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Neuroscience and Biobehavioral Reviews 29 (2005) 761–770
NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS
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Review

Endotoxin- or pro-inflammatory cytokine-induced sickness behavior as an animal model of depression: focus on anhedonia

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Abstract

In humans, exposure to endotoxins or pro-inflammatory cytokines induces a number of neuropsychological symptoms collectively referred to as 'flu-like syndrome'. The degree of overlap between flu-like syndrome and major depressive disorder is considerable and a close linkage between these has been predicted to arise due to hypersecretion of endogenous pro-inflammatory cytokines and activation of the hypothalamic pituitary adrenal axis. In animals, exposure to pro-inflammatory cytokines or endotoxins induces a 'sickness behavior' syndrome that is analogous to flu-like symptoms observed in human patients. The goal of the current paper is to review evidence implicating endotoxin- or cytokine-induced sickness behavior as an animal model of depression, with an emphasis on reduced consumption of highly palatable substances as a defining feature.
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Keywords: Anhedonia; Hedonia; Depression; Lipopolysachharide; Endotoxin; Cytokines

Contents

1. Depression is associated with a complex spectrum of changes in brain

The movement of major depressive disorder (MDD) into mainstream consciousness has led to some gross over-simplifications. For example, television advertisements for antidepressants describe depression as a result of 'a chemical imbalance in brain'. While there is no doubt that antidepressants increase synaptic levels of norepinephrine, serotonin, and perhaps also dopamine, these compounds also suppress pro-inflammatory cytokine production (e.g. interleukin-1β (IL-1β), IL-6, tumor necrosis factor-α (TNF-α)) and stress hormone release (Castanon et al., 2002; Lanquillon et al., 2000; Leonard, 2001; Yirmiya et al., 1999), and may additionally stimulate anti-inflammatory cytokine release (e.g. IL-10) (Castanon et al., 2004; Kubera et al., 2001). These data indicate that neuroimmune and neuroendocrine system perturbations likely play an important role in the etiology of depression.

In humans, exposure to endotoxins or pro-inflammatory cytokines (hereafter simply referred to as cytokines) induces a number of neuropsychological symptoms collectively referred to as 'flu-like syndrome' (Konsman et al., 2002).

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0149-7634/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neubiorev.2005.03.016

These include anhedonia, anorexia, fever, fatigue, increased pain, sleep disturbances, and confusion. The degree of overlap between flu-like syndrome and MDD in humans is considerable and a close linkage between these has been predicted to arise due to hypersecretion of endogenous cytokines (Anisman and Merali, 2003; Licinio and Wong, 1999; Maes, 1999) accompanied by chronic activation of the hypothalamic pituitary adrenal (HPA) axis (Holsboer, 2000; Meyer et al., 2001; Nemeroff et al., 1984; Pariante and Miller, 2001; Raison and Miller, 2001). Despite a predictable and deleterious side-effect profile, cytokines (e.g. interferon-α (IFN-α), IFN-β, interleukin-type-2 (IL-2)) are routinely used in the treatment of immune, autoimmune, inflammatory, infectious, and malignant disorders (Krause et al., 2003). The most striking example involves repeated IFN-α exposure (the only approved treatment for hepatitis C), which has been shown to induce depressive-like symptoms in 40% patients undergoing treatment (Asnis et al., 2003; Asnis and De La Garza, 2005; Bonaccorso et al., 2002; Zdilar et al., 2000). The recent finding that pre-treatment with the selective serotonin reuptake inhibitor (SSRI) paroxetine can prevent the onset of IFN-α-induced depression (Capuron et al., 2002; Musselman et al., 2001) has contributed to the general hypothesis that disturbances in neuroimmune and neuroendocrine system functioning are critical to the etiology of MDD.

In animals, exposure to endotoxins (e.g. lipopolysaccharide; LPS) or cytokines induces a 'sickness behavior' syndrome that is characterized by anhedonia, increased sleep, and decreases in food intake, body weight, locomotor activity, social interaction, sexual behavior and grooming (Konsman et al., 2002; Hart, 1988; Kent et al., 1992). In rodents, endotoxin- and cytokine-induced anhedonia is often described in terms of reduced intake of palatable substances (e.g. sucrose pellets or sweetened milk) (Yirmiya, 1996). An alternative and effective model for the measure of reward in rodents is responding for intracranial self-stimulation (ICSS), which is equally disrupted by stressful stimuli and endotoxin exposure (Borowski et al., 1998).

The goal of the current paper is to review evidence implicating endotoxin- or cytokine-induced sickness behavior as an animal model of depression, with an emphasis on reduced consumption of highly palatable substances as a defining feature. This will be accomplished by (1) defining anhedonia within the context of MDD in humans, (2) listing instances where anhedonia, as measured by consumption of highly palatable substances, has been used as the principal dependent measure after manipulations hypothesized to be etiologically linked to depression, (3) describing methodological considerations for measuring consumption of highly palatable substances, (4) discussing the extent to which consumption of highly palatable substances has been validated as a measure of anhedonia, (5) enumerating the advantages and disadvantages of this specific model of anhedonia, and finally by, (6) describing approaches for future studies using cytokine or endotoxin exposure for the study of the consumption of highly palatable substances and as an animal model of depression.

2. Anhedonia is a major feature of MDD

The degree of pleasantness associated with an experience or particular state was termed hedonia in the mid 1600s, and is derived from the Greek word hedonikos. For some unknown reason, it took another 250 years to specify the obvious antonym. Absence of pleasure was termed 'anhedonia' by the French psychologist T. Ribot in 1896 (Auriacombe et al., 1997), and has since been described as a behavioral construct central to depression in humans (Fawcett et al., 1983a,b; Peterson and Knudson, 1983). In fact, anhedonia is specified as a core symptom of MDD and is characterized by a loss of interest in, or ability to derive pleasure from, rewarding stimuli (or activities) (American Psychiatric Association, 2000). Anhedonia may not be present in all individuals diagnosed with MDD (Borowski et al., 1998), yet its occurrence in a significant number of depressed patients makes it a feature worth investigating in animal models.

In rodents, anhedonia has been described in terms of reduced exploratory activity (though this characterization is doubtful (Nava et al., 1997; Pare, 2000)), reduced social investigation (Fishkin and Winslow, 1997), reduced sexual behavior (Yirmiya, 1996; Pare, 2000), and reduced consumption of highly palatable substances (Yirmiya, 1996). As specified above, ICSS is also utilized as a measure of reward, and disruption of responding has been designated anhedonia (Borowski et al., 1998). Of these, the most highly utilized method involves characterizing of the consumption of highly palatable substances, which has been reported in the literature for the past several decades (Hodos, 1961; Hodos and Kalman, 1963; Katz, 1982).

