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Self-Regulation of ICSS Duration: Effects of Anxiogenic Substances, Benzodiazepine Antagonists and Antidepressants

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GERHARDT, S AND J. M LIEBMAN *Self-regulation of ICSS duration Effects of anxiogenic substances, benzodiazepine antagonists and antidepressants* PHARMACOL BIOCHEM BEHAV 22(1) 71–76, 1985 —A variety of anxiogenic substances, benzodiazepine antagonists and antidepressants were tested in a shuttlebox task in which rats interrupted infrared beams to initiate (ON latency) and terminate (OFF latency) continuous rewarding brain stimulation. It was hypothesized that substances exhibiting anxiogenic activity in animals (pentylenetetrazol and β-CCM) would selectively reduce the OFF latency, since anxiolytic drugs increase this latency β-CCM, however, did not alter the OFF latency, but instead lengthened the ON latency Pentylenetetrazol showed a similar, though not significant, trend. Ro 15-1788 did not alter ON latencies, but selectively lengthened the OFF latency at a high dose, consistent with previously reported anxiolytic activity at such doses In contrast, CGS 8216 lengthened the ON latency selectively Thus, Ro 15-1788 was differentiated from other drugs that antagonize benzodiazepines Caffeine and dopamine uptake-blocking antidepressants (amineptine and nomifensine) preferentially decreased ON latencies, while non-dopamine-blocking antidepressants (viloxazine and CGS 7525A) lengthened both latencies nonspecifically In conclusion, the OFF latency (but not the ON latency) appears refractory to reduction by various classes of psychotropic agents.

ICSS Ro 15-1788 CGS 8216 Antidepressants Beta-CCM

A wide variety of psychotropic drugs have been shown to influence intracranial self-stimulation (ICSS). The effects of neuroleptics, opiates, and psychomotor stimulants have been of particular interest [10, 11, 34]. Numerous problems of interpretation have arisen in the course of these studies, and a variety of novel research techniques have been developed in an attempt to resolve these issues [19]. One such technique is based on the ability of animals to self-regulate the duration of ICSS current when placed in a shuttlebox [2]. This method has proven particularly versatile in its ability to differentiate among a variety of psychotropic drugs, including neuroleptics, muscle relaxants, psychomotor stimulants, benzodiazepine-type anxiolytics and atypical anxiolytics [2, 15, 19] It therefore appears especially useful for psychopharmacological studies [19].

This procedure provides three indices of drug effects. First, the latency to initiate stimulation (i.e., to interrupt the ON photocell beam in a shuttlebox) correlates inversely with the reward value of stimulation [2,19]. This latency is elevated by neuroleptics and is reduced by psychomotor stimulants [2, 20, 21]. Secondly, when rats are tested in this procedure, the latency to terminate stimulation appears to correlate with aversiveness that builds up during continuous, rewarding stimulation of the lateral hypothalamus, particularly its medial aspect [30]. The evidence for this interpretation has been reviewed elsewhere (cf. [15, 19, 30]). For example, rats show flight-like behavior as they undergo initial training to terminate stimulation, suggestive of intense anxiety. Further, manipulations of ICSS parameters have demonstrated that the latency to terminate stimulation is dissociable from that to initiate stimulation. Consistent with this interpretation, anxiolytic drugs selectively elevate the termination latency but have no consistent effect on the initiation latency at doses that are free of overt sedation [4,15]. The termination latency appears to correlate with stimulation-induced aversiveness, manifested as anxiety, and not with the reward value of stimulation [19].

Finally, a concurrent elevation of both latencies appears to indicate nonspecific performance impairment. Such an effect is produced by high doses of various psychotropic drugs, by physical hindrance to shuttling, and by muscle relaxant drugs [21]. High doses of diazepam or chlordiazepoxide also elevate both latencies nonselectively [15].

