Cytokine mediation of experimental heart failure-induced anhedonia

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Grippo, Angela J., Joseph Francis, Robert M. Weiss, Robert B. Felder, and Alan Kim Johnson. Cytokine mediation of experimental heart failure-induced anhedonia. Am J Physiol Regul Integr Comp Physiol 284: R666–R673, 2003. First published November 7, 2002; 10.1152/ajpregu.00430.2002.—Immune system dysfunction is hypothesized to influence several disease states, including cardiovascular disease and psychological depression. The comorbidity of depression and coronary artery disease may be influenced by immune system-brain interactions involving proinflammatory cytokines. The present studies evaluated an index of depression in a rodent model of heart failure by measuring responses to rewarding electrical brain stimulation, which provides an experimental procedure to operationally define anhedonia in rats. Heart failure led to a rightward shift in the current-response relationship in the brain stimulation paradigm, indicative of reduced rewarding properties of the brain stimulation (i.e., anhedonia). Acute treatment with a tumor necrosis factor antagonist, etanercept, reduced circulating tumor necrosis factor-α levels in rats with heart failure and restored responding for electrical brain stimulation. The current findings have implications for the study of pathophysiological mechanisms underlying the association of cardiovascular disease and depression.

cardiovascular disease; depression; etanercept; immune system; tumor necrosis factor-α

INCREASED CLINICAL AND EXPERIMENTAL attention is being focused on the nature of interactions between psychopathology and pathophysiology. Depression occurs in combination with coronary artery disease at levels far exceeding chance (3, 6), and it is perhaps even more important that the presence of one of these disorders increases the likelihood of developing the other. Reciprocal relationships between depression and other medical conditions, such as cancer (37), have not been established. In contrast, depression is a recognized risk factor for coronary artery disease. Although the prevalence of major depression in the general population is 2–9% (1), its prevalence among postmyocardial infarct patients may be as high as 45% (34). Major depression doubles the risk that patients with newly diagnosed coronary artery disease will experience an adverse cardiovascular event within 12 mo (6), and the presence of depression is a significant predictor of mortality after myocardial infarction (18).

The mechanisms underlying the link between depression and coronary artery disease are not well established. Cardiovascular disease-induced depression is likely to result from both psychological and physiological changes. Congestive heart failure (CHF) is an outcome of certain detrimental cardiovascular events, such as ischemia and myocardial infarction (15). Furthermore, proinflammatory cytokines are components of the immune system that are important in both CHF and depression. Tumor necrosis factor-α (TNF-α), a product of activated macrophages that has anti-proliferative and anti-tumor effects (39), is one such cytokine shown to be associated with CHF. Serum levels of TNF-α are increased in humans with heart failure associated with ischemic heart disease (24) and in rats with experimental heart failure (16). This cytokine has been shown to contribute to left ventricular dysfunction, cardiomyopathy, and pulmonary edema (23).

TNF-α acts in both the peripheral and central nervous systems and thus may play an important role in depression associated with myocardial infarction and CHF. Reciprocal communication among the endocrine, immune, and central nervous systems has been established (19, 21). Immune system activation involving high levels of circulating cytokines is observed not only in depression but also in other chronic illnesses, including multiple sclerosis, rheumatoid arthritis, and type 1 diabetes mellitus (13). Excessive secretion of cytokines, such as TNF-α and interferon-α, is hypothesized to play an etiological role in depression (36). For instance, TNF-α administration results in depressive signs, such as fatigue, malaise, lethargy, and anorexia in humans (38). Similarly, central administration of interleukin-2 has been shown to produce depressive signs in rodents (2).

Because myocardial infarction and the subsequent progression of heart failure are associated with symptoms of depression in humans at greater than expected levels, it is of interest to determine whether experimental CHF in rodents is associated with depressive symptoms. The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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signs. The present experiments addressed whether coronary artery ligation to produce CHF or sham ligation (control) procedures leads to attenuated responding for rewarding electrical brain stimulation in male Sprague-Dawley rats. Impaired responding for electrical brain stimulation has been used to operationally define the reduced responsiveness to pleasurable stimuli (anhedonia) that characterizes human depression (1). Furthermore, in the present studies, we investigated the role of TNF-α in the association between CHF and anhedonia via the administration of a TNF-α antagonist, etanercept, and the direct measurement of plasma TNF-α in rats that underwent coronary artery ligation or sham ligation procedures.

