Role of IL-1 in Poststroke Depressive-like Behavior in Mice

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Background: Poststroke depression (PSD) leads to impaired functional recovery and increased mortality, yet physiological mechanisms are unknown. The present study investigates the roles of glucocorticoids and interleukin-1 (IL-1) in poststroke anhedonia.

Methods: Adult male mice underwent middle cerebral artery occlusion (MCAO), and were recovered 7 days. Mice were treated with metyrapone (100 mg/kg intraperitoneally), mifepristone (50 mg/kg subcutaneously), or vehicle injections on reperfusion days 4–7. A separate cohort of mice was implanted with cannulae and was administered IL-1 receptor antagonist (IL-1ra) or vehicle (6 µg intracerebroventricularly) on reperfusion days 6 and 7. After the final injection or infusion, sucrose consumption was recorded for 6 hours.

Results: Mice in the sham-treated group consumed significantly more sucrose solution than water, whereas MCAO-treated mice consumed similar amounts of each, suggesting anhedonia among MCAO-treated mice. A separate experiment assessed whether stroke-induced increases in corticosteroids or IL-1 contribute to anhedonia. Only IL-1ra restored sucrose consumption in MCAO-treated mice. Vehicle-MCAO–treated mice drank significantly less sucrose solution than did both IL-1ra and vehicle-sham treatment groups, whereas IL-1ra–MCAO–treated mice drank similar amounts to both sham-treated groups.

Conclusions: Poststroke anhedonia, a symptom of depression in human beings, can be reproduced in a mouse model of stroke and appears to involve altered IL-1 transmission in the brain.

Key Words: Anhedonia, cytokines, glucocorticoids, ischemia, IL-1 receptor antagonist, middle cerebral artery occlusion

Depression is a frequent consequence of stroke (Whyte et al 2004). Approximately 40% of ischemic stroke patients are diagnosed with poststroke depression (PSD), although some studies report that the incidence of PSD is as high as 72% (Hachinski 1999; Pohjasvaara et al 1998; Schubert et al 1992). Emotional distress caused by stroke-induced physical limitations may contribute to the onset of depression, but the higher occurrence of depression among stroke patients than among orthopedic patients with similar functional disability (Folstein et al 1977) suggests that PSD is not a purely psychological response to acquired motor deficits. PSD is characterized by increased cognitive deficits, social withdrawal (Langer et al 1998), sexual dysfunction (Angeleri et al 1993; Neau et al 1998), insomnia (Chemerinski and Robinson 2000), anhedonia (Piamarta et al 2004), and feelings of despair. Furthermore, PSD can influence stroke recovery; self-reports of depression before and after stroke are correlated positively with exacerbated poststroke deficits (Bogousslavsky 2005) and increased mortality (Berg et al 2003; Williams et al 2004).

Despite the high incidence of PSD and its detrimental effects on stroke recovery, the underlying causes of the disorder are not well understood (Robinson 2003). In the present study, we examine the role of stroke-induced changes in glucocorticoids (GC) and cytokines in mediating poststroke depressive-like behavior in mice. Our hypothesis is that the pathophysiological processes that occur after stroke contribute to the etiology of PSD. Indeed, stroke is associated with dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and neuromflammation, and both of these physiological alterations have been associated with depressive symptoms in nonischemic populations (Bogousslavsky 2003; Pollak and Yirmiya 2002; Wright et al 2005). Elevated corticosteroid concentrations are among the first measurable physiological responses to cerebral ischemia (Fass D et al 1994; Johansson et al 1997), and dysregulation of the HPA axis can persist for several years after stroke (Astrom et al 1999).

Stroke induces an inflammatory response, which is marked by up-regulation of cytokine expression (DeGraba 1998). Specifically, experimental stroke increases central expression of several interleukins (IL), including IL-1α, IL-1β, IL-1 receptor antagonist (IL-1ra), and IL-6 (Hill et al 1999; Legos et al 2000; Zhai et al 1997). Similarly, increased IL concentrations have been reported in both cerebrospinal fluid and blood serum of stroke patients (Ferrarese et al 1999; Tarkowski et al 1995c). Whether stroke-induced increases in cytokine expression have behavioral consequences is unknown, but there are several studies in human beings and in nonhuman animals that report an association between elevated cytokine expression and depression or sickness behavior (Anisman et al 2002a, 2002b; Dantzer et al 1999; Leonard and Song 2002; Licinio and Wong 1999; Miller et al 1999; Segreti et al 1997).

