The Corticotropin-Releasing Factor₁ Receptor Antagonist R121919 Attenuates the Behavioral and Endocrine Responses to Stress

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ABSTRACT

Corticotropin-releasing factor (CRF) is the major physiological regulator of the hypothalamic-pituitary-adrenal (HPA) axis and serves to coordinate the mammalian endocrine, autonomic, and behavioral responses to stress. Considerable literature from clinical and preclinical data suggests that hypersecretion of hypothalamic and/or extrahypothalamic CRF systems is a major factor in the pathogenesis of affective and anxiety disorders. Based on this premise, a CRF₁ receptor antagonist has been hypothesized to possess anxiolytic and/or antidepressant properties. In this study, an acute dose of the lipophilic CRF₁ receptor antagonist 3-[6-(dimethylamino)-4-methyl-pyrid-3-yl]-2,5-dimethyl-N,N-dipropyl-pyrazolo[2,3-a]pyrimidin-7-amine (R121919), administered i.v. to rats with surgically implanted jugular cannula 60 min before a 5-min restraint stress, dose dependently attenuated peak plasma adrenocorticopin hormone (ACTH) and corticosterone concentrations by 91 and 75%, respectively. In a second study, acute administration of R121919 reduced measures of anxiety in a rodent defensive withdrawal paradigm. R121919 dose dependently decreased latency to exit the tube, and total time spent in the tube 60 min after a single subcutaneous administration. In addition, the ACTH and corticosterone response to novelty was decreased by 82 and 97%, respectively, at the 10-mg/kg dose of R121919. In another study, this dose was associated with approximately an 85% occupancy of the CRF₁ receptor in the cortex measured 75-min postsubcutaneous injection. These data confirm that R121919 acts as a CRF₁ receptor antagonist in vivo, attenuates HPA axis responsivity, and possesses anxiolytic properties.

Since its discovery and characterization by Vale et al. (1981), a burgeoning database has accrued concerning the neural and endocrine roles of corticotropin-releasing factor (CRF). A preeminent role of CRF as the key regulator of the hypothalamo-pituitary-adrenal (HPA) axis, as well as the behavioral, immune, and autonomic aspects of the stress response has been clearly established (for review, see Owens and Nemeroff, 1991).

Two CRF receptor subtypes, CRF₁ and CRF₂, with distinct anatomical localization and receptor pharmacology have been identified (Chang et al., 1993; Chen et al., 1993; Lovenberg et al., 1995; Chalmers et al., 1996; Grigoriadis et al., 1996). The CRF₁ receptor is the predominant receptor in the pituitary, cerebellum, and neocortex in the rat (Primus et al., 1997), whereas CRF₂ receptors are more prevalent in subcortical regions, such as the ventromedial hypothalamus, lateral septum, and dorsal raphe nucleus. A growing body of evidence has shown that CRF₁ receptors may specifically mediate some of the anxiogenic-like behaviors observed after administration of CRF (Heinrichs et al., 1997). Several additional members of the CRF peptide family, including urocortin, urocortin II, and urocortin III have also recently been identified (Lewis et al., 2001).

Numerous studies have attempted to isolate the role of individual CRF receptor subtypes in mediating distinct behaviors. Mice with targeted knockouts of the CRF₁ receptor demonstrate an impaired stress response (Timpl et al., 1998). In contrast to the CRF₁ receptor knockouts, mice lacking CRF₂ receptors demonstrate increased anxiety-like behaviors and hypersensitivity to stress (Bale et al., 2000; Kishimoto et al., 2000). These results lead to the intriguing possibility that there are two separate CRF systems as suggested by their distinct anatomical distribution and pharmacology, and furthermore that activation of CRF₁-type receptors may be anxiogenic, whereas CRF₂ receptor activation may modu-

ABBREVIATIONS: CRF, corticotropin-releasing factor; HPA, hypothalamic-pituitary-adrenal; ACTH, adrenocorticopin hormone; CORT, corticosterone; ANOVA, analysis of variance; SNK, Student-Newman-Keuls.
late stress-coping mechanisms. Clinical data also support
dysregulation of the CRF system in the pathogenesis of af-
fective and anxiety disorders (Arborelius et al., 1999).

