Physiological Responses to Acute Psychological Stress Are Reduced by the PPARγ Agonist Rosiglitazone

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Physiological reactions to psychological stress are positively associated with several important chronic conditions including cardiovascular and neurodegenerative diseases and are linked to increased mortality. As such, the identification of cellular and molecular pathways that act to reduce stress responding may represent important targets for therapeutic intervention. Here we report that acute treatment with the peroxisome-proliferator activated receptor-γ (PPARγ) agonist rosiglitazone (RSG) blunts systemic responses to acute psychological stress in rats. Rats that had previously received oral RSG for 5 d exhibited a 40% reduction in the initial heart rate response to an acute restraint stress, compared with vehicle-treated controls, suggesting that increased PPARγ signaling blunts the acute autonomic response to stress. Rats previously treated with RSG likewise had a blunted hormonal response to this stressor, exhibiting a 30% reduction in peak corticosterone levels compared with controls. Moreover, stress-induced expression of c-Fos, a marker of early neuronal activation, was similarly reduced in the paraventricular hypothalamus, a key site for brain stress integration, facilitating both autonomic and hypothalamic-pituitary-adrenocortical responses to stress. Taken as a whole, these data suggest that PPARγ stimulation potently inhibits physiological responses to psychological stress, prescribing a novel role for PPARγ signaling in the regulation of brain stress integration. (Endocrinology 153: 1279–1287, 2012)

The systemic response to stress involves coordinated physiological and behavioral changes in reaction to a real or perceived threat to homeostasis or well-being. These physiological responses include rapid activation of the sympathetic branch of the autonomic nervous system, leading to increased heart rate and blood pressure. The hypothalamic-pituitary-adrenocortical (HPA) axis responds in a relatively slower timeframe, leading to increased circulating glucocorticoids that act at their receptors throughout the body to mobilize stored energy, maintain vasomotor tone, and provide feedback inhibition of further glucocorticoid release (reviewed in Ref. 1). Finally, in response to more prolonged or severe stress, the immune system reacts to increase production of inflammatory mediators, including cytokines, free radicals, and prostaglandins (2–4). These coordinated physiological responses facilitate both immediate and sustained context-appropriate behavioral responses.

Peroxisome-proliferator activated receptor-γ (PPARγ), a member of the nuclear hormone receptor superfamily of transcription factors, is activated by its agonist ligands to induce the transcription of target genes involved primarily in glucose and lipid metabolism (5). Its endogenous agonists are fatty acids and fat metabolites, including eicosanoids and other inflammatory lipid mediators (6–8). Thiazolidinediones, insulin-sensitizing drugs that are pharmacological agonists of PPARγ, are in therapeutic use as antidiabetic agents (9). In addition to effects on glucose...
and lipid homeostasis, PPARγ activation has potent anti-inflammatory effects, primarily by indirect interactions with other transcription factors (10).

Recent studies have identified activation of PPARγ as an important homeostatic mechanism in the central nervous system immunoinflammatory response to stress. Various psychological and physiological stressors acutely increase brain prostaglandin synthesis, cytokine release, and other markers of neuroinflammation in the cerebral cortex of rats (2, 3, 11). Activation of PPARγ by either endogenous or pharmacological agonists abrogates these effects (4, 11), suggesting that brain PPARγ plays an important homeostatic role under stressful conditions.

The role of PPARγ in systemic responses to stress is unclear. We undertook the present studies to test the hypothesis that treatment with the PPARγ agonist rosiglitazone (RSG) blunts neuroendocrine and cardiovascular responses to a psychogenic stressor ( restraint) in rats. Our data indicate that PPARγ stimulation potently inhibits both autonomic and neuroendocrine responses to stress, suggesting a novel role for PPARγ signaling in the regulation of brain stress integration.

Materials and Methods

Animals

The Institutional Animal Care and Use Committee at the University of Cincinnati approved all animal protocols. Male Long-Evans rats, weighing about 275 g at the beginning of the studies, were obtained from Harlan Labs (Indianapolis, IN). After arrival at our facility, rats were allowed to adapt to the new surroundings for at least 1 wk before surgery or other experiments were performed. Rats were singly housed and kept in temperature- and humidity-controlled rooms with a 12-h light, 12-h dark cycle (lights on at 0600 h). Rats were given ad libitum access to water and standard rat chow; food intake and body weight were recorded daily.