In the current study, we examined the roles of corticosteroids and IL-1 in poststroke depressive-like behavior. We induced experimental stroke in mice via middle cerebral artery occlusion (MCAO) and used sucrose consumption as our primary outcome measure of poststroke depressive-like behavior. A decrease in sucrose consumption indicates a state of anhedonia, a core symptom of depression, that can be evaluated effectively in rodents (De La Garza 2005; Willner et al 1992). We hypothesized that MCAO would lead to decreased poststroke sucrose consumption and examined the importance of stroke-induced elevations in corticosteroids and IL-1 in mediating this behavioral effect. If elevated corticosteroids induce anhedonia in mice recovering from experimental stroke, then metyrapone (MET; a GC synthesis inhibitor), and mifepristone (MIF; a GC receptor antagonist) should reinstate increased sucrose consumption after stroke. If the stroke-induced increase in central nervous system

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inflammation causes anhedonia, then poststroke treatment with IL-1ra (an anti-inflammatory cytokine) should reinstate sucrose consumption. Taken together, these studies will improve our understanding of the physiological mechanisms underlying PSD.

**Methods and Materials**

**Animals**

This study was conducted in accordance with the National Institute of Health guidelines for the care and use of animals in research and under protocols approved by the local institutional animal care and use committee. Adult, sexually naïve male C57 BL/6 mice (22–30 g; approximately 3 mo old) were individually housed with ad libitum access to food and water and were maintained on a 14L:10D light–dark cycle. The mice were housed with ad libitum access to food and water and were maintained on a 14L:10D light–dark cycle. Measurement of Liquid Consumption

Consumption of water or sucrose solution was monitored for 6 hours per night for 6 days before surgery (2 d of water, then 2 d of sucrose solution, then 2 d of water). To begin, each mouse received 10 mL of water or 3% sucrose solution immediately before the onset of the dark cycle. Liquid consumption (in milliliters) was determined 6 hours after introduction. The water and sucrose bottles were not presented simultaneously in the current study because MCAO is well known to produce cognitive deficits (DeVries et al. 2001b), which may prevent the stroke mice from being able to learn an association between location of the bottle in the cage and whether it contains water or sucrose. Confusion between the bottles could result in continuous sampling of both bottles in search of the preferred drink. It is important to note that in a separate cohort of unmanipulated mice (n = 11), it was confirmed that mice consume similar amounts of sucrose regardless of whether they are presented sucrose alone (1 bottle protocol) or water and sucrose simultaneously (2-bottle protocol; p = .54). As expected, mice in the two-bottle protocol consumed approximately four times as much sucrose as water (p < .01).

**Experimental Stroke**

Transient focal cerebral ischemia was induced in male mice by right MCAO as described elsewhere (Sugo et al. 2002) Briefly, the mice were anesthetized with 1%–1.5% halothane in oxygen-enriched air delivered through a face mask. Unilateral MCAO was achieved by using the intraluminal filament insertion technique, which involved inserting a 6–0 nylon monofilament into the internal carotid artery, via the external carotid artery, then positioning the filament tip (of approximate 1.0-mm length and 25-mm width) for occlusion at a distance of 6 mm beyond the internal carotid artery–pterygopalatine artery bifurcation. Once the filament was secured, the wound was sutured, and the mouse was allowed to emerge from the anesthesia in its home cage. After 60 min of occlusion, the mouse was briefly reanesthetized with halothane, and reperfusion was initiated by withdrawing the filament. This surgical protocol typically results in a core infarct that encompasses approximately 15% of the affected hemisphere (Sugo et al. 2002) and is limited primarily to the parietal cerebral cortex and caudate putamen, although diffuse neuronal damage can occur in other regions. The surgical duration and procedure was similar for MCAO and sham-group (SHAM) mice, except that in the SHAM groups, the internal carotid artery was exposed but not disturbed. Throughout the surgery, rectal temperature was maintained at 37 ± 5°C through the use of a homeothermic blanket system. All animals were given a 5-mL subcutaneous injection of lactated Ringer’s solution at the conclusion of the surgical procedure.

