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Editorial

Is there a role for resveratrol and sirtuins in the treatment of cocaine and methamphetamine addiction?

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Cocaine and methamphetamine addiction is a significant public health concern. The abuse and dependence of these drugs have a damaging impact on the life of the drug user, as well as on the user's family and community. The development of pharmacotherapies against stimulant addiction is critical, as there are no consistently-successful medications for its treatment[1]. Anti-addiction drug therapies have primarily focused on dopamine receptors and transporters and on opiate receptors. However, other protein targets, such as sirtuins, have emerged as potential targets against stimulant addiction.

Sirtuins are a family of nicotinamide adenine dinucleotide (NAD^+)-dependent histone deactylases. There are seven human homologs (SIRT1-7), but much of the sirtuin research has focused on SIRT1 and its role in regulating the aceylation state of proteins that police diverse aspects of cellular physiology. SIRT1 has been investigated in the periphery for its role in cancers and diabetes; however, it is also expressed in the central nervous system, with high levels found in cortical and limbic regions. Studies on degenerative diseases, such as Alzheimer's and Parkinson's diseases, have identified sirtuins and SIRT1 as potential therapeutic targets via their NAD^+-dependent activity in neural processes associated with learning, memory and motivation[2].

A role for SIRT1 in the neuronal changes associated with repeated cocaine administration has been identified[3;4]. Ferguson and colleagues (2013) studied the impact of repeated cocaine treatment to mice on sirtuins in the nucleus accumbens (NAc), a region critical to drug reward and the development of addiction. Repeated, but not acute, cocaine administration induced a marked increase in NAc SIRT1 expression that persisted after several days of drug withdrawal. The cocaine-induced increase is SIRT1 expression is possibly through transcriptional activation of the *Sirt1* gene by ΔFosB. The interaction of methamphetamine and *Sirt1* gene expression has not been reported; however, since methamphetamine, like cocaine, increases ΔFosB activity[5], a mechanism involving SIRT1 is probable. Ferguson and colleagues further showed that both repeated cocaine treatment and SIRT1 overexpression induced an increase in NAc dendritic spine density. This growth has been correlated by several groups with an enhanced behavioral response to cocaine and may reflect a transition from using a drug because it's "liked" to using it because it's "craved".

Drug addiction studies using rodent models have demonstrated that SIRT1 can regulate the behavioral effects of cocaine. Ferguson and colleagues observed that overexpression of SIRT1 in the NAc enhanced the development of cocaine's conditioned-rewarding properties. In contrast, SIRT1 inhibition attenuated the stimulant's conditioned-rewarding properties. Renthal and colleagues (2009) reported that NAc infusion of the sirtuin inhibitor sirtinol reduced cocaine's conditioned-rewarding properties and decreased cocaine self-administration behavior. These findings suggest SIRT1 as a target for the development of treatment agents against the pathophysiology of cocaine addiction. A promising area for additional research is the impact of SIRT1 expression on the rewarding and reinforcing properties of methamphetamine.

While pharmaceuticals can be developed, an alternative approach is the use of herbal medicine and botanical products that regulate sirtuin activity. Resveratrol (*trans*-resveratrol) is a polyphenol found in cranberries, the skin of red grapes, and herbal plants (e.g., Japanese knotweed, *fallopia japonica*). Over the past decade resveratrol use has increased worldwide in foods and supplements for its putative health-promoting effects[6]. Resveratrol is generally classified as a SIRT1 activator. Pharmacologically, it is not clear if resveratrol is a direct activator of SIRT1 or if it produces sirtuin-enhancing effects as an allosteric modulator[7]. Consistent with the research on SIRT1 and cocaine[3;4], resveratrol has been shown to enhance cocaine's effects[4;8].

Shuto and colleagues demonstrated that acute resveratrol treatment amplified cocaine-induced hyperactivity and postsynaptic dopamine signaling in mice. Renthal and colleagues demonstrated that resveratrol enhanced the conditioned-rewarding properties of cocaine. Recently, resveratrol has been shown to alter methamphetamine's behavioral and neurochemical effects [9;10]. Miller and colleagues demonstrated that repeated, but not acute, resveratrol treatment attenuated methamphetamine-induced hyperactivity in mice and diminished methamphetamine-evoked dopamine release from rat striatum. Kanthasamy and colleagues showed that in a cell culture model of methamphetamine neurotoxicity, resveratrol attenuated stimulant-induced caspase-3 activity and DNA fragmentation. This observation suggests that resveratrol may have therapeutic benefits in mitigating against dopaminergic degeneration. It is not clear why the sirtuin activator resveratrol enhances cocaine's effects, but blocks the effects of methamphetamine. The contrast is an important area for future research in understanding the role of sirtuins in stimulant pharmacology and on the development of resveratrol as an anti-addiction therapy. Investigation into resveratrol's pharmacological interaction with SIRT1 as a direct activator or as an allosteric modulator may provide insight. The difference between resveratrol's efficacy on cocaine and methamphetamine could also be explained by its action on other neuronal processes, such as its known antioxidant activity[6].

The widespread prevalence and profound impact of cocaine and methamphetamine addiction make the development of new treatments an emerging trend in pharmaceutical research. Sirtuin regulation and the use of natural products, like resveratrol, are promising areas for future investigations. Additionally, herbal medicines and botanical products may be found to have better clinical outcomes in managing substance addiction than the limited number of pharmaceuticals used for the psychopathology.

REFERENCES

1. Vocci FJ, Montoya ID. Psychological treatments for stimulant misuse, comparing and contrasting those for amphetamine dependence and those for cocaine dependence. Curr Opin Psychiatry 2009; 22: 263-268.
2. Donmez G. The neurobiology of sirtuins and their role in neurodegeneration. Trends Pharmacol Sci 1990; 33: 494-501.
3. Ferguson D et al. Essential role of SIRT1 signaling in the nucleus accumbens in cocaine and morphine action. J Neurosci 2013; 33: 16088-16098.
4. Renthal W et al. Genome-wide analysis of chromatin regulation by cocaine reveals a role for sirtuins. Neuron 2009; 62: 335-348.
5. Cornish JL et al. Regional c-Fos and FosB/DeltaFosB expression associated with chronic methamphetamine self-administration and methamphetamine-seeking behavior in rats. Neuroscience 2006; 206: 100-114.
6. Anekonda TS. Resveratrol--a boon for treating Alzheimer's disease? Brain Res Rev 2006; 52: 316-326.
7. Farghali H et al. Resveratrol and related compounds as antioxidants with an allosteric mechanism of action in epigenetic drug targets. Physiol Res 2013; 62:1-13.
8. Shuto T et al. Acute effects of resveratrol to enhance cocaine-induced dopamine neurotransmission in the striatum. Neurosci Lett 2013; 522:107-112.
9. Miller DK et al. Repeated resveratrol treatment attenuates methamphetamine-induced hyperactivity and [^{3}H]dopamine overflow in rodents. Neurosci Lett 2013; 554: 53-58.
10. Kanthasamy K et al. Neuroprotective effect of resveratrol against methamphetamine-induced dopaminergic apoptotic cell death in a cell culture model of neurotoxicity. Curr Neuropharmacol 2011; 9: 49-53.