Drugs

The high-affinity PPARγ agonist RSG (Cayman Chemicals, Ann Arbor, MI) was suspended in 0.2% methylcellulose in water (Sigma Chemical Co., St. Louis, MO) at a concentration of 1 mg/ml. RSG or its vehicle was dosed by oral gavage at 10 mg/kg body weight, considered to be a therapeutic dose for glycemic control in rats (12). To minimize outcomes potentially arising from differences in body weight, we decided on an acute course of treatment, delivering the drug once daily for just 5–6 d.

Surgical procedures

We implanted rats with radiotelemetry transmitters (Data Sciences International, St. Paul, MN) as previously described (13, 14). Briefly, under isoflurane anesthesia, the descending aorta was exposed via an abdominal incision, and a catheter extending from the transmitter capsule was placed into the descending aorta and secured with tissue adhesive (Vetbond; 3M Animal Care Products, St. Paul, MN) and a cellulose patch. The capsule was sutured to the abdominal musculature, the abdominal musculature was sutured, and wound clips were applied to the skin. Rats recovered for at least 1 wk, and wound clips were removed before beginning the experiments.

Cardiovascular parameters

Rats were allowed to fully recover from the surgical procedure (at least 1 wk) before commencement of telemetric monitoring. Baseline cardiovascular parameters [heart rate, mean arterial pressure (MAP), and systolic and diastolic pressure] and general locomotor activity were recorded continuously for 3 d. On the fourth day, we began dosing the rats with RSG or vehicle by daily gavage for 5 d, while continuing to record cardiovascular and locomotor data. For each rat, changes in these variables were calculated relative to the average of the 3-d baseline.

Restraint challenge

Restraint challenges were performed in the morning, between 1000 and 1200 h, 2 h after the fifth and final dose of RSG. We physically restrained the animals by placing them in snug, well-ventilated transparent Plexiglas tubes. For the cardiovascular studies, we noted the exact time at which rats were placed quickly into their restrainers, and cardiovascular responses were recorded continuously starting at this time (T = 0). Rats were quickly removed from the restrainers at 20 min after the onset of restraint. For the HPA axis studies, each animal was brought from the housing room into the procedure room and was placed immediately in the restrainer (T = 0), and a blood sample (T = 0; ~300 μl) was quickly taken by tail clip for later measurement of plasma ACTH and corticosterone. Care was taken to complete the T = 0 sampling in less than 3 min from first touching the rats’ cage to ensure assessment of basal, unstressed plasma hormones. A second tail-blood sample was taken quickly at 15 min after initiation of restraint. At 30 min after initiation of restraint, a tail-blood sample was taken immediately before removing the rat from the restraint tube. Additional tail-blood samples were quickly collected at 60 and 120 min from unrestrained rats. At the end of the restraint challenge, these acutely stressed rats and unstressed controls (that had remained in the home room), were given lethal injections of pentobarbital and then perfused with normal saline followed by 4% paraformaldehyde in PBS (pH 7.4). Brains were collected for immunohistochemistry, postfixed at 4 C in 1:3 series using a freezing microtome and then perfused with normal saline followed by 4% paraformaldehyde in PBS, and stored at 4 C in 30.0% sucrose/PBS.

Hormone assays

Blood samples were centrifuged (3000 × g for 15 min at 4 C), and plasma was stored at ~80 C until measurement of immunoactive ACTH and corticosterone concentrations by RIA, as described previously (15).

c-Fos immunohistochemistry

c-Fos-positive cells were identified using immunohistochemistry. Coronal hypothalamic sections (35 μm) were collected in a 1:3 series using a freezing microtome. Sections were stored in ethylene glycol cryoprotectant at ~20 C until time of use. Briefly, tissue sections were removed from cryoprotectant and washed in 0.1 M PBS. To block endogenous peroxidases, tissue was soaked in 9:1 methanol/3% hydrogen peroxide solution for 15 min and subsequently rinsed in PBS. Tissue was then preincubated in
blocking buffer (PBS plus 0.4% Triton X-100 plus 2% normal donkey serum) for 30 min at room temperature, followed by incubation with c-Fos-specific antibody (1:2500; Santa Cruz Biotechnology, Santa Cruz, CA; no. sc-52) in blocking buffer for 48 h at 4°C. After washes in PBS, tissue was incubated for 1 h in biotinylated donkey antirabbit antibody (1:300; Vector Laboratories, Burlingame, CA; no. BA-1000), and subsequently washed and incubated in avidin-biotin solution (1:600; Vector Laboratories; no. PK-6100) for 30 min. c-Fos immunoreactivity was visualized with 3,3′-diaminobenzidine-enhanced with nickel chloride.