**METHODS**

**Animals**

Twenty-eight male Sprague-Dawley rats (Harlan, Indianapolis, IN), weighing 250–350 g, were used for the experimental procedures. Animals were housed individually in suspended wire cages. Food (Purina Rat Chow 5012) and water were available ad libitum for the duration of the experiments. The temperature was maintained at 22 ± 2°C, and the light cycle was a 12:12-h light-dark cycle with lights on at 0600. Rats were allowed 1 wk to acclimate to the surroundings before any experimentation began. All procedures were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and the American Physiological Society Guiding Principles for Research Involving Animals and Human Beings and were approved by the University of Iowa Institutional Animal Care and Use Committee.

**Experimental Protocol**

Rats were instrumented with a single bipolar stimulating electrode directed to the lateral hypothalamus. Self-stimulation training was initiated, and multiple baseline measures of operant responding were recorded. After this baseline period, all rats underwent coronary artery ligation or identical surgery without ligation (sham heart failure). Responding for electrical stimulation was measured 7 days postligation. A subset of rats in each group was then treated with a TNF-α antagonist, etanercept, or saline vehicle. Responding for electrical stimulation was measured 24 h after drug treatment. At the conclusion of the protocol, left ventricular end-diastolic pressure (LVEDP) was recorded in anesthetized rats, a sample of blood was collected for cytokine analysis, and histological procedures were performed to verify the presence of CHF and proper electrode placement in the brain.

**Specific Experimental Procedures**

**Electrode placement.** A bipolar stimulating electrode (10 mm length; Plastics One, Roanoke, VA) was chronically implanted in the lateral hypothalamus. This site was chosen for use in the present study based on its reliability in producing self-stimulation behavior in rats (see Ref. 28). Under an Equithesin-like anesthetic cocktail (composed of 0.97 g pentobarbital sodium and 4.25 g chloral hydrate/100 ml distilled water; 3 ml/kg ip; University of Iowa Hospital Pharmacy, Iowa City, IA), rats were placed in a stereotaxic instrument, and the head was leveled between bregma and lambda. The electrode was implanted in the lateral hypothalamus at 3.0 mm posterior to bregma, 1.7 mm lateral to midline, and 8.5 mm ventral to the skull surface. Three jeweler’s screws and dental acrylic were used to fix the electrode to the skull. Butorphanol (3 mg/kg, sc; Bristol-Myers Squibb, Princeton, NJ) was administered to the animals for postoperative analgesia, and they recovered for a minimum of 5 days.

**Behavioral stimulation training and baseline measurements.** Rats were trained in a Plexiglas operand conditioning chamber (Skinner Box) equipped with a lever. Each lever press delivered a negative-going, square pulse train lasting 200–500 ms, at 60 or 120 Hz, through the electrode. The training procedure consisted of first placing the rat in the operand chamber and allowing it to explore the environment. The electrical parameters (train duration, frequency, and current intensity) were set to predetermined values, and the experimenter gave the rat a few “free” electrical pulses. When the rat began to approach the lever, the parameters were systematically varied, and free pulses of electricity were administered until the rat began to respond to the stimulation by pressing the lever. Once the specific parameters were determined for each rat, these were held constant throughout the entire study (with the exception of current intensity, which was varied; these methods are described below). Rats that did not respond to electrical stimulation or showed untoward motor effects that interfered with responding were not used in the study (i.e., this was a functional assessment of proper electrode placement).

After establishing consistent response rates, current-response curves were determined for each rat using procedures similar to those described by Milearessis and colleagues (25). Current was delivered in a descending series from 350 to 50 μA in discrete presentations of 25-μA decrements, and the animal was allowed to respond for 1 min at each intensity. An optimal current-response curve was generated for each rat using the following criteria: 1) the range of current intensities to which the rat responded was between 50 and 350 μA, 2) the response rate was minimal for low levels of current (e.g., ~50–100 μA) and increased monotonically, eventually reaching a stable plateau during 10 consecutive presentations of 25-μA increment current intensities, so that there was a sigmoid relationship between current intensity and behavioral responses, and 3) the maximum current intensity for which the rat would respond did not also produce a motor effect. Baseline current–response functions were generated over a 3- to 5-day period, and the results from different days were averaged for each rat.

