Epigenetic alteration a promising new drug target for heroin use disorder

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The past few years have seen an explosion of heroin abuse and deaths from opiate overdose. But little is known about the molecular underpinnings of heroin addiction. A new study in Biological Psychiatry found that heroin use is associated with excessive histone acetylation, an epigenetic process that regulates gene expression. More years of drug use correlated with higher levels of hyperacetylation. The study, led by Dr. Yasmin Hurd of the Icahn School of Medicine at Mount Sinai, New York, provides the first direct evidence of opiate-related epigenetic alterations in the human brain.

To narrow in on these alterations, first author Dr. Gabor Egervari and colleagues studied postmortem human tissue - a challenging but critical endeavor for understanding the molecular organization of the human brain - from 48 heroin users and 37 controls. They focused on the striatum, a brain region implicated in drug addiction because of its central role in habit formation and goal-directed behavior.

The acetylation changes were observed at genes that mediate glutamatergic function, specifically the glutamate receptor gene GRIA1, which has previously been implicated in drug use. The epigenetic impairments reflect changes that increase accessibility of chromatin, a process that enhances gene transcription, suggesting the impairments play an important role in addiction behavior.

"At this time, when prescription opioid use and opioid overdoses are both major threats to our public health, it is important to identify new

treatment targets, such as epigenetic processes, that help to change the way that we do business in treating opioid use disorders," said professor John Krystal, Editor of Biological Psychiatry.

"Epigenetic marks are physical alterations to the DNA that do not change the sequence of a gene, and thus have the potential to be reversed," said Hurd. So the researchers used a rat model of heroin addiction to test this idea. Importantly, rats allowed to self-administer heroin displayed the same hyperacetylation alterations that were found in the human brains.

Dr. Egervari and colleagues treated the rats with JQ1, a compound originally developed against cancer pathology, which inhibits acetylation. The drug reduced self-administered heroin taking in the rats. Importantly, JQ1 also reduced drug-seeking behavior after abstinence from heroin, suggesting it might be beneficial for long-term heroin users.

"Our findings suggest that JQ1 and similar compounds might be promising therapeutic tools for heroin use disorder," said Dr. Hurd.

The analogous epigenetic impairments found in the heroin-taking rats also indicate this animal model will be useful in further studies to identify addiction-related changes that translate to the human brain.

More information: Gabor Egervari et al. Striatal H3K27 Acetylation Linked to Glutamatergic Gene Dysregulation in Human Heroin Abusers Holds Promise as Therapeutic Target, *Biological Psychiatry* (2017). DOI: 10.1016/j.biopsych.2016.09.015

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