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Central β_1-Adrenergic Receptors Are Involved in CRF-Induced Defensive Withdrawal

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YANG, X.-M. AND A. J. DUNN. *Central β_1-adrenergic receptors are involved in CRF-induced defensive withdrawal.* PHARMACOL BIOCHEM BEHAV **36**(4) 847–851, 1990.—Previous studies indicated that peripheral administration of propranolol, a nonselective β-adrenergic antagonist, attenuated ICV CRF-induced suppression of a conditioned emotional response and defensive withdrawal behavior in rats, suggesting the involvement of a β-adrenergic receptor in the CRF-induced behavioral changes. The present study was carried out to determine whether central or peripheral β-adrenergic receptors are involved in CRF-induced defensive withdrawal behavior, and which subtype of β-adrenergic receptor is involved. *l*-Propranolol (2.5 mg/kg IP) significantly reversed CRF-induced defensive withdrawal behavior. CGP-12177 (1 mg/kg IP), a β-adrenergic antagonist with predominant effects on peripheral β-adrenergic receptors, and ICI 118,551 (0.5 mg/kg IP), a selective β_2-adrenergic antagonist, had no significant effects on CRF-induced defensive withdrawal. When administered ICV, two selective β_1-adrenergic antagonists, CGP-20712A (10 μg) and atenolol (100 μg), significantly antagonized CRF-induced defensive withdrawal. Our results suggest that a central β_1-adrenergic receptor is involved in CRF-induced defensive withdrawal in rats.

Corticotropin-releasing factor β-Adrenergic antagonists ICI 118,551 CGP-12177 *l*-Propranolol CGP-21072AI Atenolol

WHEN injected intracerebroventricularly (ICV) or directly into certain brain regions, corticotropin-releasing factor (CRF) elicits a number of neurochemical, physiological and behavioral responses resembling those observed in stress (4, 9, 15, 27, 45). These effects of CRF are independent of the activation of hypothalamic-pituitary-adrenal axis because hypophysectomy did not attenuate the CRF-induced responses (6,17). Alpha-helical CRF_{9-41} (ahCRF), a CRF antagonist, reversed various stress-induced behavioral and physiological responses (5, 8, 28). These findings and other similar evidence indicate that CRF plays a role in mediating behavioral and physiological responses in stress (16).

A recent report indicated that propranolol, a nonselective β-adrenergic receptor antagonist, significantly attenuated the CRF-induced suppression of a conditioned emotional response (10). We also found that propranolol reduced defensive withdrawal behavior in a novel environment (45), a behavior in which endogenous CRF is believed to be involved (41). Propranolol also reversed ICV CRF-induced defensive withdrawal (45). These results suggest that a β-adrenergic receptor is involved in the CRF-induced behavioral changes. It is relevant that propranolol has been used clinically to treat acute pathological panic (22).

Central administration of CRF has been shown to produce an activation of the sympathetic nervous system, increasing the plasma concentrations of norepinephrine and epinephrine, and heart rate and blood pressure (8,20). Because of its lipophilic properties, propranolol administered IP penetrates the blood-brain barrier and antagonizes both peripheral and central β-adrenergic receptors (1, 23, 29). It has been suggested that the anxiolytic actions of propranolol result from its action in the periphery, because it significantly improves autonomic symptoms in anxious patients (21), and because significant effects on the central physiological and behavioral measures are absent in normal human subjects (29). Therefore, it is important to investigate whether peripheral or central β-adrenergic receptors, or both, are involved in the CRF-induced behavioral changes. There are three subtypes of β-adrenergic receptors with distinct pharmacological (18, 30–32) and structural characteristics (39,40). It was, therefore, of interest to study which subtype of the β-adrenergic receptor is involved in the behavioral changes.

