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The anti-inflammatory mechanism of antidepressants – SSRIs, SNRIs

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A B S T R A C T

The cytokine theory of depression no longer brings about any doubts. Experiments and research studies conducted in the last ten years have confirmed that both physical and psychological (emotional) stress increases the likelihood of occurrence of mental disorders (including depressive disorders) owing to the action of a series of hormonal and biochemical mechanisms.

Selective serotonin reuptake inhibitors (SSRI) as well as serotonin and norepinephrine reuptake inhibitors (SNRIs) are some of the most commonly applied drugs in the world during pharmacotherapy of recurrent depressive disorder.

The underestimated anti-inflammatory and anti-oxidative effect may be one of the potential mechanisms of action of the preparations mentioned above. The detailed specificity of action of this mechanism still remains unknown. The aim of our work will be to perform a review of contemporary literature in order to present the latest scientific reports regarding the anti-inflammatory effects of SSRIs and SNRIs.

The mechanism of anti-inflammatory action may serve as a possible explanation for the efficacy of antidepressants from the groups of SSRIs and SNRIs.

1. Introduction

The cytokine theory of depression no longer brings about any doubts (Maes et al., 2011a; Maes et al., 2011c; Lopresti et al., 2014; Black et al., 2015; Talarowska et al., 2015). Experiments and research studies conducted in the last ten years have confirmed that both physical and psychological (emotional) stress increases the likelihood of occurrence of mental disorders (including depressive disorders) (Lindqvist et al., 2016) owing to the action of a series of hormonal and biochemical mechanisms (Finnell and Wood, 2016), as well as only recently confirmed epigenetic mechanisms (Babenko et al., 2015). For many years, attempts have been made to work out and introduce the most effective method of treating depressive disorders, which will not only bring relief to patients, but will also effectively counteract recurrence of the disease (Kamenov et al., 2017).

Selective serotonin reuptake inhibitors (SSRI) as well as serotonin and norepinephrine reuptake inhibitors (SNRIs) are some of the most commonly applied drugs in the world during pharmacotherapy of recurrent depressive disorders (Poluzzi et al., 2013). Their efficacy does not bring about any doubts of both clinicians and scientists. Moreover, the drugs are tolerated well by patients because the number of side effects is limited (Wade et al., 2014; Castellano et al., 2016; Jakobsen et al., 2017; James et al., 2017). Due to the format of this publication, the authors decided to limit the analysis conducted only to the two groups of drugs mentioned above.

The underestimated anti-inflammatory and anti-oxidative effect may be one of the potential mechanisms of action of the preparations mentioned above (Leonard, 2001; Gałecki et al., 2009). The detailed specificity of action of this mechanism still remains unknown (Baumeister et al., 2016). The aim of our work will be to perform a review of contemporary literature in order to present the latest scientific reports regarding the anti-inflammatory effects of SSRIs and SNRIs.

For the sake of this narrative review, we carried out a comprehensive search in the Pubmed/MEDLINE electronic databases from the very beginning until January 1st, 2017. The terms we looked for included: “SSRI”, “SNRI”, “Selective Serotonin Reuptake Inhibitors”, “Selective Serotonin-Norepinephrine Reuptake Inhibitor” cross-referenced with “depress∗.” We only took into consideration the articles written and published in English. The articles were taken into account and included in our study based on their overall quality of methodology. Moreover, relevant meta-analyses were included.

1.1. Selective serotonin reuptake inhibitors (SSRIs)

The participation of serotonin and its derivatives in the mechanism of development of depressive disorders has been examined for nearly 40 years (Mendels and Frazer, 1974). Preparations from the SSRI group

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were used in the pharmacotherapy of depressive disorders for the first time back in the 1980′s (Cohen et al., 2000). Henceforth, they have dominated the pharmaceutical market (Castellano et al., 2016).

Sertraline, one of the substances from the SSRI group, in a single (0.75 mg/kg) dose, decreased IL-1β mRNA expression and TNF-α expression after repeated doses (Sitges et al., 2014). On the other hand, Lindqvist et al. (2016) observed that indicators of an ongoing inflammatory process (F2-isoprostanes) were significantly higher in those of the examined patients who were characterised by a poor therapeutic response to SSRIs. Higher levels of F2-isoprostanes at baseline and after eight weeks of treatment were recorded for non-responders to SSRI antidepressant treatment. Moreover, during an eight-week-long therapy, an increase in 8-OH 2-deoxyguanosine (8-OHdG) was observed in the group with a poor therapeutic response; while a drop of the level of interleukin 6 (IL-6) was noticed in the patients with the highest indicators of improvement. Halaris et al. (2015) confirmed a beneficial effect of escitalopram on the reduction of neurotoxic metabolites of the kynurenine pathway among the examined subjects with depressive disorders. Meanwhile, Lopez-Vilchez et al. (2016) underscored the efficacy of treatment with SSRIs in case of endothelial dysfunctions in naive patients with major depression. Additionally, Rafiee et al. (2016) indicated a positive influence of pharmacotherapy with the use of fluvoxamine on the expression of genes connected with the inflammatory cascade (intercellular adhesion molecule, $ICAM_1$; vascular cell adhesion molecule, $VCAM_1$; cyclooxygenases2, COX_2; inducible nitric oxide synthase, iNOS). According to Greeson et al. (2016), citalopram reduces expression of the human immunodeficiency virus (HIV). This impact is visible irrespective of the presence of any clinical signs of depression (Greeson et al., 2016).

