Future Medicinal Chemistry

Nicotine for psychiatric disease: from nuisance to novel treatment?

"...an inflammatory component underlies synaptic impairment associated with psychiatric disease ... the use of nicotine agonists potentially ameliorates illness – from psychosis to depression through anxiety and bipolar disease – by decreasing inflammation."

Keywords: anxiety syndrome • inflammation • maladaptive synaptic plasticity • nicotinic receptors • post-traumatic stress disorder • schizophrenic psychosis

Intense and/or prolonged stress can trigger a large class of psychiatric conditions which includes schizophrenic psychoses, anxiety spectrum disorders and depression. Data of the last decade are beginning to recognize inflammation as a factor shared by this apparently inhomogeneous set of illnesses. An abnormally large percentage of patients suffering from these conditions also share nicotine-(ab)use as common habit, suggestive of an attempt at self-medication [1]. Evidence of the last two decades shows that activation of the anti-inflammatory reflex, mediated by activation of nicotinic receptors on immune cells, decreases the release of proinflammatory cytokines [2]. The pharmacological or electrophysiological activation of nicotinic receptors has unexplored potential for the treatment of such conditions, particularly for patients refractory to traditional illness-specific treatment.

In this editorial, we will discuss the hypothesis that, since an inflammatory component underlies synaptic impairment associated with psychiatric disease, the use of nicotine agonists potentially ameliorates illness – from psychosis to depression through anxiety and bipolar disease – by decreasing inflammation.

Hyperexcitability & synaptic inhibitory/excitatory ratio

Emerging research is finding a link between the onset of a large family of hyperexcitable psychiatric conditions on the one hand, and, on the other hand, the decrease in the balance between synaptic inhibition and excitation (sI/E). Clinical evidence indicates various levels of synaptic alterations, sharing a *decreased* sI/E as a critical factor triggering hyperexcitable neuropsychiatric conditions. Among these factors, an impaired development and functioning of cortical inhibitory, γ-amino butyric acid (GABA)-ergic interneurons positive for the calcium-binding protein parvalbumin (corresponding to 60% or more of the total number of GABAergic interneurons in the hippocampus and the neocortex) of genetic and/or environmental origin, has been proposed to underlie schizophrenic psychoses [3]. The assessment of a further contribution of excitatory synapses to schizophrenic psychoses is complicated by the psychotic effect of the antagonists of N-methyl D aspartate receptor (NMDAR), which is often interpreted as inhibiting preferentially the GABAergic over the glutamatergic network. In spite of this interpretative complication, evidence is gathering supporting the hypothesis that psychotic states are mostly associated with an increased glutamatergic response mediated by α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR) and at least some class of metabotropic glutamate receptors [4]. Similar to psychoses, depression and anxiety disorders have also been proposed to be linked to, and possibly caused by, a hypofunction of the inhibitory GABAergic function [5], eliciting hyperexcitable states associated with the decrease in sI/E.

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Stress & elevation in proinflammatory cytokine levels in neuropsychiatric disease

Stress is a trigger for a large set of conditions like schizophrenic psychoses, major depression, bipolar disease and anxiety spectrum disorders [6], conditions characterized by incomplete understanding of the etiology and molecular mechanisms, and by the presence of large cohorts of patients refractory to traditional pharmacological treatment.

"xxx."

A connection between stress and the appearance of psychiatric symptoms seems to implicate the activation of at least some components of the innate immune system [7], leading to stress-specific patterns of increased levels of proinflammatory cytokines-like IL-6 and/or TNF-α [8,9]. Not only are the basal levels of these pleiotropic molecules elevated [9] but these cytokines are also released in disproportionately larger amounts and during longer time spans in clinics or animal models of depression [10], schizophrenic psychoses [8], disorders of the anxiety spectrum [11] and other psychiatric disorders [12].