Reduced consumption of palatable substances has been determined in a number of animal procedures involving manipulations that are hypothesized to induce depression. These include the chronic mild stress model (Andriamampandry et al., 2002; Kim et al., 2003; Konkle et al., 2003; Pijlman et al., 2003; Willner, 1997a), the olfactory bulbectomy model (Primeaux et al., 2003), models of social stress (Von Frijtag et al., 2002; Willner et al., 1995), a model of prenatal drug (i.e. cocaine, nicotine) exposure (Sobrian et al., 2003), a model of drug (amphetamine)-induced withdrawal (Barr and Phillips, 1999), and a model of schizophrenia (that may mimic negative symptoms in psychotic patients) (Le Pen et al., 2002). Reduced consumption of palatable substances has also been reported in specific strains of rats with a genetic background associated with increased probability of depressive-like behavior (De La Garza and Liu, 2002; Sarkisova et al., 2003).

3. Methods to measure anhedonia

It is important to discuss the principal methods used to measure anhedonia in rodents since several approaches have been employed and the information that each provides is distinct. As such, this section reviews some of the most important considerations. This information is especially useful when discussing the scientific validity, and advantages or disadvantages of the proposed model.

It is well established that animals that have access to another food source (i.e. in the home cage) exhibit increased susceptibility to disruption of operant responding. For example, the effect of consumption cost (i.e. having to press a lever for reward vs. having free access) on the intake of sucrose solution (8–32%) was determined in rats when a nutritionally complete chow was concurrently freely available (Collier and Johnson, 2000). The authors were able to establish that selection appears to be guided by (1) caloric requirements and the relative cost of calories, (2) by nutrient requirements and the relative cost of nutrients, and (3) by taste. Given this information, some experimental designs include food and/or water restriction in order to increase motivation to consume the test substance. The data from this approach are useful since test and control groups are subjected to the same conditions. However, food and water restriction are proven forms of stress and are unnecessary confounds. Animals that are in a state of forced hunger or thirst will, of course, exhibit increased motivation to consume the test substance, but the reward salience of the substance is not distinguishable in these conditions. Consumption of palatable substances should be based exclusively on the reinforcing nature of the substance itself and how motivated the animal is to work for that substance. Models of basic reward are set forth to measure the desire of the animal to obtain/consume the substance that surpasses a basic need to quell hunger or thirst. An important aside to consider is that some anxiety assays involve measures of latency to consume palatable substances in a novel environment. While several investigators have similarly utilized food restriction in these assays, recent evidence demonstrates that the procedure is both sensitive and reliable in the absence of food restriction (Merali et al., 2003a).

Animals allowed unrestricted access to food and water in their home cages readily perceive highly palatable substances as rewarding and quickly discover (or can be trained) how to obtain the reward. Several such substances have been utilized by investigators, including sucrose (varying concentrations expressed as percentage), sweetened milk (e.g. Eagle Brand, Borden), sucrose pellets (e.g. Noyes, New Brunswick, NJ), saccharine, and graham crackers, to name just a few. The choice of the rewarding substance is critical since motivation (and hence behavioral performance) has been shown to be highly dependent on the rewarding substance itself. Data from our own lab confirm this supposition, since acute LPS exposure significantly reduced rate of self-administration and total reinforcers obtained for sucrose pellets, but not sweetened milk, in non-food deprived rats (De La Garza et al., 2004a). These data argue against a non-selective reduction in ingestive behaviors following endotoxin exposure, suggesting that the behavioral effects reported are most likely related to anhedonia, not anorexia.

A primary consideration in determining reward behavior is to specify exactly what will be quantified. A combination of choices must be made, including the environment in which testing will occur (home cage vs. a test chamber), the delivery medium (single bottle, two-bottle choice, food tray), and deciding on a schedule of reinforcement. The latter is especially important since the response cost for reward influences the outcome of goal-directed behaviors (Larson et al., 2002). Moreover, the schedule of reinforcement selected weighs heavily on the type of data accumulated and consequently the conclusions that can be drawn from that data. Several studies allow unlimited access to the palatable substance in the home cage and involve a basic quantification of amount consumed (volume in milliliters or weight in grams). Quantification of total amount of substance consumed is informative, but satiation may obscure fine aspects of motivated behavior that can be uncovered using other approaches. One such approach involves the testing of animals in operant chambers using fixed ratio (FR) and progressive ratio (PR) schedules of reinforcement. FR schedules measure the pleasurable or hedonic effects of a particular substance by providing important information on latency to obtain the first reinforcer, a profile of responding between reinforcers, and overall rate of reinforced behavior (specifying a maximum number of rewards to avoid satiation). One limitation of FR schedules is that absolute rates of responding do not necessarily provide a measure of reinforcement value (Hodos and Kalman, 1963). As such, PR schedules are recognized as a better tool for measuring incentive motivation or craving (Arnold and Roberts, 1997), and are used to best assess reward strength, although performance on these schedules can still be affected by satiating effects produced by the substance (Hodos, 1961; Reilly, 1999; Sclafani and Ackroff, 2003). This important topic has recently been reviewed within the context of dopamine system modulation of reward behavior (Salamone et al., 2003).

An additional methodological consideration is the need to determine home cage food (regular rodent chow) and water consumption, as well as body weight changes. One common effect of endotoxin or cytokine exposure is reduced body weight. Decreases in body weight may arise from reduced food intake, but have also been predicted to arise because of altered metabolic activity (Larson and Dunn, 2001). As such, endotoxin- or cytokine-induced behavioral effects may extend beyond changes in reward behavior (anhedonia) to include more general sickness behaviors induced by the drug, including reduced food intake

(anorexia). It is well established that humans exhibit decreased appetite during illness and disease, including depression (Plata-Salaman, 1996). In rodents, infection and inflammation are similarly accompanied by reduced food intake (Bernstein et al., 1985; McHugh et al., 1993), and endotoxins and cytokines have specifically been shown to reduce food intake (Dunn and Swiergiel, 2001; Langhans et al., 1993; McCarthy et al., 1984; Swiergiel et al., 1997a,b; Dunn and Swiergiel, 2000; Yirmiya et al., 2001). Given this information, it is important to measure home cage food and water consumption, as well as body weight changes so that these alterations can be considered within the context of behavioral changes observed in reward paradigms. Of interest, several research groups have shown that low dose endotoxin or cytokine exposure reduces consumption of palatable substances, without decreasing home cage food or water consumption (Yirmiya, 1996; Plata-Salaman et al., 1988; Shen et al., 1999; De La Garza et al., 2005a). This information is critical when considering arguments of endotoxin- or cytokine-induced anorexia vs. anhedonia.

Our laboratory has used an experimental procedure that employs a combination of the above factors (De La Garza et al., 2004; De La Garza et al., 2005a) (Fig. 1). Specifically, animals are first exposed to 3 days of partial food restriction (15 g/day) as a means of increasing initial motivation to press the lever for a reward. During the next 3 days, animals are trained to press a lever (FR-1 schedule) for a 45 mg sucrose pellet reward (Noyes, New Brunswick, NJ) in a typical two-lever operant chamber (Med-Associates, St Albans, VT). Once the task is learned (invariably by the fifth day of training), animals are returned to free-feeding.