The synthesis of the first small-molecule CRF antagonist,
butyryl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyr-
rolo[2,3-d]pyrimidin-4-yl]ethylene (CP-154,526), was re-
ported by Chen et al. (1996). The compound demonstrated
activity in blocking CRF-mediated ACTH responses (Schulz
et al., 1996), in learned helplessness models (Mansbach et al.,
1997), in the defensive withdrawal paradigm (Arborelius et
al., 2000), and in attenuating stress-induced relapse to drug
seeking in cocaine- and heroin-trained rats (Shaham et al.,
1998). Antalarmin, a methyl analog of CP-154,526, attenu-
ated the behavioral, neuroendocrine, and autonomic re-
sponses to stress in adult nonhuman primates (Habib et al.,
2000). CRA1000 and CRA1001, two other small-molecule
CRF antagonists, were able to reverse the swim stress-
induced reduction of the time spent in the light area in the
light/dark exploration, although they were ineffective in non-
stressed animals in the same paradigm (Okuyama et al.,
2000). CRA1000 and CRA1001, two other small-molecule
CRF antagonists has been recently reviewed (McCarthy et al.,
1999; Owens and Nemeroff, 1999).

R121919 is a potent small-molecule CRF1 receptor antag-
onist with high affinity for the CRF1 receptor (Kᵢ = 2–5 nM)
and over 1000-fold weaker activity at the CRF2 receptor,
CRF-binding protein, or 70 other receptor types (Grigoriadis
et al., 2000; Keck et al., 2001). Recently, the effectiveness of
R121919 in major depression was demonstrated in a small
open-label clinical study (Zobel et al., 2000). R121919 re-
duced measures of both anxiety and depression in the de-
pressed patients. In addition, two recent studies have demon-
strated anxiolytic-like effects of R121919 in rodents (Keck
et al., 2001; Heinrichs et al., 2002).

In the present set of experiments, we examined the ability
of R121919 to block restraint-stress induced activation of the
HPA axis, and whether it possesses activity in the defensive
withdrawal test. Finally, receptor autoradiography was used
to examine the blood-brain barrier penetrability and occupa-
cy of central CRF receptors by R121919 after peripheral
administration and the interaction between receptor occupa-
cy and behavioral parameters was evaluated.

Materials and Methods

Animals. Male Sprague-Dawley rats (225–250 g on arrival; Har-
lan, Prattville, AL) were housed two per cage unless otherwise noted,
with food and water available ad libitum. The animals were weighed
carefully and allowed to acclimate to the bucket for 2 days before testing.
The bucket was used to allow convenient access to the jugular can-
nula for blood sampling. On testing day, a blood sample (300 μl) was
obtained 60 min before restraint stress to determine basal ACTH
and corticosterone (CORT) values, immediately before administering
either vehicle (70% polyethylene glycol), or varying concentrations of
R121919 (0.33, 1.0, 3.3, or 10 mg/kg; n = 8–10/group) via the i.v.
cannula. An additional blood sample was then collected before plac-
ing the rodent in a plastic restraint cone for 5 min. A third blood
sample was collected immediately after restraint, before the animal
was removed from the restraint cone and returned to its bucket.
Additional samples were collected at 15, 30, 60, and 90 min after
beginning the restraint. The blood volume removed during sample
collection was replaced with 4 ml of 0.9% saline.

Animals were decapitated at 3 or 8 h after initiation of the restraint
stress, and the brains were immediately removed and frozen on dry
ice, and then kept frozen at −80°C until slicing for autoradiography.
One animal treated with 10 mg/kg R121919 was removed from analysis
because ACTH and CORT values were greater than 2 stan-
dard deviations from the mean at all time points measured. This
animal had ACTH and CORT values greater than 200 pg/ml and 200
ng/ml, respectively, at all time points measured, including the point
immediately before drug administration, indicating that the elevated
ACTH and CORT in this animal were not a direct effect of R121919
administration.