**Determination of Stroke Volume**

Brains were removed and sectioned into five 2-mm-thick coronal sections. Sections were incubated for 15 min in 2,3,5-triphenyltetrazolium (TTC; Sigma-Aldrich Corp., St. Louis, MO), with rotation to the opposite side every 2 min to allow uniform tissue staining. The TTC solution was maintained at 37°C throughout the staining process. After staining, the sections were fixed in 10% buffered formalin solution. The brain slices were photographed using Inquiry software (Loats Associates, Inc, Westminster, MD). The images were used to determine infarct size as a percentage of the contralateral hemisphere after correcting for edema, as previously described (Hattori et al. 2000).

**Experiment 1: Determination of Stroke-induced Anhedonia**

On days 1–6, baseline water and sucrose consumption were determined as described above. MCAO or sham surgery was performed on day 7. All mice were allowed ad libitum access to water on days 7 through 13. On day 14, the water bottles were removed 6 hours before behavioral testing. Bottles containing sucrose solution or water were placed in the cage at onset of the dark cycle. Half of the MCAO group (n = 10) and half of the SHAM group (n = 10) were given 10 mL of water, whereas the other half (MCAO, n = 10; SHAM, n = 10) received 10 mL of sucrose solution. The animals were allowed 6 hours of ad libitum access to the liquid, and then consumption was recorded (Figure 1). At the conclusion of the 1-week reperfusion and final sucrose–water treatment, brain tissue was collected, and infarct sizes were determined.

**Experiment 2: Reversal of Stroke-induced Anhedonia**

**Experiment 2A: Effects of Glucocorticoid Synthesis Inhibitor (MET).** After the 6-day introductory water–sucrose–water cycle described above, the mice underwent either MCAO or sham surgery on day 7 and were recovered for a 1-week reperfusion period. All animals were allowed ad libitum access to water on days 7 through 13. The experimental groups consisted of the following: (1) SHAM-VEH (sham operation with vehicle [VEH]; n = 10), (2) SHAM-MET (sham operation with MET; n = 10), (3) MCAO-VEH (MCAO operation with VEH; n = 9), and (4) MCAO-MET (MCAO operation with MET; n = 11). Injection of MET (metyrapone; 100 mg/kg; Sigma-Aldrich Corp., St. Louis, MO; Gill et al. 1995; Risedal et al. 1999; Smith-Swintosky et al. 1996) or the vehicle (.05 mL of isotonic saline given intraperito-
neally) was initiated on poststroke day 4 (60 min before the onset of the dark phase) and was continued daily through day 14. The rationale for delaying the injections until day 11 was to avoid interference with the normal progression of core infarct development that typically occurs within the first 72 hours after ischemia. On day 14, the mice were water deprived for 6 hours as described above in Experiment 1; then the final injection of MET or VEH was administered 60 min before presentation of the sucrose solution (Figure 1). After 6 hours, liquid consumption was recorded, brain tissue was collected, and infarct volumes were determined.

**Experiment 2B: Effects of Glucocorticoid Receptor Antagonist (MIF).** After the 6-day introductory water–sucrose–water cycle described above, the mice underwent either MCAO or SHAM surgery on day 7 and were recovered for a 1-week reperfusion period. All animals were allowed ad libitum access to water on days 7 through 13. The experimental groups consisted of the following: (1) SHAM-VEH (n = 8), (2) SHAM-MIF (n = 8), (3) MCAO-VEH (n = 7), and (4) MCAO-MIF (n = 6). Subcutaneous injection of MIF (50 mg/kg; Sigma-Aldrich Corp., St. Louis, Missouri; Antonawich et al 1999; Soulet and Rivest 2003) or VEH (2% ethanol in polyethylene glycol [PEG 400; Hampton Research Corp., Aliso Viejo, California]; Douma et al 1998) was initiated on day 11 (60 min before the onset of the dark phase) and was continued daily through day 14. On day 14, the mice were water-deprived for 6 hours as described above in Experiment 1; then the final injection of MET or VEH was administered 30 min before presentation of the sucrose solution (Figure 1). After 6 hours, liquid consumption was recorded, brain tissue was collected, and infarct volumes were determined.

