

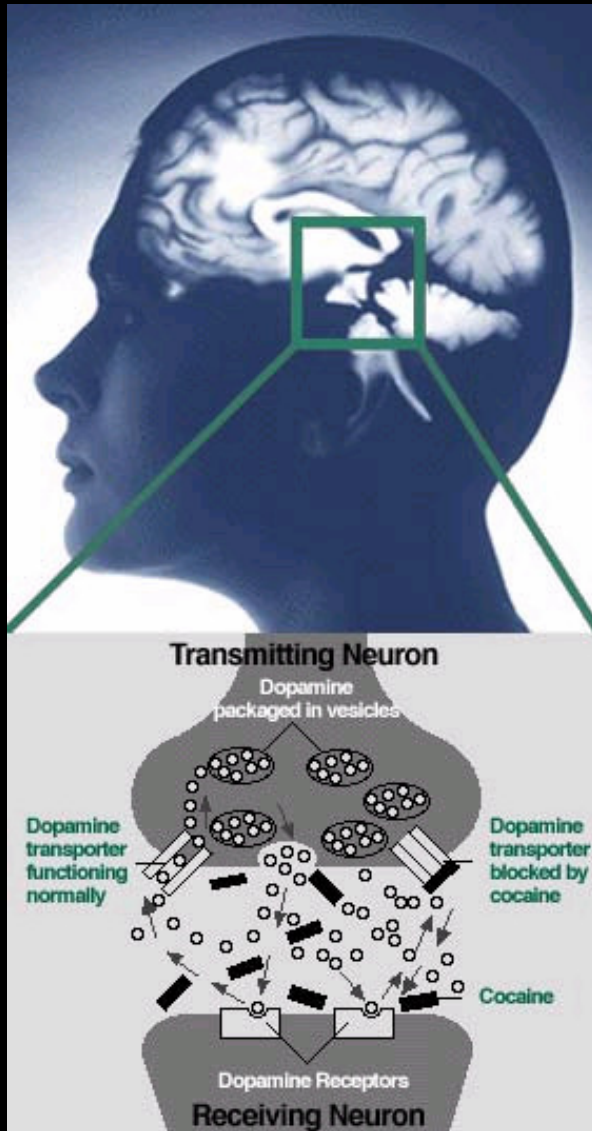


cocaine: from animal models to pharmaceutical targets

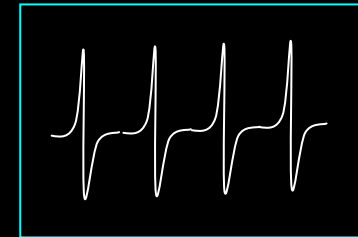
Antonello Bonci, M.D.
Gallo Center and Department of Neurology
UCSF, San Francisco, CA

Addiction & Neuroscience,
Verona, March 18

A simple hypothesis:
Any addictive behavior depends on changes in electrical activity of specific brain regions