Proinflammatory cytokines & synaptic transmission

In spite of a clear association between stress, inflammation and neuropsychiatric disorder, a causal link between inflammation and synaptic function was lacking until now. Only recent studies are suggesting that proinflammatory cytokines can directly affect synaptic function. For instance, it has been shown that TNF-α increases the size of the synaptic excitatory response of amino-propionic acid-receptor (AMPAR)-mediated currents [13], and that IL-6 decreases γ-amino butyric acid type A receptors ($GABA_A$Rs)-mediated responses [14]. Interestingly, both effects appear to be mediated by changes in density and/or distribution of synaptic receptors, possibly due to interference by the cytokines with the intracellular displacement and migration of AMPA- and $GABA_A$ receptors, respectively. In both cases, in turn, an sI/E decreased by the combined action of IL-6 and TNF-α leads to increased behavioral excitability, which in turn – if left unchecked chronically of for long periods of time – could jeopardize the functional integrity of brain circuits critically and specifically associated with different neuropsychiatric illnesses.

The association between a particular illness and the type of stress triggering a specific mode of a pathologic episode (psychotic episode in schizophrenia, aggression and flashbacks in PTSD, panic attack, seizure in epilepsy, etc) would be determined by genetics and by the particular pattern of cytokine level alteration associated with the stressor. The specificity, extent and complexity of the immune response to different types of stress prevent a one-size-fits-all solution to this problem.

These findings might be interpreted with the hypothesis that a temporary decrease in sI/E may elicit a benefit to the stressed subject in terms of behavioral hyperactivity, teleologically aimed to overcoming the stressor. The presence of overly intense, prolonged and/or repeated stress would turn such an evolutionary advantage into a risk factor associated with detrimental plasticity of multiple neural substrates caused by a sustained sI/E, taking the forms of different neuropsychiatric conditions depending on its intensity, temporal pattern and success in terms of stressor defeat [15]. An obvious corollary of this hypothesis leads to the search for treatments aimed to minimize the long-term inflammatory damage caused by prolonged and/or repeated stress.

Among the open questions critical to understanding the relationship between mental disease and inflammation: the role of inflammation of CNS elements (microglia, astrocytes and neurons themselves) versus peripheral inflammation; what is the specific contribution of the innate versus adaptive immune system and what are the transmitter/receptor systems mediating the immune–neural interactions.

Autonomic system & inflammation

The autonomic system has important and incompletely understood effects on the onset, maintenance and interruption of inflammation. While the activation of cholinergic terminals seems to activate inflammation through muscarinic receptors [16] (which are activated by nanomolar concentration of the endogenous agonist), higher concentrations of ACh – released locally by peripheral immune organs regulated by sympathetic innervation – produce the opposite effect [17]. Tracey's group and others have shown that vagal nerve stimulation reduces peripheral effects of inflammation by activating the sympathetic branch of the vagal nerve [2]. The release of epinephrine stimulates a class of splenic cholinergic T_h regulatory lymphocytes, which in turn release acetylcholine at local micromolar concentrations, sufficient to activate α_7 nicotinic receptors and eventually inhibit the release of proinflammatory cyto-

kines from a different type of splenic lymphocytes. Ongoing research is identifying similar mechanisms within the CNS [18].

Anti-inflammatory role of nicotine & neuropsychiatric illness

Nicotine use and abuse has a higher than normal incidence in the cohort of psychotic, depressed, PTSD and other neuropsychiatric disease patients. While a central contribution to nicotine addiction is clearly mediated by direct effects of nicotine on neurons, the disproportionate extent of nicotine (ab-)users among psychiatric disease sufferers may be related to activation of the anti-inflammatory pathway. The findings reported in the previous paragraphs have triggered a number of studies aimed at assessing the potential of nicotinic receptor activation in the treatment of psychiatric disease. On the one hand, electrophysiological studies have been undertaken for determining whether the stimulation of autonomic nerves like the vagal nerve can trigger peripheral responses limiting detrimental central effects of inflammation [17]. Recent work has shown that the inhibition of inflammation through vagal nerve stimulation exerts a nicotinic receptor-mediated protective effect on stress-induced synaptic impairment, at least on GABAergic synapses [19]. On the other hand, the pharmacological use of nicotinic receptors agonists might represent an important complementary viable avenue in the search of long sought-relief for at least some groups of patients suffering from hyperexcitable conditions, particularly for the unfortunately large cohorts resistant to traditional treatment. Particularly, the use of allosteric α_7 nicotinic agonists [20] has the potential to offer a solution with minimal undesirable effects associated with nicotine addiction and cardiovascular stress and other undesirable cholinergic effects like those deriving from the use of cholinesterase inhibitors.

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