Expanding Clinical Knowledge on Fluvoxamine

An international workshop, Amsterdam, November 17th 2006

Welcome to the first edition of International Medical News in 2007. Expanding Clinical Knowledge of Fluvoxamine was an international Solvay Pharmaceuticals-sponsored workshop attended by over 100 delegates from around the world and held in the unique and impressive 17th century domed Koepelchurch in central Amsterdam. An internationally renowned faculty discussed recent investigations on the role of sigma-1 receptors in the mechanism of action of the selective serotonin reuptake inhibitors (SSRIs) and evaluated the important clinical implications of this emerging mechanism of action. It is now recognised that sigma-1 receptors are involved in the modulation of the N-methyl-D-aspartate (NMDA) type of glutamate receptor, and contribute to the anti-depressant effect of the SSRIs. Intriguing new research also suggests that sigma-1 receptors are involved in neuroplasticity and cognitive function. These insights raise the possibility that patients may benefit from SSRI therapy in ways that have traditionally not been recognised. In bringing this workshop review to your attention, we hope that our scientific program may contribute to the optimal treatment of your patients with depression.

This edition of IMN is dedicated to the memory of Professor Guy Debonnel who died suddenly on the 4th of November 2006, shortly before he was due to join the faculty of this workshop. He will be remembered by his patients, students and colleagues for his kindness and generosity of spirit.

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Current knowledge on sigma receptors and their potential role in depression

Sigma receptors represent an emerging novel target for the therapeutic treatment of a diverse range of neuropsychiatric diseases including schizophrenia, depression and cognition and also brain ischaemia. Mindful that many clinicians are perhaps currently not familiar with the sigma receptor, Professor Tangui Maurice (INSERM U. 710, University of Montpellier II, EPHE, Montpellier, France) reviewed the history, distribution, activation and physiology of this dynamic intracellular protein.

First described in 1976 as opiate receptors, sigma receptors were later determined to be a distinct class of non-opiate receptors with at least two subtypes, sigma-1 and sigma-2. The sigma-1 receptor was cloned in 1996, prompting the generation of sigma-1 knockout mice and furthering the understanding of its molecular and cellular biology.

Although no endogenous ligand of sigma-1 receptors has yet been identified, the literature currently points to the involvement of neurosteroids, such as dehydroepiandrosterone sulphate or progestosterone. A biphasic bell-shaped dose response curve occurs for sigma ligands, suggesting that low doses of sigma ligands activate one subtype of sigma receptors for which they have high affinity, whereas higher doses may activate another or other subtype(s) for which they have a lower affinity. Acute activation of sigma-1 receptors triggers both G-protein-dependent and -independent signal transduction pathways that modulate K+ and Ca2+ currents (Figure 1). Sigma-1 receptor ligands also modulate neurotransmitter release, ionotropic (nicotinic) receptors, metabotropic (muscarinic, dopamine, norepinephrine, serotonin and histamine) receptors and intracellular kinase and phospholipase pathways. Chronic sigma-1 receptor activation contributes to the formation and recomposition of membrane lipids rafts, with direct consequences for neuroplasticity.

Selective sigma-1 receptor agonists show antidepressant potential in preclinical behavioural models. For example, in animal models, sigma-1 agonists may alleviate the stress response through regulation of hypothalamic-pituitary-adrenal axis activation. Electrophysiological and biochemical models demonstrate the ability of sigma receptors to modulate important factors in the pathophysiology of depression and/or the mechanisms of action of antidepressants, such as serotonergic neurotransmission in the dorsal raphe nucleus and glutamatergic transmission in the hippocampus.

Unlike the tricyclic antidepressants, SSRIs possess moderate to high affinity for sigma-1 sites (see the next presentation for comparative affinity data). It has been proposed that certain differences in the clinical effects of various antidepressants may, in part, be explained by their interaction with cerebral sigma receptors. The mechanism of action of antidepressants may involve direct or indirect (via neurotransmitter or neurotrophin metabolotropic receptors

ionotopic receptors

voltage-dependent calcium channels

neuron

nucleus

transcription factors

mito.

CAMP

InsP3

Ca2+

ER

InsP3-R

kinases

mito.

Neuron

Figure 1: Activation of the sigma-1 receptor
the brain-derived neurotrophic factor system, BDNF) interactions with sigma-1 receptors. It is likely that the ability of sigma ligands to modulate both glutamatergic and 5-HT transmissions contribute to the antidepressant effects observed in behavioural models. The molecular mechanism underlying the modulation of 5-HT and glutamatergic transmissions by sigma receptors may involve their ability to modulate Ca2+ or K+ signalling.