A new interesting direction of studies has been indicated by Hough et al. (2016). In their opinion, leucocyte telomere length (LTL) may be a factor modifying the effectiveness of action of drugs from the SSRI group, especially shorter pre-treatment LTL. However, the same authors underline that this issue requires further and more extensive research.

Branchi et al. (2013) formulated an interesting hypothesis, too. The authors claim that an increase in serotonin levels induced by SSRI may not affect mood per se, but enhances neural plasticity and, consequently, renders a given individual more susceptible to the influence of the environment. SSRI administration in a favourable environment would lead to a reduction of symptoms, while it might lead to a worse prognosis in a stressful environment (Branchi et al., 2013).

The favourable effect of pharmacotherapy using SSRIs on immune system regulation was observed not only among patients with symptoms of depression, but also in the subjects diagnosed with post-traumatic stress disorders (PTSD) (Wilson et al., 2014). During research studies on animals, sertraline inhibited inflammatory process markers to a large extent and normalised 5-HT levels in the central nervous system (CNS) (Wilson et al., 2014).

1.2. Serotonin and norepinephrine reuptake inhibitors (SNRIs)

Originally, the catecholamine theory of depression aetiology linked the occurrence of symptoms with norepinephrine (NE) deficiency (Finnell and Wood, 2016). At present, most scientific reports concentrate on the lack of balance in the action of this system of neurotransmitters as the most probable cause of depression (Marshe et al., 2017).

Venlafaxine is a strong serotonin and norepinephrine reuptake inhibitor, and a rather poor dopamine reuptake inhibitor; it has been used as an effective antidepressant for many years (Magalhães et al., 2015). It is often used as an alternative to SSRIs (Dold et al., 2016). Similarly as in case of SSRIs, venlafaxine affects the action of the immune system through regulation of a stress response (Nazimek et al., 2016). It seems that various physical and psychosocial stressors are strongly associated with an increase in norepinephrine secretion in many places of the human brain, particularly in the hypothalamus, the amygdala and the locus coeruleus (Tanaka et al., 2000).

Studies on animals made it possible to determine that the applied strategies of coping, emerging in response to psychosocial stressors, are linked with diverse patterns of activation of norepinephrine pathways (Reyes et al., 2015). Perhaps this may be an explanation for the differences in the susceptibility of each person to the occurrence of anxiety disorders (Reyes et al., 2015). What is more, the amygdala, which is strongly connected with a response to negative emotional stimuli, is also in charge of regulating the effectiveness of the norepinephrine pathway through peptide circuits (Reyes et al., 2011; Kravets et al., 2015). According to Curtis et al. (2006), how strong an anxiety reaction is depends not only on the range of coping skills a given person has, but also on gender. In the experiments conducted by the said team (Curtis et al., 2006) the intensity of stress reactions was significantly greater among the examined women. This phenomenon may be observed independently of hormonal factors. A similar correlation with reference to favourable/unfavourable environmental factors is being sought by Alboni et al. (2016).

It turns out that venlafaxine limits renovascular hypertension, which leads not only to endothelial dysfunction, serum oxidative and nitrosative stress, brain and aortic oxidative stress, but also is a cause of cognitive deficits (Singh and Sharma, 2016). Reports compatible with the ones presented above were also delivered by Minaiyan et al. (2015) and Hajhashemi et al., 2015. The results seem to be particularly important for the elderly diagnosed with late-life depression (Sigurdsson et al., 2015). Meanwhile, Dubovický et al. (2014) indicate a weak yet significant impact of venlafaxine on major pro-inflammatory parameters of microglia. According to the quoted authors, venlafaxine's inhibitory effect on superoxide generation can contribute to the prevention of harmful effects of oxidative and nitrosative stress involved in the pathogenesis of depression. Moreover, the protective effect of VEN on the viability of microglia can prevent a rapid reduction of these cells.