Receptor Autoradiography. Using the atlas by Paxinos and
Watson (1986), brains from the restraint stress and defensive with-
drawal studies were sectioned at the level of the prefrontal cortex
and lateral septum to determine CRF1, and CRF₂ receptor binding,
respectively. The prefrontal cortex has been shown via in situ hy-
bridization to express predominantly CRF₁ receptors, whereas the
lateral septum only expresses CRF₂ receptors in rodents (Van Pett et
al., 2000). For both experiments, 15-μm rat brain sections containing
the prefrontal cortex and the lateral septum were sectioned at ap-
proximately −20°C and mounted on Superfrost Plus Slides (Fisher
Scientific, Pittsburgh, PA) and stored at −80°C until the assay.

After a modification of the techniques of De Souza et al. (1985) and
Primus et al. (1997), ex vivo CRF receptor autoradiography was

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Aventis, Strasbourg, France) in 0.3% tartaric acid (Sigma-Aldrich,
St. Louis, MO). The solution was sonicated for at least an hour to
allow the drug to dissolve. Small amounts of glacial acetic acid
(≤10%) were added to increase solubility, until the powder was completely in
solution. Both the vehicle and all concentrations of the antagonists
used in the studies were adjusted to a final pH of ~4.5. R121919 was a gift of Janssen Pharmaceuticals (Beerse, Belgium).

Restraint Stress. For the restraint stress study, the rats were canulated 5 days before the experiment. Rats were implanted with
chronic jugular venous cannulae under aseptic conditions, as de-
scribed in detail previously (Thrivikraman et al., 2000). Briefly,
animals were anesthetized with a mixture of acepromazine (1.5
mg/kg s.c.; Tech America, Fermenta Animal Health Co., Kansas
City, MO), ketamine (37 mg/kg s.c.;Vetalog, Aveco Co., Inc., Fort
Dodge, IA), and xylazine (7.4 mg/kg s.c.; Rompun, Miles Laborato-
ries Inc., Shawnee, KS), and the jugular vein was exposed by blunt
dissection and a small incision made using iridectomy scissors.
The cannula, consisting of a piece of polyethylene 50 tubing (Clay Adams,
Sparks, MD) with a tip of silicone tubing (T5715-3; Baxter, McGaw
Park, IL), was inserted into the vein approximately 3 cm in the
caudal direction, ligated to the vessel, and tunneled subcutaneously
to emerge from the neck of the animal. The wounds were closed with
metal clips and 200 to 250 μl of 120 μg/ml gentamicin was added to the
cannula (Schein Pharmacy, Port Washington, NY) and flushed
every 3rd day. The rats were then housed singly for 2 days to recover
from the surgery.

Three days after surgery, the animals were moved from their cage
into a polyethylene bucket (28 cm in diameter and 37 cm in height)
with food and water available ad libitum. The animals were weighed
and then allowed to acclimatize to the bucket for 2 days before testing.

Drug Preparation. For the restraint stress, R121919 was dis-
solved in an aqueous 70% (v/v) polyethylene glycol 400 solution, and
serially diluted in this vehicle to the appropriate concentrations. The
drug was injected i.v. in a volume of 1 ml/kg. For the defensive with-
drawal experiments, R121919 solutions were made fresh the
night before each experiment. R121919 was dissolved in a vehicle
consisting of 5% (v/v) polyethoxylated castor oil (Alkamuls EL-620;

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performed on 15-μm rat brain sections. Sections were removed from the -80°C freezer and allowed to warm to room temperature in a desiccator. Brain sections were fixed for 2 min in 0.1% paraformaldehyde, pH 7.5, followed by a 15-min incubation in assay buffer (50 mM Tris, 10 mM MgCl₂, 2 mM EDTA, 0.1% bovine serum albumin, 0.1 mM bacitracin, and 0.1% aprotinin, pH 7.5). Next, triplicate slides containing adjacent brain sections were incubated in one of three conditions: 1) 0.1 nM radiolabeled [125I]sauvagine (PerkinElmer Life Sciences, Boston, MA) to determine total binding at both the CRF₁ and CRF₂ receptor subtypes; 2) 0.1 nM radiolabeled [125I]sauvagine + 1 μM CP-154,526 (Pfizer, Groton, CT), a CRF₁ receptor specific antagonist, to determine CRF₂ receptor-specific binding; or 3) 0.1 nM radiolabeled [125I]sauvagine + 1 μM unlabeled sauvagine (American Peptide Co., Inc., Sunnyvale CA) to determine nonspecific binding. After a 2-h incubation, unbound radioligand was removed by two 5-min rinses in ice-cold phosphate-buffered saline + 1% bovine serum albumin on a rotating platform at 60 rpm, followed by two brief dips in ice-cold distilled, deionized H₂O. Slides were then rapidly dried using a cold air blow dryer and apposed to Kodak Biomax MR film (Eastman Kodak, Rochester, NY) with [125I]-microscale standards (Amersham Biosciences, Inc., Piscataway, NJ) for 80 to 90 h.

**Image Analysis.** Images from the receptor autoradiography films were digitized with a CCD-72 (Dage-MTI, Michigan City, IN) image analysis system equipped with a Nikon camera. Semi-quantitative analysis was performed using AID software (version 4.0; Imaging Research, St. Catherines, ON, Canada). Optical densities were calibrated against coexposed [125I]-microscale standards (Amersham Biosciences, Inc.) and expressed in terms of nanocuries per gram of tissue. Receptor-specific binding was calculated as total binding − CRF₁ receptor binding, and CRF₂ receptor-specific binding was calculated as CRF₂ receptor binding − nonspecific binding. Receptor binding data are expressed as a percentage of the control values. The percentage of binding was subtracted from 100 to estimate percentage of receptor occupancy by R121919 relative to control values. The mean averages were 0.96 ± 0.34 pg/ml and 18.22 ± 6.9 ng/ml, respectively. R121919 had no effect on baseline ACTH or CORT levels measured 1 h after the single injection. Ten minutes after a 5-min restraint stress both ACTH and CORT were not different between groups, and the percent ACTH and CORT responses to restraint stress are presented in Fig. 1, A and B. Pretreatment baseline values of ACTH and CORT were not different between groups, and the mean averages were 0.96 ± 0.34 pg/ml and 18.22 ± 6.9 ng/ml, respectively. R121919 had no effect on baseline ACTH or CORT levels measured 1 h after the single injection. Ten minutes after a 5-min restraint stress both ACTH and CORT were significantly increased in vehicle-treated animals, with nearly a 40- and 11-fold increase, respectively, relative to pretreatment concentrations. The maximum or peak responses in ACTH and CORT in vehicle animals were at 10 and 15 min, respectively. R121919 dose dependently decreased ACTH and CORT responses to restraint stress. Peak plasma ACTH and corticosterone concentrations at a dose of 10 mg/kg R121919 were 9 and 25%, respectively, of vehicle controls.

**Restraint Stress: Ex Vivo Binding.** Calculated inhibition of binding ex vivo, which was used as a surrogate for receptor occupancy, at 3 and 8 h after i.v. administration of R121919 are displayed in Fig. 1C. At the highest dose tested, 10 mg/kg, R121919 occupied approximately 75% of CRF₁ receptors in the cortex at 3 h, and 45% at 8 h. At both time points an increase in CRF₁ ex vivo binding occurred with increasing dosage. In contrast, CRF₂ ex vivo binding by R121919 in the lateral septum remained under 20% and was not statistically different from controls (at any dose), and did not exhibit dose dependence.

**Defensive Withdrawal: Behavior.** One-hour pretreatment with a single subcutaneous injection of R121919 produced a dose-dependent decrease in the latency to the first
four-paw transition in defensive withdrawal testing (Fig. 2A). For the highest dosage tested (10 mg/kg), the latency to the first transition decreased by over 55% compared with vehicle-treated rats. Moreover, 10.0 mg/kg R121919 produced a 5-fold decrease in the total amount of time spent in the tube compared with control (Fig. 2B). Thirty-seven percent of the vehicle-treated animals failed to make a single transition during the 600-s trial, although 100% of the animals receiving 10 mg/kg R121919 made at least one transition. Total time spent in the tube was also significantly decreased after treatment with R121919 (Fig. 2B). The average length per transition was also calculated, and showed a nonsignificant trend toward increased trip duration with increasing dosage (data not shown).