**Experiment 2C: Effects of IL-1 Receptor Antagonist.** A cannula, aimed at the right lateral ventricle, was implanted 1 week before experimental stroke surgery. The mice were anesthetized with 1%–1.5% halothane in oxygen-enriched air and were placed in a stereotaxic apparatus (David Kopf Instruments, Tujunga, CA). An incision was made along the midline to locate the bregma. The cannula (26-G, 1.75 mm below pedestal; Plastics One, Inc., Roanoke, VA) was positioned at +.02 posterior and −95 lateral of bregma, and secured with glue. Once the glue was dry, a dummy cannula with a dust cap was inserted into the cannula, and the mouse was placed back into its home cage for recovery. One day after cannulae implants, the mice began the 6-day introductory water–sucrose–water cycle. Then, the mice underwent either MCAO (n = 17) or SHAM (n = 16) surgery (day 0) and were recovered for a 7-day reperfusion period. On postsurgical days 6 and 7, the mice were given an infusion of either the VEH (artificial cerebrospinal fluid; 3.6 μL; Sigma-Aldrich Corp., St. Louis, MO) or recombinant mouse IL-1 receptor antagonist (IL-1ra; 1.8 μg/μL dose of IL-1ra; R&D Systems Inc., Minneapolis, MN; Bluthe et al 1997). The solutions were administered over 30 sec via a 5-μL Hamilton syringe connected to an internal cannula. The experimental groups consisted of the following: (1) SHAM-VEH (n = 8), (2) SHAM-IL-1ra (n = 8), (3) MCAO-VEH (n = 8), and (4) MCAO-IL-1ra (n = 9). On day 14, the mice were water deprived for 6 hours as described above in Experiment 1; administered the final injection intracerebroventricularly, then presented the sucrose solution (Figure 1). After 6 hours, liquid consumption was recorded, brain tissue was collected, and infarct volumes were determined.

**Statistical Analysis**

The water and sucrose consumption amounts for the 6-hour readings were analyzed by one-way analysis of variance (ANOVA). One-way ANOVA also was used to assess infarct size and glucose concentrations. Fisher’s least significant difference (LSD) test was used for post hoc analysis of significantly different means. Corticosteroid concentrations were analyzed by t test, followed by post hoc analysis by Fisher’s protected least significant difference (PLSD) test. Effects were considered significant at p < .05.

**Results**

Across each experiment, presurgical sucrose consumption was significantly increased relative to baseline water consumption in each experimental group, with no significant difference in sucrose consumption between groups (p < .05). Furthermore, postsurgical water consumption was similar between SHAM and MCAO groups in all experiments at postsurgical day 7 (p > .05), suggesting that MCAO mice were not impaired in their ability or motivation to drink from the bottles on the experimental test day.

**Experiment 1**

Mean sucrose consumption was compared with the mean water consumption for MCAO and SHAM mice. Liquid consumption values were based on a 6-hour ad libitum period, during which mice were presented with either 10 mL of sucrose or 10 mL of water immediately after 6 hours of water deprivation. There was a significant treatment effect on liquid consumption [F(3,39) = 6.79, p < .01] (Figure 2). Post hoc analysis by Fisher’s LSD revealed a significant increase in consumption of sucrose solution consumption relative to water in SHAM (p < .05) mice but not in MCAO (p > .05) mice. Furthermore, SHAM mice drank significantly more sucrose solution than did MCAO mice (p < .05).
.05), but water consumption was similar for MCAO and SHAM mice (p > .05).

Reversal of Poststroke Depressive-like Behavior

Experiment 2A: MET. Overall, there was a significant treatment effect on sucrose consumption [F(3,39) = 4.15; p < .01]. When treated with VEH injections, SHAM mice consumed significantly more sucrose solution (4.88 ± .33 mL) than did MCAO mice (3.07 ± .27 mL), replicating the poststroke anhedonic response that was observed in experiment 1. Treatment with MET, however, significantly decreased consumption of sucrose solution in SHAM mice (3.81 ± .29 mL) compared with VEH-injected SHAM mice (p < .05) and had no effect on consumption in MCAO mice (2.50 ± .24 mL) compared with the case of VEH-injected MCAO mice [F(3,39) = 10.3; p < .01]. There was no effect of group on water consumption [F(3,39) = .351; p > .05]. Infarct size was similar between VEH-treated and MET-treated MCAO mice (22.3% ± 2.93% and 20.0 ± 4.89%, respectively) [t(14) = .393; p > .05].