The present experiment compared the ability of nonselective β-adrenergic antagonists propranolol and CGP-12177 to antagonize ICV CRF-induced defensive withdrawal. These antagonists exhibit a similar affinity for β-adrenergic receptors in vitro. However, CGP-12177 is hydrophilic relative to *l*-propranolol (38), and penetrates the central nervous system less well (34). A selective β_2-adrenergic receptor antagonist ICI 118,551 IP (2, 7,

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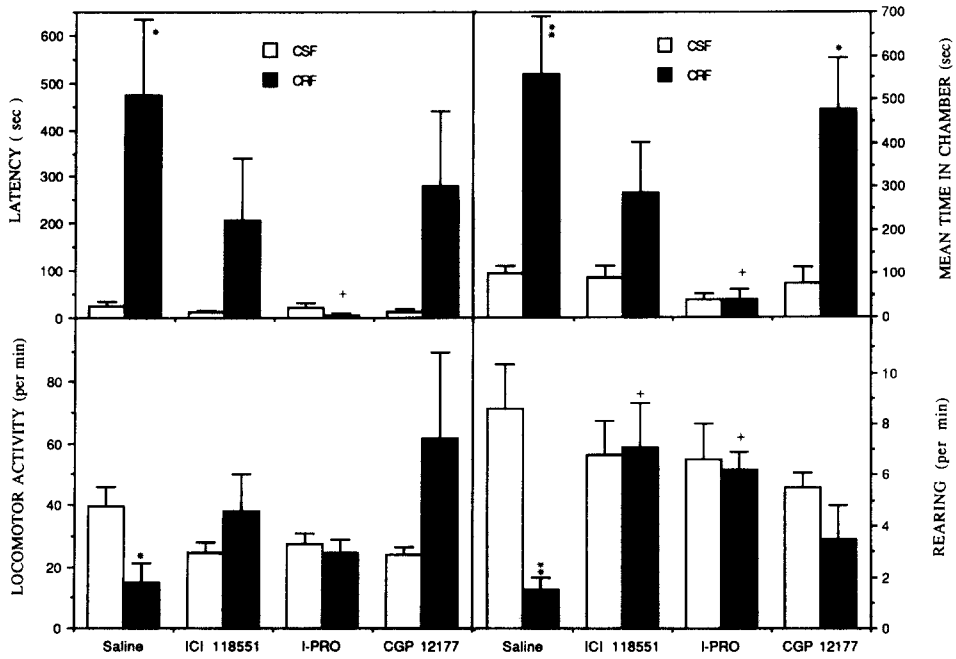

FIG. 1. Effects of ICI 118,551 (0.5 mg/kg), *l*-propranolol (*l*-PRO, 2.5 mg/kg) and CGP-12177 (1 mg/kg) on CRF-induced defensive withdrawal and exploratory behavior in rats. Rats were injected IP with saline or drugs 15 min before ICV injection of aCSF or CRF (50 ng). Twenty-five minutes later, rats were placed in the small enclosed chamber and behavior scored. N = 7–8 per group. Compared with aCSF control, $*p<0.05$; $**p<0.01$; compared with saline-CRF control, $+p<0.05$; $++p<0.01$.

42), and the β_1-adrenergic receptor antagonists, CGP-20172A and atenolol ICV (3, 13, 14, 25) were used to examine which subtype of β-adrenergic receptors is primarily involved.

METHOD

Animals

Adult male Sprague-Dawley rats (250–300 g), obtained from Harlan Laboratories, were housed individually in plastic cages placed in a temperature- and light-controlled room (light on from 6:00 a.m. to 5:30 p.m.) for one week before surgery. Food and water were available continuously in the home cages.

Surgery and Infusion Procedure

Two 9-mm 23-gauge stainless steel guide cannulae were implanted with their tips 1.0 mm above the lateral ventricles and secured to the skull with two stainless steel screws and dental cement. Surgery was performed under pentobarbital anesthesia (55 mg/kg IP). Stereotaxic coordinates were: A-P −0.5 mm, L ±2.0 mm, and 3.2 mm below the skull surface at the point of entry. Rats were allowed at least 5 days to recover from surgery before being tested.