*The Rat Brain Atlas* by Paxinos and Watson (46) was used to identify hypothalamic sections at the level of −1.3 to −3.7 mm caudal to bregma. Using a Zeiss Axioplan 2 microscope coupled with a Zeiss Axiocam camera, adjacent images of c-Fos were obtained at ×5 using Axiovision version 4.8 software. Using Scion Image version 4.0.3.2, images were uploaded and background was subtracted. Positive cells were counted in the paraventricular hypothalamus (PVH), arcuate hypothalamus (ARH), and dorsomedial hypothalamus (DMH), using standard anatomical landmarks to define nuclear boundaries for regions of interest (third ventricle, fornix, and mammillothalamic tract). The number of c-Fos-positive cells was averaged across each nucleus. An individual blind to the experimental treatment groups scored the sections. Display images were adjusted for brightness and contrast.

**Statistical analysis**

Data are presented as means ± st. Data were analyzed using repeated-measures (RM) ANOVA or ANOVA followed by Tukey’s post hoc test or by t test, as indicated, using Prism (GraphPad, San Diego CA) or SigmaStat (SYSTAT, San Jose CA) software, with the critical value, α, set at P < 0.05.

**Results**

**Changes in basal (unstressed) cardiovascular variables**

During the active (dark) phase of the light-dark cycle, RSG elicited a reduction in MAP [RM ANOVA, F(1,33) = 14.07; P < 0.01], encompassing both systolic [RM ANOVA, F(1,33) = 7.61; P < 0.05] and diastolic [RM ANOVA, F(1,33) = 20.27; P < 0.001] pressures, with no changes in heart rate or locomotor activity (Fig 1, A–E). Changes in these variables during the inactive (light) phase were in a similar direction (Fig. 1, F–J), but only the reduction in diastolic pressure reached statistical significance [RM ANOVA, F(1,33) = 5.20; P < 0.05].

**Cardiovascular responses to acute restraint stress**

The cardiovascular response to acute restraint stress was calculated as the change from baseline, defined here as the 60 min before the investigators entering the room to begin the experiment. There were no differences during this 1-h interval between the groups for any of the variables (light phase, data not shown). In response to the acute physical restraint, activation of the sympathetic branch of the autonomic nervous system led to a rapid increase in both heart rate and MAP. Control rats increased their heart rate by about 180 beats/min, reaching a peak heart rate of about 525 beats/min within the first 5 min. This acute response was markedly blunted in RSG-treated rats, increasing by only 60% (108 beats/min) in the first 5 min compared with vehicle-treated controls. RM ANOVA indicated a significant interaction between time and the RSG treatment [F(11,121) = 2.855; P < 0.01], and post hoc analysis using Tukey’s honestly significant difference indicated that the change in heart rate over the first 5 min was significantly lower in RSG-treated rats (P < 0.001, Fig. 2A). On the other hand, there were no differences between the two groups in their blood pressure and locomotor responses to the restraint (Fig. 2, B and C).

**FIG. 1.** Acute RSG treatment and basal cardiovascular parameters. A–C, Rats treated with oral RSG (10 mg/kg body weight per day) over the course of 4 d of treatment exhibited a significant reduction (relative to individual baseline measurements) in MAP (A), systolic pressure (B), and diastolic pressure (C) during the dark phase of the light-dark cycle, beginning as early as d 2 of treatment compared with rats treated with its vehicle alone. D and E, There was no significant effect of RSG on heart rate (D) or locomotor activity (E) during the dark phase. H, Rats treated with oral RSG exhibited a significant reduction in diastolic pressure during the light phase of the light-dark cycle compared with rats treated with its vehicle alone. F–J, There was no significant effect of RSG on MAP (F), systolic pressure (G), heart rate (I), or locomotor activity (J) during the light phase. *, P < 0.05; ***, P < 0.001; n = 6–7 rats per group.
There were no differences between the groups in basal ACTH or corticosterone (Fig. 3, A and B) or in the stress-induced increase in plasma ACTH (Fig. 3A). However, stress-induced increases in circulating corticosterone were reduced by about 30% in the RSG-treated rats. RM ANOVA indicated a significant main effect of the RSG treatment \( F(1,52) = 7.17; P < 0.05 \) and a significant interaction between the RSG treatment and time \( F(4,52) = 2.903; P < 0.05 \). Post hoc analyses using Tukey’s honestly significant difference indicated that RSG-treated animals had a lower peak plasma corticosterone at 60 min after the onset of restraint (\( P < 0.001 \), Fig. 3B). The integrated corticosterone response to restraint was also significantly blunted, as calculated by area under the curve \( (T_{13} = 2.59; P < 0.05 \), Fig. 3C).}