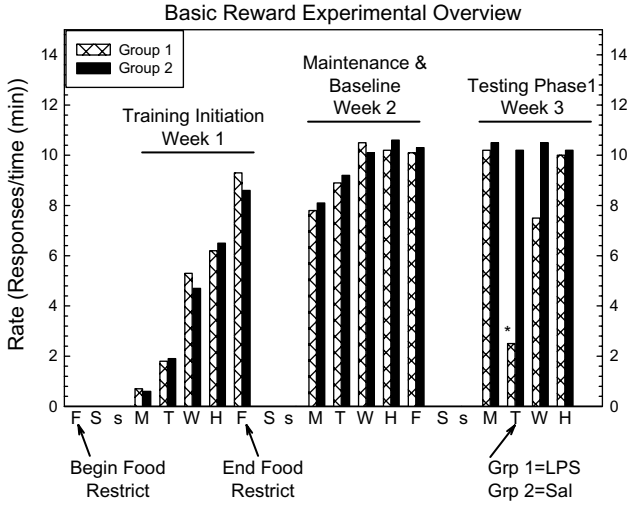

Fig. 1. Overview of the basic experimental design. The figure represents predicted (not actual) data for distinct groups of rats (Grp 1 vs. Grp 2) trained to press a lever for a 45 mg sucrose pellet. Training occurs Monday to Friday (M, T, W, H, F) and a steady baseline is achieved by the end of the second week. During the third week, after another training day has elapsed, testing can ensue by exposing half the animals to an injection of saline and half to the test substance (LPS). Acute LPS exposure produces robust changes in behavior that return to baseline 24–48 h after initial exposure.

Training is not necessary on weekends to maintain this behavior, and is resumed once daily for an additional week (Week 2) to obtain a steady baseline ($\pm$10% last three consecutive sessions). Each session lasts for a maximum of 30 min or is terminated upon the acquisition of 30 reinforcers. Rate is the principal dependent variable and is calculated as #reinforcers obtained divided by time in minutes. We have calculated rate after 5, 10, 20 and 30 reinforcers and have not detected significant differences for any of these targets. Animals that have achieved a steady baseline average one lever press per 5.5 s, and this robust responding is noteworthy given that the animals are not food or water restricted. As such, this behavioral output is driven by the rewarding properties produced by the substance itself, and are therefore likely to be a measure of hedonia. After the initial 2-week training period, animals are ready for testing (Week 3). For example, 2–4 h after acute exposure to LPS (20 μg/kg, ip), responding for reward is reduced to 20% of baseline. This effect is relatively short-lived since animals recover to 80% within 24 h, and return to 100% responding by 48 h. The testing phase can be used for acute challenges, or continue for several days or weeks with no significant alterations to baseline performance and this is useful for testing of repeated antidepressant pre-exposure. In fact, we have shown that this basic reward behavior is readily sustained for at least 30 days (De La Garza et al., 2005b).

4. Validation of the model

Determining the scientific validity of endotoxin- or cytokine-induced anhedonia as an animal model of depression is essential. The striking similarities between symptoms of MDD in humans and the behavioral and physiological alterations induced by endotoxin or cytokine exposure in rodents offer a convincing ‘face validity’ for this model (described above). For predictive validity, animal models for antidepressant drug effects have to fulfill a number of pharmacological criteria, including therapeutic class specificity and dose-dependent sensitivity. A number of examples can be given to demonstrate the predictive validity of the model. For example, chronic, but not acute, treatment with either the tricyclic antidepressant imipramine, or the SSRI fluoxetine, abolished the reduction in preference for saccharin produced by acute LPS exposure (Yirmiya, 1996; Yirmiya et al., 2001). Similarly, IFN-α-induced reductions in sucrose consumption (Sammut et al., 2002), and IL-1β-induced reductions in responding for sucrose using a PR schedule (Merali et al., 2003b) were each reversed by chronic fluoxetine pre-treatment. Further, chronic treatment with the atypical antidepressant tianeptine attenuated LPS and IL-1β-induced sickness behaviors (Castanon et al., 2001). Of interest, the antidepressant responses in these behavioral assays are similar to those reported in rats exposed to chronic mild stress. Specifically,

chronic mild stress-induced reductions in consumption of palatable substances were prevented by chronic, but not acute, administration of antidepressants, including SSRIs and tricyclics (Katz, 1982; Monleon et al., 1995; Muscat et al., 1990; Willner, 1997b). It is important to mention, however, that the chronic mild stress procedure has been shown to be largely unreliable with many failures to replicate (Harris et al., 1997; Hatcher et al., 1997).

Some investigators have failed to observe anti-anhedonia effects by imipramine, venlafaxine, paroxetine or desipramine in animals exposed to endotoxins or cytokines (Dunn and Swiergiel, 2001; Shen et al., 1999). As such, it is not possible to unequivocally conclude that acute endotoxin- or cytokine-induced anhedonia is an appropriate model of depression. The ambiguities may be related to the manner in which testing has been conducted. In particular, all of the investigations mentioned above have relied exclusively on testing healthy, adult animals after acute endotoxin or cytokine exposure. This is considered an inferior means to test the model since it is improbable that MDD arises due to a single harmful event, but is more likely the result of numerous environmental insults (e.g. stressors) that combine with a genetic predisposition to ultimately give rise to the disease state.

5. Advantages and disadvantages of the endotoxin or cytokine model of anhedonia

The advantages of the model are straightforward, and include ease of implementation, low cost, and minimal training of animals. The most important advantage is that both endotoxin- and cytokine-induced alterations occur rapidly, and these changes occur at several levels, including changes in brain neurochemistry, neuroendocrine and neuroimmune function, and behavioral changes—all of which coincide with MDD in humans.

There are some disadvantages to the proposed model. Foremost, it must be conceded that this model, like all others currently available, is not a specific test for depressive-like behavior. A second disadvantage of using endotoxin of cytokine exposure to induce anhedonia is the lack of long-term effects produced by acute treatment, despite a robust profile of changes the first several hours after exposure. In fact, some data suggest that the effects observed are present only when the drugs are ‘on board’ (Nagano et al., 1999; Takemura et al., 1997), though this has not been rigorously tested by examining long-term changes several days or weeks after exposure. The short-lived acute effects are considered a disadvantage to developing an animal model since the human disease state (of MDD) is characterized by a chronic, recurring pattern of brain and behavioral changes, and is operationally defined by the American Psychiatric Association as a series of symptoms that persist for at least 2 consecutive weeks (Peterson and Knudson, 1983).