Recent evidence has shown that persistent hippocampal atrophy can accompany major depression. Such atrophy could be due to a regression of dendritic processes, an inhibition of neurogenesis, or the loss of hippocampal neurons. One theory concerning the action of antidepressants relates to the drugs’ ability to induce an adaptive plasticity in neurons such as neurite sprouting. Sigma-1 receptors may play a significant role in cell morphological changes, specifically in the initiation of neurite outgrowth and sprouting. In cultured PC12 cells, fluvoxamine potentiated the effects of nerve growth factor (NGF); these effects were antagonised by the selective sigma-1 antagonist NE100, indicating that the effects were mediated via sigma-1 receptors (Figure 2). Chronic treatment of cells with fluvoxamine also increased the number of sigma-1 receptors.

Preclinical studies have also shown that the efficacy of sigma-1 receptor agonists is dependent on endogenous neurosteroidal tonus. Circulating steroids appear to exert a tonic modulatory effect on the sigma-1 receptor and therefore on sigma-1 receptor-mediated antidepressant-like effects. It has thus been proposed that the potency of sigma-1 agonists as antidepressants is highly dependent on endogenous neurosteroidal tonus. Depressed patients such as the elderly with decreased levels of neurosteroids, which would be tonically inhibiting sigma receptors to a lesser degree, might be particularly sensitive to such treatments. Other appropriate patients include those with neurodegenerative conditions associated with depression and those with post-partum depression, both associated with depleted neuro(active) steroid tonus.

**Sigma-1 receptors and SSRLs: clinical implication**

Despite several decades of research, and many interesting and promising leads, the changes induced by the antidepressants in the brain remain largely unclear. Several recent lines of evidence, however, suggest that sigma-1 receptors play a role in the pathophysiology of psychiatric diseases, as well as in the mechanism of action of certain SSRIs and some antipsychotic drugs. Professor Kenji Hashimoto (Chiba University Center for Forensic Mental Health, Japan) discussed the multiple emerging roles of sigma-1 receptors in psychiatric diseases, with particular reference to fluvoxamine. Amongst the SSRIs, fluvoxamine has the highest affinity at the sigma-1 receptor (Table 1).

**Table 1: In vitro affinity of various agents for rat sigma-1 binding sites**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Ki (nM)</th>
<th>Sigma-1</th>
<th>Sigma-2</th>
<th>Ki ratio (sigma-1/sigma-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SSRIs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>36</td>
<td>8,439</td>
<td>234</td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>57</td>
<td>5,297</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>S(+)-Fluoxetine</td>
<td>120</td>
<td>5480</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>(+)-Fluoxetine</td>
<td>240</td>
<td>16,100</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>292</td>
<td>5,410</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>1,893</td>
<td>22,870</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td><strong>Tricyclic antidepressants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipramine</td>
<td>343</td>
<td>2,107</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Desipramine</td>
<td>1,987</td>
<td>11,430</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2: Fluvoxamine may facilitate neuronal sprouting in the brain via sigma-1 receptors** (Adapted from Takebayashi et al., 2002)
The neurotrophic hypothesis of depression and antidepressant action was originally based on findings in rodents that acute or chronic stress decreases expression of BDNF in the hippocampus and that diverse classes of antidepressant treatment produce the opposite effect and prevent the actions of stress (Figure 3). These observations led to the suggestion that such changes in BDNF could mediate the structural damage and reduced neurogenesis seen in the hippocampus after stress and the prevention of these effects by antidepressant treatments. Preclinical evidence suggests that the action of antidepressants involves neuroplasticity; for example, antidepressants may exert their therapeutic effects by stimulating neuronal remodelling in the brain. As discussed by Professor Maurice, sigma-1 receptors were shown to play a role in the mechanism of stimulation of NGF-induced neurite sprouting by fluvoxamine. Interestingly, the SSRI sertraline appeared to act as a sigma-1 receptor antagonist in cultured PC12 cells; in combination with fluvoxamine, sertraline reduced to control levels the number of cells with neurite outgrowth.

The role of sigma-1 receptors in cognitive defects suggests promising new therapeutic applications, as revealed by recent preclinical data (Hashimoto et al. 2006). The effects of fluvoxamine and paroxetine on cognitive deficits in mice were investigated after repeated administration of the NMDA receptor antagonist phencyclidine (PCP), known to induce cognitive deficits in healthy human subjects. PCP-induced cognitive deficits were significantly improved by subsequent subchronic (2-week) administration of fluvoxamine (20 mg/kg/day), but not paroxetine (10 mg/kg/day). This effect of fluvoxamine was antagonised by co-administration of NE100, suggesting that the effects of fluvoxamine are mediated via agonistic activity at sigma-1 receptors. These data therefore raise the possibility that sigma-1 receptor agonists such as fluvoxamine may have important clinical potential for the treatment of cognitive deficits in a variety of psychiatric and neurological conditions.