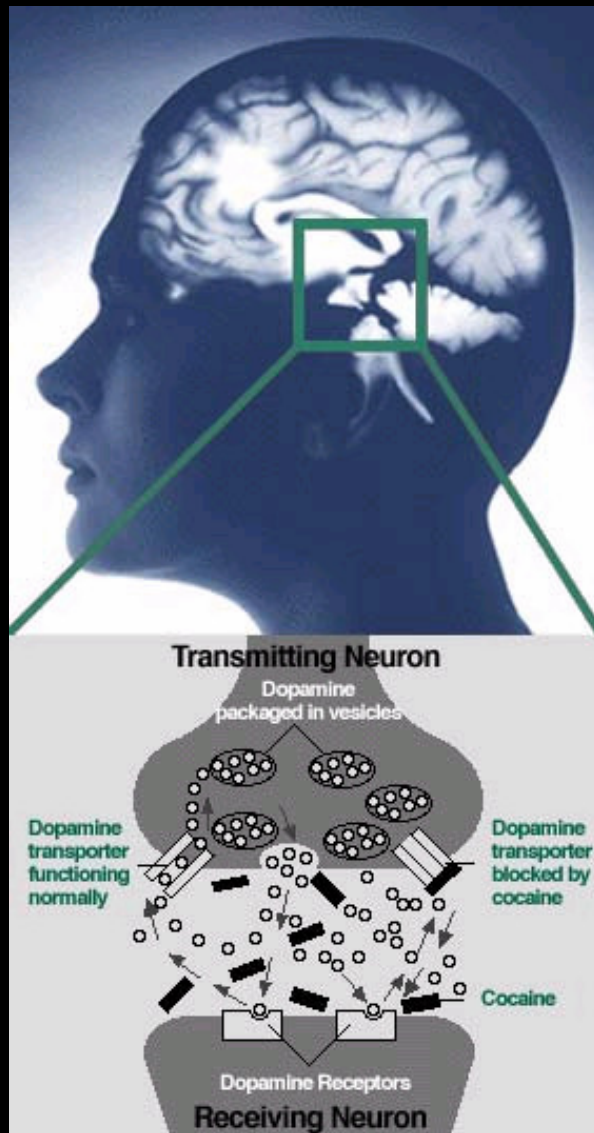


Genetic background

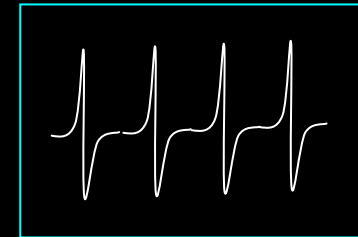


Environmental stimuli

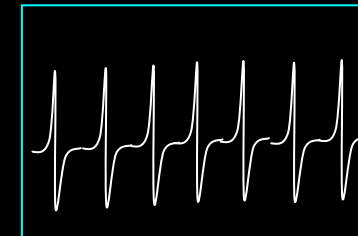
A simple hypothesis:
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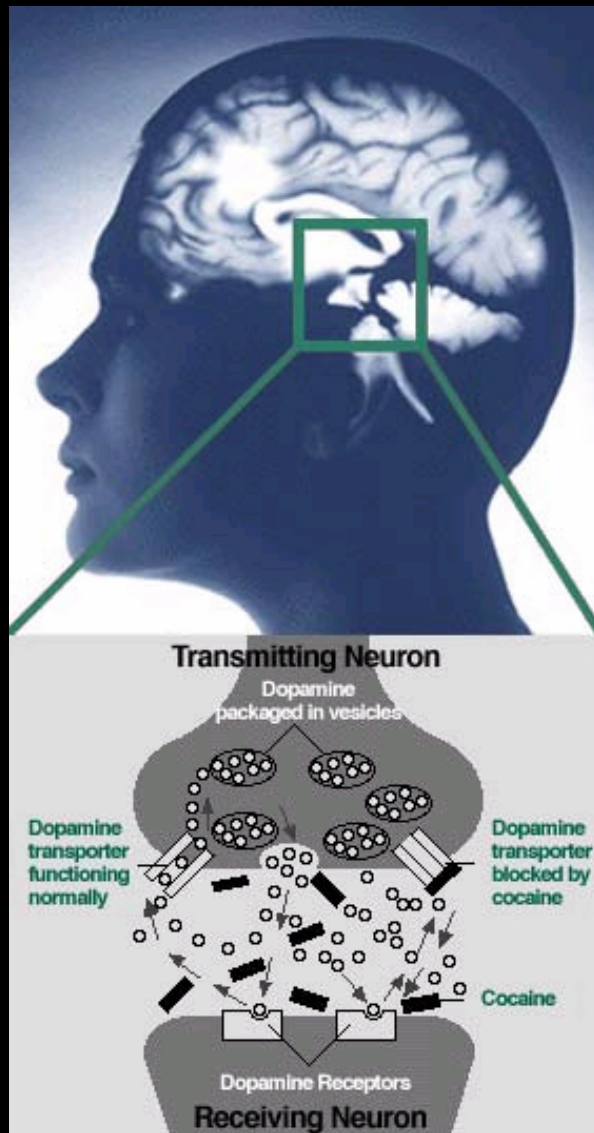
Genetic background



