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Full-Length Review

Insights from interferon-α-related depression for the pathogenesis of depression associated with inflammation

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ABSTRACT

Interferon-α (IFN-α) is a pleiotropic cytokine that is administered as a therapeutic in highly prevalent medical conditions such as chronic hepatitis C and B virus infection, melanoma and lymphoma. IFN-α induces, to a clinically relevant degree, concentration, memory, drive and mood disturbances in almost half of all patients. For this reason, IFN-α is increasingly being replaced by more specifically acting drugs. In the past decades, IFN-α has offered a valuable insight into the pathogenesis of major depression, particularly in settings associated with inflammation. IFN-α triggers immune responses, hypothalamo–pituitary–adrenal axis abnormalities and disturbances of brain metabolism resembling those in other depression states. IFN-α stimulates indoleamine-2,3 dioxygenase-1, activating the kynurenine pathway with reduced formation of the neurotransmitters serotonin and dopamine, excessive formation of the NMDA agonist quinolinic acid, and reduced formation of the NMDA antagonist kynurenic acid. In addition, IFN-α disturbs neurotrophic signaling and impedes neurite outgrowth, synaptic plasticity, endogenous neurogenesis and neuronal survival. Consequently, IFN-α-related depression may represent a model for the neurodegenerative changes that are noticed in late-life major depression. Indeed, the observation that brain responses in IFN-α-related depression resemble idiopathic depression is supported by the existence of common genetic signatures, among which of note, a number of neuronal survival and plasticity genes have been identified. In view of the high incidence of depressive symptoms, IFN-α-related depression is an attractive model for studying links between neuronal plasticity, neurodegeneration and depression. We predict that in the latter areas new targets for anti-depressant therapies could be identified, which may deepen our understanding of idiopathic major depression.

Interferon-α (IFN-α) is a pleiotropic cytokine released by the innate immune system in response to viruses, bacteria, parasites and tumor cells. Due to its wide range of action, IFN-α is widely administered as a therapeutic in several medical conditions, such as chronic hepatitis C virus (HCV) infection, hepatitis B virus (HBV) infection, melanoma, lymphoma and acquired immune deficiency syndrome (AIDS)-related Kaposi's sarcoma. In chronic HCV infection, a particularly prevalent condition affecting 170 million persons worldwide (Hoofnagle, 2002), pegylated IFN-α combined with the polymerase inhibitor ribavirin has been the standard therapy for many years. This has recently changed with the availability of direct antiviral agents (Feld, 2014). In light of these agents, IFN-α will remain important both as part of combination therapies and in patients suffering from multidrug resistant infections.

Since the introduction of IFN-α in clinical therapy, side-effects have raised concerns. As many as 30–50% of the patients undergoing longer lasting IFN-α monotherapy exhibit depressive symptoms (Capuron and Miller, 2004). Patients eligible for IFN-α therapy may already suffer from psychomotor slowing, loss of appetite or fatigue as part of their infectious or tumor disease. Upon IFN-α treatment, these vegetative symptoms exacerbate almost immediately, whereas mood disturbances, anxiety and cognitive deficits normally develop after a delay of several days to weeks (Capuron et al., 2002; Amodio et al., 2005; Hilsabeck et al., 2005; Reichenberg et al., 2005; Miller, 2009; Rodrigue et al., 2011; Byrnes et al., 2012). Mild forms of energy loss or fatigue are highly prevalent in IFN-α therapy. They have been described in as many as 80–90% of melanoma patients (Nashan et al., 2012). More severe states of major depression are noted in 23–45% of HCV infected patients (Keefe, 2007; Fontana et al.,

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2008; Udina et al., 2012). Some patients receiving IFN-α develop an acute confusional state, which may comprise of pronounced cognitive disturbances, psychotic symptoms and hallucinations (Raison et al., 2005). Past history of depression or subclinical depression at onset of IFN-α therapy have been recognized as risk factors for IFN-α-related depression (Raison et al., 2005).

Similar to other types of depression, IFN-α-related depressive symptoms, but not the vegetative symptoms, respond to antidepressant drugs. Thus, prophylactic prescription of selective serotonin reuptake inhibitors (SSRI) reduced the incidence and severity of depression in most (Musselman et al., 2001; Raison et al., 2007; Kraus et al., 2008; de Knegt et al., 2011; McNutt et al., 2012; Schaefer et al., 2012) but not all (Morasco et al., 2007, 2010; Diez-Quevedo et al., 2011) controlled randomized clinical studies. In chronic HCV infection, the efficacy of prophylactic SSRI prescription against IFN-α-related depression was recently confirmed in two meta-analyses (Hou et al., 2013; Sarkar and Schaefer, 2013).

Previous reviews have thoroughly evaluated the clinical presentation of IFN-α-related depression (e.g., Capuron and Miller, 2004; Keefe, 2007; Udina et al., 2012) and examined the role of immune signals, neurotransmitter systems and oxidative stress in depression associated with inflammation (e.g., Muller and Schwarz, 2007; Miller et al., 2009; Miller, 2010; Loftis et al., 2010; Maes et al., 2011b; Leonard and Maes, 2012; Felger and Lotrich, 2013). These reviews thoroughly evaluated the role of cytokines and pointed out the central role of indoleamine-2,3 dioxygenase-1 (IDO1) in models of IFN-, cytokine- and lipopolysaccharide (LPS)-induced depression. With the availability of directly acting antiviral drugs, the question arises regarding the lessons the scientific community has learned from research on IFN-α-related depression. The present review summarizes pathomechanisms of this unique depression subtype, evaluating in more depth links between inflammation, neurotransmitter dysbalance, neurodegeneration and neuroplasticity, which had been a focus of more recent studies.