Unpublished positron emission tomography studies provide clear evidence that fluvoxamine, but not paroxetine, binds to sigma-1 receptors in the human brain (Figure 4). Preclinical studies previously revealed that sigma-1 receptor is more abundant in the dentate gyrus of the hippocampal formation, facial nucleus and various thalamic and hypothalamic nuclei. Although clinical evidence of the implications of SSRI interaction with sigma-1 receptors are currently lacking, the available preclinical evidence suggests that selective sigma-1 receptor agonists may have potential as cognitive enhancers during ageing. The sigma-1 receptor also appears to exert a potent neuromodulatory role in the brain that may have relevance in the response to anxiety and stress, depression, learning and cognitive processes, neuroprotection and antipsychotic activity. As fluvoxamine has the highest affinity for sigma-1 receptors amongst the SSRIs, this drug may have particular benefits in the treatment of depressed patients who show features of anxiety/stress, and for whom memory impairment is particularly undesirable, such as in depressed elderly patients, and also in treating psychotic depression.
An intact memory and good cognitive function are necessary essentials for psychological well being. The underpinnings of an intact cognitive system are an integrated central nervous system. Aside from natural age-related cognitive decline, explained Professor Emeritus Ian Hindmarch (University of Surrey, UK), cognitive impairment is a well established and characteristic feature of patients with major depressive disorder and also those with depression and comorbid anxiety. This impairment of cognitive function is most likely a direct consequence of the structural changes caused by neural atrophy that occurs particularly in the hippocampus, amygdala and prefrontal cortex in patients with depression, and is evident by PET imaging (Figure 5).

The problem is compounded by the observation that several antidepressant drugs have intrinsic neurotoxic potential. These drugs can, via direct pharmacological action on alpha-1, anti-cholinergic and anti-histaminic receptors, cause significant neural atrophy. The resulting behavioural toxicity is not only counter-therapeutic but also increases the chance of cognitive failure and/or accident in patients using them. For example, potent alpha-1 receptor blockade by tricyclic antidepressants (amitriptyline has a Ki for alpha-1 blockade of 25) is associated with an increased incidence of falls and poor sensory-motor coordination. The SSRIs typically have a much lower alpha-1 receptor affinity; the Ki for sertraline is 400 and that for fluvoxamine is 7,500. Potent antihistaminic activity causes CNS sedation that may result in meaningful cognitive impairment (mirtazepine Ki = 0.5; amitriptyline Ki = 20; paroxetine ki = 250; fluvoxamine Ki > 10,000). Potent anticholinergic activity may produce features of dementia including cognitive impairment and memory loss (amitriptyline Ki = 1; fluvoxamine Ki > 10,000). Comparative effects of antidepressants on critical flicker frequency (CFF) as a function of anticholinergic activity are illustrated in Figure 6. In contrast to other antidepressants, fluvoxamine, with relatively low anticholinergic activity, has a neutral impact on CFF.

Antidepressants can broadly be classified on the basis of their effects on cognitive function. Whilst many agents may be described as causing either excitation or sedation, others may have neutral or even cognitive enhancing properties. Based on clinical circumstances, it is therefore good practice to avoid using drugs that possess behavioural toxicity and these include the tricyclics, noradrenergic and specific serotonergic antidepressants (NASSAs) and some SSRIs. In this context it is valuable to consider the fact that ligands of sigma-1 receptors not only possess anti-depressant activity but that they can also improve cognitive function and learning and initiate or promote neurogenesis.

Based on currently available data, fluvoxamine appears to be neutral as regards to cognitive effects, with studies demonstrating it has no effect on choice reaction time (CRT, a reliable indicator of psychomotor retardation; Figure 7a) (Hindmarch, 1995). Moreover, fluvoxamine may actually aid learning. In a double-blind, rando-
mised study, fluvoxamine significantly improved performance in the digit symbol substitution test (p = 0.02 vs baseline; Figure 7b) (Perez & Ashford, 1990). Fluvoxamine is also associated with a very low incidence of sexual dysfunction, one of the most fundamental ‘cognitive’ symptoms of depression. These observations likely reflect the fact that fluvoxamine has the highest affinity, of current antidepressants, for the sigma-1 receptor. This creates clinically relevant augmentation of antidepressant action, neurogenesis, cognition (memory and learning) and anxiolysis. Such properties account for the low incidence of behavioural toxicity and underpin the therapeutic utility of fluvoxamine in diverse patient groups with risks for cognitive impairment.

### Suggested further reading

**Current knowledge on sigma receptors and their potential role in depression**


**Sigma-1 receptors and SSRIs: clinical implication**


**Cognition and antidepressants: beyond behavioural toxicity**