A third disadvantage of this model concerns the difficulty in drawing a parallel between human and animal studies. In humans, cytokine treatment (IFN-α, IL-1β) takes place over several weeks and it is this exposure regimen that is most associated with the onset of symptoms of MDD. In contrast, animal models used to date often involve only a single administration of an endotoxin or cytokine. A related concern is that tolerance develops to repeated exposure to endotoxins or cytokines. Since acute exposure produces robust but ephemeral changes, sustained neurobiological effects produced by repeated exposure might be predicted to serve as a better animal model for MDD. Available data reveal that while acute LPS produces a robust fever response, a reduction in locomotor activity, and anorexia, these effects diminish with repeated exposure. Recent evidence also showed that acute LPS induced a dramatic loss of ICSS, however, rats developed a tolerance to this effect after repeated exposure (Barr et al., 2003). While this may signal caution for the use of repeated endotoxin exposure to measure anhedonia behavior (at least for ICSS), some biological responses do not show tolerance after repeated exposure (see below). As these assays are currently being used, behavioral tolerance is reported only during treatment (with the drug on board). The unanswered question is whether some of the long-term neurobiological changes that persist after repeated exposure are capable of altering behavior some time later (e.g. days or weeks after initial exposure and which may have greater relevance to an animal model of depression). This is an important consideration since it has been speculated that MDD arises not because of a single traumatic event (or even multiple insults), but is the result of many factors that work together over time to produce changes in brain that ultimately give rise to the disease state (Anisman and Merali, 2003).

Long-term biological changes following repeated endotoxin exposure include significant increases in serum IL-1 (Zuckerman et al., 1991). Additional data showed that repeated LPS exposure led to sustained elevations in plasma IL-1β and increased IL-1β protein in hypothalamus, hippocampus and pituitary (Nagano et al., 1999). These findings may be especially important to consider for long-term studies since IL-1β infusion directly into the hippocampus has been show to induce HPA axis activity (Linthorst et al., 1994). Repeated LPS exposure also produced sustained elevations in pro-opiomelanocorticotropin hormone (POMC) gene expression in anterior pituitary and corticotropin releasing hormone (CRH) gene expression in the paraventricular nucleus of the hypothalamus, as well as decreased glucocorticoid receptor mRNA in hippocampus (Takemura et al., 1997; Grinevich et al., 2001). Sustained elevations in cytokines may have long-term functional consequences that are not immediately apparent upon cessation of treatment, and may only be manifest using specific behavioral paradigms. Another example of sustained biological effects produced by repeated LPS exposure includes increased adrenal

weight (the principal end organ of the HPA axis) (Takemura et al., 1997; Grinevich et al., 2001; Bumiller et al., 1999). This is important to consider since adrenal hypertrophy has been observed in human patients with depression (Nemeroff et al., 1992). Finally, a careful examination of the literature reveals that although tolerance develops to acute LPS-induced elevations in corticosterone and ACTH, these responses often remain significantly elevated above baseline levels (saline-treated animals) (Nagano et al., 1999; Takemura et al., 1997).

To this point, endotoxin and cytokine effects have been spoken of as if they are identical. It is known that acute exposure to endotoxins, IL-1β, IL-6 or TNF-α, each disrupt consumption of palatable substances (Anisman et al., 2002). Despite these similarities and those pertaining to neuroendocrine and neuroimmune activation, there are sufficient differences such that they should not be casually regarded as identical. For example, endotoxins and IL-1 have been shown to induce a full spectrum of sickness behaviors, including reduced consumption of palatable substances, while IL-6 and TNF-α seldom produces potent sickness syndrome changes (Larson and Dunn, 2001; Swiergiel et al., 1997b). In addition, unlike endotoxins or IL-1β, IL-2 provokes only modest effects on HPA axis activation and has minor effects on sickness behaviors (Anisman et al., 2002). Recent evidence demonstrates that chronic IL-2 treatment resulted in sustained decreases in chocolate milk consumption, while regular home cage chow consumption remained unaffected (Anisman and Merali, 2003; Anisman et al., 2002). In addition, repeated cytokine exposure produced persistent alterations in HPA axis functioning (Linthorst et al., 1994; van der Meer et al., 1996), effects not yet reported for endotoxins.

A final concern worth noting is the difficulty in dissociating anhedonia vs. reduced motivation to consume palatable substances secondary to more global effects produced by the sickness syndrome. As mentioned previously, endotoxins and cytokines do much more than just induce anhedonia, increase stress hormones and increase pro-inflammatory cytokines. They also reduce locomotor activity, increase fever, cause body weight reductions, and sometimes decreases home cage water and food consumption. It is, therefore, critical to consider (and to control where possible) these changes in order to make more accurate conclusions regarding anhedonia (De La Garza et al., 2005a).

6. Future studies of endotoxin or cytokine exposure as a model of anhedonia

The question whether endotoxin- or cytokine-induced reduction in consumption of palatable substances serves as a model anhedonia is easy to answer. The unequivocal answer is Yes. It is clearly established that endotoxin or cytokine exposure induces a profound disruption of basic reward behavior in rats, mice, and in non-human primates. However robust these behavioral responses may be, there is some question whether the anhedonia effects have relevance to the bigger picture of MDD.

As such, a second and perhaps more important question is whether endotoxin- or cytokine-induced reductions in consumption of palatable substances can be considered an animal model of depression. There is compelling evidence that the behavioral effects produced by endotoxins and cytokines, including also alterations to brain neurochemistry, and neuroendocrine and neuroimmune function, collectively mimic the profile of MDD observed in humans (Konsman et al., 2002; Anisman and Merali, 2003; Larson and Dunn, 2001; Leonard and Song, 2002). A major limitation of currently published research, however, is that a majority of these studies have been conducted in 'healthy' adult animals. While this is an obvious first step for most scientific research, a key goal for future studies should be to determine the effects of endotoxin or cytokine exposure in animals during prenatal or early postnatal development, in animals previously exposed to chronic stress or cytokines, in animals exhibiting compromised immune system functioning, or in animals with a genetic predisposition to exhibit anxiety or depressive-like behavior. After all, it has long since been hypothesized that MDD (and probably most neuropsychiatric disorders) in humans likely arises not because of a single traumatic event (or an abrupt turning on of a malevolent gene), but is the result of multiple factors (genetic and environmental) that work together *over time* to produce changes in brain that ultimately give rise to the disease state (Anisman and Merali, 2003). Given this information, the use of acute endotoxin or cytokine exposure in healthy adult animals is likely not the best means to determine the suitability of the model for the measure of depressive-like behavior.

As such, there are a number of unexplored scenarios that could serve as rationale for future studies using endotoxin or cytokine exposure to model depression. A first consideration is prenatal exposure to endotoxins or cytokines, which may increase susceptibility of animals to develop depressive-like behavior in adulthood. For example, recent evidence showed that LPS exposure during a critical developmental window leads to a profound and permanent loss of dopamine neurons in brain and increased production of TNF-α (Carvey et al., 2003). Increased circulating levels of pro-inflammatory cytokines have been reported in depression (Zorrilla et al., 2001), though this has not been always consistent, and reductions in dopamine may give rise to anhedonia. In a separate study, maternal endotoxemia increased the incidence of obesity, insulin resistance, and serum levels of leptin in adult male offspring (Nilsson et al., 2001). This may be an important outcome for animal models since obesity in humans has been strongly associated with depression (Onyike et al., 2003).