**Coronary artery ligation.** Rats underwent either coronary artery ligation to induce CHF (n = 15; CHF group) or identical sham ligation (n = 13; sham heart failure group), using procedures described previously (15). Rats were anesthetized with ketamine (100 mg/kg ip; Abbott Laboratories, Chicago, IL), endotracheally intubated, and mechanically ventilated with room air (respiratory rate 50–55 breaths/min, tidal volume 2.5 ml). Under sterile conditions, a left thoracotomy was performed to expose the heart. The pericardium was opened, and the heart was exteriorized. The left anterior descending coronary artery was ligated between the pulmonary outflow tract and the left atrium with a 6–0 suture that was passed through the superficial layers of myocardium. The heart was returned to the chest cavity, lungs were reinflated, and the chest incision was closed. Sham heart failure rats were prepared in the same manner but did not undergo the ligation. After completion of the surgical procedures, rats were removed from the ventilator, and the endotracheal tube was removed. After surgery, animals were given benzathine penicillin (30,000 units im; Phoenix Pharmaceuticals, St. Joseph, MO) and lidocaine (2 mg im every
4 h for 2 doses; AstraZeneca Pharmaceuticals, Wilmington, DE). The rats were allowed to recover for 7 days.

**Postcoronary artery ligation behavioral measurements.** Seven days after induction of heart failure, anhedonia was assessed by generating current-response curves in CHF and sham heart failure groups in the same manner as the baseline measurements. Current was delivered in a descending series from 350 to 50 µA in discrete presentations of 25-µA decrements, and the animal was allowed to respond for 1 min at each intensity.

**Etanercept treatment and postetanercept behavioral measurements.** Immediately after the generation of current-response curves (on day 7 after coronary artery ligation), a subset of rats was given a single dose of etanercept (n = 6 CHF and 5 sham heart failure; 2.5 mg/kg ip; Wyeth-Ayerst Laboratories, Philadelphia, PA) or distilled water vehicle (n = 5 CHF and 4 sham heart failure). Twenty-four hours after etanercept treatment (on day 8 after coronary artery ligation), current-response curves were generated in these rats in the same manner as the baseline and 7-day postligation measurements.

**Measurement of LVEDP.** Left ventricular pressure was recorded according to procedures described by Francis et al. (15). The animals were anesthetized with pentobarbital (50 mg/kg ip; Abbott Laboratories), the right carotid artery was exposed, and a PE-50 catheter attached to a pressure transducer was advanced through the carotid artery, across the aortic valve, and into the left ventricular chamber. Pressure was recorded while the catheter was positioned at a site within the left ventricle where left ventricular pressure could be recorded accurately (i.e., the onset of the rapid rise in left ventricular pressure after atrial contraction could be observed) and left ventricular systolic pressure was not higher than aortic pressure upon entering the left ventricle (i.e., there was no evidence of ventricular outflow obstruction by the catheter). Left ventricular pressure was recorded continuously for 2 min using Spike II data acquisition software (Cambridge Electronic Design, Cambridge, UK). An estimate of LVEDP was obtained by adjusting a horizontal cursor to lie across the end-diastolic pressure of several sequential left ventricular pressure waveforms.

**Cytokine measurements.** Blood (3 ml) was collected transcardially from the left ventricle with a 5-ml syringe and a 21-gauge needle and put immediately in a chilled EDTA tube. The sample was centrifuged at 4°C. The separated plasma sample was stored at −70°C until assayed for TNF-α. Plasma TNF-α levels were measured using an ultrasensitive ELISA kit (Biosource International, Pottsboro, TX). Ninety-six-well microplates were coated with an antibody specific to rat TNF-α. Duplicate aliquots of each sample (100 µl) were added to the wells of the microplates, incubated for 2 h, and then washed five times. Subsequently, 100 µl of biotinylated anti-TNF-α antibody solution were added and incubated for 45 min. Plates were then washed, and 100 µl of streptavidin-horseradish peroxidase conjugate solution were added and incubated for 45 min. The plates were washed and, finally, 100 µl chromogen solution were added and incubated in the dark for 15 min. The reaction was stopped with HCl, and the plates were read at 450 nm using an ELISA plate reader. The minimum concentration of TNF-α detectable was <0.1 pg/ml.

