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Recombinant human interferon-α does not alter reward behavior, or neuroimmune and neuroendocrine activation in rats

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Abstract

Recombinant human interferon-α (IFN-α) induces depression, and neuroendocrine and neuroimmune activation, in a significant number of patients undergoing treatment for viral illnesses (e.g., hepatitis C), yet these effects have not been consistently reproduced in rodents. As such, we sought to determine the effects of acute or chronic IFN-α treatment on basic reward and immobility in the forced swim test (FST), neuroendocrine and neuroimmune activation, and monoamine turnover in brain. In the first experiment, male Wistar rats ($N=7$/group) treated with human recombinant IFN-α (100,000 IU/kg, i.p.), as compared to saline, did not exhibit alterations to rate of sucrose pellet self-administration or total reinforcers obtained, corticosterone release, plasma IL-6 release, IL-1β or IL-6 mRNA expression in hippocampus, or monoamine turnover in prefrontal cortex, striatum, nucleus accumbens, or amygdala. However, acute IFN-α decreased body weight and produced a trend toward reduced food consumption in the home cage 2 h after injection. In the second experiment, Wistar rats ($N=4$/group) were subjected to a chronic treatment regimen of saline or IFN-α (100,000 IU/kg, i.p.) once daily for 14 consecutive days. The data reveal that animals exposed to chronic IFN-α exhibited similar amounts of time immobile and similar latencies to primary immobility in the FST as compared to saline-treated controls. Chronic IFN-α did not induce corticosterone release, plasma TNF-α, or IL-6 release. Tissue monoamine analysis revealed that chronic IFN-α reduced DA levels in prefrontal cortex, and decreased 5-HT levels and increased 5-HT turnover in amygdala. In the third experiment, Wistar rats ($N=4$/group) were exposed to either acute or chronic pegylated IFN-α (pegIFN-α: 3.25, 10 or 75 mg/kg, i.p.) at one of several time points from 1 h to 23 days. The data reveal that neither acute nor chronic pegIFN-α induced corticosterone release. Overall, the current report demonstrates that neither acute nor chronic IFN-α induced depressive-like behavior and neither IFN-α nor peg-IFN-α was capable of inducing neuroendocrine or neuroimmune activation. Despite the neurochemical alterations observed in the chronic treatment regimen, the data indicate that recombinant human IFN-α does not produce a robust model of depressive-like behavior in rodents.

Keywords: Anhedonia; Corticosterone; Depression; IL-1β; IL-6; Interferon-α

Abbreviations: CNS, central nervous system; DA, dopamine; DOPAC, 3,4 dihydroxyphenylacetic acid; FST, forced swim test; 5-HIAA, 5-hydroxyindole acetic acid; 5-HT, 5-hydroxytryptophan (serotonin); HPA axis, hypothalamic–pituitary–adrenal axis; HPLC, high-performance liquid chromatography; IFN, interferon; LPS, lipopolysaccharide; NE, norepineherine; PCR, polymerase chain reaction; Peg-IFN, pegylated interferon.

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1. Introduction

In humans, exposure to endotoxins or pro-inflammatory cytokines activates neuroendocrine and neuroimmune systems and causes a number of neuropsychological disturbances, including anhedonia, anorexia, fever, fatigue, increased pain, sleep disturbances, and confusion (Licinio et al., 1998; Konsman et al., 2002). Collectively, these alterations have been termed "flu-like syndrome." Striking similarities between flu-like syndrome and major depressive disorder have been noted and are predicted to arise from hypersecretion of pro-inflammatory cytokines (Anisman and Merali, 2002; Irwin, 2002; Licinio and Wong, 1999; Maes, 1999), and/or chronic activation of the hypothalamic–pituitary–adrenal (HPA) axis (Holsboer, 2000; Nemeroff et al., 1984; Pariante and Miller, 2001). Interferon-α (IFN-α) is a pro-inflammatory cytokine commonly utilized in clinical practice because of its antiviral and immunomodulatory properties (Poynard et al., 2003). Despite its beneficial properties, IFN-α treatment is hampered by a deleterious side effect profile, including neuropsychiatric and neurotoxic side effects, such as depression, anxiety, insomnia, lethargy, confusion, and psychosis (Asnis et al., 2003).