A second consideration is exposure to endotoxins or cytokines postnatally during early brain development, which may increase susceptibility of animals to

develop depressive-like behavior in adulthood. For example, repeated injections of IL-1β or LPS in the newborn rat resulted in increased adrenal weight and decreased thymus weight (Bumiller et al., 1999). Also, endotoxin exposure to rats during early development increased HPA responsiveness to stress, suggesting that exposure to LPS in early life may predispose these same animals to stress-related pathology in adulthood (Shanks et al., 1995). Also, maternal deprivation (routinely used as a model of early life stress) has been shown to modify the response of the HPA axis induced by IL-1β in an age-dependent fashion (Kent et al., 1997). These neuroendocrine and neuroimmune alterations may alter basic reward behavior in adult animals, though this has not yet been tested.

A third, and especially intriguing, consideration is endotoxin or cytokine exposure in animals exposed to stressors or cytokines. Anisman and Merali have previously hypothesized that a history of stressful experiences or cytokine activation can augment the response to later challenges and possibly induce the onset of depression (Anisman and Merali, 2003; Anisman et al., 2003). Importantly, these authors have shown sensitization effects (at several levels) induced by endotoxin and cytokine exposure (Hayley et al., 2001, 2002). This finding has been corroborated by other groups, who have shown that prior stress exposure sensitizes LPS-induced cytokine effects (Johnson et al., 2003). Similarly, a single exposure to IL-1 induced long-lasting HPA sensitization responses, and these are associated with prolonged activation of CRH and CRH-R1 mRNA expression in the paraventricular nucleus (Schmidt et al., 2003).

A fourth consideration is endotoxin or cytokine exposure in animals exhibiting a vulnerable phenotype. For example, one could test the effects of endotoxin or cytokine exposure in rats predicted to be hyper-reactive to stress or susceptible to experimental inflammatory/autoimmune diseases (Wei et al., 2003). Similarly, it would be of interest to investigate endotoxin or cytokine exposure in animals with chronic inflammatory disease. For example, in a model of adjuvant-induced arthritis (AA), LPS-induced increases in plasma IL-1β and IL-6 were markedly increased in AA rats compared to control rats (Grinevich et al., 2002). Finally, it may be useful to determine the effects of endotoxin or cytokine exposure in animals exhibiting a phenotype of heightened anxiety- (e.g. Wistar Kyoto rats) (Pare, 2000; De La Garza and Liu, 2002) or depressive-like behavior (e.g. High DPAT Sensitive rats) (Overstreet et al., 2003).

7. Summary and conclusions

Major depressive disorder is an extraordinarily complex disease that involves perturbations to brain neurochemistry, and neuroendocrine and neuroimmune systems, and also includes changes at the level of second messenger systems and transcription elements (Nestler et al., 2002). In animals, exposure to cytokines or endotoxins induces a 'sickness behavior' syndrome that mimics several components of MDD in humans. The current review set forth evidence implicating endotoxin- or cytokine-induced sickness behavior as a manipulation that induces depression-like behaviors, with an emphasis on reduced consumption of highly palatable substances as a defining feature. While it is clearly established that endotoxin or cytokine exposure induces a profound disruption of basic reward behavior, there is some question whether the anhedonia effects have relevance to the bigger picture of MDD. A number of recommendations are set forth for future studies. Overall, looking beyond studies involving healthy, adult animals, alternative approaches may prove more useful for determining the extent to which endotoxin or cytokine exposure may serve as an animal model of depression.

Acknowledgements

The author gratefully acknowledges Dr Gregory M. Asnis (Albert Einstein College of Medicine, Montefiore Medical Center) for insightful scientific conversations on this topic. Support for RD provided by National Institute on Drug Abuse (DA 15126-01).

References

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders, fourth ed. TR, Washington, DC.

Andriamampandry, C., Muller, C., Schmidt-Mutter, C., Gobaille, S., Spedding, M., Aunis, D., Maitre, M.., 2002. Mss4 gene is up-regulated in rat brain after chronic treatment with antidepressant and down-regulated when rats are anhedonic. Mol. Pharmacol. 62, 332–338.

Anisman, H., Merali, Z., 2003. Cytokines, stress and depressive illness: brain–immune interactions. Ann. Med. 35, 2–11.

Anisman, H., Kokkinidis, L., Merali, Z., 2002. Further evidence for the depressive effects of cytokines: anhedonia and neurochemical changes. Brain Behav. Immun. 16, 544–556.

Anisman, H., Merali, Z., Hayley, S., 2003. Sensitization associated with stressors and cytokine treatments. Brain Behav. Immun. 17, 86–93.

Arnold, J.M., Roberts, D.C., 1997. A critique of fixed and progressive ratio schedules used to examine the neural substrates of drug reinforcement. Pharmacol. Biochem. Behav. 57, 441–447.

Asnis, G.M., De La Garza II, R., 2005. Interferon–induced depression: Strategies in treatment. Progr. Neuropsychopharmacol. Biol. Psych. (in press).

Asnis, G.M., De La Garza II, R., Kohn, S.R., Reinus, J.F., Henderson, M., Shah, J., 2003. IFN-α-induced depression: a role for NSAIDs. Psychopharmacol. Bull. 37, 29–50.

Auriacombe, M., Reneric, J.P., Le Moal, M., 1997. Animal models of anhedonia. Psychopharmacology 134, 337–338.

Barr, A.M., Phillips, A.G., 1999. Withdrawal following repeated exposure to d-amphetamine decreases responding for a sucrose solution as measured by a progressive ratio schedule of reinforcement. Psychopharmacology 141, 99–106.

Barr, A.M., Song, C., Sawada, K., Young, C.E., Honer, W.G., Phillips, A.G., 2003. Tolerance to the anhedonic effects of lipopolysaccharide is associated with changes in syntaxin immunoreactivity in the nucleus accumbens. Int. J. Neuropsychopharmacol. 6, 23–34.

Bernstein, I.L., Treneer, C.M., Goehler, L.E., Murowchick, E., 1985. Tumor growth in rats: conditioned suppression of food intake and preference. Behav. Neurosci. 99, 818–830.

Bonaccorso, S., Marino, V., Puzella, A., Pasquini, M., Biondi, M., Artini, M., Almerighi, C., Verkerk, R., Meltzer, H., Maes, M., 2002. Increased depressive ratings in patients with hepatitis C receiving interferon-alpha-based immunotherapy are related to interferon-alpha-induced changes in the serotonergic system. J. Clin. Psychopharmacol. 22, 86–90.

Borowski, T., Kokkinidis, L., Merali, Z., Anisman, H., 1998. Lipopolysaccharide, central in vivo biogenic amine variations, and anhedonia. Neuroreport 9, 3797–3802.

Bumiller, A., Gotz, F., Rohde, W., Dorner, G., 1999. Effects of repeated injections of interleukin 1beta or lipopolysaccharide on the HPA axis in the newborn rat. Cytokine 11, 225–230.

Capuron, L., Gumnick, J.F., Musselman, D.L., Lawson, D.H., Reemsnyder, A., Nemeroff, C.B., Miller, A.H., 2002. Neurobehavioral effects of IFN-alpha in cancer patients: phenomenology and paroxetine responsiveness of symptom dimensions. Neuropsychopharmacology 26, 643–652.