Defensive Withdrawal: Endocrine. R121919 dose dependently attenuated ACTH and CORT concentrations obtained 5 min after the termination of the 10-min defensive withdrawal test (Fig. 2D). ACTH and CORT concentrations in the 10-mg/kg treatment group were 16 and 2%, respectively, of the control group values. This effect was statistically significant (p < 0.01) at both the 3.3- and 10.0-mg/kg groups versus control for CORT, and at the 10.0-mg/kg dosage for ACTH measurements. Basal concentrations of ACTH and CORT taken from animals raised under the same conditions as the test groups were 37.3 ± 12.3 pg/ml and 2.6 ± 2.4 ng/ml, respectively.

Defensive Withdrawal: Ex Vivo Binding. R121919 (3.33 and 10 mg/kg) occupied nearly 80 to 85% of cortical CRF1 receptors 75 min after a single s.c. injection (Fig. 2C). In contrast, CRF2 ex vivo occupancy in the lateral septum ranged from 5 to 20% at the 0.33, 1.0, and 3.33 mg/kg R121919. CRF2 ex vivo occupancy increased to approximately 24% at the 10.0-mg/kg dose, but this was not statistically different from any other treatment group. Representative autoradiographs are shown in Fig. 3.

Discussion

Although several small-molecule CRF1 receptor antagonists have been developed over the past 5 years, much of the pioneering preclinical work in the field used peptide-based antagonists that needed to be directly infused into target brain regions. α-Helical CRF9–41 was one of the first compounds used as a CRF receptor antagonist and demonstrated activity in several animal models of anxiety. These and many other studies clearly demonstrated that CRF1 receptor antagonists exhibit anxiolytic activity in a variety of animal models (Arborelius et al., 1999; Holsboer, 1999).

Exploratory behavior, as measured by the time an animal spends investigating objects in a novel environment, is often used as a measure of innate fearfulness or anxiety in rodents. Prior exposure to stressors such as restraint or shock reduces the amount of exploratory behavior. Direct i.c.v. injection of CRF similarly reduces exploratory behavior in this paradigm. This effect can be reversed by pretreatment with α-helical-CRF9–41. Furthermore, α-helical-CRF9–41 also attenuates the response to laboratory stressors, e.g., restraint stress and defensive withdrawal, in the absence of exogenous CRF, presumably by blocking the effects of endogenously released CRF (Berridge and Dunn, 1987; Berridge and Dunn,
1989; Takahashi et al., 1989). These data clearly support a preeminent role for CRF in modulating the behavioral response to stress and provided one of the major rationales for the development of small-molecule CRF antagonists with enhanced bioavailability.

Small-molecule lipophilic CRF antagonists exhibit important pharmacological differences compared with peptide antagonists due to the widespread distribution of the former class of compounds both peripherally and throughout the central nervous system. Small-molecule antagonists may exert both central and peripheral effects on CRF systems. Peptides, because of their polar nature and relative inability to permeate the blood-brain barrier, need to be infused directly, either i.c.v. or into specific brain nuclei, which limit the neuroanatomically accessible targets.

As noted above, the results from transgenic studies with knockout mice have indicated that CRF₁ receptors seem to specifically mediate the anxiogenic affects of CRF. CRF₁ receptor knockout mice exhibit a reduced stress response, whereas CRF₂ receptor knockout mice seemed to be more anxious than controls (Timpl et al., 1998; Bale et al., 2000; Kishimoto et al., 2000), although this view is by no means universal. There is a general consensus that CRF₁ receptor antagonists may represent a new class of psychotherapeutic agents for the treatment of mood and anxiety disorders (Holsboer, 1999).

Ideally, any clinically useful CRF₁ receptor antagonist should demonstrate efficacy in attenuating anxiety and/or depressive-like symptomatology, possess a favorable pharmacokinetic and bioavailability profile, and exhibit a low incidence of side effects. R121919 is a small-molecule CRF₁ receptor-selective antagonist that shows good solubility and readily crosses the blood-brain barrier (Keck et al., 2001). Concurrent with our own research, the first open-label study with R121919 in human patients with major depressive disorder has recently been completed (Zobel et al., 2000). This study showed an overall improvement in anxiety and depressive symptomatology after 30 days of treatment with R121919, and a worsening of affective symptomatology after drug discontinuation. Although this was a small open-label study, taken together with the present findings in rodent models, it supports CRF antagonists as novel treatments for both depression and anxiety disorders.

