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Tyrosine metabolism during interferon-alpha administration: Association with fatigue and CSF dopamine concentrations

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ABSTRACT

Chronic exposure to interferon (IFN)-alpha, an innate immune cytokine, produces high rates of behavioral disturbances, including depression and fatigue. These effects may be mediated by the actions of IFN-alpha on dopamine (DA) metabolism in the basal ganglia. Diminished conversion of phenylalanine (Phen) to tyrosine (Tyr), the primary amino acid precursor of DA, has been associated with inflammation, and may reflect decreased activity of the enzyme phenylalanine-hydroxylase (PAH). This study investigated the peripheral Phen/Tyr ratio in relation to cerebrospinal fluid (CSF) concentrations of DA and its metabolites in subjects treated with IFN-alpha plus ribavirin for hepatitis C and controls awaiting IFN-alpha therapy. Plasma Phen/Tyr ratios were significantly increased in IFN-alpha-treated subjects ($n = 25$) compared to controls ($n = 9$), and were negatively correlated with CSF DA ($r = -0.59$, df = 15, $p < 0.05$) and its metabolite, homovanillic acid ($r = -0.67$, df = 15, $p < 0.01$), and positively correlated with fatigue ($r = 0.44$, df = 23, $p < .05$) in IFN-alpha-treated patients but not controls. Given the role of tetrahydrobiopterin (BH4) in the PAH conversion of Phen to Tyr, CSF concentrations of BH4 and its inactive oxidized form, dihydrobiopterin (BH2), were examined along with CSF interleukin (IL)-6 in a subset of patients. BH2 concentrations were significantly increased in IFN-alpha-treated patients ($n = 12$) compared to controls ($n = 7$), and decreased CSF BH4 concentrations correlated with increased CSF IL-6 ($r = -0.57$, df = 12, $p < 0.05$). These results indicate that IFN-alpha is associated with decreased peripheral conversion of Phen to Tyr, which in turn is associated with reduced DA in the brain as well as fatigue. These alterations may be related to oxidation of BH4 secondary to IFN-alpha-induced activation of a CNS inflammatory response.

1. Introduction

Activation of the innate immune system has been shown to affect behavior through changes in neurocircuitry and neurotransmitter systems in the brain, mediated in part by effects of inflammatory cytokines on monoamine neurotransmission (Dantzer et al., 2008; Haroon et al., 2012; Miller et al., 2009). Recent evidence indicates that the basal ganglia and dopamine (DA) may be primary targets of inflammatory cytokines leading to cytokine-induced behavioral changes (Capuron et al., 2007, in press; Haroon et al., 2012; Liu and Hong, 2003; Theodore et al., 2006, 2008). The basal ganglia are key subcortical structures regulating motivation and motor activity (Grace, 2002), and cytokine effects on basal ganglia DA may contribute to the development of depression and fatigue, as well as psychomotor disturbances, in both medically ill and medically healthy subjects.

Numerous studies have reported elevated inflammatory cytokines in depressed individuals (Maes, 1999; Sluzewska, 1999), and patients exposed to increased inflammation during chronic illness experience significantly higher rates of depression and fatigue than the general population (Yirmiya, 2000; Yirmiya et al., 2000, 1999). Evidence that inflammatory cytokines can cause behavioral alterations exists in numerous reports of the neuropsychiatric symptoms induced by chronic administration of the inflammatory cytokine, interferon (IFN)-alpha, used to treat certain cancers and viral infections. Indeed, IFN-alpha produces an array of behavioral disturbances, many of which are consistent with decreases in basal ganglia DA function including anhedonia, fatigue, and psychomotor

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slowing (Bersano et al., 2008; Capuron et al., 2009, 2002; Majer et al., 2008; Sunami et al., 2000). Interestingly, whereas anxiety and some depressive symptoms in IFN-alpha-treated patients are alleviated by selective serotonin reuptake inhibitor (SSRI) therapy, fatigue and psychomotor retardation are less responsive to SSRIs (Capuron et al., 2002; Morrow et al., 2003; Raison et al., 2005). Of note, fatigue is also one of the primary residual symptoms in SSRI-treated medically healthy depressed patients (Nierenberg et al., 1999; Targum and Fava, 2011), who, as noted above, have been shown to exhibit evidence of increased inflammation. These findings suggest that neurotransmitter systems other than serotonin, such as DA, may be involved in these SSRI-resistant, inflammation-related symptoms, and substantiate further investigation of cytokine effects on DA in the basal ganglia.

Accordingly, recent studies in our laboratory and others have investigated the effects of inflammatory cytokines and innate immune activation on the basal ganglia and DA function. Positron emission tomography (PET) imaging in IFN-alpha-treated patients revealed increased basal ganglia glucose metabolism (consistent with Parkinson's disease) that correlated with symptoms of fatigue (Capuron et al., 2007). Moreover, functional magnetic resonance imaging (fMRI) demonstrated decreased neural activation to a hedonic reward task during IFN-alpha treatment (Capuron et al., in press). Similarly, lipopolysaccharide (LPS) and typhoid vaccination have been shown to have effects on basal ganglia activity (Brydon et al., 2008; Eisenberger et al., 2010), including decreased ventral striatal activation to a reward task (Eisenberger et al., 2010), suggesting that the effects on basal ganglia function generalize to multiple inflammatory stimuli. In regard to DAergic mechanisms of cytokine effects on the basal ganglia, PET studies have also revealed increased uptake and decreased turnover of [18F]fluorodopa (FDOPA) in the caudate and putamen of IFN-alpha-treated patients, both of which correlated with depression and fatigue scores (Capuron et al., in press). Additionally, decreased cerebrospinal fluid (CSF) concentrations of the DA metabolite, homovanillic acid (HVA), have been observed in rhesus monkeys that display anhedonic, depressive-like huddling behavior during chronic IFN-alpha administration (Felger et al., 2007). Together, these findings support the idea that alterations in DA neurotransmission in the basal ganglia during exposure to inflammatory cytokines contribute to the development of depression and fatigue.