Carvey, P.M., Chang, Q., Lipton, J.W., Ling, Z., 2003. Prenatal exposure to the bacteriotoxin lipopolysaccharide leads to long-term losses of dopamine neurons in offspring: a potential, new model of Parkinson's disease. Front. Biosci. 8, s826–s837.

Castanon, N., Bluthe, R.M., Dantzer, R., 2001. Chronic treatment with the atypical antidepressant tianeptine attenuates sickness behavior induced by peripheral but not central lipopolysaccharide and interleukin-1beta in the rat. Psychopharmacology 154, 50–60.

Castanon, N., Leonard, B.E., Neveu, P.J., Yirmiya, R., 2002. Effects of antidepressants on cytokine production and actions. Brain Behav. Immun. 16, 569–574.

Castanon, N., Medina, C., Mormede, C., Dantzer, R., 2004. Chronic administration of tianeptine balances lipopolysaccharide-induced expression of cytokines in the spleen and hypothalamus of rats. Psychoneuroendocrinology 29, 778–790.

Collier, G., Johnson, D.F., 2000. Sucrose intake as a function of its cost and the cost of chow. Physiol. Behav. 70, 477–487.

De La Garza II, R., Liu, X., 2002. Wistar–Kyoto rats exhibit reduced intravenous nicotine self-administration behavior: implications for an animal model of depression. Drug Alcohol Depend. 66, S42.

De La Garza II, R., Fabrizio, K.R., Radoi, G.-E., Vlad, T., Asnis, G.M., 2004. The non-steroidal anti-inflammatory drug diclofenac sodium attenuates lipopolysaccharide-induced alterations to reward behavior and corticosterone release. Behav. Brain Res. 149, 77–85.

De La Garza, II, R., Fabrizio, K.R., Pedrosa, E., Asnis, G.M., 2005a. Acute diclofenac treatment attenuates lipopolysaccharide-induced alterations to reward behavior, and HPA axis activation. Psychopharmacol. (in press).

De La Garza II, R., Asnis, G.M., Pedrosa, E., Stearns, C.M., Migdal, A.L., Reinus, J.F., Paladugu, R., Vemulapalli, S., 2005b. Recombinant human interferon-a does not alter reward behavior, or neuroimmune and neuroendocrine activation in rats. Progr. Neuropsychopharmacol. Biol. Psych. (in press).

Dunn, A.J., Swiergiel, A.H., 2000. The role of cyclooxygenases in endotoxin- and interleukin-1-induced hypophagia. Brain Behav. Immun. 14, 141–152.

Dunn, A.J., Swiergiel, A.H., 2001. The reductions in sweetened milk intake induced by interleukin-1 and endotoxin are not prevented by chronic antidepressant treatment. Neuroimmunomodulation 9, 163–169.

Fawcett, J., Clark, D.C., Scheftner, W.A., Gibbons, R.D., 1983a. Assessing anhedonia in psychiatric patients. Arch. Gen. Psychiatry 40, 79–84.

Fawcett, J., Clark, D.C., Scheftner, W.A., Hedeker, D., 1983b. Differences between anhedonic and normally hedonic depressive states. Am. J. Psychiatry 140, 1027–1030.

Fishkin, R.J., Winslow, J.T., 1997. Endotoxin-induced reduction of social investigation by mice: interaction with amphetamine and anti-inflammatory drugs. Psychopharmacology 132, 335–341.

Grinevich, V., Ma, X.M., Herman, J.P., Jezova, D., Akmayev, I., Aguilera, G., 2001. Effect of repeated lipopolysaccharide administration on tissue cytokine expression and hypothalamic–pituitary–adrenal axis activity in rats. J. Neuroendocrinol. 13, 711–723.

Grinevich, V., Harbuz, M., Ma, X.M., Jessop, D., Tilders, F.J., Lightman, S.L., Aguilera, G., 2002. Hypothalamic pituitary adrenal axis and immune responses to endotoxin in rats with chronic adjuvant-induced arthritis. Exp. Neurol. 178, 112–123.

Harris, R.B., Zhou, J., Youngblood, B.D., Smagin, G.N., Ryan, D.H., 1997. Failure to change exploration or saccharin preference in rats exposed to chronic mild stress. Physiol. Behav. 63, 91–100.

Hart, B.L., 1988. Biological basis of the behavior of sick animals. Neurosci. Biobehav. Rev. 12, 123–137.

Hatcher, J.P., Bell, D.J., Reed, T.J., Hagan, J.J., 1997. Chronic mild stress-induced reductions in saccharin intake depend upon feeding status. J. Psychopharmacol. 11, 331–338.

Hayley, S., Lacosta, S., Merali, Z., van Rooijen, N., Anisman, H., 2001. Central monoamine and plasma corticosterone changes induced by a bacterial endotoxin: sensitization and cross-sensitization effects. Eur. J. Neurosci. 13, 1155–1165.

Hayley, S., Wall, P., Anisman, H., 2002. Sensitization to the neuroendocrine, central monoamine and behavioural effects of murine tumor necrosis factor-alpha: peripheral and central mechanisms. Eur. J. Neurosci. 15, 1061–1076.

Hodos, W., 1961. Progressive ratio as a measure of reward strength. Science 134, 943–944.

Hodos, W., Kalman, G., 1963. Effects of increment size and reinforcer volume on progressive ratio performance. J. Exp. Anal. Behav. 6, 387–392.

Holsboer, F., 2000. The corticosteroid receptor hypothesis of depression. Neuropsychopharmacology 23, 477–501.

Johnson, J.D., O'Connor, K.A., Hansen, M.K., Watkins, L.R., Maier, S.F., 2003. Effects of prior stress on LPS-induced cytokine and sickness responses. Am. J. Physiol. Regul. Integr. Comp. Physiol. 284, R422–R432.

Katz, R.J., 1982. Animal model of depression: pharmacological sensitivity of a hedonic deficit. Pharmacol. Biochem. Behav. 16, 965–968.

Kent, S., Bluthe, R.M., Kelley, K.W., Dantzer, R., 1992. Sickness behavior as a new target for drug development. Trends Pharmacol. Sci. 13, 24–28.

Kent, S., Tom, C., Levine, S., 1997. Effect of interleukin-1beta on pituitary–adrenal responses and body weight in neonatal rats: interaction with maternal deprivation. Stress 1, 213–230.

Kim, H., Whang, W.W., Kim, H.T., Pyun, K.H., Cho, S.Y., Hahm, D.H., Lee, H.J., Shim, I., 2003. Expression of neuropeptide Y and cholecystokinin in the rat brain by chronic mild stress. Brain Res. 983, 201–208.

Konkle, A.T., Baker, S.L., Kentner, A.C., Barbagallo, L.S., Merali, Z., Bielajew, C., 2003. Evaluation of the effects of chronic mild stressors on hedonic and physiological responses: sex and strain compared. Brain Res. 992, 227–238.

Konsman, J.P., Parnet, P., Dantzer, R., 2002. Cytokine-induced sickness behaviour: mechanisms and implications. Trends Neurosci. 25, 154–159.