**Histology.** At the conclusion of the protocol, the hearts were removed under anesthesia. The heart and lungs were removed, and heart-to-body weight and lung-to-body weight ratios were determined. In a subset of rats, the hearts were fixed using 10% buffered formalin. The brains were cut into four transverse sections and photographed. The brains were removed from a subset of rats and fixed in 10% buffered formalin. Brain sections were taken at 50-µm intervals throughout the hypothalamus. The sections were mounted on slides, stained with cresyl violet solution, and examined by light microscopy. The slides were evaluated for proper electrode placement in the lateral hypothalamus based on Paxinos and Watson (31).

**Statistical procedures.** Current-response functions were calculated for each individual rat at different time points (baseline, 7 days postligation, and 24 h postetanercept). Data points from individual rats were plotted using Sigma Plot (Jandel Scientific, Chicago, IL), and a three-parameter sigmoidal function was fit to the data. Mean current-response functions were calculated by averaging the response rate for each rat at each current intensity and plotting the mean data using Sigma Plot. A three-parameter sigmoidal function was similarly fit to these data.

From each individual fit curve, the following three parameters were calculated: 1) maximum rate of responding and corresponding current intensity, 2) threshold or current intensity that supports 50% of the maximum response rate (EC50), and 3) minimum rate of responding. Mean EC50 and maximum response values were statistically compared in CHF and sham heart failure groups using mixed-design ANOVAs and Student’s t-tests and a Bonferroni correction for multiple comparisons. Anhedonia was operationally defined as an increase in EC50, representing a rightward shift in the current-response relationship relative to the baseline current-response relationship.

**LVEDP, body weight, and organ-to-body weight ratios were compared statistically in CHF vs. sham heart failure groups using Student’s t-tests. Levels of TNF-α were compared in CHF vs. sham heart failure groups using mixed-design ANOVAs and Student’s t-tests. For all ANOVAs and t-tests, a probability value <0.05 was considered to be statistically significant.

**RESULTS**

**Behavioral Responses to Electrical Stimulation in CHF vs. Sham Heart Failure**

There was a sigmoidal current-response relationship between current intensity and response rate for rewarding electrical brain stimulation. That is, as current intensity increased, response rates increased and reached an asymptote. Figure 1 shows raw data points and the three-parameter fit curves from a representative CHF (A) and control (B) rat.

Coronary artery ligation resulted in reduced responding for electrical stimulation across a range of current intensities, relative to baseline responding (i.e., the current-response function generated before coronary artery ligation) and the responses of shamligated rats (Fig. 2A). Table 1 displays the curve parameters for the current-response curves shown in Fig. 2. At 7 days after coronary artery ligation, a parallel rightward shift was observed in the current-response function of the CHF group compared with baseline and sham heart failure responses.

Figure 2B presents the mean EC50 responses for CHF and sham heart failure groups relative to each group’s respective baseline responses. An ANOVA revealed significant main effects of time and group and a significant interaction. The baseline EC50 values did not differ between CHF and sham heart failure groups.
The CHF group displayed a significantly higher ECu50 than its respective baseline value and the sham heart failure group. The sham ECu50 value did not differ significantly from its respective baseline value.

An ANOVA yielded no significant main effects or interaction for the maximum response rate in CHF vs. sham heart failure groups. CHF and sham heart failure maximum response rates did not differ from the groups’ respective baseline values or each other (data not shown).

Behavioral Responses to Electrical Simulation

After Etanercept Treatment

The CHF group displayed a significantly higher ECu50 than its respective baseline value and the sham heart failure group. The sham ECu50 value did not differ significantly from its respective baseline value.

An ANOVA yielded no significant main effects or interaction for the maximum response rate in CHF vs. sham heart failure groups. CHF and sham heart failure maximum response rates did not differ from the groups’ respective baseline values or each other (data not shown).