Compounds requiring ICV injection were administered with a 30-gauge infusion cannula extending 1 mm beyond the tip of the guide cannulae and connected to a 10 μl Hamilton syringe by 25 cm polyethylene tubing. The rate of infusion was about 1 μl in 15 seconds and the infusion cannula were left in the guide cannula for about 20 seconds.

At the end of behavioral testing, rats were anesthetized with sodium pentobarbital and infused ICV with 2–4 μl blue dye. After 20 min, brains were removed and cannula placements verified by visual inspection of coronal sections.

Behavioral Testing Procedure

After surgery, rats were habituated to handling by stroking their dorsal surface for about 1 min every day until the test day. Testing was conducted in an opaque Plexiglas open field (110 × 110 × 35 cm), the floor of which was marked with 20 × 20 cm squares and illuminated by a fluorescent lamp. A cylindrical galvanized chamber, open at one end and measuring 15 cm deep and 13 cm in diameter, was secured to the floor of open field next to the wall in a lengthwise direction 40 cm away from a corner of the open field. The following behaviors were observed during the 15-min test session: the latency to leave the chamber, defined as the placement of all four paws in the open field; the mean time in the small chamber; locomotor activity, defined as the number of lines on the floor of open field crossed per min; and the number of rears per min. After each test, the testing apparatus was cleaned with 1% acetic acid to prevent olfactory cues from affecting the behavior of rats tested subsequently.

All tests were conducted with rats familiar with the apparatus. Thirty-eight rats (n = 38) were used in a two-factor repeated-measure design. On the first experimental day, rats received an ICV injection of artificial cerebrospinal fluid [(aCSF, made according to (26)] and ICV or IP injections of β-adrenergic receptor antagonists or vehicle. The following day, the same procedure was repeated with the same drugs, except that CRF was substituted for aCSF.

Drugs

Atenolol and *l*-propranolol were obtained from Sigma Chemi-

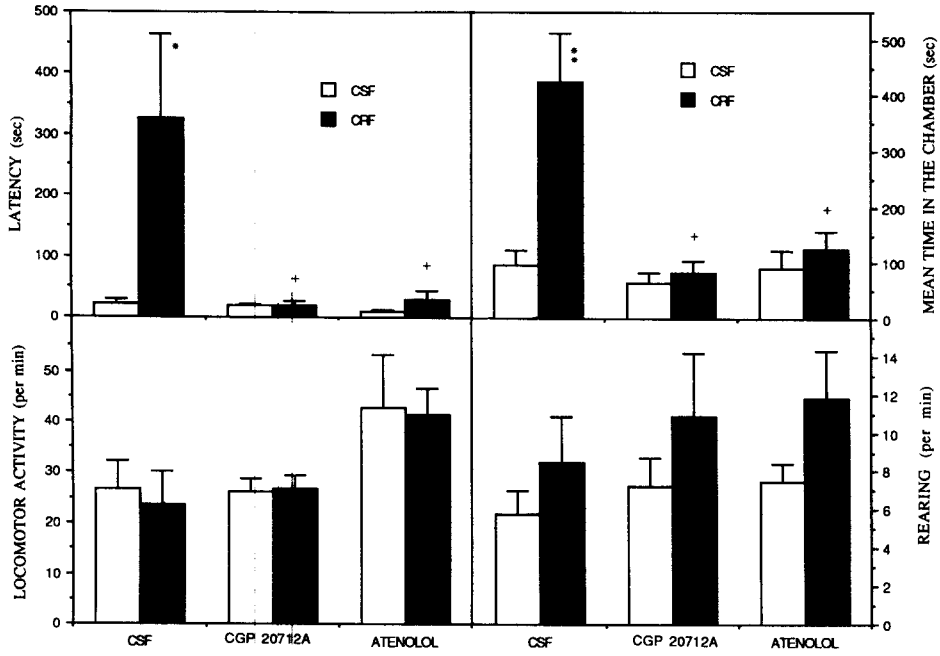

FIG. 2. Effects of CGP-20712A (10 μg) and atenolol (100 μg) on CRF-induced defensive withdrawal and exploratory behavior in rats. Rats were injected ICV with aCSF or drugs 5 min before an ICV injection of 50 ng aCSF (Day 1) or CRF (Day 2). Twenty-five minutes after ICV injection of CRF, rats were placed in the small enclosed chamber. N = 7–8 per group. Compared with aCSF-aCSF, *$p<0.05$; **$p<0.01$; compared with aCSF-CRF, +$p<0.05$.