Krause, I., Valesini, G., Scrivo, R., Shoenfeld, Y., 2003. Autoimmune aspects of cytokine and anticytokine therapies. Am. J. Med. 115, 390–397.

Kubera, M., Lin, A.H., Kenis, G., Bosmans, E., van Bockstaele, D., Maes, M., 2001. Anti-inflammatory effects of antidepressants through suppression of the interferon-gamma/interleukin-10 production ratio. J. Clin. Psychopharmacol. 21, 199–206.

Langhans, W., Savoldelli, D., Weingarten, S., 1993. Comparison of the feeding responses to bacterial lipopolysaccharide and interleukin-1 beta. Physiol. Behav. 53, 643–649.

Lanquillon, S., Krieg, J.C., Bening-Abu-Shach, U., Vedder, H., 2000. Cytokine production and treatment response in major depressive disorder. Neuropsychopharmacology 22, 370–379.

Larson, S.J., Dunn, A.J., 2001. Behavioral effects of cytokines. Brain Behav. Immun. 15, 371–387.

Larson, S.J., Romanoff, R.L., Dunn, A.J., Glowa, J.R., 2002. Effects of interleukin-1beta on food-maintained behavior in the mouse. Brain Behav. Immun. 16, 398–410.

Leonard, B.E., 2001. The immune system, depression and the action of antidepressants. Prog. Neuropsychopharmacol. Biol. Psychiatry 25, 767–780.

Leonard, B.E., Song, C., 2002. Changes in the immune system in rodent models of depression. Int. J. Neuropsychopharmacol. 5, 345–356.

Le Pen, G., Gaudet, L., Mortas, P., Mory, R., Moreau, J.L., 2002. Deficits in reward sensitivity in a neurodevelopmental rat model of schizophrenia. Psychopharmacology 161, 434–441.

Licinio, J., Wong, M.L., 1999. The role of inflammatory mediators in the biology of major depression: central nervous system cytokines modulate the biological substrate of depressive symptoms, regulate stress-responsive systems, and contribute to neurotoxicity and neuroprotection. Mol. Psychiatry 4, 317–327.

Linthorst, A.C., Flachskamm, C., Holsboer, F., Reul, J.M., 1994. Local administration of recombinant human interleukin-1 beta in the rat hippocampus increases serotonergic neurotransmission, hypothalamic–pituitary–adrenocortical axis activity, and body temperature. Endocrinology 135, 520–532.

Maes, M., 1999. Major depression and activation of the inflammatory response system. Adv. Exp. Med. Biol. 461, 25–46.

McCarthy, D.O., Kluger, M.J., Vander, A.J., 1984. The role of fever in appetite suppression after endotoxin administration. Am. J. Clin. Nutr. 40, 310–316.

McHugh, K.J., Weingarten, H.P., Keenan, C., Wallace, J.L., Collins, S.M., 1993. On the suppression of food intake in experimental models of colitis in the rat. Am. J. Physiol. 264, R871–R876.

Merali, Z., Levac, C., Anisman, H., 2003a. Validation of a simple, ethologically relevant paradigm for assessing anxiety in mice. Biol. Psychiatry 54, 552–565.

Merali, Z., Brennan, K., Brau, P., Anisman, H., 2003b. Dissociating anorexia and anhedonia elicited by interleukin-1beta: antidepressant and gender effects on responding for 'free chow' and 'earned' sucrose intake. Psychopharmacology 165, 413–418.

Meyer, S.E., Chrousos, G.P., Gold, P.W., 2001. Major depression and the stress system: a life span perspective. Dev. Psychopathol. 13, 565–580.

Monleon, S., D'Aquila, P., Parra, A., Simon, V.M., Brain, P.F., Willner, P., 1995. Attenuation of sucrose consumption in mice by chronic mild stress and its restoration by imipramine. Psychopharmacology 117, 453–457.

Muscat, R., Sampson, D., Willner, P., 1990. Dopaminergic mechanism of imipramine action in an animal model of depression. Biol. Psychiatry 28, 223–230.

Musselman, D.L., Lawson, D.H., Gumnick, J.F., Manatunga, A.K., Penna, S., Goodkin, R.S., Greiner, K., Nemeroff, C.B., Miller, A.H., 2001. Paroxetine for the prevention of depression induced by high-dose interferon alfa. N. Engl. J. Med. 344, 961–966.

Nagano, I., Takao, T., Nanamiya, W., Takemura, T., Nishiyama, M., Asaba, K., Makino, S., De Souza, E.B., Hashimoto, K., 1999. Differential effects of one and repeated endotoxin treatment on pituitary–adrenocortical hormones in the mouse: role of interleukin-1 and tumor necrosis factor-alpha. Neuroimmunomodulation 6, 284–292.

Nava, F., Calapai, G., Facciola, G., Cuzzocrea, S., Marciano, M.C., De Sarro, A., Caputi, A.P., 1997. Effects of interleukin-10 on water intake, locomotory activity, and rectal temperature in rat treated with endotoxin. Int. J. Immunopharmacol. 19, 31–38.

Nemeroff, C.B., Widerlov, E., Bissette, G., Walleus, H., Karlsson, I., Eklund, K., Kilts, C.D., Loosen, P.T., Vale, W., 1984. Elevated concentrations of CSF corticotropin-releasing factor-like immunoreactivity in depressed patients. Science 226, 1342–1344.

Nemeroff, C.B., Krishnan, K.R., Reed, D., Leder, R., Beam, C., Dunnick, N.R., 1992. Adrenal gland enlargement in major depression. A computed tomographic study. Arch. Gen. Psychiatry 49, 384–387.

Nestler, E.J., Barrot, M., DiLeone, R.J., Eisch, A.J., Gold, S.J., Monteggia, L.M., 2002. Neurobiology of depression. Neuron 34, 13–25.

Nilsson, C., Larsson, B.M., Jennische, E., Eriksson, E., Bjorntorp, P., York, D.A., Holmang, A., 2001. Maternal endotoxemia results in obesity and insulin resistance in adult male offspring. Endocrinology 142, 2622–2630.

Onyike, C.U., Crum, R.M., Lee, H.B., Lyketsos, C.G., Eaton, W.W., 2003. Is obesity associated with major depression? Results from the third national health and nutrition examination survey. Am. J. Epidemiol. 158, 1139–1147.

Overstreet, D.H., Commissaris, R.C., De La Garza, R., File, S.E., Knapp, D.J., Seiden, L.S., 2003. Involvement of 5-HT1A receptors in animal tests of anxiety and depression: evidence from genetic models. Stress 6, 101–110.

Pare, W.P., 2000. Investigatory behavior of a novel conspecific by Wistar Kyoto, Wistar and Sprague–Dawley rats. Brain Res. Bull. 53, 759–765.

Pariante, C.M., Miller, A.H., 2001. Glucocorticoid receptors in major depression: relevance to pathophysiology and treatment. Biol. Psychiatry 49, 391–404.