### c-Fos immunohistochemistry

Consistent with the blunted cardiovascular and corticosterone response, RSG blunted the Fos response to acute restraint stress by about 30% in the PVH \( (T_{14} = 2.411; P < 0.05 \), Fig. 4, A and C) and by about 35% in the ARH \( (T_{7} = 2.75; P < 0.05 \), Fig. 5B). There were no significant differences in stress-induced Fos immunoreactivity in the DMH (Fig. 5D). Among unstressed control rats, there was minimal Fos immunoreactivity in any of these brain regions and no differences between the RSG- and vehicle-treated rats (Figs. 4, A and B, and 5, A and C).

### Food intake, body weight, and plasma volume

Consistent with previous studies (16, 17), rats treated with RSG consumed more food \( T_{28} = 2.79, P < 0.01 \) and gained an additional 8 g body weight over the course of the 5-d treatment \( T_{28} = 3.66; P < 0.01 \), Fig. 6, A and B) compared with vehicle-treated rats, providing a positive control for RSG action. However, we note that this weight gain is modest relative to total body weight, representing just a 2–3% increase. Importantly, the RSG and vehicle groups therefore never differed in absolute body weight, including on the day of the restraint stress testing. For the telemetry studies, on the day of the restraint challenge, the average body weights (± SE) for the vehicle and RSG groups, respectively, were 338.6 ± 8.5 and 360.7 ± 18.09 g. For the HPA studies, on the day of the restraint challenge, the average weights were 318.0 ± 7.02 and 324.1 ± 6.7 g. Although chronic RSG administered over longer periods of time can lead to increased plasma volume (18), we did not observe any effect of RSG on hematocrit, mea-

![Figure 2. Acute RSG treatment and the cardiovascular response to restraint stress.](https://academic.oup.com/endo/article-abstract/153/3/1279/2423990)

![Figure 3. Acute RSG treatment and the HPA response to restraint stress.](https://academic.oup.com/endo/article-abstract/153/3/1279/2423990)
sured on d 6, 2 h after a sixth dose of RSG (t test, Fig. 5C), indicating no differences in plasma volume between the groups with this acute course of treatment.

Discussion

The present data support the hypothesis that treatment with the PPARγ agonist RSG blunts the systemic response to acute restraint, a potent psychogenic stressor, in rats. Specifically, we found that RSG-treated rats exhibited a blunted heart rate response, a blunted glucocorticoid response, and blunted stress-induced neuronal activity in the ARH as well as the PVH, the latter being a key site for integrating both HPA and autonomic responses to stress (1, 19). The data indicate that PPARγ stimulation is sufficient to inhibit central responses to restraint in rats, further suggesting a possible role for endogenous agonists (e.g., free fatty acids and fat metabolites) in stress inhibition.

We first examined the effect of RSG on cardiovascular responses to stress. Consistent with previous reports that PPARγ activation by RSG and by other agonist ligands reduces blood pressure (20–22), we found that MAP and systolic and diastolic pressures were reduced (in the basal, unstressed state) beginning as early as d 2 of treatment (Fig. 1, A–C). We did not find any significant effect of RSG on the blood pressure response to acute restraint stress (Fig. 2B), but the initial heart rate response was reduced by 40% (Fig. 2A). In contrast, when the rats were released from their restrainers, the two groups equally increased their heart rates in parallel with increased locomotor activity (Fig. 2, B and C). Because the elimination half-life of RSG in rats is greater than 4 h (23), it seems unlikely that this pattern results from clearance of the drug. Rather, it appears RSG-treated rats retained the capacity to increase heart rate in response to increased physical demands, whereas the heart rate response to a psychological stressor was specifically abrogated.