Although cytokines may affect multiple aspects of DA neurotransmission, increased FDOPA uptake and decreased DA metabolites during IFN-alpha administration suggest that chronic exposure to inflammatory cytokines may decrease DA synthesis. One mechanism by which inflammatory cytokines may impact DA synthesis is by reducing the availability of the enzyme co-factor, tetrahydrobiopterin (BH4). BH4 is necessary for phenylalanine (Phen) hydroxylase (PAH) conversion of Phen to tyrosine (Tyr), the primary amino acid precursor of DA, as well as for the activity of Tyr hydroxylase (TH), the rate-limiting enzyme in DA synthesis. BH4 is also a co-factor for nitric oxide synthases (NOS), which convert L-arginine to NO (Cunnington and Channon, 2010). Additionally, BH4 is highly redox-sensitive and is readily oxidized to dihydrobiopterin (BH2) (Landmesser et al., 2003), which can be regenerated to BH4 by dihydrofolate reductase (Cunnington and Channon, 2010; Dumitrescu et al., 2007; Haroon et al., 2012). Although inflammation and cytokines have been shown to induce GTP-cyclohydrolase I, the enzyme necessary for BH4 synthesis, inflammation-induced increases in inducible NOS (iNOS) activity and the production of reactive oxygen and reactive nitrogen species (ROS and RNS) can ultimately lead to decreased BH4 availability (Kitagami et al., 2003; Neurauter et al., 2008b). When BH4 is readily usurped and oxidized to BH2, less BH4 is available for the conversion of Phen to Tyr and Tyr to DA. The Phen/Tyr ratio, as indication of PAH activity and Tyr metabolism, as well as BH4 and BH2 concentrations, can be assessed in blood or CSF, and serve as indirect measures of changes in DA synthesis (Capuron et al., 2011; Hashimoto et al., 2004; Neurauter et al., 2008b).

In the present study, Tyr metabolism in the periphery (the plasma Phen/Tyr ratio) was examined to determine whether it predicted reduced DA and HVA concentrations in the CSF and the development of neuropsychiatric disturbances in IFN-alpha-treated patients. To identify whether changes in Tyr metabolism and CSF DA/HVA concentrations were related to inflammation-mediated increases in the oxidation of BH4, BH4 (and its inactive form, BH2) was also examined in CSF from a subset of subjects and correlated with CSF IL-6. Increases in circulating IL-6 have been demonstrated to predict development of IFN-alpha-induced depression (Prather et al., 2009; Wichers et al., 2007, 2006), and we have previously reported IL-6 to be the inflammatory cytokine with the greatest increase in the CSF of IFN-alpha-treated subjects (Raison et al., 2009). Therefore, IL-6 was chosen for correlation with CSF BH4 because it is a behaviorally relevant marker of immune activation in the CNS.

2. Methods and materials

2.1. Participants

Thirty-seven HCV-positive subjects (19 males, 18 females) were enrolled. Exclusion criteria included decompensated liver disease; liver disease from any cause other than HCV; unstable cardiovascular, endocrinologic, hematologic, renal or neurologic disease (as determined by physical exam and laboratory testing); infection with HIV (as reported by the subjects' treating physician); and history of schizophrenia or bipolar disorder and/or a diagnosis of major depression or substance abuse/dependence within 6 months of study entry (determined by Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition) (First et al., 1997). Patients were required to be off all antidepressant, antipsychotic, or mood stabilizer medications for at least 4 weeks prior to study entry (8 weeks for fluoxetine). Subjects were also required to discontinue other agents that might affect study results (i.e., narcotic analgesics, benzodiazepines, and anti-inflammatory agents) at least 2 weeks prior to sample collection. The subjects reported on herein represent a subsample of subjects included in previous studies on effects of IFN-alpha on cognitive performance, neuroendocrine function, gene expression, and inflammatory responses (Felger et al., 2011, in press; Raison et al., 2009, 2010a,b). All subjects provided written informed consent, and study procedures were approved by the Emory University Institutional Review Board.

2.2. Study design

Study participants were enrolled in a longitudinal study examining immune, neuroendocrine, and neuropsychiatric variables at baseline and 12 weeks of either no treatment or treatment with IFN-alpha/ribavirin. For purposes of this study, plasma ($n = 34$) and CSF ($n = 24$) was obtained between 11–12 weeks from a subset of HCV + patients treated with IFN-alpha plus ribavirin ($n = 26$) and untreated HCV + patients awaiting IFN-alpha/ribavirin therapy (control subjects, $n = 11$). All subjects who underwent IFN-alpha treatment received either pegylated IFN-alfa-2b (Pegintron, Schering Plough, Kenilworth, NJ; 1.5 μg/kg) ($n = 15$) or pegylated IFN-alfa-2a (Pegasys, Roche-Genentech, San Francisco, CA; 180 mg) ($n = 11$) administered subcutaneously plus ribavirin (800–1400 mg/day). Participation in the treatment versus control group was determined by patients and their physicians based on