

## **Targeting serotonin-1A receptors for improving therapeutic use of opioid analgesics.**

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Morphine and some other opioids are amongst most effective prescription medications for the treatment of pain. However, addiction and hyperalgesia associated with long term use limits the clinical utility of these drugs. Evidence suggests an important role of 5-hydroxytryptamine (5-HT; serotonin), and particularly 5-HT<sub>1A</sub> receptors in addiction as well as analgesic effects of opiate drugs. Studies targeting 5-HT<sub>1A</sub> receptors for the modulation of dopamine and opioid neurotransmission may help to improve therapeutics in pain.

### **Drug Addiction**

Drug addiction is a chronic and relapsing brain disorder, which is characterized by compulsive drug seeking and use, despite its known negative consequences. In general the initial decision to take drugs is voluntary, though it may be a consequence of many biological, psychological and sociocultural factors [1]. However, with continued use, a person's ability on self-control is impaired resulting in escalated drug use as the hallmark of addiction. Emergences of negative emotional states further escalate drug use and abuse [2].

### **Opioid Analgesics and Addiction**

Morphine and other opioid based drugs are amongst most effective prescription medications for pain management [3,4]. However, the risk for misuse and development of opioid addiction is of particular concern for clinicians, community and researchers. There are reports that the prevalence of chronic pain is much higher in subjects with opiate or substance abuse disorder than in the general population [5,6] and that patients treated with morphine like drugs show dependence and drug overuse [7]. The increasing diversion of opioid drugs from therapeutic to non therapeutic use, indicative of addiction, is due to the rewarding and reinforcing effects of these compounds. Opioid agonist based treatments known to reduce some aspects of opioid addiction, often lead to the high relapse rate when discontinued [8]. To improve therapeutics in pain, there is growing need of drugs which

can reduce opioid addiction without reducing its pain killing effects. Understanding opioid neurotransmission in addiction and studies at the interface of opioidergic, dopaminergic and serotonergic systems are equally important. To draw research interest in improving therapeutic use of opioid drugs is the aim of this editorial article.

### **5-HT<sub>1A</sub> Receptors in Opioid Analgesia and Hyperalgesia**

A number of studies show that a significant reduction in the analgesic effects of morphine and other opioid drugs is produced on repeated administration. This is also associated with an increase in the sensitivity to other nociceptive stimuli [9]. The phenomenon often described as hyperalgesia limits the clinical use of these drugs. Although the exact mechanism of morphine-induced hyperalgesia remains not fully understood, modulation of mu as well as delta opioid receptors sensitivity is implicated in this phenomenon [10].

Evidence suggests that increases in the activity of the brain and spinal cord serotonin neurons are associated with analgesia and enhanced antinociceptive drug potency, whereas decreases in the activities of these neurons may lead to hyperalgesia and diminished analgesic drug potency [11]. Cell bodies of serotonin containing neurons are located in the midbrain raphe [12], and administration of morphine and other opioid analgesics to experimental animals increases extracellular serotonin in brain regions innervated by dorsal raphe neurons [13]. Multiple types and subtypes of 5-HT receptors exist in the CNS. The 5-HT<sub>1A</sub> receptor subtypes are located both presynaptically on the soma and dendrites of serotonin neurons and postsynaptically in terminal regions innervated by serotonin neurons. Dorsal raphe, a somatodendritic region of serotonergic neurons, is particularly rich in 5-HT<sub>1A</sub> receptors. It has been also shown that antinociceptive effects of morphine are abolished by pretreatment with p-chlorophenylalanine [14], a serotonin synthesis inhibitor.

Receptor research shows a role of 5-HT<sub>1A</sub> receptors in morphine analgesia and tolerance [15]. The pain reducing effects of atypical antipsychotic aripiprazole are also mediated via its agonist activity at 5-HT<sub>1A</sub> receptors and antagonist activity at dopamine D<sub>2</sub> receptors [16]. Studies targeting 5-HT<sub>1A</sub> receptors may help to understand adaptations in nociceptive pathway which occur after long term use of opioid drugs.

### **5-HT<sub>1A</sub> Receptors in Rewarding and Reinforcing Effects of Drugs of Abuse**

Studies from our laboratory show that specific adaptations in the functional activity of somatodendritic 5-HT<sub>1A</sub> receptors are involved in the reinforcing and rewarding effects of alcohol [17] and apomorphine [18-20]. Adaptations in 5-HT<sub>1A</sub> receptors have been also shown to occur following the administration of morphine. Acute morphine disinhibits serotonergic neurons and facilitates somatodendritic as well as postsynaptic 5-HT<sub>1A</sub> receptor function [21]. Following chronic administration of morphine firing rate of serotonergic neurons decreased [22] because of an increase in the sensitivity of somatodendritic 5-HT<sub>1A</sub> receptors [23], and this is associated with a compensatory upregulation of postsynaptic 5-HT<sub>1A</sub> receptors function [24].

### **5-HT<sub>1A</sub> Influences on Dopamine Neurotransmission**

It is now well recognized that an increase in dopamine neurotransmission via mesolimbic pathway resulting in the activation of particularly dopamine D<sub>2</sub> receptors plays a key role in rewarding and reinforcing effects of drugs of abuse including opioid drugs [25]. Thus morphine is not rewarding in dopamine D<sub>2</sub> receptor knockout mice [26]. Evidence suggests that euphoric effects of drug of abuse are mediated via an increase in dopamine neurotransmission while serotonin seems to play a critical role in 'drug wanting' to contribute to transition to addiction [12,27].

Studies on 5-HT<sub>1A</sub> influences on dopamine neurotransmission suggest that activation of 5-HT<sub>1A</sub> receptors can modulate dopamine neurotransmission by at least two mechanisms. Activation of somatodendritic 5-HT<sub>1A</sub> receptors releases dopamine neurons from the inhibitory influence of 5-HT and enhances dopamine neurotransmission [12]. Activation of postsynaptic 5-HT<sub>1A</sub> receptors also facilitates dopamine neurotransmission via GABA and glutamate dependent mechanism and seems important for mesolimbic pathway [12]. It would suggest that drugs targeting 5-HT<sub>1A</sub> receptors can modulate euphoric effects of opioid drugs and may be useful in treating opioid addiction.

### **Conclusion**

Pre and postsynaptic 5-HT<sub>1A</sub> receptors seem important targets for manipulating opioid analgesia and addiction. Studies addressing role of 5-HT<sub>1A</sub> receptors in opioid analgesia, hyperalgesia, euphoria and reward may provide

a greater understanding of neurobiology of addiction to improve and extend therapeutics in pain and other therapeutically important drugs which are abused.

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