1.3. Kynurenine pathway – will it dispel all doubts?

One of the probable hypotheses that explain the effectiveness of SSRIs and SNRIs is the kynurenine pathway hypothesis (Maes et al., 2011b; Dantzer, 2017). The relationship between tryptophan, serotonin, and depression has a long history in psychiatry. Tryptophan is the precursor of serotonin, and due to the fact that tryptophan hydroxylase is not saturated by its substrate, the bioavailability of tryptophan regulates the amount of serotonin produced in the brain (Remus and Dantzer, 2016).

Based on the kynurenine pathway hypothesis of depression aetiology, inflammatory factors cause excessive activation of indoleamine-2,3 dioxygenase (IDO) – an enzyme present in microglia, astrocytes and neurons (Anderson, 2016). This enzyme catabolises tryptophan, the source of serotonin, into kynurenine (KYN), a neurotoxic substrate which increases the risk of neurodegenerative and neurotoxic processes. This way, IDO reduces the amount of tryptophan available for the production of serotonin (Anderson, 2016).

Connecting the activity of kynurenine pathways with the efficiency of cognitive functions seems an interesting direction of studies (Allison and Ditor, 2014). The highest concentration of kynurenic acid in the human brain was observed and confirmed in the caudate nucleus and the thalamus; lower concentration was found in the hippocampus and the frontal cortex, while the lowest – in the cerebellum (Maddison and Giorgini, 2015).

The activity of proinflammatory cytokines and inflammation enzymes is significant not only during an immune response, but is also of importance for the neuroprotective and neurodegenerative processes (Talarowska et al., 2015). Mood disorders and deterioration of cognitive processes are the symptoms of dysfunction of the same neuronal mechanism (Rosenberg et al., 2010). Hence a question arises about the common denominator of these changes. An inflammatory process,

Table 1
The possible effect of anti-inflammatory action of SSRIs and SNRIs (Caiaffo et al., 2016).

SSRIs	SNRIs
• Neuroprotection • Anti-inflammatory properties similar to standard drugs for the treatment of inflammatory conditions • Antioxidant properties, contributing to its therapeutic action and an important intracellular mechanism underlying the protective pharmacological effects seen in clinical practice in the treatment of different stress-related adverse health conditions • Anti-apoptotic properties, with greater neuron survival and a reduction in apoptosis mediators as well as oxidative substances, such as superoxide dismutase and hydrogen peroxide	• Attenuate renovascular-hypertension induced cognition impairment, endothelial dysfunction, serum nitrosative stress, brain and aortic oxidative stress, cholinergic function, inflammation as well as cerebral damage

alongside its functional and structural consequences, taking place in the organism of the patients suffering from depression, may be one of the possible explanations. Functional disorders within the area of the anterior and medial cingulate gyrus, the dorsolateral and ventromedial prefrontal cortex, and the anterior part of the insula and the amygdala, are considered the neurobiological foundation of deficits in the scope of the so-called “cold” (attention, memory, executive functions) and “hot” (emotions) mental processes as well as in the scope of social cognition in depression (Schmaal et al., 2015; Talarowska and Gałecki, 2016).

1.4. Controversies – is it possible to avoid them?

According to Warner-Schmidt et al. (2011), commonly used anti-inflammatory drugs may act – on the biochemical level – as antagonists of preparations from the SSRI group. Additionally, preclinical findings in rodents exposed to SSRIs during development point to an increase in depression- and anxiety-like behaviour, and alteration in social behaviours in the offspring (Gur et al., 2013). Moreover, according to Nulman et al. (2012), the children of mothers treated during pregnancy with venlafaxine and SSRIs had consistently, but not to a significant extent, higher rates of most problematic behaviours than the children of non-depressed mothers. However, in this case the very diagnosis of depressive disorders may be significant. During the same study, the authors demonstrated that the emotional functioning of the children of the mothers who had not undergone any pharmacotherapy during pregnancy due to the presence of depression symptoms revealed a similar level of emotional functioning as the children of the mothers treated with both venlafaxine and SSRIs (Nulman et al., 2012). The team led by Nulman et al. confirmed the results obtained earlier during successive studies conducted with the participation of relatives (Nulman et al., 2015). Eriksen et al. (2015) claim, however, that prenatal exposure to SSRIs does not have any impact on the level of intelligence in a child.

2. Summary

To sum up, it is worth underlining one benefit resulting from the use of drugs from the SSRI and SNRI groups – the indicators of an ongoing inflammatory process do not have an impact on their metabolism (Hefner et al., 2015), which additionally increases their effectiveness of action.

The issue of the anti-inflammatory action of SSRIs and SNRIs is still open, especially in the clinical aspect. It also enables conducting further research (Table 1).

3. Conclusions

The mechanism of anti-inflammatory action may serve as a possible explanation for the efficacy of antidepressants from the groups of SSRIs and SNRIs.

Conflict of interest

None to declare

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