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Studies explain adolescents' vulnerability to addictive drugs

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Researchers have discovered one reason why adolescents are more prone to drug addiction than adults, with findings that could lead to new treatments for addictive disorders.

In two studies with mice and humans to be published together in the journal *eLife*, the investigators from Baylor College of Medicine, US, have found that the ability to produce (or synthesize) new proteins, regulated by the molecule eIF2, accounts for adolescents' hypersensitivity to both cocaine and nicotine.

"In humans, adolescence, namely the period between the early teenage years and early twenties, is a time of heightened susceptibility to the effects of addictive drugs, but previous studies have struggled to explain why. Our studies support the idea that regulation of protein synthesis by eIF2 might be the underlying cause," says senior author Mauro Costa-Mattioli.

In the first study, the team injected adolescent and adult mice with saline or a low dose of cocaine. Their results showed that in adolescents, but not adults, cocaine reduces the activity of eIF2α. This leads to an increase in the strength of the connections, or synapses, between dopamine-storing neurons in a part of the midbrain that is rich with these cells.

"This greater communication between dopamine-rich neurons gives a greater sense of pleasure from taking the drug and encourages behaviors

related to addiction," says lead author Wei Huang.

"Only higher doses of cocaine led to similar responses in adult mice, proving that adolescents have a lower threshold for the effects of cocaine on these neurons."

With the combined use of genetics and pharmacology, the investigators altered the production of proteins controlled by eIF2α in adult mice, essentially converting them into adolescents by making them more susceptible to cocaine-induced changes in synaptic strength and behavior. Conversely, adolescent mice with increased eIF2α activity in the brain became more resistant to the effects of cocaine, as seen in adults.

"It's truly remarkable that by manipulating the processes surrounding eIF2α in this way, we can rejuvenate brain activity. This could hold significant promise for developing new treatments for drug addiction and related disorders," says Costa-Mattioli.

For the second paper, the team carried out similar experiments in mice with different doses of nicotine instead of cocaine, showing that the same effects are also true for this drug.

In the study, they also identified a variation in the gene encoding eIF2α and found that such variation affects how human smokers' brains respond to reward, as determined by changes seen in functional magnetic resonance imaging.

"Our findings are clinically relevant as they identify a novel addiction target in rodents, along with parallel supporting evidence from brain imaging studies in human addicts," explains Andon Placzek, lead author of the nicotine study.

"In the US, the indirect financial costs of smoking and the costs of enforcing the drug control system are estimated at more than $300 billion and $100 billion per year, respectively. To help bring down both these and the human costs of addiction, our new insights could help educate adolescents about the risks of recreational drug use and experimentation, discouraging these behaviors as a result. They could also help discover a new way to fight addiction in both adolescents and adults, for example by altering the activity of eIF2α in the brain."

More information: 'Translational control by eIF2α phosphorylation regulates vulnerability to the synaptic and behavioral effects of cocaine' DOI: 10.7554/eLife.12052

'Translational control of nicotine-evoked synaptic potentiation in mice and neuronal responses in human smokers by eIF2α' DOI: 10.7554/eLife.12056

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