly in DMI treated rats in comparison to DMI + saline treated group. This combination of propranolol + quipazine produced no significant change in SEF in saline treated group in comparison to the pretest level. These results suggested that propranolol + quipazine act synergistically at low doses to inhibit the increased SEF seen in DMI treated rats and might have therapeutic implications for the management of irritable aggression or mania.

Shock-elicited fighting Propranolol Quipazine

TRICYCLIC antidepressants (TCA), the major agents used in treating depression, produce a variety of pharmacological effects on brain biogenic amines. However, their mechanism of action in depression remains unclear. The increase in aggressive behavior resulting from chronic, but not acute, administration of TCA drugs may provide a useful behavioral model to study changes which are brought about by chronic as opposed to acute administration. An increase in shock elicited fighting (SEF) in rats was observed after chronic administration of several antidepressant drugs, e.g., imipramine (IMI) desipramine (DMI) and amitriptyline (AMI) [2,6]. We have observed that this significant and reliable increase in SEF occurs in rats within 72 hours of desipramine (DMI) treatment [7]. We now report further investigations into the role of agents which modify norepinephrine (NE) and serotonin (5-HT) systems on this enhanced SEF.

A possible role for the B-adrenergic system has been shown by experiments with propranolol, a B-adrenergic antagonist, where acute doses of 10 or 20 mg/kg produced an inhibition of SEF [9]. Eichelman [3] has reported, however, that repeated treatment with propranolol produces an increase in SEF. This occurs despite the fact that each individual dose of propranolol continues to inhibit SEF [3]. Propranolol, in addition to B-adrenoceptor blocking activity, has some alpha-adrenergic antagonist and serotonin agonist properties. Quipazine which acts as a 5-HT agonist [5] in addition to having both an uptake blocking and slight inhibitory effect upon monoamine oxidase (MAO) [4] has also shown a dose dependent inhibitory effect upon SEF with significant inhibition at doses of 5.0 and 7.5 mg/kg [10]. The present study was undertaken to observe the effect of propranolol and quipazine either alone or in combination on desipramine treated rats.

METHOD

All animals were experimentally naive male rats of Sprague-Dawley Strain (Charles River Co.) weighing between 300–370 g at the time of the experiment and paired on the basis of weight. Rats were housed three to a cage of non-fighting members in a colony room maintained on a 12:12 light-dark (7 a.m.–7 p.m.) cycle. Food and water were freely available.

The shock-elicited fighting (SEF) apparatus has been described previously [8]. Essentially it consisted of a Plexiglas box (30×28×24 cm) with a grid floor of 0.5 mm parallel bars. This cage was housed in a dimly lighted Lehigh Valley sound attenuated chamber. Fighting was observed through a window from a darkened room. Fights were defined as a directed movement toward the opponent resulting in contact plus one of the following: biting, sparring, upright attack posturing or supine, submissive posturing adopted by the attacked rat. A Lehigh Valley shocker and scrambler delivered 30 shocks at 1.0 mA, 0.5 sec duration and the intershock interval was 7 sec.

Animals received intraperitoneal (IP) injections of DMI (10 mg/kg) (USV Pharmaceutical Corp., Tuckahoe, NY) and control injections of 0.9% saline. DMI,dl-propranolol (Ayerst Lab, Inc., NY) and quipazine (Miles Labs, Inc. Elkart, IN) were dissolved in 0.9% saline (injection volume 1 ml/kg). Doses were measured as the salt.