Behavioral Responses to Electrical Simulation

After Etanercept Treatment

The behavioral responses to electrical stimulation after drug treatment were analyzed separately in CHF and sham heart failure groups. Figure 3A displays the mean current-response functions of CHF rats treated with etanercept or vehicle at 24 h after drug/vehicle treatment relative to baseline (i.e., the current-response function generated before coronary artery ligation). Table 2 shows the curve parameters for the current-response curves shown in Fig. 3. The current-response function for CHF rats treated with etanercept was similar to the baseline curve. In contrast, the current-response function for the sham heart failure group was similar to the baseline function. Data are displayed with a sigmoid curve fit to mean values. At the midpoint of each curve is a large filled circle with vertical and horizontal SE bars. A combined baseline curve for both CHF and sham heart failure groups is depicted. B: mean + SE effective current (ECu50) values for CHF and sham heart failure groups, relative to each group’s respective baseline ECu50 value, on day 7 after coronary artery ligation. There was an elevated ECu50 in the CHF group (t(14) = 8.17). *P < 0.05 vs. baseline CHF.

Table 1. Curve parameters defining current-response functions in CHF and sham HF rats

<table>
<thead>
<tr>
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<th>Maximum, responses/min</th>
<th>Midpoint, standardized current level</th>
<th>Minimum, responses/min</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>28 68.05 ± 3.38</td>
<td>4.91 ± 0.23</td>
<td>2.09 ± 0.48</td>
</tr>
<tr>
<td>CHF</td>
<td>15 72.18 ± 3.46</td>
<td>7.84 ± 0.37*</td>
<td>0.15 ± 0.08</td>
</tr>
<tr>
<td>Sham HF</td>
<td>13 81.95 ± 3.82</td>
<td>4.86 ± 0.57</td>
<td>1.35 ± 0.31</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of rats. CHF, congestive heart failure; Sham HF, sham heart failure. *P < 0.05 vs. respective sham HF value.
The EC_{50} value significantly differed from baseline maximum response rates. Rats at 24 h after drug treatment did not differ significantly from baseline. Conversely, CHF rats treated with etanercept, relative to control rats, indicated hypertrophy of the myocardium. The heart-to-body weight ratio was elevated significantly in CHF rats relative to control rats, which is an indication of heart failure-induced congestion. Coronary artery ligation used to induce heart failure has been validated previously by our laboratories (15–17). Therefore, in the present study, an assessment of the physical consequences of myocardial infarction was made on a macroscopic level. An observer who was blind to the experimental conditions examined each heart upon its removal to determine whether an infarct was present. All CHF rats had observable infarcts, whereas control rats had no physical damage. Figure 5 displays transverse sections from a typical CHF and control rat, showing the necrotic tissue and thinned myocardial wall in the CHF rat.

Cytokine Analysis

Enzyme immunoassay of plasma TNF-α was performed at the conclusion of the experiments from blood collected 24 h after the last anhedonia test. Plasma TNF-α was elevated significantly in the CHF group relative to the sham heart failure group (Fig. 5). Additionally, the dose of etanercept used in the present experiments was effective in reducing TNF-α levels in the CHF group. The etanercept treatment had no effect on the TNF-α levels in the sham heart failure group (data not shown).

Table 2. Curve parameters defining current-response functions in CHF rats receiving etanercept or vehicle

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Maximum, responses/min</th>
<th>Midpoint, standardized current level</th>
<th>Minimum, responses/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>11</td>
<td>68.99 ± 7.27</td>
<td>4.94 ± 0.28</td>
<td>2.19 ± 0.58</td>
</tr>
<tr>
<td>CHF + vehicle</td>
<td>5</td>
<td>68.29 ± 0.67</td>
<td>7.94 ± 0.19</td>
<td>0.08 ± 0.08</td>
</tr>
<tr>
<td>CHF + etanercept</td>
<td>6</td>
<td>68.69 ± 3.11</td>
<td>5.69 ± 0.48</td>
<td>0.00 ± 0.00</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of rats. *P < 0.05 vs. respective CHF + vehicle value.
DISCUSSION

Humans have been the central focus in traditional studies of altered mood and cardiovascular regulation, and, consequently, descriptive analyses have been the general practice in these investigations. The present studies, in contrast, examined the mediating role of TNF-α in anhedonia resulting from experimental CHF in rats. Anhedonia is a product of experimental heart failure, similar to that which is observed in humans with cardiovascular disease and depression. Furthermore, the presence of anhedonia in rats with CHF is associated with increased plasma TNF-α levels. By blocking TNF-α with an antagonist, we demonstrated a reversal of anhedonia in rats with heart failure.

