Mechanism of action of agomelatine: a novel antidepressant exploiting synergy between monoaminergic and melatonergic properties

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ISSUE:

A striking and unexpected pharmacologic synergy has been shown between antagonist actions at serotonergic 5HT2C receptors, and agonist actions at melatonergic receptors by agomelatine, a drug that has both of these properties.

Take-Home Points

1. Blocking serotonergic 5HT2C receptors causes the enhanced release of both dopamine and norepinephrine in the prefrontal cortex.

2. Stimulating melatonergic MT1 and MT2 receptors causes synchronization of circadian rhythms.

3. When 5HT2C antagonism is combined with MT1 and MT2 agonism, this results in unexpected synergistic actions, including much greater dopamine and norepinephrine release in the prefrontal cortex than with 5HT2C antagonism alone, as well as several actions not seen at all with either action alone, including increases in brain derived neurotrophic factor (BDNF) in the prefrontal cortex, and reduction of stress-induced glutamate release in the amygdala.

4. In theory, this synergy accounts for the antidepressant actions of the monoaminergic/melatonergic agent agomelatine and may account for its unique clinical profile.

The new antidepressant agomelatine, marketed in many countries but not in the U.S., has a mechanism of action quite different from any other antidepressant. It combines antagonist actions at serotonergic 5HT2C receptors with agonist actions at melatonergic MT1 and MT2 receptors (Figure 1). Neither mechanism alone has any evidence of efficacy in depression, but when combined in a single molecule, agomelatine has proven antidepressant actions.

Pharmacologic Synergy of Agomelatine

Normally, 5HT2C receptors inhibit downstream dopamine and norepinephrine release from the prefrontal cortex (Figure 2A). When these 5HT2C receptors are blocked, dopamine and norepinephrine release is disinhibited in the prefrontal cortex, and the levels of dopamine and norepinephrine increase (Figure 2B). 5HT2C antagonist action is one of the multiple pharmacologic properties of many antidepressants, and may thus contribute to the antidepressant efficacy of quetiapine, olanzapine, mirtazapine, and possibly asenapine; some tricyclic antidepressants; and other known antidepressants.

Normally, stimulating melatonergic receptors has the effect of “resynchronization” circadian rhythms without altering monoamines. However, when MT1/MT2 stimulation is combined with 5HT2C antagonism, a striking and unexpected potentiation of dopamine and norepinephrine release occurs in the prefrontal cortex (Figure 3). This is not the only example of synergy between these 2 mechanisms. A serendipitous finding of synergy between 5HT2C antagonism and
MT1/MT2 agonism has now been demonstrated as well for increases in brain derived neurotrophic factor (BDNF) (Figure 4)6 and for blocking stress-induced release of glutamate (Figure 5).7

How does this synergy occur, and what are the functional consequences of combining 5HT2C antagonism with MT1/MT2 agonism in depressed patients? It is possible that the actions of agomelatine are especially targeted at the suprachiasmatic nucleus, the brain’s pacemaker; this is where circadian rhythms are regulated and where both 5HT2C receptors and MT1/MT2 receptors are expressed in abundance.1,2
It is also possible that separate actions in different brain areas may also account for some of the observed pharmacologic synergies. Where these various receptors exist in close physical contact, there is even the possibility of interaction of the receptors through heterodimerization. However, the exact mechanism of how simultaneous actions at 5HT2C and MT1/MT2 receptors is synergistic remains under active investigation.

**Monoaminergic–Melatonergic Synergy and the Clinical Profile of Agomelatine**

To the extent that restoring dopamine and norepinephrine neurotransmission results in antidepressant action, this may explain in part the antidepressant mechanism of agomelatine, which combines 5HT2C antagonism with MT1/MT2 agonism (Figure 1). Indeed, this could theoretically underlie the observation...
that agomelatine has robust actions in treating anhedonia,9 emotional blunting,10 daytime sleepiness,11 cognition, attention, and psychomotor retardation,12 without causing sexual dysfunction.13

These clinical actions of agomelatine in depression are consistent with its known pharmacologic effects on dopamine and norepinephrine—and not on serotonin—as dopamine and norepinephrine deficiencies have been theoretically linked to “reduced positive affect,”1,8 namely depressed mood, loss of happiness/joy, loss of interest/pleasure, loss of energy/enthusiasm, decreased alertness/cognitive functioning/attention/concentration, and decreased self-confidence.8 Clinical studies of agomelatine’s actions have the profile of improving reduced positive affect,9–13 and this differentiates agomelatine from serotonergic antidepressants

Figure 2B. 5HT2C antagonists increase dopamine and norepinephrine release. When serotonergic 5HT2C receptors on GABA-ergic interneurons in the brainstem are blocked by a 5HT2C antagonist such as agomelatine, this disinhibits downstream dopamine and norepinephrine release in the prefrontal cortex.1–3
such as selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) that do not have particularly robust actions on restoring reduced positive affect, but are more consistent in their therapeutic effects in reducing the increased negative affects that characterize some depressed patients, such as guilt/disgust, fear/anxiety, hostility, irritability, and loneliness.

Summary
Agomelatine is an antidepressant with a novel mechanism of action, namely the blockade of 5HT2C receptors with simultaneous stimulation of MT1/MT2 receptors. These actions are synergistic for various pharmacologic effects associated with antidepressant efficacy, and define a unique clinical profile of an antidepressant that not only reduces negative affects such as guilt and anxiety but has particularly robust clinical actions on improving positive affect, namely targeting the improvement of anhedonia, emotional blunting, daytime sleepiness, cognition, attention, and clinical retardation without causing sexual dysfunction.

References
5. Chenu F, El Mansari M, Blier P. Electrophysiological effects of repeated administration of agomelatine on the...


