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Why are depressed patients inflamed? A reflection on 20 years of research on depression, glucocorticoid resistance and inflammation

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Abstract
Studies over the last 20 years have demonstrated that increased inflammation and hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis are two of the most consistent biological findings in major depression and are often associated: but the molecular and clinical mechanisms underlying these abnormalities are still unclear. These findings are particularly enigmatic, especially considering the accepted notion that high levels of cortisol have an anti-inflammatory action, and therefore the coexistence of inflammation and hypercortisolemia in the same diagnostic group appears counter-intuitive. To celebrate the 2015 Anna-Monika Foundation Award to our laboratory, this review will discuss our own 20 years of research on the clinical and molecular evidence underlying the increased inflammation in depression, especially in the context of a hyperactive HPA axis, and discuss its implications for the pathogenesis and treatment of this disorder.

1. Introduction

Winning the prestigious Anna-Monika Foundation Award has been an ideal opportunity for me to reflect on the research that has been coming out of our laboratory over the last 20 years, especially since this long period of time has seen a very important theoretical advance in psychiatry: the transformation of *psychoneuroimmunology* (or, as it has been more recently called, *immunopsychiatry*) from a niche area of biological psychiatry and psychosomatics to an established mainstream research and translational area in mental health and clinical neuroscience (Pariante, 2015). Because of the focus of this review on our scientific production within the larger immunopsychiatry framework, the narrative and the citations are self-referential. However, this scientific production would not exist

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if we had not been supported by a number of friends, colleagues and collaborators who have shaped psychoneuroimmunology over the years.

2. Inflammation and the glucocorticoid receptor: love at first sight

Although my first publication on depression and immune system dates back to 1991 (Bartoloni et al., 1991), what really defined my future as researcher in this field was my encounter with the glucocorticoid receptor (GR) in the laboratory of Andrew H Miller at Emory University in Atlanta, in the years 1995–1997. At that time, it was well known that a hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis can be consistently identified in at least a subgroup of depressed patients. The prevailing model at that time – which is pretty much still unchanged today – was based on the notion of "glucocorticoid resistance". In a nutshell, the glucocorticoid receptor (one of the two receptors for the human glucocorticoid hormone, cortisol) physiologically mediates the HPA axis negative feedback, that is, the ability of cortisol to inhibit its own secretion, especially during an increased production due to stress; in contrast, in depression, a dysfunction of the GR leads to an impaired HPA axis negative feedback (a phenomenon called glucocorticoid resistance), which in turn leads to the HPA axis hyperactivity (Pariante and Lightman, 2008; Pariante and Miller, 2001). While this theoretical model was already established at that time, very little was known on the molecular mechanisms that could underpin these presumed GR abnormalities. To address this question, we started using a scientific approach that has continued to deliver many interesting findings over the years: we exploited *in vitro* models utilising fibroblasts, human blood cells, and neurons.

In the first paper on this topic, we found that incubating L929 mouse fibroblasts cells with the pro-inflammatory cytokine interleukin (IL)-1 leads to glucocorticoid resistance, *i.e.*, to an impairment of GR activation and translocation from the cytoplasm to the nucleus, resulting in reduced expression of GR-stimulated genes (Pariante et al., 1999). Interestingly, at the same time we also demonstrated that antidepressants *in vitro increase* GR activation and function, that is, reverse glucocorticoid resistance, thus confirming the crucial role of the GR as a target of both depressogenic (inflammation) and therapeutic (antidepressants) stimuli (Pariante et al., 1997). Two subsequent papers demonstrated similar findings in human peripheral blood mononuclear cells (Carvalho et al., 2008, 2010).

An interesting side-story following these initial findings was a series of subsequent studies (conducted in London) in which we demonstrated that the effects of antidepressants potentiating GR translocation and function is not only directly mediated through steroid-independent activation of the GR, but also indirectly by inhibition of the p-glycoprotein transporter that expels cortisol from cells (and, *in vivo*, from the brain). We found that, *in vitro*, these effects are common to all tested antidepressants and are present not only in mouse fibroblasts but also in rat neurons (Pariante et al., 2001, 2003a. 2003b, 2004b). In subsequent animal studies, we were able to demonstrate that p-glycoprotein regulates the effects of antidepressants on GR expression (Yau et al., 2007) but not, however, that p-glycoprotein or indeed antidepressants regulate cortisol levels in the brain (Mason et al., 2008, 2011).

3. From cells to humans

After moved to London in 1997, I expanded my research portfolio to include clinical studies. In 2008 we described increased plasma cortisol levels and increased inflammation (plasma IL-6) in the same depressed individuals, a group of severely depressed inpatients with treatment-resistant depression (Carvalho et al., 2008); moreover, these same subjects have glucocorticoid resistance, as shown by a reduced *in vitro* ability of their peripheral blood mononuclear cells to respond to dexamethasone and cortisol during an immune stimulus (Carvalho et al., 2009). Patients with the highest IL-6 levels are also the least likely to respond to antidepressants (Carvalho et al., 2013). These findings confirmed the notion that glucocorticoid resistance, cortisol hypersecretion and increased inflammation are indeed coexistent and related biological abnormalities. In two studies in healthy volunteers, we were also able to confirm that antidepressants reverse GR resistance, that is, increase GR function as measured by the HPA axis negative feedback (Pariante et al., 2004a) and the effects of cortisol on the EEG (Pariante et al., 2012). But these studies, while confirming that these biological changes are operating in man, did not help elucidate the potential molecular mechanisms underlying GR resistance in depression, nor its reversal by antidepressants.

To try to understand such molecular mechanisms, we measured the expression of candidate genes in the peripheral blood mRNA of patients with major depression (and healthy controls) from the GENDEP sample, a large European study funded by the European Commission. In this study, we found two noticeable results: first, we replicated the increased inflammation in depression as shown by increased mRNA expression of proinflammatory cytokines (IL-1, IL-6, TNF-alpha and macrophage inhibiting factor, MIF) together with a reduced expression of the anti-inflammatory cytokines, IL-4; and, second, we showed that these same patients also have molecular evidence of GR resistance as shown by a reduced expression of GR mRNA together with an increased expression of the GR chaperone protein, FKBP5 (Cattaneo et al., 2013). Both these findings indicate the possible molecular signature underlying GR resistance and increased inflammation in depression: a reduced GR expression (that is, less receptor available) together with a decreased GR responsivity (as FKBP5 binds to the GR and maintains it in an unresponsive state).

We subsequently tested the same hypotheses in an independent study, in which we measured HPA axis activity and inflammation in a group of older depressed patients with coronary heart disease. We were particularly interested in this group, as coronary heart disease is characterised by higher levels of chronic inflammation, and hence we hypothesised that depression in this context would have shown clear abnormalities of the immune system. And, indeed, this is exactly what we found: depressed patients with coronary heart disease have higher inflammation (higher IL-6 mRNA and higher levels of c-reactive protein (CRP), an acute phase response protein produced by the liver in response to IL-6) together with a reduced expression