EFFECTS OF TREATMENTS WITH CO-ADMINISTERED ANTIDEPRESSANTS AND ANTIINFLAMMATORY DRUGS ON SERUM CYTOKINES LEVELS

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Abstract. This paper briefly presents researches regarding decrease of serum cytokines levels as a possible effect of antidepressants and involvement of inflammation in depressive disorders. Investigations have shown high levels of IL-6, IFN-gamma and TNF-alfa in patients with depressive disorders. Also, chronic diseases are co-morbid with depression, for instance rheumatoid arthritis. Researches on possible antidepressants' effects of decreasing cytokines' levels, were carried out in patients and by using experimental models. On the other hand, there is specialized literature supporting benefits of anti-inflammatory drugs as adjunctive treatment in depression, which is contradictory to results showing that anti-inflammatory agents antagonize therapeutic efficacy of antidepressants in patients with depressive disorders. The inflammatory hypothesis of depression could mark a major shift in the study of depression and development of new antidepressant agents.
Keywords: pro-inflammatory cytokines, antidepressants, anti-inflammatory agents.

Rezumat. Lucrarea prezinta sumar cercetari privind posibilul efect al unor antidepresive, de scadere a concentratiilor citokinelor proinflamatorii si implicarea inflamatiei in aparitia depresiei. O serie de astfel de investigatii au evidentiat concentratii mari de interleukina IL-6 , TNF alfa, interferon gamma, la pacienti cu tulburari depresive. De asemenea, mai multe boli cronice printre care artrita reumatoida sunt prezente concomitent cu depresia. Cercetarile asupra efectului catorva antidepresive, de reducere a concentratiilor IL-6, TNF alfa au fost efectuate prin includerea de subiecti in studii, sau experimental, utilizand animale de laborator. Pe de alta parte, exista literatura de specialitate care sustine actiunea benefica a unor antiinflamatoare ca adjuvante in tratamentul cu antidepresive, ceea ce este in dezacord cu rezultatele care atesta ca efectul antiinflamatoarelor in relatie cu efectul terapeutic al antidepresivelor este de scadere a efectului terapeutic al agentilor antidepresivi, daca sunt co-administrate. Ipoteza implicarii procesului inflamator in aparitia tulburarilor depresive poate sa reprezinte o modificare importanta in studiul depresiei, cu implicatii in ceea ce priveste producerea unor noi agenti antidepresivi.
Cuvinte cheie: citochine pro-inflamatorii, antidepresive, agenti anti-inflamatori.

BACKGROUND

Researches have investigated effects of various antidepressants on pro-inflammatory cytokines levels in depression. It has been shown that treatments with selective serotonine re-uptake inhibitors (SSRI) diminished serum IL-6 levels, while levels of TNF-alpha and IL-6 significantly increased in patients with resistant depression compared with those in healthy subjects /1/.

Literature documenting efficacy of anti-inflammatory agents as adjunctive treatments for depression appears contradictory to data showing that anti-inflammatory drugs reduce effectiveness of antidepressants. It has been considered as well that the inflammatory hypothesis of depression could mark a significant shift away from monoamine-based approaches and be a step towards directly targeting a causal factor of depression (Li M., 2011). Cytokines and their receptors, intracellular inflammatory mediators, glucocorticoid receptors, may all be considered possible therapeutic targets in the treatment of depression (Catena-Dell'Osso M, 2011). Schiepers (2005) underlined that even though effects of pro-inflammatory cytokines appear to account for depression symptoms, it could be that cytokines only

subsume epiphenomena, the etiology and pathophysiology of major depression still being less clear (Li M., 2011; Catena-Dell'Osso M, 2011; Schiepers, 2005).

Findings from clinical practice have shown that a large number of patients with major depression do not respond adequately to current antidepressant pharmacological treatments. Moreover, currently available antidepressants are effective in less than two thirds of depressed patients, with even lower remission rates in those with co-morbid medical illnesses (Li M. et. al, 2011). It has been pointed out in addition that several medical illnesses, which are characterized by chronic inflammatory responses, are accompanied by depression, for instance rheumatoid arthritis (Schiepers, 2005). Administration of pro-inflammatory cytokines in cancer or hepatitis C therapies, has also been found to induce depressive symptomatology and sickness behavior . In experimental models sickness is taken into account as a pattern of behavioral alterations that is similar to symptoms of depression in humans. Actions of cytokines may induce the hypothalamic-pituitary-adrenal (HPA) axis hyperactivity by inhibiting the corticosteroids exerted negative feed-back on the HPA axis.

Increased plasma cortisol levels and enlarged adrenals and anterior pituitary reflect dysregulation of the hypothalamic–pituitary–adrenal axis in major depression. The aforementioned HPA dysregulation suggested impairment of the glucocorticoid receptor (GR)-mediated negative feedback, which is known as glucocorticoid resistance. Increased cortisol levels in patients with depression but not accompanied by physical signs of Cushing's syndrome are in further support to the notion of glucocorticoid resistance (Carvalho, 2010; 2008).

Carvalho et al. (2008, 2010) further showed that antidepressants may reverse glucocorticoid receptor changes specific of depression by directly acting on the GR. In laboratory animals, antidepressants increase GR receptor expression and so there is a stronger negative feedback on the HPA axis. As well, her experimental research pointed out that antidepressants increase intracellular concentrations of some glucocorticoids by inhibiting membrane transporters that actively expel glucocorticoid from cells, and increase GR function in cells where these transporters are present. In contrast, Carvalho et al. (2008) also found out that clomipramine decreased GR function in human peripheral blood cells — not expressing functional glucocorticoid transporters. This effect of clomipramine, which appears in patients with major depression who are clinically resistant to treatment, suggested that antidepressants may regulate GR function in relation to their therapeutic action. Glucocorticoid resistance in peripheral blood cells from patients with depression leads to enhanced inflammation. Patients with depression had reduced GR function in peripheral blood cells and increased levels of interleukin-6, possibly reflecting a pro-inflammatory state of monocytes. The above findings showed that some antidepressants are likely to correct both glucocorticoid resistance and monocytes' pro-inflammatory states in major depression.

