EXTENDING THERAPEUTIC UTILITY OF PSYCHOSTIMULANTS

CNS stimulants (Psychostimulants) are psychoactive drugs which induce temporary improvements in either mental or physical function or both. Although considered as drugs of abuse, psychostimulants could also be used for the pharmacotherapy of various pathological conditions. They are considered as drugs of choice especially in cases where resistance to primary treatment develops and patients stop responding to those pharmacotherapeutic agents [1]. Psychostimulants, have the edge in this regard as few of them (like apomorphine) produce sensitization (a potentiation of behavior) rather than tolerance [2]. This makes them potential candidates for the treatment of various disorders like use of apomorphine for the treatment of Parkinson’s/related motor disorders [3], methylphenidate for the treatment of attention-deficit hyperactivity disorder (ADHD), depressive symptoms, narcolepsy, obesity and postural orthostatic tachycardia syndrome [4].

Depression is one of the largest health issues worldwide. In many of the physical and psychological disorders, depression is an underlying cause and treatment of depression in these individuals is very necessary for the recovery. A wide variety of drugs has been implicated lately for the treatment of depression, like tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and others. However, these antidepressant therapies do not work in around 30% of patients with clinical depression [5]. This resistance to antidepressant therapies may result due to inappropriate dose/treatment duration as well as loss of potency or efficacy over the period of time [6]. However, psychostimulants could be the drugs of choice in these patients and patients with treatment-resistant depression, respond to psychostimulants. Since monoaminergic hypothesis of depression suggests the prognosis of depression due to the deficits of monoamines in synapse, an increased availability of monoamines in synapse, could prevent depression. Psychostimulants although are supposed to increased dopaminergic release in synapse, some other mechanisms might also be involved. Pae et al (2007) have suggested an important role of CART (cocaine- and amphetamine-regulated transcript); a brain-enriched mRNA with a protein product(s) in the treatment of treatment-resistant depression [7].

A role of psychostimulant, for the treatment of fatigue is also suggested by the researchers. Hardy (2009) has reported that methylphenidate at low doses, could be safely used for the treatment of adults with depression, fatigue or apathy [8]. Minton et al (2011) have also reported use of methylphenidate for the management of cancer-related fatigue [9]. However, a major limitation associated with pharmacotherapeutic use of psychostimulants, is their high abuse potential and their self-administration could not be recommended. A safer strategy, therefore, could be, to implant infusion pumps, to supply psychostimulant at a constant rate, without allowing patients to control it. However,
when apomorphine infusion pumps were implanted in patients with Parkinson’s disease \[11\], this resulted in problematic skin reactions and multiple subcutaneous abscesses and necroses resulted due to the multiple apomorphine pump infusions \[12\]. Therefore, future research in this area should focus on lowering the reinforcing effects of psychostimulants, while keeping their therapeutic profiles unaffected. So that these psychostimulants could be administered safely, in combination with other adjuvant therapies, to increase the quality of life in patients with conditions treatable with psychostimulants only.

Dopamine is the primary neurotransmitter involved in the pathophysiology of addiction, and drugs of abuse increase dopaminergic neurotransmission mainly in the Nucleus Accumbens, irrespective of their initial targets. However, 5-Hydroxytryptamine (5-HT; serotonin) could also play an important role in the attenuation/normalization of reinforcing effects of drugs of abuse. We also have proposed an involvement of somatodendritic 5-HT\(_{1A}\) receptors in the pathophysiology of addiction \[2\]. Since somatodendritic 5-HT\(_{1A}\) receptors are found to be supersensitized in drug addicts and psychostimulant addiction is more common in depressed individuals; a desensitization of somatodendritic 5-HT\(_{1A}\) receptors, could lead to the attenuation of psychostimulant addiction. So, desensitization of these somatodendritic 5-HT\(_{1A}\) receptors seems to be one of the common mechanisms underlying the pathophysiology of both addiction and depression. This idea is further strengthened by the fact that prevalence of depression is high in addicts.

In line with this hypothesis, we administered buspirone at the dose of 1.0 mg/kg, along with the apomorphine, to monitor its effects on apomorphine-induced sensitization \[2\]. Repeated administration of buspirone at this dose produces a desensitization of somatodendritic 5-HT\(_{1A}\) receptors. We have observed that a desensitization of these receptors by the repeated co-administration of buspirone could attenuate apomorphine-induced sensitization (a component of addiction). So a formulation containing apomorphine and buspirone could safely be prescribed for the self-administration in individuals with Parkinson’s and related disorders. Another advantage of using buspirone as adjuvant therapy is, that it is clinically prescribed anxiolytic and could be used safely in the human subjects. Further validation of these results and clinical trials are required to implicate these results in humans.

REFERENCES: