Towards A Multimodal Treatment of Depression: A Minireview on the Potential Role of Antibiotics

B. Yulug*[,1,2] and W.-R. Schäbitz[3]

[1]*Neuron-Neuropschiatry Center, Izmir, Turkey;* [2]*Brain Research Laboratory, University of Yeditepe, Istanbul, Turkey*

[3]*Department of Neurology, Evangelisches Krankenhaus Bielefeld, Teaching Affiliate of University of Munster, Bielefeld, Germany*

Abstract: In regard of increasing rates of post-stroke mood disorders and evidences of a neuroprotective effect of antbiotics after cerebral ischemia we have reviewed the clinical relevance of the neuroprotective and mood stabilizing effects of antibiotics in the light of the basic pathophsiology of depression.

Keywords: Cerebral ischemia, post-stroke mood disorders, neuroprotection, antibiotics.

INTRODUCTION

The overwhelming progress in basic neuroscience research has led to many therapeutic advances for neurological and psychiatric diseases including a potentially improved perspective for a neuroprotective therapy. Antibiotics are interesting candidates as besides their well known antiinfectious activity they possess an array of neuroprotective functions such as prevention of neuroinflammation, mitochondrial mediated cytochrome c release, microglial activation and glutamate neurotoxicity [1-4]. Their attenuating effect on glutamate excitotoxicity has recently been associated with the stimulating effect on astroglial protein expression that is responsible for removing glutamate from the extracellular space [4]. Antibiotics may have a therapeutic potential for several types of neurological and psychiatric disorders such as cerebral ischemia, depression and schizophrenia.

In addition to excessive release of excitatory neurotransmitters and deficient neurotrophic support, preclinical and clinical studies have demonstrated that major depression is also associated with an impaired inflammatory response [6-12]. This includes activation of the inflammatory response system resulting in an increased production of proinflammatory cytokines during the course of major depression [13]. Moreover, recent evidence suggests that the role of glutamate, and its receptors in antidepressant activity is rapidly replicating [14-16]. This was suggested by preclinical and clinical studies showing that antidepressant drugs directly or indirectly reduce N-methyl-D-aspartate glutamate receptor function and drugs that reduce glutamatergic activity or glutamate receptor-related signal transduction may also exert mood stabilizing effects [17-22,56].

These findings could be also important for post-stroke depression, one of the most frequent complications of a stroke [5,23]. It has recently been hypothesized that post-stroke depression is associated with the release of proinflammatory cytokines and indoleamine 2,3-dioxygenase which may lead to a depletion of serotonin in paralimbic regions. These findings suggest, for example, a therapeutic role of selective serotonin re-uptake inhibitors [24]. Although the postischemic neuroprotective effect of antibiotics has been already shown in various studies [25-33], the antidepressant effect of antibiotics is relatively unknown.

THE ANTIDEPRESSANT ROLE OF ANTIBIOTICS

Minocycline

Minocycline is a second-generation tetracycline and one of the most promising neuroprotective agents currently in clinical trials in several neurodegenerative diseases [1,35-40]. In addition to its anti-inflammatory effects in central nervous system disorders, it has also been shown to have multiple beneficial effects in brain injury. This includes the inhibition of microglial activation, glutamate toxicity and caspase-1-activated apoptosis and decreasing activity of p38 mitogen activated protein kinase (p38 MAPK). Minocycline also attenautes the release of inducible nitric oxide synthetase [1,34]. These actions of minocycline altogether are thought to be responsible for its success in various brain injury models including focal and global cerebral ischemia [25-33]. Interestingly, recent studies of minocycline reveal that it has also neurogenesis inducing activity and antidepressant-like neuroprotective actions [41,42].

Recent studies reported that pro-inflammatory mediators are consistently increased in patients with major depression and are normalized after the antidepressant treatment [43-45]. In this respect, it can be hypothesized that inflamation modulating effects of antibiotics decrease the deleterious effects of neuroinflamation on newborn neurons which may in turn provoke hippocampal neurogenesis in the context of a major depression.

*Address correspondence to this author at the Neuron-Neuropsychiatry Center, Izmir-Turkey; Tel: 0090 506 406 97 14; Fax: +90 216 5780575; E-mail: yulug@gmx.de

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Molina-Hernandez *et al*., showed that minocycline reduced immobility and synergized the antidepressant actions of subthreshold doses of desipramine and glutamate receptor antagonists using the forced swimming test in mice [46]. These findings are supported by a very recent animal study showing that intracerebroventricularly infused minocycline reduced not only the neuronal damage, but also the anxiety-like behavior which was found to correlate with measures of microglial activation [47]. Both studies suggested that a modulation of inflammation may be beneficial in protecting the brain and preventing the development of affective disorders.

Additional animal studies suggested a role of minocycline also in cognitive and pain disorders which is important in the light of increasing evidence for cognitive and somatic symptoms during the course of a major depression. In this respect, Hunter *et al*., showed that minocycline protected basal forebrain cholinergic neurons from immunotoxic injury in mice and reversed the lesion associated cognitive impairment [48]. Intrathecal given minocycline has been also found to attenuate peripheral inflammation-induced hyperalgesia by inhibiting p38 MAPK in experimental models of tissue injury and inflammation-evoked pain [49]. These findings altogether suggest its potential effectiveness in treating somatic symptoms commonly found in patients with major depression and somatoform disorders.

Interestingly, these preclinical findings are supported by pivotal clinical data. Levine *et al*., described that the addition of minocycline 150 mg/day to clomipramine not only led to significant improvement of depressive symptoms but was also associated with the resolution of facial pain [50].

ßeta-Lactam Antibiotics

Beta-lactam group antibiotics are potent antibiotics inhibiting bacterial synthetic pathways [31]. It has been shown that ßeta-lactam antibiotics are the first practical pharmaceuticals capable of increasing the expression and activity of glutamate transporters which are important in preventing glutamate neurotoxicity [3,4,31]. In this respect, Beta-lactam antibiotics were found to be neuroprotective when used in models of ischaemic injury and motor neuron degeneration [4,31,51,52]. Interestingly, recent findings showed that excessive glutamatergic transmission is associated with a depressive-like behavior that can be balanced by enhanced glutamate uptake [53-57]. This underlines not only the role of glutamate overload during depression but also the capability of beta-lactam antibiotics to stimulate glutamate uptake which may be responsible for their antidepressant-like activity.

The first study, conducted by Volchegorskii and Trenina showed that injection of reterpen, ceftazidime, and thienam in mice led to significant shortening of the duration of behavioral despair measured by the tail test, and intensified the exploratory and orientation activity in the open field test which was found to relate to changes in serotonin sensitivity [58]. Despite small differerences in frequency and amount of dosages between the administered drugs, this study provided strong preclinical evidence for the antidepressant effect of beta-lactam antibiotics. These findings were supported by another study investigating the antidepressant-like effect of ceftriaxone in mice. Mineur *et al*., showed that ceftriaxone increased immobility and freezing in the forced swim and tail suspension tests in mice, which is consistent with the hypothesis that enhanced uptake of glutamate might have antidepressant-like effects [59].

Rapamycin

Rapamycin is a macrolid group antibiotic widely used in clinical routine as an immunosuppressant after organ transplantation [60-62]. A well-documented action of rapamycin is its activity to inhibit mammalian target of rapamycin (mTOR), which is an important regulator of autophagy. Autophagy is a cell death process that plays a crucial role by controlling the levels of accumulation of aggregate proteins and toxic substances [63-65]. The important role of autophagy in neurodegenerative disorders has been already shown and there is rapidly increasing evidence suggesting that the increased process of autophagy can lead to prominent neuroprotective effect [66-73]. Additionally, enhanced autophagy has been also found to correlate with the mood stabilizing effect of lithium which is a well known neuroprotective agent [74]. These findings suggest not only the neurodegenerative nature of mood disorders but also a possible association between the neuroprotective effect of mood stabilizer agents and autophagy. Interestingly, rapamycin has been recently shown to interact with signaling pathways which are activated through depression and/or stress related decrease of neurotrophic support leading to the destabilization of the mitochondrial membrane which may in turn result in neuronal cell death [75-78]. These findings were supported by an interesting study demonstrating that subchronic administration of rapamycin resulted in an antidepressant-like activity in two different but widely accepted models of depression in mice and rats [79].

The study also suggested that mTOR inhibition may be a potential new target for the treatment of affective disorders.

However, it should be also noted that albeit acting *via* different mechanisms, the similar effects of lithium and rapamycin on autophagy give us strong evidence for the important role of these pathways for the development and the treatment of effective disorders.

CONCLUSION

In addition to their interesting antidepressant effects, all above mentioned antibiotics have been already shown to be neuroprotective in various *in vivo* and *in vitro* models of cerebral ischemia [25-32,72]. The neuroprotective effect is supported by a recent study showing that patients with acute stroke had significantly better outcome after minocycline treatment [80].

As summary, this review summarizes the current data that some antibiotics in common with mood stabilizators may have antidepressant and neuroprotective actions which should be evaluated with further studies.

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