cal Co. (St. Louis, MO). CRF was provided by Dr. Jean Rivier (Salk Institute). ICI 118,551 [(erythro-*dl*-1C7-methylindan-4-yloxyl)3-isopropylaminobutan-2-*O*-1, Imperial Chemical Industries, Cheshire, England], CGP-21072A {1-[2((3-carbamoyl-4-hydroxy)phenoxy)-ethylamino]-3-[4-(1-methyl-4-trifluoromethyl-2-imidazolyl)phenoxy]-2-propanol methanesulfonate} and CGP-12177 [4-(3-*tert*-butylamino-2-hydroxypropoxy)-benzimidazole-2-one hydrochloride] (Ciba-Geigy Ltd, Basel, Switzerland) were generous gifts from Dr. James M. O'Donnell. Materials for ICV injections (atenolol, CGP-21072A and CRF) were dissolved in CSF and those for IP injections (ICI 118,551, *l*-propranolol and CGP-12177) were dissolved in normal saline.

Statistical Analysis

The data are represented as the means ± S.E.M. Statistical analysis was performed by ANOVA using the SAS program. The comparison of multiple means was accomplished by Duncan's test.

RESULTS

Effects of IP Injections of l-Propranolol, ICI 118,551 and CGP-12177 on CRF-Induced Defensive Withdrawal

CRF 50 ng ICV was used to induce defensive withdrawal behavior (45). On each day, normal saline, *l*-propranolol (2.5 mg/kg), ICI 118,551 (0.5 mg/kg) or CGP-12177 (1 mg/kg) were injected IP 15 min before aCSF (Day 1) or 50 ng CRF (Day 2) was injected ICV. As shown in Fig. 1, 50 ng CRF significantly increased the latency, $F(1,15)=8.27$, $p<0.05$, the mean time in the chamber, $F(1,15)=14.04$, $p<0.01$, and decreased locomotor activity, $F(1,15)=8.28$, $p<0.05$, and rears, $F(1,15)=9.20$, $p<0.05$. Compared with saline-aCSF, none of the drugs had significant effects on the latency, the mean time in the chamber, or the locomotor activity or rears in aCSF-injected rats. *l*-Propranolol significantly reversed the CRF-induced increases in the latency, $F(1,13)=7.22$, $p<0.05$, the mean time in the chamber, $F(1,13)=12.62$, $p<0.01$, and the decrease in rears, $F(1,13)=10.37$, $p<0.01$, but had no effect on the CRF-induced decrease in locomotor activity. Except for the significant antagonism by ICI 118,551 of the CRF-induced decrease in rears, $F(1,13)=6.49$, $p<0.05$, CGP-12177 and ICI 118,551 had no significant effects on CRF-induced defensive withdrawal.

Effects of ICV CGP-21072A and Atenolol on CRF-Induced Defensive Withdrawal

CGP-21072A (10 μg) and atenolol (100 μg) were injected ICV in a volume of 2 μl each side 5 min before aCSF (Day 1) or 50 ng CRF (Day 2) was injected ICV. As shown in Fig. 2, 50 ng CRF significantly increased the latency to emerge, $F(1,10)=4.97$, $p<0.05$, and the mean time in the chamber, $F(1,10)=16.17$, $p<0.01$, but had no significant effects on locomotor activity and rears. We have no explanation for the lack of effect on locomotor activity, although CRF-induced changes in this measure have not been particularly consistent in our studies in mice. CGP-21072A and atenolol significantly antagonized the CRF-induced increases in the latency, $F(1,10)=5.03$, $p<0.05$; $F(1,11)=5.52$, $p<0.05$, respectively, and the mean time in the chamber, $F(1,10)=12.42$, $p<0.01$; $F(1,11)=10.34$, $p<0.01$, respectively, but had no effects on locomotor activity and rears.

