Agomelatine: Protecting the CNS from the Effects of Stress

Stefania Maccari¹ & Ferdinando Nicoletti^{2,3}

¹ NeuroPlasticity Team, UMR 8576 CNRS, University Lille, North of France

² Department Human Physiology and Pharmacology, Sapienza University of Rome, Italy

³ I.N.M. Neuromed, Pozzilli, Italy

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Major depression affects about 10% of the population worldwide, and is currently treated with drugs that enhance monoaminergic transmission in the CNS, for example, serotonin/noradrenaline uptake blockers or inhibitors of monoamino oxydase. However, drug treatments for depression are far from ideal, and often inadequate. Despite the increase in the available therapeutic armamentarium 50% of depressed patients remain untreated. In addition to the need to administer the drugs for weeks or months before seeing clinical benefit, side effects are still a serious problem even with the newer monoaminergic medications. There is still a great need for new effective drugs with faster onset of clinical activity and better profile of safety and tolerability. For this reason, the field has moved beyond monoamines in an attempt to identifying new therapeutic tools. Agomelatine, a synthetic analogue of the pineal hormone, melatonin, is one of the products of this new avenue. Agomelatine acts as a potent agonist of MT1 and MT2 melatonin receptors, and can also block 5HT2c serotonin receptors. By activating melatonin receptors, agomelatine corrects the desynchronization of circadian rhythms, which contributes to the pathophysiology of mood disorders [1–5]. The anti-5HT2c receptor activity likely accounts for the anxiolytic properties of agomelatine [6]. In patients with moderate and severe depression, agomelatine (25–50 mg/day) shows clear-cut efficacy in short- and long-term placebo-controlled studies [7–10]. In addition, recent studies show that the antidepressant activity of agomelatine is comparable or even superior to that exhibited by classical antidepressants, such as venlafaxine, fluoxetine, or sertraline [11–13]. Because of its unique pharmacological profile, agomelatine does not cause adverse effects that are typical of selective serotonin reup-

take inhibitors (SSRIs) or other classical antidepressants, such as weight gain, sexual dysfunction, and sleep problems. All this led to the approval of agomelatine by EMEA (the European Medicines Agency) for the treatment of major depression.

In preclinical studies, agomelatine attenuates depression-like behavior induced by a learned helplessness paradigm or chronic mild stress, and reduces the immobility time in the forced swim test [5,14–15]. The basic research on agomelatine has been extended to models that take into account the impact of stressful life events on the pathophysiology of depression and anxiety. Rats exposed to prenatal restraint stress (chronically administered to the mothers during pregnancy) develop (mal)adaptive changes in neuroplasticity that have been related to their depression- and anxiety-like behavior in the adult life. These changes include a reduced neurogenesis in the hippocampal dentate gyrus, changes in the expression of brain-derived neurotrophic factor (BDNF) and glucocorticoid receptors in the hippocampus, and changes in the expression and/or activity of mGlu2/3 and mGlu5 metabotropic glutamate receptor subtypes, which have been linked to the pathophysiology of anxiety and depression. All these changes are reversed by chronic agomelatine treatment [16]. Agomelatine also dampens the increase in glutamate release induced by acute stress in the rat frontal/prefrontal cortex [17]. In line with these data, Dagyte et al. have found that agomelatine treatment reverses the reduction in Fos protein expression in the hippocampus of adult rats exposed to daily footshock stress. As c-fos induction is an established marker of neuronal activation, these data demonstrate that agomelatine normalizes the pathological changes in neuronal activity induced by chronic stress [18].

All together these studies show a protective action of agomelatine against the harmful effect of stress on the CNS. Agomelatine appears to correct the “allostatic” changes in neuroplasticity that develop to chronic stress, and eventually lead to behavioral abnormalities, mood disorder, and anxiety. The identification of the precise mechanisms by which activation of MT1/MT2 receptors and 5HT2c receptor blockade restores neuronal homeostasis is a challenge for the near future.

Conflict of Interests

The authors have no conflict of interest.

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