Novel mechanism of antidepressant action: norepinephrine and dopamine disinhibition (NDDI) plus melatonergic agonism

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All known antidepressants enhance monoamine neurotransmission, and most do so by blocking one or more of the reuptake transporters for serotonin, norepinephrine and/or dopamine (Stahl, 2000). Now comes agomelatine, a new agent that enhances norepinephrine and dopamine neurotransmission by a unique mechanism, namely 5-HT$_{2C}$ antagonism (Millan et al., 2003; Millan, 2005). Agomelatine is also a direct agonist at melatonin 1 (MT$_1$) and MT$_2$ receptors and a 5-HT$_{1B}$ antagonist (Millan et al., 2003).

First reuptake inhibitors, now disinhibitors

Clinicians are well aware of how the popular monoamine reuptake inhibitors enhance synaptic actions of serotonin, norepinephrine and dopamine. That is, serotonin selective reuptake inhibitors (SSRIs) enhance the synaptic action of serotonin by blocking the serotonin transporter (SERT); serotonin norepinephrine reuptake inhibitors (SNRIs) enhance the synaptic action of serotonin and norepinephrine by blocking both SERT and the norepinephrine transporter (NET); norepinephrine and dopamine reuptake inhibitors (NDRIs) enhance the synaptic actions of norepinephrine and dopamine by blocking both NET and the dopamine transporter DAT, and so on (Stahl, 2000).

A new concept now arises from agents with a novel psychopharmacological mechanism, namely disinhibition. That is, certain monoamine circuits are under tonic inhibition by serotonin (Figure 1a), and when that inhibition is removed, these circuits can now release their neurotransmitters (Figure 1b) (Dremencov et al., 2005; Filip and Cunningham, 2003; Millan, 2005; Porras et al., 2002). Circuits no longer under tonic inhibition are said to be ‘disinhibited’. This is not psychopharmacological double-talk, but a term of art that also means ‘turned on’.

Serotonin inhibits norepinephrine and dopamine release in prefrontal cortex

Normally, noradrenergic circuits arising from the brainstem locus coeruleus that project to the prefrontal cortex are under tonic inhibition from GABA interneurons either in the brainstem as depicted in Figure 1a or in the prefrontal cortex (Dremencov et al., 2005; Filip and Cunningham, 2003; Millan, 2005; Porras et al., 2002). Serotonin provides excitatory input to 5-HT$_{2C}$ receptors to drive these GABA interneurons. GABA interneurons in turn tonically inhibit norepinephrine circuits (Figure 1a). The same thing occurs at dopamine circuits arising from the brainstem ventral tegmental area that project to the prefrontal cortex (Figure 1a) (Dremencov et al., 2005; Filip and Cunningham, 2003; Millan, 2005; Porras et al., 2002). Thus, norepinephrine and dopamine circuits are inhibited by the normal tonic release of serotonin onto 5-HT$_{2C}$ receptors (Figure 1a).

5-HT$_{2C}$ antagonists are norepinephrine and dopamine disinhibitors (NDDIs)

If the 5-HT$_{2C}$-mediated inhibition of norepinephrine and dopamine release is blocked, neurotransmission at these neurons is ‘disinhibited’ or turned on (Figure 1b) (Dremencov et al., 2005; Filip and Cunningham, 2003; Millan, 2005; Porras et al., 2002). Thus, 5-HT$_{2C}$ antagonists are norepinephrine and
dopamine disinhibitors or NDDIs (Figure 1b). Although the combination of 5-HT<sub>2C</sub> antagonism with melatonergic agonist actions by agomelatine is a novel mechanism for an antidepressant, numerous agents with proven antidepressant actions are known to have 5-HT<sub>2C</sub> antagonist properties, including fluoxetine, mirtazapine, trazodone, various tricyclic antidepressants and numerous atypical antipsychotics (Millan et al., 2003; Millan, 2005; Ni and Miledi, 1997; Shayegan and Stahl, 2004; Stahl, 1998). However, until recently, these 5-HT<sub>2C</sub> antagonist actions have largely been ignored and antidepressant actions of these drugs have been attributed to other pharmacological properties. With agomelatine, there is now increasing attention being paid to 5-HT<sub>2C</sub> antagonism itself as a mechanism of enhancing norepinephrine and dopamine neurotransmission in the prefrontal cortex since this shows ‘antidepressant’ actions in animal models (Bourin et al., 2004; Millan et al., 2003; Millan, 2005). The question now is whether this novel NDDI mechanism of monoamine enhancement via 5-HT<sub>2C</sub> antagonism causes antidepressant actions in humans.

**Melatonergic actions**

Agomelatine combines NDDI actions as a 5-HT<sub>2C</sub> antagonist with direct agonist actions at MT<sub>1</sub> and 2 MT<sub>2</sub> receptors (Millan et al., 2003; Millan, 2005). Melatonergic actions are much more potent than the 5-HT<sub>2C</sub> actions of agomelatine, and have been shown to change sleep physiology in experimental animals (Armstrong et al., 1993; Millan et al., 2003; Millan, 2005). Although melatonergic actions are not known to cause antidepressant effects in humans (Srinivasan et al., 2006), the question now is whether agomelatine causes circadian phase shifts or hypnotic effects.