Experiment 2B: MIF. Overall, there were significant group differences in sucrose consumption [F(3,28) = 6.45; p < .01]. SHAM mice drank similar volumes of sucrose solution when injected with the VEH (4.75 ± .22 mL) or MIF (4.15 ± .29), which suggests that MIF does not alter sucrose consumption in mice that have not experienced ischemia. MCAO mice injected with the VEH consumed significantly less sucrose solution than did VEH-injected SHAM mice, as predicted from the results of experiment 1. However, MCAO mice that were injected with MIF drank significantly less sucrose (2.60 ± .60 mL) than did VEH-treated MCAO mice (3.74 ± .25 mL). Thus, after ischemia, treatment with a GC receptor antagonist increases anhedonia. MIF had no effect on postischemic corticosterone concentrations [F(3,26) = .240; p > .05] and did not alter percentage infarct volume (MCAO-VEH = 19.4% ± 5.85%; MCAO-MIF = 20.0% ± 5.92%) [t(11) = .071; p > .05] at 7 days of reperfusion.

Experiment 2C: IL-1ra. Treatment with IL-1ra significantly altered sucrose consumption in MCAO mice. Mean sucrose consumption after 6 hours was statistically different among experimental groups [F(3,52) = 3.61; p < .05] (Figure 3). Post hoc analysis with Fisher’s LSD indicated that there was no difference in mean consumption between VEH-treated and IL-1ra–treated SHAM mice, which suggests no effect of IL-1ra on sucrose consumption in non-ischemic animals. In contrast, SHAM mice drank significantly more sucrose solution than those in the VEH-treated MCAO group (p < .05). Post hoc analysis also indicated that IL-1ra–treated MCAO mice drank significantly more sucrose solution than did VEH-treated MCAO mice (p < .05). As expected, infarct size was similar between VEH-treated and IL-1ra–treated MCAO mice (12.9 ± 4.21% and 10.0 ± 2.90%, respectively) [t(124) = .523; p > .05].

Discussion

Depression is a frequent consequence of stroke and is associated with increased morbidity and mortality (Berg et al 2003; Bogousslavsky 2003; Whyte et al 2004; Williams et al 2004). However, the mechanisms underlying PSD are not well understood and research on this topic has been hindered by a dearth of animal models of PSD. The data from the current study suggest that it is possible to induce and study anhedonia as an index of poststroke depressive-like behavior in mice. At baseline, all mice in our study consumed more sucrose solution than water. SHAM surgery did not affect the natural sucrose preference relative to water (Figure 2). In contrast, experimental stroke eliminated the preference for sucrose solution, such that MCAO mice drank equivalent amounts of water and sucrose (Figure 2). Furthermore, the MCAO group drank significantly less sucrose solution than the SHAM group. It is important to note that MCAO and SHAM mice consumed equivalent amounts of water, thereby ruling out physical limitations or stroke-induced differences in drinking behavior as potential confounding factors. There is a remote possibility that the decrease in sucrose consumption in the current study reflects a stroke-induced alteration in taste perception; however, the reversal of anhedonia through IL-1ra treatment in Experiment 2C (described two paragraphs below) makes this interpretation unlikely. Taken together, these data suggest that mice can be used to study poststroke anhedonia.

Stroke produces sustained elevations in corticosteroid concentrations in human beings (Fassbender et al 1994; Johansson et al 1997) and other animals (Craft et al 2005; DeVries et al 2001a; DeVries et al 2001b). Although there is substantial evidence suggesting that dysregulation of the HPA axis can contribute to depression in human beings (Holsboer and Barden 1996; Muselman and Nemeroff 1996) and to depressive-like behavior in rodents (reviewed in Arborelius et al 1999; Stenzel-Poore et al 1999), it does not appear that anhedonia in the present study was mediated by a stroke-induced increase in corticosterone concentrations. MET, which is a GC synthesis inhibitor, did not have an effect on sucrose consumption among MCAO mice in the present study. In contrast, MIF, which is a GC receptor antagonist, induced anhedonia in the MCAO-MIF group relative to the MCAO-VEH group but did not affect sucrose consumption among SHAM mice. Thus, neither decreasing endogenous GC synthesis (MET) nor blocking activation of GC receptors (MIF) reinstated the sucrose preference in mice after stroke. However, these results do not preclude a role for other HPA-axis hormones.
in affecting stroke-induced anhedonia. Indeed, elevated corticotropin-releasing factor (CRF) concentrations also have been associated with anhedonia in rats (Stout et al. 2000). Although MET suppresses GC synthesis, it causes an elevation of other HPA-axis hormones, including CRF, adrenocorticotropic hormone, and vasopressin (Rollant and Armario 2000; Rollant et al. 2002), which could explain why MET induced anhedonia in the SHAM-MET group relative to the SHAM-VEH group. Furthermore, the doses of MET and MIF that were used in the current study were based on doses that were effective in altering other ischemic outcomes; thus, it remains possible that a change in the dose or timing of MET or MIF treatment could produce different behavioral effects.