Peterson, C.A., Knudson, R.M., 1983. Anhedonia: a construct validation approach. J. Pers. Assess. 47, 539–551.

Pijlman, F.T., Wolterink, G., Van Ree, J.M., 2003. Physical and emotional stress have differential effects on preference for saccharine and open field behaviour in rats. Behav. Brain Res. 139, 131–138.

Plata-Salaman, C.R., 1996. Anorexia during acute and chronic disease. Nutrition 12, 69–78.

Plata-Salaman, C.R., Oomura, Y., Kai, Y., 1988. Tumor necrosis factor and interleukin-1 beta: suppression of food intake by direct action in the central nervous system. Brain Res. 448, 106–114.

Primeaux, S.D., Wilson, M.A., Wilson, S.P., Guth, A.N., Lelutiu, N.B., Holmes, P.V., 2003. Herpes virus-mediated preproenkephalin gene transfer in the ventral striatum mimics behavioral changes produced by olfactory bulbectomy in rats. Brain Res. 988, 43–55.

Raison, C.L., Miller, A.H., 2001. The neuroimmunology of stress and depression. Semin. Clin. Neuropsychiatry 6, 277–294.

Reilly, S., 1999. Reinforcement value of gustatory stimuli determined by progressive ratio performance. Pharmacol. Biochem. Behav. 63, 301–311.

Salamone, J.D., Correa, M., Mingote, S., Weber, S.M., 2003. Nucleus accumbens dopamine and the regulation of effort in food-seeking behavior: implications for studies of natural motivation, psychiatry, and drug abuse. J. Pharmacol. Exp. Ther. 305, 1–8.

Sammut, S., Bethus, I., Goodall, G., Muscat, R., 2002. Antidepressant reversal of interferon-alpha-induced anhedonia. Physiol. Behav. 75, 765–772.

Sarkisova, K.Y., Midzianovskaia, I.S., Kulikov, M.A., 2003. Depressive-like behavioral alterations and c-fos expression in the dopaminergic brain regions in WAG/Rij rats with genetic absence epilepsy. Behav. Brain Res. 144, 211–226.

Schmidt, E.D., Aguilera, G., Binnekade, R., Tilders, F.J., 2003. Single administration of interleukin-1 increased corticotropin releasing hormone and corticotropin releasing hormone-receptor mRNA in the hypothalamic paraventricular nucleus which paralleled long-lasting (weeks) sensitization to emotional stressors. Neuroscience 116, 275–283.

Sclafani, A., Ackroff, K., 2003. Reinforcement value of sucrose measured by progressive ratio operant licking in the rat. Physiol. Behav. 79, 663–670.

Shanks, N., Larocque, S., Meaney, M.J., 1995. Neonatal endotoxin exposure alters the development of the hypothalamic–pituitary–adrenal axis: early illness and later responsivity to stress. J. Neurosci. 15, 376–384.

Shen, Y., Connor, T.J., Nolan, Y., Kelly, J.P., Leonard, B.E., 1999. Differential effect of chronic antidepressant treatments on lipopolysaccharide-induced depressive-like behavioural symptoms in the rat. Life Sci. 65, 1773–1786.

Sobrian, S.K., Marr, L., Ressman, K., 2003. Prenatal cocaine and/or nicotine exposure produces depression and anxiety in aging rats. Prog. Neuropsychopharmacol. Biol. Psychiatry 27, 501–518.

Swiergiel, A.H., Smagin, G.N., Dunn, A.J., 1997a. Influenza virus infection of mice induces anorexia: comparison with endotoxin and interleukin-1 and the effects of indomethacin. Pharmacol. Biochem. Behav. 57, 389–396.

Swiergiel, A.H., Smagin, G.N., Johnson, L.J., Dunn, A.J., 1997b. The role of cytokines in the behavioral responses to endotoxin and influenza virus infection in mice: effects of acute and chronic administration of the interleukin-1-receptor antagonist (IL-1ra). Brain Res. 776, 96–104.

Takemura, T., Makino, S., Takao, T., Asaba, K., Suemaru, S., Hashimoto, K., 1997. Hypothalamic–pituitary–adrenocortical responses to single vs. repeated endotoxin lipopolysaccharide administration in the rat. Brain Res. 767, 181–191.

van der Meer, M.J., Sweep, C.G., Pesman, G.J., Tilders, F.J., Hermus, A.R., 1996. Chronic stimulation of the hypothalamus–pituitary–adrenal axis in rats by interleukin 1beta: central and peripheral mechanisms. Cytokine 8, 910–919.

Von Frijtag, J.C., Van den Bos, R., Spruijt, B.M., 2002. Imipramine restores the long-term impairment of appetitive behavior in socially stressed rats. Psychopharmacology 162, 232–238.

Wei, R., Listwak, S.J., Sternberg, E.M., 2003. Lewis hypothalamic cells constitutively and upon stimulation express higher levels of mRNA for pro-inflammatory cytokines and related molecules: comparison with inflammatory resistant Fischer rat hypothalamic cells. J. Neuroimmunol. 135, 10–28.

Willner, P., 1997a. Validity, reliability and utility of the chronic mild stress model of depression: a 10-year review and evaluation. Psychopharmacology 134, 319–329.

Willner, P., 1997b. Validity, reliability and utility of the chronic mild stress model of depression: a 10-year review and evaluation. Psychopharmacology 134, 319–329.

Willner, P., D'Aquila, P., Coventry, T.L., Brain, P., 1995. Loss of social status: preliminary evaluation of a novel animal model of depression. J. Psychopharmacol. 9, 207–213.

Yirmiya, R., 1996. Endotoxin produces a depressive-like episode in rats. Brain Res. 711, 163–174.

Yirmiya, R., Weidenfeld, J., Pollak, Y., Morag, M., Morag, A., Avitsur, R., Barak, O., Reichenberg, A., Cohen, E., Shavit, Y., Ovadia, H., 1999. Cytokines, "depression due to a general medical condition," and antidepressant drugs. Adv. Exp. Med. Biol. 461, 283–316.

Yirmiya, R., Pollak, Y., Barak, O., Avitsur, R., Ovadia, H., Bette, M., Weihe, E., Weidenfeld, J., 2001. Effects of antidepressant drugs on the behavioral and physiological responses to lipopolysaccharide (LPS) in rodents. Neuropsychopharmacology 24, 531–544.

Zdilar, D., Franco-Bronson, K., Buchler, N., Locala, J.A., Younossi, Z.M., 2000. Hepatits C, interferon alpha, and depression. Hepatology 31, 1207–1211.

Zorrilla, E.P., Luborsky, L., McKay, J.R., Rosenthal, R., Houldin, A., Tax, A., McCorkle, R., Seligman, D.A., Schmidt, K., 2001. The relationship of depression and stressors to immunological assays: a meta-analytic review. Brain Behav. Immun. 15, 199–226.

Zuckerman, S.H., Evans, G.F., Butler, L.D., 1991. Endotoxin tolerance: independent regulation of interleukin-1 and tumor necrosis factor expression. Infect. Immun. 59, 2774–2780.