The present data indicate that rats with experimental CHF display anhedonia as evidenced by reduced responding for electrical stimulation relative to baseline values and sham-ligated rats. The anhedonia observed on day 7 after coronary artery ligation is a specific hedonic deficit. A greater EC50 in the CHF group is an indication of a rightward shift in the current-response function such that responding is reduced at the same level of current that previously supported the responses (i.e., baseline responding), and a greater current intensity is required to produce the same level of previously recorded responding (see Fig. 2). Parallel shifts in current- or frequency-response functions in self-stimulation paradigms have been cited as evidence for a change in the reinforcing efficacy of the electrical stimulation (25).

Importantly, although the EC50 was shifted in the CHF group, the maximum response rate was not altered significantly by coronary artery ligation. The fact that rats with CHF demonstrated maximum response rates similar to baseline maximum rates indicates the absence of confounding motor/performance effects. This conclusion is consistent with other research employing curve shift paradigms for the analysis of self-stimulation (12, 25). For instance, it has been suggested that changes in asymptotic performance in self-stimulation indicate that the manipulation in question has interfered with the animal’s ability to perform the task, whereas a shift in the midpoint of the curve (i.e., the EC50) infers a change in the sensitivity to the rewarding properties of the stimulus (12).

The presence of CHF was verified by several methods in the present study. There was evidence of congestion indicated by an elevated lung-to-body weight ratio in the CHF group. Furthermore, there was morphological evidence of myocardial hypertrophy and functional evidence, as indicated by elevated LVEDP. Also, CHF rats weighed less than control rats, which may be an indication of cachexia. These findings are in supported the responses (i.e., baseline responding), and a greater current intensity is required to produce the same level of previously recorded responding (see Fig. 2). Parallel shifts in current- or frequency-response functions in self-stimulation paradigms have been cited as evidence for a change in the reinforcing efficacy of the electrical stimulation (25).

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Table 3. LVEDP, body weights, heart-to-body weight ratios, and lung-to-body weight ratios in CHF and sham HF rats

<table>
<thead>
<tr>
<th></th>
<th>LVEDP, mmHg</th>
<th>Body Wt, g</th>
<th>Heart/Body Wt</th>
<th>Lung/Body Wt</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF</td>
<td>19.72 ± 2.32*</td>
<td>342 ± 8*</td>
<td>0.0045 ± 0.0002*</td>
<td>0.0081 ± 0.0011</td>
</tr>
<tr>
<td>Sham HF</td>
<td>6.06 ± 1.35</td>
<td>381 ± 11</td>
<td>0.0035 ± 0.0001</td>
<td>0.0061 ± 0.0003</td>
</tr>
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</table>

Values are means ± SE; n, no. of rats. LVEDP, left ventricular end-diastolic pressure. *P < 0.05 vs. respective sham HF value.

Fig. 4. Transverse sections from the heart of a CHF rat (A) and a sham heart failure rat (B). The infarct involves predominantly the anterior and lateral walls of the heart, sparing the septum and portions of the inferior wall. The lighter tissue is necrotic, and parts of the myocardial wall are thinned in the CHF heart. The sham heart failure sections show the normal “doughnut-shaped” left ventricle (LV), with symmetrical wall thickness throughout the section. The LV and right ventricle (RV) are labeled.

Fig. 5. Mean ± SE plasma tumor necrosis factor-α (TNF-α) levels in rats with CHF (n = 4), sham heart failure rats (n = 4), and CHF rats treated with etanercept (n = 6). TNF-α levels were elevated in the CHF group relative to the sham heart failure group [t (6) = 4.86] and the CHF rodents treated with etanercept [t (8) = 5.99]. *P < 0.05 vs. CHF.
line with previous investigations of CHF in rats, which showed large infarcts, increased LVEDP and left ventricular end diastolic volume, decreased left ventricular ejection fraction, elevated heart-to-body weight ratio, and elevated lung-to-body weight ratio within 1–2 wk after coronary artery ligation (15, 17). These changes are considered to be important markers of the condition of CHF that progresses after myocardial infarction.