Because little data are currently in the public domain regarding the pharmacology of R121919, our first goal in this experiment was to characterize the ability of R121919 to block restraint stress-induced HPA axis activation. Restraint stress is a potent activator of the HPA axis that has been blocked via CRF antagonists in past studies (Krahn et al., 1986; Berridge and Dunn, 1987, 1989; Cole et al., 1990; Smagin et al., 1996). R121919 dose dependently attenuated restraint-induced HPA axis activation (Fig. 1, A and B). Both basal levels before infusion of drug, and 1 h after administration were nearly identical between the treatment groups, indicating R121919 did not affect ACTH and CORT levels under basal, nonstressed conditions. Significant effects of

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**Fig. 2.** A, latency to exit the tube in the defensive withdrawal paradigm was significantly reduced by treatment with 10.0 mg/kg R121919 60 min before the onset of defensive withdrawal. *p < 0.05 versus 0.00 (vehicle) and 0.33-mg/kg doses; one-way ANOVA, followed by SNK post hoc analysis. B, total time spent in the tube was significantly decreased after treatment with 10.0 mg/kg R121919 60 min before the onset of defensive withdrawal. **p < 0.01 versus 0.00 (vehicle), 0.33 mg/kg, p < 0.01 versus 1.00-mg/kg doses; one-way ANOVA, followed by SNK post hoc analysis. C, estimated receptor occupancy as determined by autoradiography 75 min after defensive withdrawal. D, ACTH and CORT responses 15 min after the onset of 10 min of defensive withdrawal. An additional group of rats (basal) that did not undergo defensive withdrawal is included for comparison. Both ACTH and CORT were significantly decreased relative to vehicle-treated animals that underwent defensive withdrawal. *p < 0.05.
In our experiments, R121919 clearly attenuated the scored measures of anxiety in the novel environment. Although the effect was only statistically significant compared with vehicle control at the highest dose tested (10.0 mg/kg), both total time spent in the tube and latency to exit showed clear dose-dependent effects (Fig. 2, A and B). Regression analysis yielded an R² value of approximately 0.93 between dosage and both latency and time spent in the tube, further validating the dose dependence of this observation. It seemed that optimal behavioral effects occurred at a receptor occupancy of CRF₁ receptors between 60 and 80%. Furthermore, other studies have shown that R121919 does not seem to have sedating effects in the doses used, so these effects do not seem to be related to changes in spontaneous locomotor activity (Keck et al., 2001). Preliminary studies in our laboratory have also not shown gross changes in spontaneous locomotor activity after acute administration of R121919.

After successfully demonstrating that R121919 possesses anxiolytic activity in the defensive withdrawal paradigm and the ability to block restraint stress-induced HPA axis activation, we also examined the HPA axis response to defensive withdrawal. A separate set of rats was handled and maintained in the animal facility under conditions identical to the experimental group, but did not undergo defensive withdrawal. Figure 2D clearly demonstrates that the novel defensive withdrawal arena acted as a fairly potent stressor that activated the HPA axis under our testing conditions; furthermore, R121919 dose dependently attenuated the HPA response to defensive withdrawal (Fig. 2D).

Because the cannula in the restraint stress experiments allowed venous access without having to disturb the animal, we used polyethylene glycol as our initial vehicle. For the defensive withdrawal experiments, the tartaric vehicle proved more amenable to subcutaneous injection for the concentrations we used. In spite of the differences in route of administration and differences in the vehicles used between the two experiments, these data are revealing on the pharmacokinetics of R121919.

First, R121919 seems to fairly rapidly cross the blood-brain barrier. Second, even 8 h after a single administration there was still a marked blockade of CRF₁ receptors in the cortex (Figs. 1C, 2C, and 3). Thus, R121919 and/or an active metabolite retain its ability to block central CRF₁ receptors for a significant amount of time. In contrast, CRF₂ receptors were also explored the effects of long-term administration of R121919 on behavioral and endocrine measures, as well as the concomitant changes in CRF receptor function.

Our findings with R121919 further support the hypothesis that peripherally administered small-molecule CRF₁ receptor antagonists act as anxiolytics in animals. Currently, we are exploring the effects of long-term administration of R121919 on behavioral and endocrine measures, as well as the concomitant changes in CRF receptor function.

References