These experimental results suggest additional applications of this procedure to the characterization of several other drug classes. For example, it would be expected that

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drugs that antagonize the actions of benzodiazepines would reduce the latency to terminate stimulation, opposite to the known effects of anxiolytic drugs [15] Dihydromethyl β-carboline (β-CCM) is an inverse agonist [7] with anxiogenic properties at subconvulsive doses [27]. CGS 8216 blocks the actions of classical benzodiazepines [6,35] and has been characterized as an inverse benzodiazepine agonist [7] Ro 15-1788 appears to be a benzodiazepine antagonist with only minimal propensity to cause anxiety [13] These drugs were evaluated in the shuttlebox ICSS procedure

For comparison with these novel agents, caffeine and pentylenetetrazol were also tested. These two substances antagonize some of the actions of benzodiazepines [6] and have anxiogenic activity in animal models [12,28] and in humans [16,29] Therefore, they might be expected to decrease the OFF latency. At the same time, however, both drugs have stimulant properties [16], suggesting that a specific decrease might also occur in the ON latency Such an effect is produced by the psychomotor stimulants, *d*-amphetamine and pipradrol, and by bupropion [1,20]

A further objective of the present experiments was to explore in more detail the possible association between psychomotor stimulation and selective decreases in the ON latency. For this purpose, several antidepressants representing different neurochemical mechanisms were assessed These included nomifensine and amineptine, which have dopamine uptake blocking properties and are clinically useful as antidepressants, and viloxazine, a preferential norepinephrine uptake blocker [32] An alpha-2 adrenoceptor antagonist, CGS 7525A (aptazapine) was also tested, as this substance should elevate mood by increasing the synaptic availability of norepinephrine [22]. It was of interest to determine whether these substances would also decrease the ON latency selectively

METHOD

Animals and Surgical Procedures

Male Fischer (F-344, Charles River) rats weighing 250–300 g were anesthetized with 20 mg ketamine HCl IM to which acepromazine (0.75 mg/ml) had been added to induce muscle relaxation Stainless steel bipolar electrodes having a diameter of 0.2 mm each (Plastic Products, Roanoke, VA) were stereotaxically implanted in the lateral hypothalamus (coordinates· AP=+4.8; L=1.0 to 1.3; DV=−3.5 from stereotaxic zero, according to the atlas of Konig and Klippel [18]). At least one week of recovery was allowed before initiation of behavioral testing. Following experimentation, a representative sample of rats (approximately one-third of the total group) was sacrificed and perfused with fixative Brains were removed, sectioned and stained with cresyl violet Examination of slides showed that the stereotaxic coordinates used yielded reliable placement of electrodes in the dorsomedial area of the lateral hypothalamus

Behavioral Procedures

The shuttlebox procedure has been previously described [21] Animals were tested in a chamber containing an infrared beam at each end. An Inter-Act (BRS-LVE, Beltsville, MD) computer system controlled the experiment such that interruption of one photocell beam (the ON beam) caused rectangular pulses to be delivered continuously through the implanted electrode until the other photocell beam (the OFF beam) was interrupted by the rat. Brain stimulation was delivered by a Haer 4bp stimulator according to the following parameters· pulse duration 0 4 msec, pulse frequency 100 Hz, current intensity 40 to 200 μA

After initial training, rats underwent daily 10 min test sessions The first beam that the rat interrupted became the ON beam. The total number of crossing cycles in the next 10 min was recorded, as were the cumulative latencies to break the ON and the OFF beams The task was programmed so that if the rat allowed the ON latency to reach 60 sec at any time, brain stimulation was automatically activated and the normal programming contingency then resumed Conversely, if the OFF latency reached 60 sec at any time, stimulation was automatically terminated Thus, the cut-off latency value was 60 sec

A total of 35 rats yielded performance suitable for drug testing In these rats, current intensity was individually adjusted so as to yield between 35 and 80 crossing cycles per session, as previously described [21] Each drug treatment was administered only after at least two days of stable baseline responding (i e , no more than 10% variation in the number of crossing cycles) occurred within these limits At least five days elapsed between treatments, during which time stable baseline responding was reestablished An additional constraint was that drug data were not collected if either the mean ON or OFF latency was less than two sec These short latencies were previously found to be refractory to drug-induced reductions in latencies [21] Under the present experimental conditions, the group mean ON latencies ranged from 4 7 to 6.4 sec, and the group mean OFF latencies ranged from 4 8 to 8 5 sec

Drug Treatments

Drugs and sources were. viloxazine HCl (Stuart, Wilmington, DE), caffeine sodium benzoate (Sigma, St. Louis, MO), pentylenetetrazol (Knoll, Whippany, NJ), amineptine, nomifensine, dihydro methyl beta-carboline (β-CCM), Ro 15-1788, CGS 7525A and CGS 8216 (synthesized by CIBA-GEIGY chemists) Pentylenetetrazol was dissolved in physiological saline β-CCM was suspended in saline to which two drops of Tween 80 had been added [31] Other drugs were prepared in a 3% colloidal cornstarch suspension containing 5% PEG-400 and 0 34% Tween 80