Recent reports of adverse cardiovascular outcomes among patients taking RSG for the treatment of type 2 diabetes have led to a black-box warning and considerable controversy over continued clinical use of this drug (24–26). It is interesting to consider our data in this context. According to the stress reactivity hypothesis, larger-than-normal cardiovascular responses to acute stress are markers of subclinical disease or contribute to increased risk for immediate cardiovascular events (27, 28). Within this framework, the ability of this PPARγ agonist to blunt heart rate reactivity, particularly among individuals that have larger-than-normal re-

![FIG. 4. Acute RSG treatment and the c-Fos response to restraint stress in the PVH. Among unstressed rats (A), there was no significant difference (C) in the number of c-Fos-positive cells observed in the PVH, regardless of whether the rats had been previously treated with oral RSG (10 mg/kg body weight per day) for 5 d or its vehicle alone. Among stressed rats (B), those previously treated with RSG exhibited significantly fewer c-Fos-positive cells in the PVN (D) compared with rats treated with vehicle alone. Pictures taken at $\times 5$ magnification. Scale bar, 100 $\mu$m; n = 8 animals per group. *, $P < 0.05$.](https://academic.oup.com/endo/article-abstract/153/3/1279/2423990)

![FIG. 5. Acute RSG treatment and the c-Fos response to restraint stress in the ARH and DMH. Among unstressed rats, there were no significant differences in c-Fos immunoreactivity in either the ARH or DMH (A and C) after RSG treatment. Among rats subjected to a 30-min restraint challenge, rats previously treated with oral RSG (10 mg/kg body weight per day) for 5 d exhibited significantly fewer c-Fos-positive cells in the ARH (B) but not the DMH (D). *, $P < 0.05$; n = 3–6 animals per group.](https://academic.oup.com/endo/article-abstract/153/3/1279/2423990)
responses, could be seen as protective. In light of this, and despite the controversy surrounding clinical use of RSG, further investigation of the underlying cellular and molecular mechanisms responsible for the observed effects might identify downstream mediators as alternate targets for therapeutic intervention and/or support ongoing efforts to develop selective modulators of PPARγ signaling (29–31). In this way, it may be possible to avoid the cardiovascular risk associated with RSG, while reaping potential therapeutic benefits derived by manipulating selected aspects of PPARγ signaling with other pharmacological agents. On the other hand, it has recently been suggested that the relationship between acute stress reactivity and disease may not be linear (32–34). Several studies report that smaller-than-normal stress reactivity is associated with adverse clinical events (35–37), including mortality. Within this alternate framework, depressed autonomic responses to stress, such as those observed here, may be seen as pathological and may potentially contribute to the adverse cardiovascular outcomes observed with clinical use of RSG.

We next examined the effect of RSG on the HPA response to stress. We did not find any differences between the two groups in basal (unstressed) plasma ACTH or plasma corticosterone. Consistent with a general effect of RSG to blunt stress reactivity, however, we did observe that the corticosterone response to 30 min of restraint was reduced by about 30% (Fig. 3, B and C) in RSG-treated rats. A previous study (16) reported that rats dosed with RSG for 7 d had reduced expression of CRH mRNA in the PVH and lower plasma ACTH at the time of killing. However, that group did not report the specific protocol used to kill their rats. If the investigators did not specifically take precautions to prevent psychogenic stress immediately before killing, it is possible that the reported differences in CRH and ACTH reflect differences in stress reactivity rather than an alteration in basal HPA status.

In a series of recent studies, Garcia-Bueno and colleagues (3, 4, 11) have convincingly demonstrated that PPARγ plays an important homeostatic role in the neuroinflammatory response to stress. In the rat cerebral cortex, PPARγ activity is increased after a 6-h restraint stress. Furthermore, direct activation of central nervous system PPARγ by endogenous or pharmacological ligands was associated with a reduction in stress-induced oxidative-nitrosative species and cytokine release, suggesting a neuroprotective effect (4). No differences were observed in baseline or 6-h plasma corticosterone in these experiments, leading the authors to conclude that there were no differences in the general HPA response to stress. The data we present in this manuscript, however, indicate that in addition to direct antiinflammatory actions of PPARγ in cortex, the neuroprotective effect they observed with PPARγ activation may additionally result from a systemic reduction in stress reactivity at earlier time points, leading secondarily to reduced neuroinflammation.