In the preparation of this review, we performed a detailed PubMed literature analysis, combining the terms 'interferon', 'depression' or 'depressed', and 'inflammation', 'immune', 'cytokine', 'hypothalamo–pituitary–adrenal', 'neurotransmitter', 'serotonin', 'indoleamine-2,3 dioxygenase-1', 'glutamate', 'glucose metabolism', 'functional activation', 'neuronal plasticity', 'neurogenesis', 'neuronal survival', 'neuronal degeneration', 'neuronal death' or 'neuronal apoptosis'.

1. IFN-α interactions with inflamed tissue environments

Considering that IFN-α is administered as a therapeutic in chronic viral infection or cancer, which are *per se* inflammatory conditions, IFN-α induces a depression phenotype that is associated with high levels of inflammation. In the meantime, this depression subtype is regarded as its own disease entity, controlled by specific cytokines, cell signaling pathways and neurotransmitter systems (Raison and Miller, 2013). Depression associated with inflammation typically presents itself with pronounced vegetative symptoms, including sickness, loss of appetite or fatigue. The genetic signature which predisposes to depression associated with inflammation originates from an immune defense, representing a behavioral correlate of host responses to pathogens (Raison and Miller, 2013).

The development of depressive symptoms during IFN-α therapy strongly depends on the underlying disease for which IFN-α is administered. Interestingly, IFN-α-related depression in chronic HCV infection is more severe than IFN-α-related depression in other pathologies, such as HBV infection, melanoma or other cancers (Fried et al., 2002; Fletcher et al., 2012). HCV is able to cross the blood–brain barrier and replicate in cerebral endothelial cells, microglia, macrophages and astrocytes (Wilkinson et al., 2009; Fletcher et al., 2012), provoking the release of pro-inflammatory cytokines, such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), which are also elevated in the blood of depressed HCV patients (Loftis et al., 2008).

Tissue responses to HCV are at least partly mediated by Toll-like receptor-3 (TLR-3), which is expressed on human neurons and activated by double-stranded RNA, resulting in the expression of cytokines (IL-6, TNF-α, IL-1β), chemokines (C–C motif ligand-5 [Ccl-5], C-X-C motif ligand-10 [Cxcl-10]) and type I IFN (IFN-α, IFN-β) (Lafon et al., 2006; Cunningham et al., 2007; Field et al., 2010). In adult rats, the brain injection of the TLR-3 agonist polyinosinic:polycytidylic acid (poly(I:C)) induced an acute inflammatory response, associated with alterations in the expression of molecules involved in axonal and synaptic plasticity, namely of TAR DNA binding protein-43, α-synuclein and postsynaptic density protein-95 (Deleidi et al., 2010). In primary prefrontal cortical and hippocampal neurons, poly(I:C) potentiated the IFN-α-induced expression of pro-inflammatory cytokines (namely IL-6, IL-1β and TNF-α) (Schlaak et al., 2012; Hoyo-Becerra et al., 2013).

In organotypic hippocampal slices, TLR-3 activation by poly(I:C) induced spontaneous electrophysiological activity of CA1 pyramidal neurons that was associated with reduced phosphorylation of the NMDA receptor 2B (NR2B) subunit and reduced abundance of the astrocytic glutamate/aspartate transporter (GLAST) (Costello and Lynch, 2013). These responses were abrogated in IFN-α/β receptor (IFNAR)-1 deficient mice, indicating that the effects of TLR-3 activation were mediated by type I IFN (Costello and Lynch, 2013). Importantly, the activation of TLR-3 did not influence long-term potentiation (LTP) of CA1 neurons (Costello and Lynch, 2013). In this respect, the role of TLR-3 might differ from TLR-4, a sensor for bacterial LPS, which reduced LTP on CA1 neurons and induced memory deficits in object recognition tests upon activation (Costello et al., 2011; Mazarati et al., 2011).

Hence, different TLR apparently influence neuronal responses in diverse ways depending on the pathophysiological setting. This observation is noteworthy, since type I IFN may be induced by various TLR (O'Neill and Bowie, 2007). Type I IFN induction by TLR occurs through the adaptor protein toll or interleukin-1 receptor (TIR) domain-containing adaptor inducing IFN-β (TRIF) that activates IFN transcription via IFN-regulatory factors (IRF) (O'Neill and Bowie, 2007).

2. Role of IFN receptor signaling

Specificities in IFNAR binding are considered responsible both for tissue selective therapeutic and for harmful effects of IFN-α and IFN-β in the brain (Owens et al., 2014). Although IFN-α and IFN-β act via the same receptor, a heterodimer consisting of IFNAR-1 and -2 proteins, receptor interaction is influenced by protein sequences within recognition sites, which differ between IFN proteins (Fish et al., 1989; Kumaran et al., 2007). Intracellular signaling of IRNAR is furthermore influenced by the composition of receptor heterodimers, which may contain three different IFNAR-2 isoforms, IFNAR-2a, IFNAR-2b or IFNAR-2c, in addition to a common IFNAR-1 protein (Kumaran et al., 2007).

IFN-α appears to be a particularly potent inducer of depressive symptoms. Comparing HCV patients receiving pegylated IFN-α plus ribavirin with those receiving non-pegylated IFN-β plus ribavirin, Nomura et al. (2012) found that depressive symptoms were more prevalent following IFN-α than IFN-β treatment. In patients already diagnosed with depression before antiviral treatment, IFN-β/ribavirin co-treatment did not exacerbate depressive

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