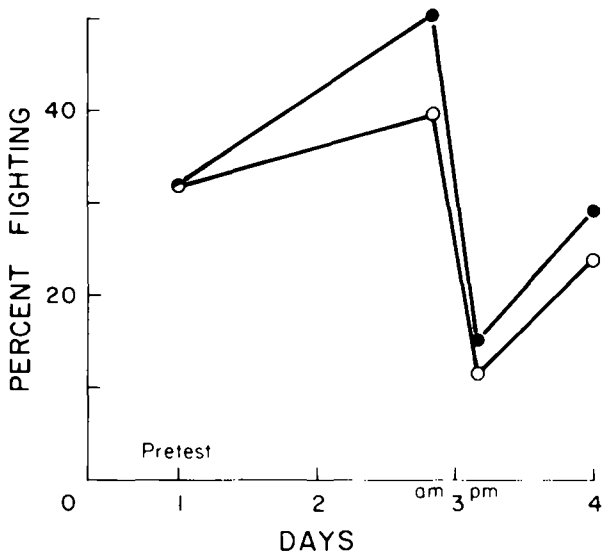

FIG. 1. Mean percent fighting for pairs of rats treated with saline + DMI (10 mg/kg) ○—○, or propranolol (20 mg/kg) + DMI (10 mg/kg) ●—●. On Day 3 testing was performed in a.m. 18 hours after last injection and again in p.m. 15 min after propranolol (20 mg/kg). Each point shows mean of 12 pairs.

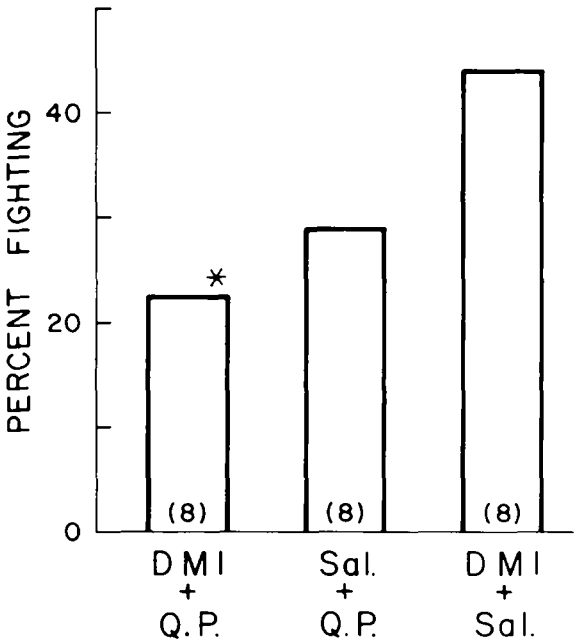

FIG. 2. Bar graph comparing precent fighting in 3 groups of rats. 1. DMI + Propranolol, (5 mg/kg) + Quipazine (1.25 mg/kg). 2. Saline + Propranolol, (5 mg/kg) + Quipazine (1.25 mg/kg). 3. DMI + saline. Numbers of pairs used for each treatment are given in parenthesis. *The level of significance was determined by independent t test: $p<0.05$, in comparison to DMI + saline group.

Prior to drug treatment 24 naive rats were paired and pretested to determine the baseline levels of SEF. Based on total number of fights, rats were divided into two groups of six pairs each having similar mean levels of SEF. Pretesting as well as subsequent testing was always carried out between 10:00–13:00 hours, except otherwise mentioned. Injections of saline + DMI or drug + DMI, started the same day as the pretest, were given between 15:00–16:00 hours.

PRELIMINARY EXPERIMENTS

Preliminary experiments tested various doses of propranolol and quipazine on saline and DMI treated groups of rats to establish doses which would not have any effect. Propranolol, 5 mg/kg, and quipazine, 1.25 mg/kg or 2.5 mg/kg, were found to have no significant effect on saline or DMI treated rats. An additional experiment showed that the combination of propranolol 20 mg/kg + DMI for two days showed a significantly greater increase in SEF than two days of propranolol alone.

Experiment 1. Repeated Propranolol + DMI

Six pairs of rats received saline and another six pairs dl-propranolol (20 mg/kg, IP) and 30 min later all rats received DMI. The above injection schedule was repeated on day 2. On day 3 all rats were retested in the morning approximately 18 hours after last injection. Four hours later all rats received dl-propranolol (20 mg/kg) and were tested after 15 min. Rats were retested again on day 4.

Experiment 2. Combined Propranolol + Quipazine

Prior to drug treatment, 24 naive rats were paired and pretested to determine the baseline levels of SEF. Based on total number of fights, rats were divided into three matched groups of four pairs each having similar mean levels of SEF. Pretesting, as well as subsequent testing was always carried out between 10:00–13:00 hours. Injections of saline or DMI, started the same day as pretest, were given between 15:00–16:00 hours.