One possible interpretation of our data are that RSG augments glucocorticoid negative feedback at the brain and/or pituitary, such that corticosterone levels at earlier time points provide a greater brake on the ongoing HPA response of RSG-treated rats, leading to the decrement in plasma corticosterone we observed at 60 min after the onset of restraint. We consider this possibility unlikely because we do not observe an accelerated ACTH off response (Fig. 3A) preceding the difference in circulating corticosterone. Rather, we observed no differences in plasma ACTH at any time, despite robust decreases in peak plasma corticosterone (Fig. 3). This pattern indicates that blunted HPA reactivity may result in part from reduced responsivity of the adrenal cortex to stimulation by ACTH. If the observed reduction in the heart-rate response to restraint stress reflects a more general reduction in stress-induced sympathetic tone, then the ACTH-independent reduction in plasma glucocorticoids by RSG might be secondary to a reduction in sympathetic drive to the adrenal (38, 39). Alternatively, immunoreactive ACTH measures may differ somewhat from bioactive ACTH (40), or because ACTH is rapidly increased in re-
response to restraint stress, we may simply have missed the important time point to observe differences in this outcome. Nonetheless, taken together, these studies support that activation of PPARγ leads to a blunted HPA hormonal response in rats.

To further assess the role of the central nervous system to drive blunted stress reactivity, we next asked whether RSG led to reduced neuronal activation in the hypothalamus, a key site for integrating both the HPA and autonomic responses to stress (1, 19). c-Fos, a marker of early neuronal activation, is robustly induced in the hypothalamus of rats after an acute stressor. To compare c-Fos activity in the hypothalamus of RSG- and vehicle-treated rats, we killed a cohort of animals at 2 h after the onset of a 30-min restraint and collected their brains for immunohistochemistry. RSG-treated rats had reductions in ARH and PVH Fos immunoreactivity (Figs. 4 and 5). Although it remains unknown whether RSG has more widespread effects on other stress-regulatory regions that might communicate with the hypothalamus, these data clearly suggest that the central nervous system is playing an important role to mediate the blunted stress reactivity observed in this study. Consistent with this, PPARγ is expressed in key regions of the central nervous system involved in the HPA and autonomic responses to stress, including the PVH and ARH (41, 42). We (17) and others (43) have recently demonstrated that PPARγ in these brain regions plays an important role as a nutrient sensor involved in the regulation of energy homeostasis and at least partially mediates the weight gain observed with oral RSG treatment. The data presented here further suggest a potential role for hypothalamic PPARγ in brain stress integration. Alternatively, differences in stress-induced neuronal activity may arise indirectly if increased PPARγ signaling alters neural or hormonal signals from the periphery that act secondarily on brain stress neurocircuitry. Additional studies will be necessary to explicitly parse these alternate hypotheses.

Physiological reactions to psychological stress have been positively associated with chronic conditions including neurodegenerative and cardiovascular diseases and are linked to increased mortality. The data we present here support that acute treatment with the PPARγ agonist RSG blunts cardiovascular and HPA responses to acute psychological stress in rats. Further investigation of the underlying cellular and molecular mechanisms responsible for the observed effects might identify downstream mediators as targets for therapeutic intervention in stress-associated chronic diseases. Moreover, recent efforts to develop selective modulators of PPARγ signaling offer the potential to engage beneficial pathways downstream of PPARγ, possibly including those identified here, while avoiding detrimental side effects. For example, it is now understood that cyclin-dependent kinase-5 phosphorlates PPARγ at Ser-273 to alter its regulation of a subset of target genes and that this phosphorylation is blocked by RSG and other thiazolidinediones, independent of classical receptor agonism (44). This has led to the development of promising new therapeutic compounds targeting this mechanism (45). Additional studies would be necessary to test whether alternate PPARγ ligands likewise blunt physiological responses to psychological stress. In addition to the possible therapeutic implications, our data indicate that PPARγ stimulation is sufficient to inhibit central responses to restraint in rats, further suggesting a potential physiological role for its endogenous agonists (e.g. fatty acids and fat metabolites) in stress inhibition.

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