To extend our findings in the present investigation, we examined a possible mechanism for the occurrence of anhedonia in rodents with experimental CHF. A subset of rats in each group was treated with a single dose of the TNF-α antagonist etanercept, and responses to electrical stimulation were measured 24 h later. Rats with heart failure treated with etanercept displayed normal (i.e., similar to baseline) response rates for electrical stimulation. Conversely, CHF rats treated with the vehicle remained anhedonic. Neither etanercept nor vehicle treatment affected the current-response functions in the sham heart failure group (that is, this group did not deviate from baseline response rates at any point during the protocol). These results indicate that a TNF-α antagonist is effective in reversing CHF-induced anhedonia in rodents. Enzyme immunoassay of plasma TNF-α levels at the conclusion of the experiments indicated that TNF-α was elevated significantly in CHF rats relative to sham heart failure rats. Thus anhedonia in rodents with heart failure appears to be related to levels of TNF-α, suggesting that this cytokine plays an important role in depressive signs associated with coronary artery disease.

Although the present results suggest that TNF-α is involved in CHF-induced anhedonia and that antagonism of this cytokine results in a reversal of the depressive sign, they do not address the mechanisms by which elevated TNF-α levels in the plasma translate into central nervous system alterations that are associated with changes in the rewarding value of electrical stimulation. An animal’s behavior can be reinforced by electrical stimulation in several brain areas, including prefrontal cortex, nucleus accumbens, thalamic and hypothalamic nuclei, caudate, putamen, reticular formation, amygdala, ventral tegmental area, substantia nigra, locus coeruleus, and olfactory bulbs (29). Activation of underlying neural systems (or lack thereof) associated with these structures may mediate the hedonic sensitivity to electrical brain stimulation in rats with CHF. A dopaminergic component of the medial forebrain bundle that innervates structures such as the amygdala, septum, nucleus accumbens, and frontal cortex has been implicated in the reinforcing effects of electrical stimulation (8). Similarly, norepinephrine originating in the locus coeruleus and innervating the hippocampus, thalamus, hypothalamus, basal forebrain, olfactory nuclei, cortex, and septum has also been associated with the reinforcing effects of self-stimulation via its contribution of axons to the medial forebrain bundle (29). Interestingly, antidepressants and dopamine agonists (e.g., tricyclics), affect self-stimulation behavior in rodents (20, 27). Serotonergic mechanisms are also probably involved in influencing self-stimulation behavior resulting from interactions with the dopaminergic system (26).

Communication between the immune system and the nervous system is becoming increasingly well characterized (10). Cytokines are located in both the peripheral and central nervous systems. Receptors for interleukin-1, -2, and -6, as well as TNF-α, have been localized in brain areas such as the hippocampus and hypothalamus (21, 33). Central cytokines were not measured in the present study, but it is possible that plasma TNF-α produces anhedonia by acting on the central nervous system. Cytokines produced in the periphery can gain access to the central nervous system by way of the circumventricular organs, through the blood-brain barrier by selective saturable transport systems, or perhaps via neurally mediated mechanisms involving sensory nerves (4, 9). TNF-α may act directly or indirectly to affect key neurotransmitters that are involved in the reinforcing effects of electrical stimulation. This cytokine has been shown to alter central dopamine directly (7) and serotonin via its effects on tryptophan (11). Cytokines such as TNF-α, among others, may also change the reinforcing properties of electrical stimulation through their effects on fatigue (30) or sickness behavior (2). The large molecular mass of etanercept (150 kDa) likely precludes it from crossing the blood-brain barrier (40); however, by binding to TNF-α in the periphery, it may affect the ability of this cytokine to communicate with the central nervous system.

Another unanswered question is whether anhedonia can be shown to influence the progression of heart failure in rats with experimental CHF. Depression is an established risk factor for coronary artery disease in humans, independent of many traditional risk factors such as hypertension, high cholesterol, and increased body mass index (5, 32). Immune alterations have been shown to influence the pathogenesis of several cardiovascular diseases via effects on platelet activation (14), atherosclerotic plaque formation (22), and vascular resistance (35), among others. The methodological approach used here, if applied to other studies of cardiovascular regulation and depressive disorders, might provide insight regarding the role of immune mediators in the risk of coronary artery disease in individuals with psychological depression and may contribute to improved interventions for these patients.

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