A separate cohort of mice was used to determine whether a stroke-induced increase in IL-1 contributes to anhedonia. Elevated IL-1 has been reported in the brains of rodents (Hill et al. 1999; Legos et al. 2000; Zhai et al. 1997) and in cerebrospinal fluid (CSF) of human beings (Tarkowski et al. 1995c) after stroke. In the current study, mice were injected centrally with IL-1ra or VEH (sterile artificial CSF), beginning the day before the sucrose consumption test. VEH-treated MCAO mice ingested significantly less sucrose solution than did the IL-1ra-MCAO, IL-1ra-SHAM, and VEH-SHAM groups. In contrast, there was no significant difference in mean sucrose consumption between IL-1ra-MCAO mice and either SHAM group. Thus, IL-1ra reinstates the hedonic response to sucrose among mice that have had strokes and suggests that the inflammatory response that often accompanies stroke may contribute to anhedonia and possibly other symptoms of PSD. IL-1ra antagonizes the actions of both IL-1α and IL-1β, so it is not possible to definitively attribute the effects of stroke-induced anhedonia to either form of IL-1; however, most evidence to date lends support to the hypothesis that IL-1β plays a more central role in neurodegeneration than does IL-1α (Rothwell et al. 1997).

The extent to which stroke elevates inflammatory cytokines depends on several factors, including existence of subclinical infection, vascular disease, environment, and genes (Acalovschi et al. 2003; Rothwell and Luheshi 2000). Such individual differences in poststroke cytokine expression may be one factor contributing to the apparent variability in emergence of PSD among the stroke patient population (approximately 50%). There is converging evidence from clinical and nonhuman studies that cytokines are capable of provoking or exacerbating several affective disorders, including depression and sickness behavior (Anisman et al. 2002a; Anisman et al. 2005; Dantzer et al. 1999; Leonard and Song 2002; Licinio and Wong 1999; Miller et al. 1999; Segreti et al. 1997). Indeed, cytokine immunotherapy among cancer and hepatitis patients precipitates symptoms of depression that are indistinguishable from those found in major depressive disorders (Capuron et al. 2002). The symptomatic similarities between depression and cytokine-induced sickness behavior has led to formulation of the so-called cytokine hypothesis of depression (Dunn et al. 2005). Furthermore, antidepressant therapy alleviates depression among cancer patients receiving cytokine immunotherapy (Musselman et al. 2001) and attenuates sickness behaviors in rodent models of depression (Castanon et al. 2002). Antidepressant therapy also improves functional recovery and survival of human stroke patients (Gupta et al. 2002; Shima 1997), although it remains to be determined whether this effect is being achieved, in part, through antidepressant modulation of the immune system (Castanon et al. 2002).

Anhedonia is one of the fundamental symptoms of depression and has been well-characterized in rodent models of depression (reviewed in Willner et al. 1992; De La Garza, 2002; Anisman and Matheson, 2005). The data from the current study suggest that IL-1 mediates poststroke development of anhedonia (Figure 3). These data complement a previous study that used a different model of depression (chronic mild stress) in which proinflammatory cytokine concentrations in the brain and periphery were negatively correlated with sucrose intake (Grippo et al. 2005). Furthermore, the anhedonic and anorexie effects of IL-1β are dissociable; treatment with fluoxetine reinstates responding for sucrose reward (using a progressive ratio schedule) but does not alter chow consumption (available ad libitum) after IL-1β administration (Merali et al. 2003) Future studies are needed to determine whether fluoxetine, or other antidepressants, are as effective as IL-1ra in reversing the effects of stroke on anhedonia.

