How does stress initiate drug relapse?

Drug relapse can be initiated by environmental cues and stress even after extended periods of abstinence, leading to the failure of drug rehabilitation programs. Currently, there are few effective treatments to prevent drug relapse. Therefore, drug relapse is not only an unmet medical need but also an important socioeconomic concern, especially stress-induced drug relapse. The mechanisms by which stress initiates drug relapse remain unclear. The study group led by Prof. Lih-Chu Chiou at the Department of Pharmacology at the Medical College of National Taiwan University revealed a novel mechanism for stress-induced cocaine relapse. This may shed light on the prevention of stress-related drug relapse.

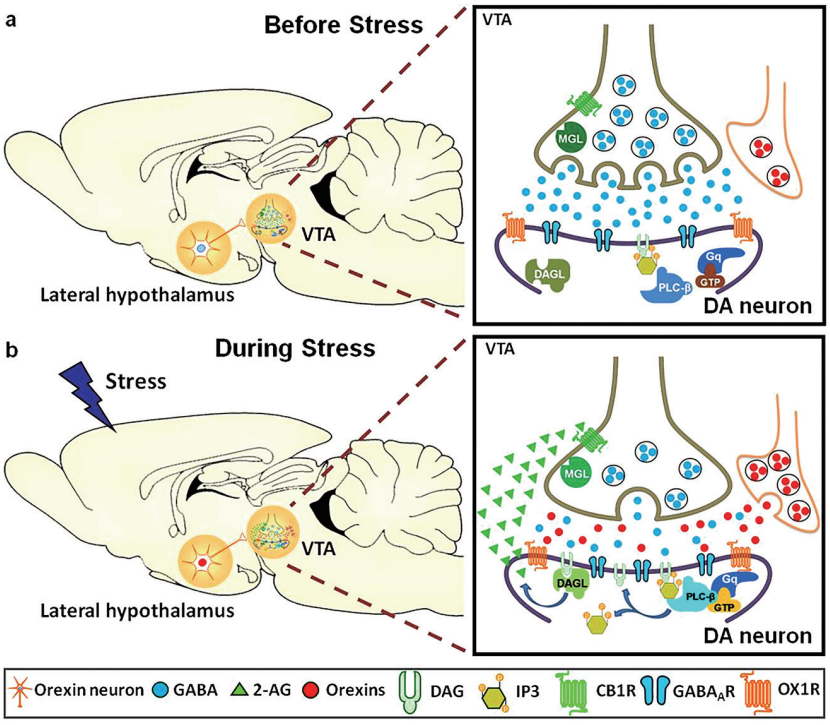

Figure 1. How does stress induce an endocannabinoid-mediated disinhibition in the ventral tagmental area, leading to cocaine relapse?

This scheme describes the neuronal processing that occurs in the lateral hypothalamus (LH) and ventral tagmental area (VTA) circuits (a) before stress and (b) during stress. The boxes on the right are enlarged portions of the synaptic events that occur in a GABAergic synapse onto a dopaminergic neuron in the VTA. During stress, LH orexin neurons are activated and release orexins. The released orexins then activate postsynaptic OX1 receptors on dopaminergic neurons in the VTA. Activation of the OX1 receptor, a Gq-protein coupled receptor, leads to PLC activation, generating DAG that is converted into 2-AG, an endocannabinoid, by DAGL. 2-AG travels retrogradely across the synapse to inhibit GABA release by activating presynaptic CB1 receptors on the GABAergic terminal. Inhibition of GABAergic synaptic neurotransmission onto dopaminergic neurons in the VTA results in activation of the mesolimbic dopaminergic circuitry, leading to a reinstatement of extinguished cocaine CPP, modeling cocaine relapse in humans. Finally, 2-AG is degraded by MAGL, which is located in GABAergic terminals. Thus, the MAGL inhibitor potentiates and prolongs orexin A-induced IPSC depression.

This work was mainly performed by Dr. Li-Wi Tung during his PhD study period at the Graduate Institute of Pharmacology at NTU. The research group found that stress can reinstate extinguished cocaine preference in mice in a conditioned place preference (CPP) training task. The CPP score in this animal model is usually used to evaluate the degree of drug craving. Their results suggest that this stress-reinstated cocaine relapse is mediated by a sequential cascade involving orexins and endocannabinoids.

Orexins consist of a pair of neuropeptides, orexin A and B (also named hypocretin 1 and 2). They are generated by a group of neurons in the hypothalamus, especially in the perifornical area (PeF) and lateral hypothalamus (LH). Their receptors, OX1R and OX2R, are widely distributed throughout the brain, including the ventral tegmental area (VTA), an important brain region for reward processing where dopamine neuron plasticity can be altered by addictive substances. Orexins have been known to play a role in drug seeking behavior in animals. However, the mechanisms by which orexins regulate the VTA dopaminergic activity to provoke drug craving, especially under stressful conditions, remain unclear. Previously, Prof. Chiou's group found that orexins can be released under stress from the

LH to activate a pain-regulating region, the periaqueductal gray (PAG), leading to analgesia. This stress-induced analgesic effect is mediated by a signaling cascade in the PAG, i.e., orexins activate postsynaptic OX1Rs, a family of Gq-protein coupled receptors, resulting in the synthesis of 2-arachydonoylglycerol (2-AG) via the phospholipase C (PLC)-diacylglycerol lipase (DAGL) enzymatic pathway. 2-AG is an endogenous cannabinoid that can produce retrograde inhibition of GABA release (disinhibition) by activating presynaptic cannabinoid 1 receptors (CB1Rs)[1,2].

Inspired by the previous finding in the PAG, Tung et al.[3] validated a hypothesis that this OX1R-PLC-DAGL-2-AG retrograde disinhibition signaling also exists in VTA dopamine neurons and can contribute to stress-induced extinguished cocaine seeking behavior in mice using both electrophysiological and behavioral approaches. Indeed, they found that orexin A inhibited GABAergic transmission via a presynaptic mechanism in dopamine neurons of VTA slices. This effect of orexin A was prevented by the antagonist of OX1Rs or CB1Rs, and by internal inhibition of G protein. It was also prevented by inhibiting the enzymes involved in 2-AG synthesis, PLC and DAGL, and potentiated by inhibiting 2-AG degradation. Furthermore, they found that acute restraint stress activated orexin neurons in the LH, increased both orexin A and 2-AG levels in the VTA, and reinstated extinguished cocaine CPP in mice. This stress-reinstated cocaine CPP was prevented by intra-VTA injection of the antagonist of OX1Rs, CB1Rs or DAGL and was abolished in CB1R-knockout mice. These results suggest a novel mechanism for stress-induced cocaine relapse: acute restraint stress activates LH orexin neurons, releasing orexins to activate postsynaptic OX1Rs on VTA dopaminergic neurons and, through a Gq-protein-PLC-DAGL cascade, generating 2-AG that retrogradely inhibits GABA release through presynaptic CB1Rs, leading to VTA dopaminergic disinhibition and reinstating cocaine CPP.

This finding provides a prospective in the development of OX1R antagonists as a novel therapeutic approach in the prevention of stress-induced cocaine relapse.

References

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