eIF2α-mediated translational control regulates cocaine-and nicotine-induced synaptic potentiation in mouse midbrain dopamine neurons and neuronal responses in human smokers

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Adolescents are especially prone to drug addiction, but the underlying biological basis of their increased vulnerability remains unknown. Using adolescent and adult mice, we show that translational control by phosphorylation of the translation initiation factor eIF2α (p-eIF2α) accounts for adolescent hypersensitivity to cocaine. In adolescent (but not adult) mice, a low dose of cocaine reduced p-eIF2α in the ventral tegmental area (VTA), potentiated synaptic inputs to VTA dopaminergic neurons, and induced drug-reinforced behavior. Like adolescents, adult mice with reduced p-eIF2α-mediated translational control were more susceptible to cocaine-induced synaptic potentiation and behavior. Conversely, like adults, adolescent mice with increased p-eIF2α became more resistant to cocaine's effects. Accordingly, metabotropic glutamate receptor-mediated long-term depression (mGluR-LTD)—whose disruption is postulated to increase vulnerability to drug addiction—was impaired in adolescent mice, and in adult mice with reduced p-eIF2α mediated translation. We also found that in mice with reduced p-eIF2α levels, cocaine induces a persistent LTP in VTA dopamine neurons. Moreover, selectively inhibiting eIF2α-mediated translational control with the small molecule drug ISRIB, or by knocking down oligophrenin-1 (Ophn1)—an mRNA whose translation is controlled by p-eIF2α—in the VTA also prolongs cocaine-induced LTP. This persistent LTP is mediated by the insertion of GluR2 subunit-lacking AMPARs. These findings suggest that eIF2α-mediated translational control regulates compulsive drug seeking by acting as a defense mechanism that prevents the conversion from transient to persistent cocaine-induced LTP. Furthermore, systemic injection of multiple drugs of abuse (ethanol, methamphetamine and nicotine) was shown to reduce p-eIF2α levels in mouse VTA. Since adolescents are particularly vulnerable to nicotine, the principal addictive component driving tobacco smoking, we studied the effect nicotine-induced potentiation of excitatory synaptic transmission in ventral tegmental area dopaminergic neurons in adolescent mice compared to adults. Adult mice with genetic or pharmacological reduction in p-eIF2α-mediated translation are more susceptible to nicotine’s synaptic effects, like adolescents. When we investigated the influence of allelic variability of the

Eif2s1 gene (encoding eIF2α) on reward-related neuronal responses in human smokers, we found that a single nucleotide polymorphism in the *Eif2s1* gene modulates mesolimbic neuronal reward responses in human smokers. These findings suggest that p-eIF2α regulates synaptic actions of nicotine in both mice and humans, and that reduced p-eIF2α may enhance susceptibility to nicotine (and other drugs of abuse) during adolescence. Collectively, our findings suggest that during addiction, multiple drugs of abuse hijack translational control by p-eIF2α, initiating synaptic potentiation and addiction-related behaviors.