In rodents, endotoxins (e.g., lipopolysaccharide: LPS) and pro-inflammatory cytokines (e.g., interleukin-1β: IL-1β) activate the HPA axis and stimulate the synthesis and release of pro-inflammatory cytokines. Moreover, LPS and IL-1β induce a "sickness behavior" syndrome that has been equated to flu-like syndrome in humans (Hart, 1988; Kelley et al., 2003; Konsman et al., 2002; Larson and Dunn, 2001). Sickness behaviors include anhedonia, increased sleep, and decreased food intake, body weight, locomotor activity, social interaction, sexual behavior, and grooming. Since IFN-α is a pro-inflammatory cytokine, acute or chronic exposure in rodents may be predicted to ellicit neuroendocrine and neuroimmune activation, including behavioral alterations indicative of depression. While there are reports of behavioral (Bethus et al., 2003; Makino et al., 2000; Sammut et al., 2001), neuroendocrine (Menzies et al., 1996), and neurochemical (Kumai et al., 2000; Shuto et al., 1997) alterations following acute and chronic IFN-α exposure in rodents, the results are remarkably inconsistent and have seldom been replicated (Dunn, 1992, 2000). As such, the question remains whether recombinant human IFN-α can be used in developing a model of depressive-like behavior in rodents. To address this issue, we utilized a multidisciplinary approach to assess the effects of acute or chronic IFN-α on behavior, neuroendocrine or neuroimmune activation, or brain neurochemistry.

2. Methods

2.1. Experimental design

The first experiment (Experiment 1) was designed to test whether acute IFN-α reduces basic reward behavior ("anhedonia": used as a measure of depressive-like behavior), or alters neuroimmune, neuroendocrine or neurochemical function. IFN-α was predicted to alter basic reward behavior on the basis of reports demonstrating that acute IFN-α treatment reduced consumption of a sucrose solution (Sammut et al., 2001, 2002). In the current experiment, male Wistar rats (250–275 g, 8 weeks of age, Charles-River, NC, $N=7$/group) were trained to press a lever for a 45 mg sucrose pellet reward (Noyes, New Brunswick, NJ) in a typical two-lever operant chamber (Med-Associates, St. Albans, VT). We have previously measured basic reward behavior using sucrose pellet self-administration and have shown that it is readily disrupted by acute LPS exposure (De La Garza et al., 2004, 2005). Animals were tested once daily for 2 weeks during which time a steady baseline was achieved. Each session lasted for a maximum of 30 min or were terminated upon the acquisition of 30 reinforcers (utilized as a means of avoiding the potential confound of satiation). For each animal, RATE (# Reinforcers/time (min)) and total reinforcers obtained (# Reinforcers) were recorded. Baseline measures reflect the performance of rats during the last regular training session (though injections were not given at that time). The effects of acute LPS (20 μg/kg, i.p.) are shown as a positive control and derived from a study where the training, testing and injection timing were identical to that used in the current study (De La Garza et al., 2005); however, these data are not included in the statistical analysis. On the test day, after the initial 2-week training period, animals were exposed to an acute injection of saline (1 ml/kg, s.c.) 30 min prior to a second injection of either saline (1 ml/kg, i.p.) or human recombinant IFN-α (100,000 IU/kg, i.p.: Biosource International, Camarillo, CA; Cat.# PHC 4814). IFN-α was diluted in phosphate-buffered saline (PBS) containing 0.1% bovine serum albumin (BSA) from a stock concentration of 3.8×10^8 units/mg, which was shipped as 5×10^6 units in 100 μl. A dual injection regimen (with a saline injection preceding the test injection) was used as a "control injection" since future studies were projected to include pre-treatment with antidepressants or non-steroidal anti-inflammatory drugs. The dose and type of IFN-α were based on previously published behavioral reports (Bethus et al., 2003; Sammut et al., 2002). All rats were tested for sucrose pellet self-administration behavior 2 h after the second injection. Upon completion of the behavioral test (2.5 h after the second injection), animals were sacrificed by rapid decapitation and trunk blood was collected. The time point for behavioral testing and sacrifice was based on our own published reports showing robust behavioral, neuroendocrine, and neuroimmune alterations after LPS exposure at this time point (De La Garza et al., 2004, 2005). Additionally, the 2-h time point was based on a report that used human recombinant IFN-α to assess alterations to sucrose pellet consumption in mice (Crnic and Segall, 1992).