**Figure 1.** (a) Serotonin inhibits dopamine and norepinephrine release at 5-HT<sub>2C</sub> receptors. Tonic release of serotonin (red circle at the bottom) excites GABA (gamma amino butyric acid) neurons in the brainstem, causing tonic inhibition of both norepinephrine and dopamine release in the prefrontal cortex (red circles at the top). (b) Mechanism of action of a 5-HT<sub>2C</sub> antagonist: norepinephrine and dopamine disinhibition (NDDI). NDDI actions are shown here, with a 5-HT<sub>2C</sub> antagonist blocking serotonin at 5-HT<sub>2C</sub> receptors on GABA interneurons (red circle at the bottom). This removes the tonic inhibition of serotonin on norepinephrine and dopamine release, so the levels of both of these monoamines are increased in the prefrontal cortex (red circles at the top). [Reproduced with permission from Stahl SM, Essential Psychopharmacology (3rd edn), In Press. New York: Cambridge University Press. © Neuroscience Education Institute.]
in depressed patients that may contribute to the therapeutic profile of an NDDI such as agomelatine (Lewy et al., 2006).

Antidepressant and sleep properties of agomelatine

In this issue of IJNP Olié and Kasper report the results of a pivotal trial of agomelatine in major depressive disorder that establish the novel mechanism of agomelatine as having clinical antidepressant effects. In fact, this study is one of three such positive trials (Kennedy and Emsley, 2006; Loo et al., 2002; Olié and Kasper, 2007). So far, the clinical profile of agomelatine—hypothetically acting through disinhibition of prefrontal norepinephrine and dopamine—is that of antidepressant actions without sexual dysfunction or weight gain. This is not surprising, since duloxetine, a proven antidepressant with this same profile, appears to enhance these same neurotransmitters but through reuptake inhibition (norepinephrine and dopamine reuptake inhibition or NDRIs) rather than through norepinephrine and dopamine disinhibition (NDDI actions) (Stahl et al., 2004). Hopefully further clinical research will clarify whether the enhancement of norepinephrine and dopamine release by agomelatine is associated with improvement of symptoms of reduced positive affect theoretically linked to dysfunctional dopamine neurotransmission such as depressed mood but also loss of happiness, joy, interest, pleasure, alertness, energy, enthusiasm and self-confidence (Nutt et al., 2006). These symptoms may be less well targeted by serotonin reuptake inhibitors, or may even be side-effects caused by serotonin reuptake inhibitors (Nutt et al., 2006). It will be necessary for agomelatine to be extensively tested in head-to-head comparisons with NDRIs, SSRIs and SNRIs in order to determine whether there are any advantages or disadvantages to agomelatine compared to standard antidepressants. It will also be interesting to see the results of adding agomelatine to serotonin reuptake inhibitors in patients with major depressive disorder.

In this issue of IJNP Quera Salva et al. (2007) provide the first evidence that the sleep effects of agomelatine in major depressive disorder may be unique and consistent with the unique mechanism of action of this drug at 5-HT\textsubscript{2C}, MT\textsubscript{1} and MT\textsubscript{2} receptors. Both 5-HT\textsubscript{2C} antagonism as well as melatonergic agonism could theoretically enhance sleep in major depressive disorder, something that might enhance remission rates as suggested in recent studies combining a hypnotic with a SSRI (Fava et al., 2006). Hypothetically, a melatonergic agent given once daily at night, as agomelatine was in all three positive pivotal trials in major depressive disorder (Kennedy and Emsley, 2006; Loo et al., 2002; Olié and Kasper, 2007) might be expected to cause phase advance, and ‘synchronize’ biological rhythms, especially in those depressed patients with phase delays in their circadian rhythms (Lewy et al., 2006). Although the study of Quera Salva et al. was not designed to show chronobiological actions, sleep onset did advance. Perhaps more interesting is the increase in slow-wave sleep after agomelatine in depressed patients, especially during the first sleep cycle. This latter action is consistent with 5-HT\textsubscript{2C} antagonist effects of agomelatine, since increased slow-wave sleep is reported in association with other 5-HT\textsubscript{2C} antagonists such as trazodone and ritanserin, but is not caused by melatonergic actions (Declerck et al., 1987; Mouret et al., 1988). However, it should be pointed out that the study of Quera Salva et al. is an open-label study, and the results should be interpreted with caution, as mentioned by the authors. Double-blind studies with larger sample sizes are needed to confirm the novel sleep properties of agomelatine in depressed patients suggested in the open-label study of Quera Salva et al.

Agomelatine, an antidepressant with novel NDDI and melatonergic actions

The reports of Olié and Kasper, and Quera Salva et al. together confirm the antidepressant actions of agomelatine and are consistent with its putative novel pharmacological mechanism of action as a 5-HT\textsubscript{2C} antagonist that acts as an NDDI, causing release of both norepinephrine and dopamine in the prefrontal cortex, in addition to directly stimulating both MT\textsubscript{1} and MT\textsubscript{2} melatonin receptors. Further research will hopefully clarify the differences between the profiles of depressed patients who might best benefit from agomelatine compared to those who might best benefit from monoamine reuptake inhibitors as it is likely that an agent with a novel mechanism of action will find novel uses and niches in the treatment of major depressive disorder and beyond.

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Statement of Interest

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