Drugs were administered intraperitoneally 30 min before testing, except for Ro 15-1788 (orally, 15 min before testing) and β-CCM (intravenously, immediately before testing) In a limited set of additional experiments, CGS 8216 was administered orally 30 min before testing for comparison with IP results. Oral doses were given in a volume of 10 ml/kg of body weight; intraperitoneal and intravenous injections were given in a volume of 1 0 ml/kg. Drug doses were expressed as the respective free base equivalents. Each animal received all doses of a given drug in counterbalanced order. At least five days elapsed between drug treatments.

Analysis of Data

The cumulative ON and OFF latencies for each rat during a given experimental session were divided by the total number of response cycles to yield individual mean ON and OFF latencies for that session. Drug effects for each session were assessed by comparing mean ON and OFF latencies with those during the baseline session of the preceding day For purposes of analysis, group mean ON and OFF data were computed from individual results To determine whether significant dose-response relationships existed for the drug-induced changes in ON and OFF latencies, regres-

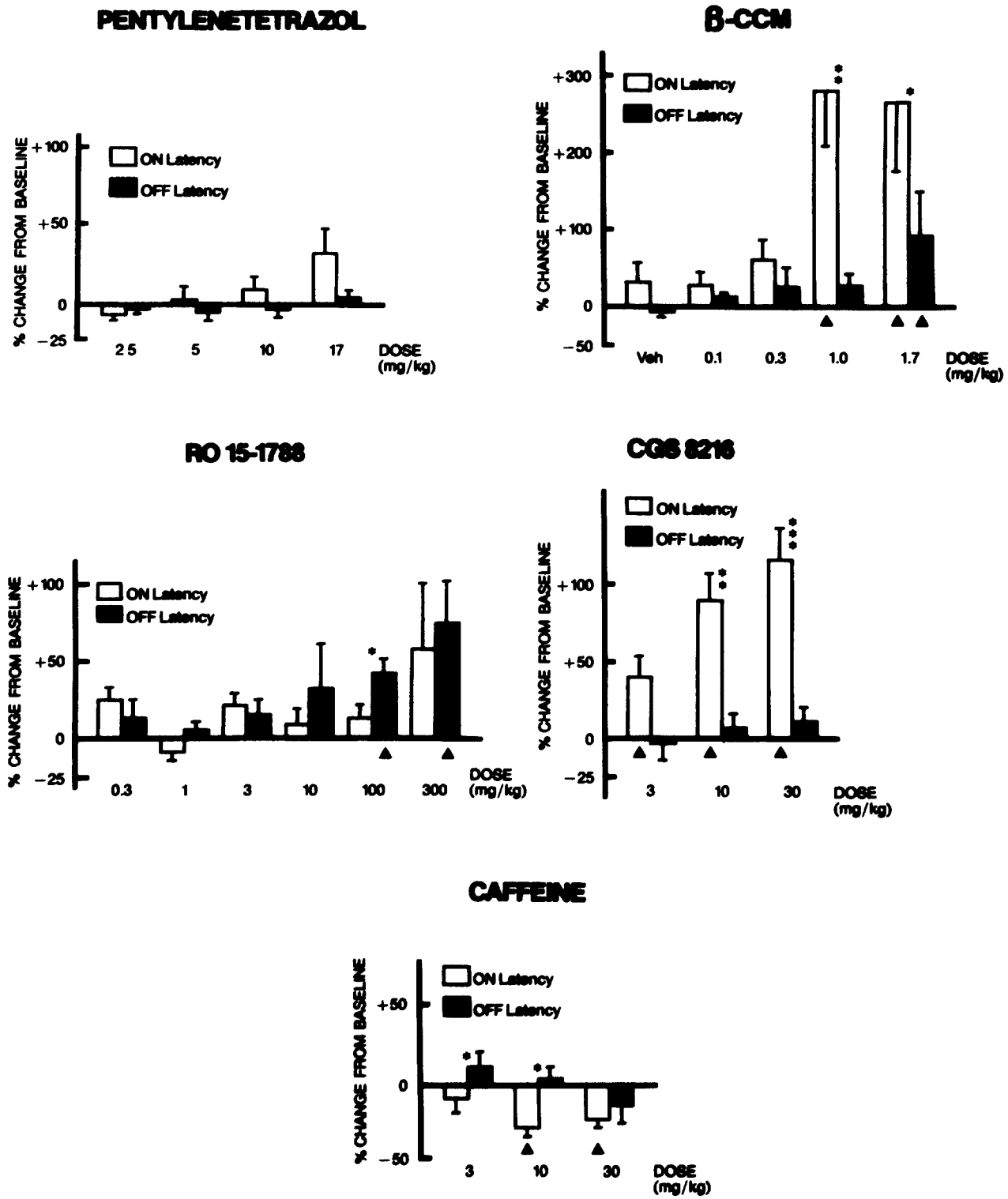

FIG 1 The effects of pentylenetetrazol (n=10), β-CCM (n=6), CGS 8216 (n=9), Ro 15-1788 (n=9) and caffeine (n=8) on mean self-stimulation ON and OFF latencies in the shuttlebox. *$p<0.05$ for difference between ON and OFF latencies, matched pair two-tailed t-test **$p<0.01$, ***$p<0.001$ ▲ Significantly different from baseline by trend test at $\alpha=0.05$. Analyses were performed on transformed data

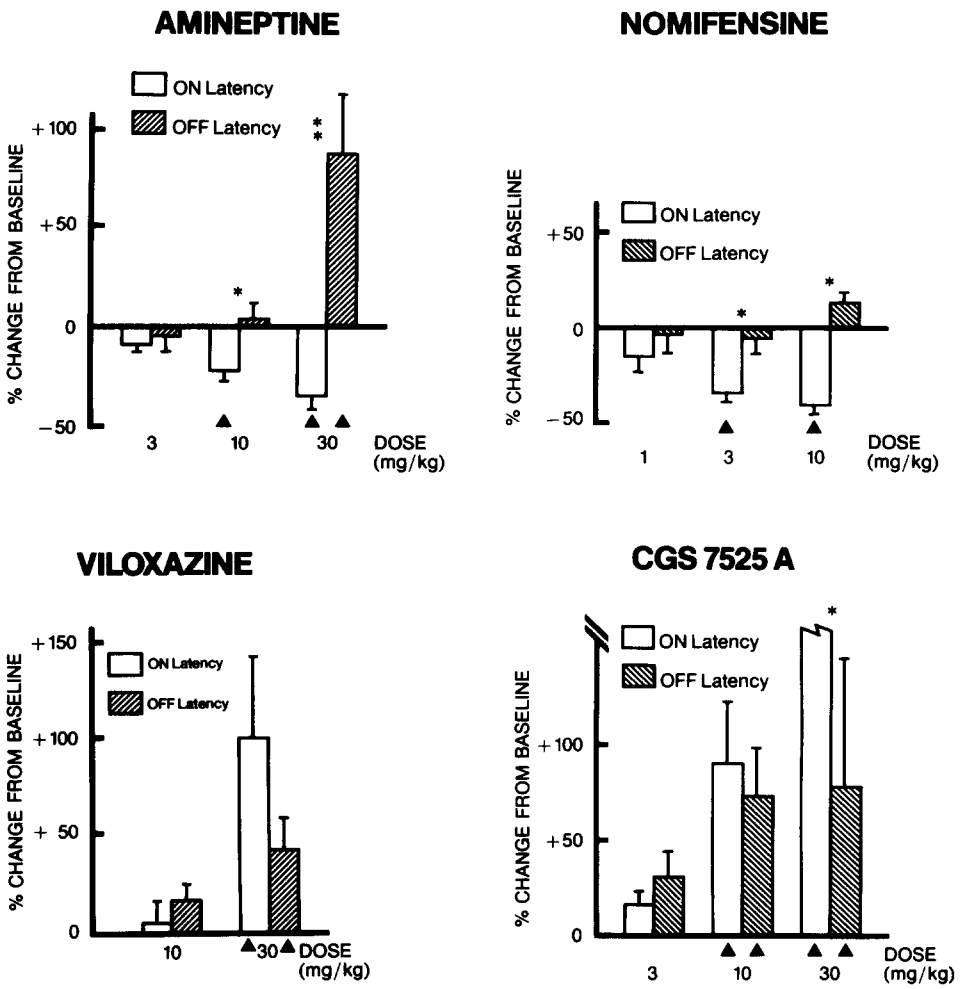

FIG 2 The effects of amineptine (n=8), nomifensine (n=9), CGS 7525A (n=8) and viloxazine (n=7) on mean self-stimulation ON and OFF latencies in the shuttlebox $*p<0.05$ for difference between ON and OFF latencies, matched pair two-tailed t-test $**p<0.01$ ▲ Significantly different from baseline by trend test at $\alpha=0.05$ Analyses were performed on transformed data