Four pairs of rats received saline and another eight pairs DMI (10 mg/kg, IP) injection for two days. On day 3, approximately 18 hours after the last injection, saline controls and one group (4 pairs) of DMI rats received a combination of dl-propranolol (5 mg/kg) + quipazine (1.25 mg/kg, IP) and another DMI injected group received saline IP and all rats were tested 15 min after the injection.

RESULTS

No significant change in the body weight was observed over the days of drug administration.

Experiment 1

Testing on Day 3 morning showed an increase in SEF in both DMI and DMI + Propranolol groups in comparison to pretest fighting level. However, the magnitude of increase was much higher in the DMI + propranolol group, though this did not reach statistical significance. Acute injection of propranolol (20 mg/kg) produced a marked inhibition of both DMI and DMI + Propranolol groups (Fig. 1). Testing on day 4 showed that the SEF had returned close to the pretest level.

To assess the statistical reliability of the results, the data were analyzed with a two-way factor analysis of variance with propranolol drug treatment as a between subject factor and repeated test trials as a within subject factor. There was a highly significant within group effect, $F(2,44)=21.07$, $p<0.001$, indicative of the increase in SEF 18 hours after and

a decrease 15 minutes after injections of propranolol. A significant change in SEF after repeated test trials, $F(2,22)=10.66$, $p<0.001$. Subsequent individual comparisons by Dunnett's test showed that SEF was significantly inhibited by acute propranolol administration, $t(1,22)=3.23$, $p<0.005$. Overall there was a significant change in SEF in propranolol + DMI group, $F(2,22)=23.64$, $p<0.001$. Subsequent individual comparison by Dunnett's test showed a significant increase in SEF 18 hours after repeated propranolol, $t(1,22)=3.75$, $p<0.005$ and a significantly inhibited SEF 15 minutes after single propranolol, $t(1,22)=3.13$, $p<0.005$.

Experiment 2

The DMI group of rats treated with the combination of propranolol + quipazine showed significantly less fighting as compared to the DMI group treated with saline $t(14)=1.74$, $p<0.05$. The fighting of the DMI + propranolol + quipazine group did not differ significantly from the group which received saline + propranolol + quipazine. Finally, the fighting in the saline + propranolol + quipazine group did not differ significantly from pretest levels (Fig. 2).

DISCUSSION

The results of this experiment demonstrate a significant increase in shock-elicited fighting with repeated injection of propranolol given in combination with DMI and a significant decrease in SEF following a single injection of propranolol (Fig. 1). The enhancement of SEF seen with DMI is presumably related to increases in functional NE at critical brain regions serving as the substrate for irritable aggression. We speculate this increase in functional NE is presumably amplified at critical time periods following the NE antagonist properties of propranolol. It is most likely too early for measurable B-adrenergic supersensitivity to have developed, but the time is about right. It is also too early for other types of receptor supersensitivity to have developed to DMI. In this study two injections of propranolol at a 24-hr interval did not enhance SEF, whereas Eichelman [3] has reported an increase with more than two. Changes in pain threshold might be a possible explanation for these changes, but we have not found pain threshold useful as an explanation for drug effects on SEF since changes in SEF do not covary with changes in pain threshold. The action of propranolol in increasing DMI enhancement of SEF may also reside partially in its alpha-antagonistic property since it has been reported that irritable aggression is enhanced by administration of alpha-adrenergic antagonists into regions near the septum [1].

The results also show that the combination of propranolol (5 mg/kg) + quipazine (1.25 mg/kg) can block the increase in SEF seen in DMI treated rats, while failing to alter fighting in control rats significantly. That this combination of low doses of propranolol + quipazine can act to inhibit the fighting in DMI treated rats points to an important synergism between these two drugs. This synergism might be dependent on their combination of B-adrenergic antagonist and 5-HT agonist activity. Propranolol also possesses some 5-HT agonist activity and this would enhance the combined inhibitory action. The combination of B-adrenergic antagonist with 5-HT agonist property might have therapeutic implications for the management of irritable aggression or mania.

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