DISCUSSION

As reported previously, ICV administration of CRF enhanced defensive withdrawal behavior in rats (41,45). Moreover, *l*-propranolol completely antagonized ICV CRF-induced defensive withdrawal in rats familiar with their environment [(45) and Fig. 1], suggesting that β-adrenergic receptors are involved in CRF-induced defensive withdrawal. This finding is consistent with the report that propranolol blocked the ICV CRF-induced suppression of a conditioned emotional response (10).

The failure of CGP-12177 to antagonize CRF-induced defensive withdrawal (Fig. 1) suggests that central, as opposed to peripheral, β-adrenergic receptors are primarily involved in the CRF-induced behavioral changes. CGP-12177 at the same dose (1 mg/kg) antagonized the operant behavioral responses to clenbuterol (34). CGP-12177 has been shown to have high affinity for both β_1- and β_2-adrenoceptors in the brain and peripheral membrane preparations (11, 19, 37, 44). However, it penetrates cells poorly and this lack of penetration has been ascribed to its hydrophilic nature (38). Even though some evidence indicates that CGP-12177 is not highly hydrophilic, the ability of CGP-12177 to inhibit the in vivo binding of [^{125}I]pindolol, a nonselective lipophilic β-adrenergic antagonist, is considerably lower than would be expected based on its capacity to displace pindolol binding in vitro (11). Intraperitoneal CGP-12177 was approximately 100-fold less potent than propranolol at inhibiting the binding of [^{125}I]pindolol in cerebral cortex and cerebellum, and 40-fold less potent than propranolol at antagonizing the behavioral effects of the β-adrenergic agonist clenbuterol (34). This evidence suggests that CGP-12177 acts predominantly at peripheral β-adrenergic receptors when given systemically.

ICI 118,551 possesses a high degree of selectivity and specificity for the central and peripheral β_2-adrenoceptors (7, 12, 24). As little as 0.01 mg/kg of ICI 118,551 IV significantly displaced the binding of pindolol to β_2-adrenergic receptors in the cerebellum (42). In the present study, a dose of 0.5 mg/kg of ICI 118,551 IP (i.e., 50-fold larger than the IV dose) did not significantly affect CRF-induced defensive withdrawal (Fig. 1), indicating that central β_2-adrenergic receptors do not play a major role in the CRF-induced behavioral changes.

CGP-20712A and atenolol are selective β_1-adrenergic antagonists (3, 13, 25). Because of their hydrophilic properties, they were injected ICV, after which they both significantly attenuated the CRF-induced increases in the latency and the mean time in the small chamber (Fig. 2). This suggests that central β_1-adrenergic receptors are involved in CRF-induced defensive withdrawal. Unfortunately, we have not been able to test agonists, because of the lack of suitable β_1-selective drugs.

Our conclusion that central β_1-adrenergic receptors are involved in CRF-induced defensive withdrawal is consistent with the finding that the β_1-receptor is the major subtype in most areas of the rat brain, although the β_2-receptor subtype predominates in the cerebellum (32, 35, 36). Most of the adaptive changes of β-adrenergic receptors following perturbations of the central nervous system, for example, those following chemical destruction with 6-hydroxydopamine and chronic administration of antidepressants, have been attributed to changes in the β_1-receptor subtype (14, 31, 33, 43). There were no significant changes of β_2-receptor subtype in cortex, hippocampus or striatum following noradrenergic denervation (14, 31, 33). However, the present results do not provide evidence to indicate how CRF interacts with central β_1-adrenergic receptors, and in what way this interaction induces defensive-withdrawal in rats.

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