Investigating dopaminergic/serotonergic mechanism during synthetic opioid use

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Over 40 million in the US suffer from substance use disorder (SUD) and overdoses have quadrupled since 2000. Opioids are the main contributor to drug overdose death resulting in more than 100,000 overdose deaths and more than 800,000 nonfatal overdoses in 2022. Not only is SUD associated with other serious psychiatric conditions, it also has a significant impact on the healthcare system and the economy. A key feature of addiction is intensified drug craving that occurs in addicts after repeated drug use, leading to frequent relapses despite best medical treatment. Dopamine (DA), a mediator for the reward pathway, and serotonin (5-HT), a neurotransmitter related to the emotion, learning and memory, have been shown to be an important component in addiction, which can be seen as the result of automated habitual behaviors with diminished reliance on reinforcement. In addition, deep brain stimulation (DBS) of the nucleus accumbens (NAc) has recently been shown to be an effective treatment for subjects with long-term opioid addiction, but the mechanism of action remains unknown. We developed a novel voltammetric technique termed multiple cyclic square wave voltammetry (MCSWV) and N-shaped multiple cyclic square wave voltammetry (N-MCSWV). These techniques allow quantification of tonic (basal) extracellular levels of DA and 5-HT in the brain in near real-time that surpass the capabilities, in terms of temporal and spatial resolution, of conventional neurochemical recording techniques such as in vivo microdialysis. Preclinical evidence strongly supports the use of NAc DBS therapy for treatment-refractory drug addiction. Our previous publications have shown that cocaine and oxycodone increase tonic DA levels in the NAc and DBS of the NAc or ventral tegmental area (VTA) can markedly alleviate these increases in DA levels and, importantly, reverse opioid-induced respiratory depression. Our preliminary data on fentanyl also altered tonic DA level increase, as well as tonic 5-HT level in the brain. These results support the possibility of using neuromodulation technology for treatment of drug addiction.