sion analyses were performed separately on group mean ON and OFF latencies, transformed to log of the ratio, post-drug/baseline. Whenever these analyses indicated a significant dose-response relationship, the trend test [3] was then applied to identify doses that produced a significant ($\alpha=0.05$) increase in latency over the pre-drug baseline.

RESULTS

Neither pentylenetetrazol (IP) nor β-CCM (IV) decreased OFF latencies significantly at any dose tested (Fig. 1) Surprisingly, ON latencies instead were selectively increased over baseline by 1 0 mg/kg β-CCM, a dose that produced no increases in OFF latencies. At 1 7 mg/kg β-CCM, OFF latencies did increase significantly. The magnitude of the increase in the ON latencies exceeded that in the OFF latencies at this dose, however Similar, although nonsignificant, trends were also apparent following pentylenetetrazol treatment Higher doses of these substances could not be tested because of the emergence of seizures

The benzodiazepine antagonist, Ro 15-1788, produced no changes in either the ON or OFF latencies at doses from 1.0 to 10 mg/kg PO (Fig 1) At 100 mg/kg, the OFF latency was significantly lengthened as compared with baseline, but the ON latency remained unchanged. Both latencies increased nonselectively at 300 mg/kg Ro 15-1788 A different, and unexpected, pattern of ICSS responding was produced by CGS 8216 This drug caused a dose-related and highly selective increase in ON latencies when administered IP (Fig. 1) Similar effects were produced by PO administration of CGS 8216 (data not shown)

Caffeine did not reduce the OFF latency significantly at any dose tested (Fig. 1). Modest, significant reductions in the ON latency occurred at 10 and 30 mg/kg The ON and OFF latencies differed significantly at 3.0 and 10 mg/kg At 100 mg/kg, caffeine produced nonselective increases in both ON and OFF latencies (data not shown)

Moderate doses of nomifensine (3 0 and 10 mg/kg IP) and

amineptine (10 and 30 mg/kg IP) significantly decreased the ON latency from baseline in a dose related fashion (Fig. 2). At all of these doses, the ON and OFF latencies differed significantly. The OFF latency was not significantly reduced by any of these treatments In fact, the OFF latency increased significantly from baseline following 30 mg/kg amineptine. Higher doses of each drug (30 mg/kg nomifensine; 100 mg/kg amineptine) markedly lengthened both latencies, suggesting behavioral impairment (data not shown)

Neither CGS 7525A nor viloxazine reduced ON or OFF latencies at any dose (IP) tested (Fig. 2). Instead, ON and OFF latencies both increased in a virtually nonselective fashion (Fig. 1). At the highest dose of CGS 7525A, the increase in the ON latency significantly exceeded that in the OFF latency, but both latencies were significantly lengthened as compared with baseline.

DISCUSSION

The most striking finding was that none of the experimental drugs decreased the OFF latency significantly at any dose tested. This was true of pentylenetetrazol, β-CCM and CGS 8216. Intense anxiety in humans may be induced by administration of pentylenetetrazol [29] and FG 7142, a β-carboline analog [9]. Therefore, anxiogenic activity per se apparently is not sufficient to decrease the OFF latency in the shuttlebox test of ICSS duration self-regulation. The inverse benzodiazepine agonist, CGS 8216, also did not reduce the OFF latency. Although this substance has been reported to have anxiogenic activity in animal models [14, 23, 24], no anxiogenic activity of CGS 8216 is apparent in clinical investigations [5].

These three drugs did have an unanticipated, but consistent, effect on performance in this task. CGS 8216 and β-CCM significantly increased the ON latency at doses that had little or no effect on the OFF latency, and a similar (although nonsignificant) trend was evident for pentylenetetrazol. In view of this selectivity for the ON latency, a nonspecific disruption of performance does not seem likely. Selective elevation of ON latencies is also induced by low to moderate doses of drugs that interfere with dopaminergic neurotransmission, and indicates impaired initiation of ICSS [21]. The present results are consistent with a very recent report that CGS 8216 and FG 7142 (a β-carboline analog) each reduced ICSS responding in a variable interval lever-pressing test [25] The effects of FG 7142 were reported to occur at a dose that had little or no effect on locomotor activity, which would again argue against mediation by nonspecific motor deficit.

As a possible explanation, it was suggested [25] that FG 7142 may reduce ICSS by enhancing an aversive component of lateral hypothalamic ICSS. If so, it would have been expected that the closely related β-carboline, β-CCM, would have reduced the OFF latency The absence of such an effect in the present experiments indicates that the aversive component of hypothalamic ICSS is not directly intensified by the anxiogenic β-carbolines

An alternative possible explanation for the increase in the ON latency is that the occurrence of anxiety (whether drug- or situation-induced) may directly inhibit the neuronal system(s) that mediate the initiation of ICSS. This hypothesis would predict that a selective inhibition of the positive motivating properties of ICSS would also be apparent if these drugs were tested in other ICSS test procedures [19].

Another finding of interest was the dissociation between Ro 15-1788 and the other drugs investigated. No increase in the ON latency was produced by Ro 15-1788 except at a dose (300 mg/kg) that also increased the OFF latency. However, at 100 mg/kg, Ro 15-1788 slightly (but significantly) elevated the OFF latency without changing the ON latency significantly. This profile is suggestive of weak anxiolytic activity at a high dose. A recent report [24] indicated that Ro 15-1788 at high doses increases ICSS responding in a manner similar to the effects of anxiolytic benzodiazepines Another report has shown that Ro 15-1788 at a high dose (40–80mg/kg) may generalize to a benzodiazepine (chlorazepate) in animals trained to discriminate chlorazepate from saline [8]. These observations suggest that, in addition to its benzodiazepine antagonist properties, Ro 15-1788 may have weak benzodiazepine agonist activity at high doses. No such properties have been reported for the inverse benzodiazepine agonist, CGS 8216 [7].

Amineptine and nomifensine, which have dopamine uptake blocking properties [32], reduced ON latencies at doses that did not reduce OFF latencies. In fact, a 30 mg/kg dose of amineptine increased OFF latencies at the same time that ON latencies were decreased. Bupropion, another antidepressant linked to possible dopamine uptake blockade [32], has been reported to have a similar profile [20] The dissociation of ON and OFF latencies rules out the possibility of nonspecific motor stimulation as an explanation for the drug effects.

Viloxazine, an antidepressant that blocks norepinephrine uptake but not dopamine uptake [32], did not reduce ON latencies at any dose tested. CGS 7525A, an alpha-2 autoreceptor antagonist [22], also failed to reduce the ON latency. Similar results have been reported for a related antidepressant, mianserin [17]. The ability to decrease the ON latency selectively therefore appears not to be a property of antidepressants in general, but seems related to facilitation of DA transmission.

Caffeine is known to have stimulant and anxiogenic properties [16], and antagonizes some of the effects of benzodiazepines [6,26]. It was hypothesized that caffeine would reduce both ON and OFF latencies, the latter effect corresponding to its anxiogenic activity. However, moderate doses of caffeine decreased ON latencies without altering OFF latencies appreciably. Caffeine therefore resembled stimulant drugs and dopamine uptake-blocking antidepressants. Enhancement of brain dopamine neurotransmission by caffeine has been reported using a rotational behavior model [33] and may account for the apparent enhancement of reward.

To date, no drug has been shown to decrease OFF latencies selectively in the shuttlebox ICSS duration self-regulation test. In fact, concurrent reductions in the ON and OFF latencies have not been convincingly demonstrated. The only drug that has reduced OFF latencies for hypothalamic ICSS is *d*-amphetamine, and that reduction was seen concurrently with a larger reduction in the ON latency [20]. Obviously, the OFF latencies generated by rats performing an ICSS duration self-regulation task cannot serve as a simple index of anxiogenic activity. If drugs can be discovered that selectively reduce the latency to terminate hypothalamic brain stimulation, these drugs may permit new insights into the nature of brain stimulation-induced aversiveness and/or anxiety

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