PHARMACOLOGICAL TARGETS ON THE CORTICO-ACCUMBENS GLUTAMATERGIC PROJECTION: A PROMISE FOR COCAINE ADDICTION THERAPY

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INTRODUCTION

There is a lot of interest in identifying how drugs affect Central Nervous System, and possible strategies to counteract their effects. Pharmacotherapies acting over mechanisms mediating drug craving, withdrawal syndrome or relapse, are being proposed.

OBJECTIVE

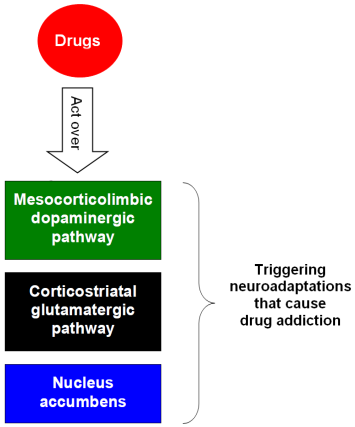
Identifying cell-surface receptors in the glutamatergic corticostriatal pathway between prefrontal cortex (PFC) and nucleus accumbens (NAc) proposed as therapeuthical targets, as well as the pharmacotherapies targeting them, analyzing their efficacy on preventing relapse from cocaine-addiction, according to literature.

METHODS

Search in PMC with keywords "accumbens + prefrontal cortex + cocaine + addiction + glutamate + pharmacotherapy" was performed. 2 reviews were chosen among the results (Kalivas PW, 2011; Haile CN, see Portfolio for complete references).

Thereon, specific searches about each pharmacotherapy and target were made (for more information see Portfolio, Annex 3).

MECHANISM OF ACTION OF ADDICTIVE DRUGS



PFC PROJECTION TO Nac: FUNCTIONAL PHYSIOLOGY AND PROPOSED PHARMACOTHERAPIES

Regulation of glutamatergic corticostriatal pathway has shown more promise than any other for possible treatments of cocaine dependence, being the main targets proteins regulating glial glutamate release and uptake, and glutamate receptors.

KEY for Figure 1 and Table 1:

- Proteins regulating glial glutamate release and uptake, and therapies targeting them
- Metabotropic glutamate receptors (mGluRs), and therapies targeting them
- Ionotropic glutamate receptors (AMPAR, NMDAR), and therapies targeting them

MGLURII

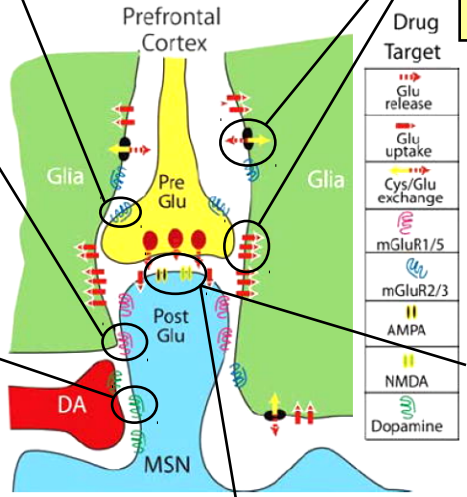
mGluRII are autoreceptors. They regulate glutamate release. Cocaine intake reduces extrasynaptic glutamate, causing mGluRII tone to decrease, thus increasing glutamate release from the presynaptic terminal. Chronic cocaine intake also downregulates mGluRII expression.

GLUTAMATE TRANSPORTERS

Cocaine downregulates the presence and function of the cystine-glutamate exchanger (xCT) and GLT-1 in NAc. Their impairment causes a reduction of extrasynaptic levels of glutamate.

MGLURI

mGluR5 and mGluR1 are postsynaptic receptors. Like mGluRII, they can regulate glutamate transmission.



DOPAMINE TRANSPORTERS

Dopamine transporters are important modulators of glutamate transmission, acting like a "gate".

AMPA RECEPTORS (AMPAR)

Chronic Increased AMPAR levels in MSN, are highly related with cocaine addiction and relapse.

NMDA RECEPTORS (NMDAR)

NMDAR are the mediators of LTP and LTD, by the regulation they exert over AMPAR expression on cell surface. NMDAR upregulation in MSN is also related to memory consolidation.

Figure 1. Glutamatergic tripartite synapse between projections from PFC (yellow) with MSN (blue) and glia (green) in NAc. The surface receptors that have been pinpointed as targets for treating drug addiction are situated in their most common position, and identified in the key. In red, a dopaminergic terminal from the VTA.

Image modified from: Kalivas PW, Volkow ND. New medications for drug addiction hiding in glutamatergic neuroplasticity. Mol Psychiatry. 2011; 16(10):974-986.

Therapy	Action	Behavioral outcome
N-acetylcisteine	xCT activator	Inhibits cue-induced cocaine seeking in rats. Reduces cocaine craving in humans
Ceftriaxone	Promotes GLT-1 expression	Prevents cocaine consumption and seeking in rats
Modafinil	Dopamine transporter blocker?	Narcolepsy treatment, cognitive enhancer. Improves working memory and attention. Cross-sensitization with cocaine
mGluRII antagonists	Inhibit mGluRII action	Alleviates withdrawal dysphoria
LY379268	mGluRII agonist	Prevents stress-induced cocaine seeking
mGluR5 NAM	Inhibit mGluR5 action	Reduce self-administration and relapse in animal models
mGluR1 PAM	Promote mGluR1 action	Inhibit cue-induced cocaine seeking in "incubation" models
Topiramate, Lamotrigine	Antiepileptic, AMPAR antagonists	Reduce craving in humans
D-cycloserine	NMDAR partial agonist	Reduces cocaine CPP, causes self-administration extinction in rats
Acamprosate	NMDAR activator	Alcohol-dependence treatment. Reduces cocaine reinforcement in preclinical models

Table 1. Pharmacotherapies targeting surface receptors in PFC glutamatergic projection to NAc.

CONCLUSIONS

Mechanisms elicited in NAc glutamatergic inputs from the corticostriatal pathway in addiction animal models offer potential targets for drug addiction therapy.

The projection from the PFC to NAc is an important site for addiction, but other neural pathways also modify NAc MSN homeostasis. This could explain some paradoxical results.

Pharmacological therapy can be a support for behavioral therapy, but will probably not become a substitute for it. Extinction learning is an active process and the cocaine-dependent subject must "learn" not to use the drug.

Usually, pharmacotherapies that inhibit one type of addiction are beneficial in other addictions, and even psychiatric disorders. The study of addiction might explain how are these processes related.

The study of these mechanisms may provide more insight into the processes implicated in different animal species: brain pathways, neuronal function and learning, reward and reinforcement mechanisms.