LABORATORY FINDINGS

It has been shown as well, that actions of antidepressants may involve the cAMP pathways. Allen et al. (2007) found out that besides interacting with membrane steroid transporters, antidepressants may partially exert their therapeutic action by altering a component of the membrane that is associated with lipid rafts. Lipid rafts are specialized structures on the plasma membrane with an altered lipid composition that link to the cytoskeleton. Although chronic antidepressant treatment does not alter membrane cholesterol content, treatment with chemically distinct antidepressants results in the movement of G protein stimulatory subunit - Gas out of lipid rafts and into a closer association with adenylyl cyclase. This association

might explain the increased cAMP and synaptic changes that were observed after chronic antidepressants administration. Cyclic AMP/protein kinase A (PKA) signal transduction pathways were pointed out to increase GR function and PKA agonists were found to have the capacity to increase GR transcription and function.

Muller and Schwartz (2007) reported as well data at molecular level related to pro-inflammatory cytokines and neurotrans-mitters in depression. Interleukin-2, interferon-gamma, or tumor necrosis factor-alpha activate indoleamine 2,3-dioxygenase (IDO), which is a tryptophan- and serotonin-degrading enzyme. Activation of both IDO and its subsequent enzyme kynurenine monooxygenase by pro-inflammatory cytokines leads to an incresed production of quinolinic acid, a strong agonist of the glutamatergic N-methyl-D-aspartate receptor. Neurotoxic effects of quinolinic acid might be antagonized by cyclooxygenase-2 inhibitors. Activated IDO preferentially metabolizes tryptophan to quinolinic acid in microglial cells, whereas astrocytes lack enzymes for metabolizing tryptophan. Astrocytes and microglia are the major cell types implicated in inflammation as sources of cytokines and so, microglial cells may have been overlooked for the study of major depression etiology (Muller and Schwartz, 2007).

Several researches have investigated effects of antidepressants on the glial production of inflammatory mediators “in vitro”. Vollmar et al. (2008) measured by ELISA, IL-6, IL-10, IFN-gamma and TGF concentrations in an astroglia-microglia co-culture treated with venlafaxine for sixteen hours. The culture system used allowed mimicking of an inflammatory milieu and demonstrated augmentation of TGF-release with a concomitant reduced secretion of IL-6 and IFN-gamma. Further, Hashioka (2007) demonstrated in vitro that tricyclic antidepressants, SSRI and SNRI inhibited induced microglial production of IL-6 and NO. These inhibitions were reversed by inhibitors of the cyclic AMP.

Maes M. (2008) pointed out that some animal models of depression have been based on induced inflammation. His research showed that depression is accompanied by an IgM-related (auto)immune response directed against disrupted lipid membrane components, such as phosphatidyl-inositol, malondialdehyde as by-product of lipid peroxidation and nitric oxide-modified amino-acids, which become immunogenic.

Vismari L and Alves J (2012) in an attempt to point out effects of amitriptyline on nitric oxide, evaluated effects of amitriptyline co-administered with a NO synthase inhibitor (L-NAME) on some parameters of acute inflammatory response in rats. Effects of amitriptyline were potentiated by L-NAME in the paw edema model, which was not abrogated when L-arginine substituted for L-NAME. Both decreases in leukocytes in the peritoneal exudate and a reduction in nitrates serum levels were reported after L-NAME and amitriptyline co-administration. These researches also reported a significant decrease of IL-1beta and TNF-alfa serum levels in experimental groups. Hence, a possible effect of amitriptyline of decreasing NO production could be pointed out.

Johansson D et al. (2012) also provided experimental evidence regarding treatment with co-administered anti-inflammatory drug celecoxib, a cyclo-oxygenase-2 (COX-2) inhibitor which blocks prostaglandins PGE (2)-production and two antidepressants. To examine the neurobiological substrate, Johansson et al. by using in vivo microdialysis, studied in awake freely moving rats, acute effects of a combined treatment with celecoxib and reboxetine on cortical noradrenaline and dopamine output, as well as celecoxib and fluoxetine on 5-HT output in the prefrontal cortex. Effects of reboxetine and fluoxetine on cortical noradrenaline and 5-HT output were significantly potentiated by celecoxib

but not the reboxetine-induced dopamine output. These findings supported the utility of combined treatment with antidepressants and anti-inflammatory drugs in major depression. Considering these results, mechanisms of action of anti-inflammatory drugs will probably be taken into account in further developments of antidepressants.

It is very important to highlight limitations of investigations with regard to antidepressants' effects on pro-inflammatory cytokines. Kennis and Maes (2002) pointed out technical difficulties in detection of human serum and plasma cytokines levels, since circulating cytokine concentrations are very low. Moreover, the meta-analysis of J Hannestad et al. (2011) pointed out heterogeneity of results of studies which measured IL-6 and TNF-alpha and even publication bias for TNF-alpha studies.

The aforementioned analysis underscores that levels of pro-inflammatory cytokines do not decrease even though symptoms in patients with depression ameliorate after administration of antidepressants. Hannestad (2011) noted that researches reported effects of antidepressants (SSRI) on IL-1beta and possibly IL-6 levels but not TNF-alpha concentrations.

In conclusion, it has been emphasized that the need is to carefully balance therapeutic benefits of anti-inflammatory drugs versus potentially negative consequences of antagonizing therapeutic efficacy of antidepressants in patients with depression.

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