The results from the current study suggest that IL-1, but not corticosterone, influences the expression of poststroke anhedonia. The immune system and HPA axis, however, cannot be viewed as separate in the etiology of stroke and PSD. A growing body of literature has demonstrated the highly integrated functioning of the HPA axis and inflammatory response system as well as their role in the development of physiological and neuropsychiatric disorders (Raison and Miller 2001). Indeed, hypercortisolism after stroke is correlated positively with several inflammatory markers (Johansson et al. 1997; Slowik et al. 2002; Szczudlik et al. 2004), whereas no correlation exists between cortisol concentrations and catecholamine or glucose concentrations (Slowik et al. 2002). Thus, postischemic increases in GC concentrations may be related to the inflammatory response that is elicited by dying neurons. Indeed, corticosteroid concentration is correlated with infarct size 24 hours after experimental stroke (DeVries et al. 2001a), whereas corticosteroid concentrations are not elevated after global cerebral ischemia if neurodegeneration is prevented via hypothermia (Neigh et al. 2004). Furthermore, IL-1α can alter GR translocation and hormone-induced GR-mediated gene transcription, suggesting that cytokines are capable of mediating GC resistance, as observed in some depressed patients (Miller et al. 1999). Taken together, these studies suggest that disruption of either the HPA axis or immune system has long-term consequences on both neuroendocrine and immune feedback regulation, which may contribute to the development of neuropsychiatric disorders, such as depression after stroke (Raison and Miller 2001).

Although there are several conflicting reports, incidence of PSD in human beings has been correlated with stroke severity (Berg et al. 2003; Poliajvavra et al. 1998; Schwartz et al. 1993; Sharpe et al. 1990) and with location of ischemic brain lesions (Carson et al. 2000; Narushima et al. 2003; Robinson et al. 1984; Starkstein and Robinson 1990). Alterations in either peri-ischemic corticosteroid concentrations (DeVries et al. 2001a; May et al. 2002; Rami et al. 1998; Sugio et al. 2002) or IL-1 (Garcia et al. 1995; Mulcahy et al. 2003; Relton and Rothwell 1992; Yang et al. 1997) can influence infarct size and functional recovery after stroke. Therefore, in the current study, treatment with MET, MIF, or IL-1ra was not initiated until after the core infarct had formed by poststroke day 4. Thus, injections given from days 4–7 would potentially impact only a small number of damaged neurons in the ischemic penumbra. Indeed, infarct size was similar for vehicle-treated and drug-treated groups within each experiment, ruling out drug-induced alterations in infarct volume as a potential confound in the behavioral testing in each of the three experiments of the current study. It remains possible that the location of the infarct could influence the extent of the inflammatory response and susceptibility to cytokine induced-behav-
ioral changes. There is accumulating evidence supporting later-
ization of brain-immune interactions and the effects of
cytokines on behavior (Gao et al 2000; Neveu et al 1998).
Furthermore, localization of the brain lesion affects cutaneous
inflammatory responses in stroke patients (Tarkowski et al, 1991,
1995a, 1995b, 1998). Whether location of the infarct affects
cytokine expression in the brain and anhedonia after stroke
remains to be determined.

In summary, stroke is associated with anhedonia, as indicated
by a decrease in sucrose consumption relative to nonischemic
mice. Treatment with central IL-1ra restores sucrose consump-
tion among stroke mice but does not alter sucrose ingestion
among sham-operated mice. Although the data from the current
study do not support a role for corticosteroids in poststroke
anhedonia, it remains possible that stroke-induced dysregulation
of the HPA axis may contribute to other depression-related
behavioral changes that have been observed among stroke
patients, including cognitive deficits, social withdrawal, sexual
dysfunction, and insomnia. Taken together, these studies suggest
that the pathophysiological changes that accompany stroke,
including inflammation, can induce depressive-like behavior.

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anhedonia, it remains possible that stroke-induced dysregulation
of the HPA axis may contribute to other depression-related
behavioral changes that have been observed among stroke
patients, including cognitive deficits, social withdrawal, sexual
dysfunction, and insomnia. Taken together, these studies suggest
that the pathophysiological changes that accompany stroke,
including inflammation, can induce depressive-like behavior.

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