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Review

A critical review of the mechanism of action for the selective serotonin reuptake inhibitors: Do these drugs possess anti-inflammatory properties and how relevant is this in the treatment of depression?

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ABSTRACT

The selective serotonin reuptake inhibitors (SSRIs) are the most widely prescribed pharmacological treatment for depression. Since their introduction many have considered the primary mechanism by which the SSRIs produced therapeutic improvement in depression is their effect on monoaminergic signalling. In recent years, however, the credibility of the monoamine theory and the therapeutic efficacy of these compounds in the treatment of depression has been extensively criticized. In the current review the legitimacy of these criticisms is critically examined, in many instances the evidence base used to support these criticisms is found to be weak. Nevertheless, the apparent 'failure' of the monoamine theory has been of benefit in motivating research into alternative mechanisms through which the SSRIs may act. Given research demonstrating that depressive symptoms are intimately linked with disturbances in pro-inflammatory signalling, perhaps the most promising discovery has been the realisation that SSRIs posses significant anti-inflammatory properties. These recent findings are discussed and contextualised with respect to the neurogenic, neurotrophic and gluatamatergic effects that these drugs also possess.

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1. Introduction

The prescription of selective serotonin reuptake inhibitors (SSRIs) is a major component in the medical treatment of mood related psychopathology. Despite the widespread prescription of these medications, their use has been a constant subject of controversy and sometimes heated debate. The safety, tolerability, efficacy, and mechanism of action of SSRIs have all been extensively scrutinized, criticized, and re-evaluated. It is against this complicated background that a compelling body of literature has emerged describing the ability of SSRIs to modulate inflammatory processes. The significance of these findings is directly linked with evidence supporting the idea that depression may emerge and be maintained by inflammatory processes. For those interested in the area these recent developments raise many challenging questions. For instance, how credible is the evidence that these medications possess anti-inflammatory activities, and what is the mechanism of action through which they exert these putative effects? It is also important to recognize that interest in these issues presupposes that SSRIs should in fact actually be used to treat depression. Accordingly, this review will begin by describing the landscape of facts that relate to the use of SSRIs, which will be followed by a detailed investigation of the evidence that has examined their tolerability, safety and efficacy. Criticisms associated with the use of antidepressants, and the monoamine theory will be investigated. This will then be followed by an expansive review of what is known about the anti-inflammatory effects of these compounds before concluding with how the anti-inflammatory actions of these compounds align with their other recognized mechanisms of action.

2. Depression, the monoamine theory and the arrival of the SSRIs

Globally, depression represents a massive health challenge affecting over 120 million people (2001), is the leading cause of disability, and the third leading contributor to the global burden of disease (WHO, 2004). Unsurprisingly, depression is also associated with a heavy economic burden, accounting annually for over $1.8 billion in Australia and $44 billion in the United States in direct and indirect costs (Greenberg and Birnbaum, 2005; Greenberg et al., 2003; Hu, 2004; Lim et al., 2000). At present, clinical guidelines in most western countries recommend that individuals with moderate to severe depression be treated with a psychological intervention, such as cognitive behaviour therapy, in combination with either an SSRI or a serotonin norepinephrine reuptake inhibitor (SNRI) (Ellis, 2004; NICE, 2009). In line with this recommendation tens of millions of prescriptions are filled each year for these medications, the majority of which are for the SSRIs (Mant et al., 2004; Pirraglia et al., 2003).

From 1990, when the SSRIs were introduced to the Australian market, to 2002, antidepressant use increased phenomenally, rising by approximately 350%, averaging 13.4% growth annually, with the SSRIs accounting for the majority of this growth from 1995 onwards (Mant et al., 2004). Similar trends have also been observed in the United States (Olfson and Marcus, 2009; Pirraglia et al., 2003). Today there are six marketed SSRI antidepressants: fluoxetine; sertraline; paroxetine; citalopram; escitalopram and fluvoxamine. The term SSRI relates to the fact that these agents bind with very high affinity to the serotonin transporter (5-HTT), inhibiting its reuptake of serotonin (5-HT). However, each of the SSRIs also binds to the norepinephrine (NE) transporter, albeit with a significantly lower affinity than for 5-HTT (Owens et al., 1997). Further, while all the SSRIs possess a comparable ability to inhibit 5-HT reuptake, they are substantially differentiated by their secondary actions on muscarinic, adrenergic, serotonergic and cholinergic neurotransmitter receptors (Owens et al., 1997; Stahl and Felker, 2008).

3. A recognized role in modulating monoaminergic activity

The SSRIs, tricyclic antidepressants (TCAs) and SNRIs are all recognized to alter monoaminergic signalling by blockading 5-HT reuptake, NE reuptake or both (Hyttel, 1993; Owens et al., 1997; Shank et al., 1988). With respect to detailed molecular mechanisms, the SSRIs are perhaps the best characterized. This group of related compounds exhibits extremely high affinity for 5-HTT (Owens et al., 1997). Binding of these drugs to the transporter effectively inhibits the ability of the transporter proteins to remove 5-HT released into the synaptic cleft. While it is commonly assumed that blockade of 5-HTT increases synaptic levels of 5-HT, the actual extracellular increase is quite modest. Indeed, in the short term blockade of 5-HT reuptake results in an inhibition of 5-HT neuronal discharge, decreased 5-HT synthesis and decreased 5-HT release (Adell and Artigas, 1991; Aghajanian and Wang, 1987; Barton and Hutson, 1999; Hjorth and Auerbach, 1994). These inhibitory effects are primarily driven by the fact that increased extracellular levels of 5-HT engage a negative feedback loop involving the 5-HT_{1A} autoreceptors located at somatodendritic sites (Bosker et al., 1997; Ceci et al., 1994; Hajos et al., 1999). In contrast to these acute effects, persistent administration of SSRIs is recognized to downregulate and desensitize 5-HT_{1A} receptors, effectively dampening the level of negative feedback on 5-HT release. This situation results in a progressive resumption of neuronal discharge, and in turn an increase in 5-HT release that raises synaptic levels of 5-HT, ultimately inducing *postsynaptic* 5-HT receptors to become desensitized (Richelson, 2001). The increased availability of 5-HT reduces the degree of negative feedback exerted on release potentials, thus increasing the probability of further 5-HT release.