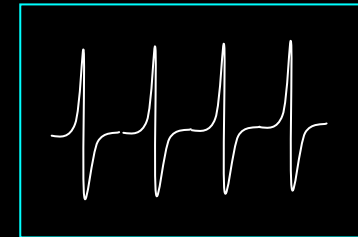
Environmental stimuli



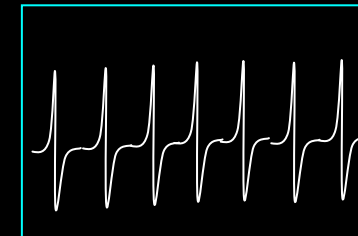
A simple hypothesis:
Any addictive behavior depends on changes in electrical activity of specific brain regions



Genetic background



Environmental stimuli



Substance abuse

Why dopamine neurons?

Addiction

Apathy

Aggressive behaviors

Sexual, appetitive behaviors

Parkinson's disease

Schizophrenia

Working memory

Depression

Reward Deficiency Syndrome

ADHD

Dementias

Behaviors produced by cocaine are modulated by dopamine neuron activity

Behavioral sensitization

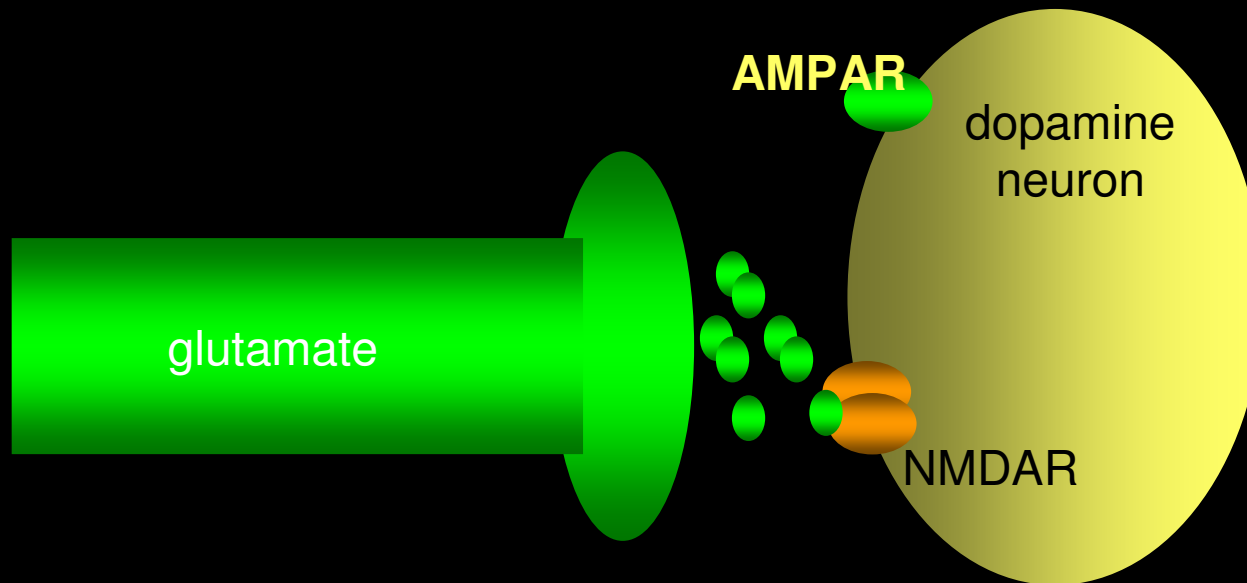
Cocaine self-administration

Relapse to cocaine seeking

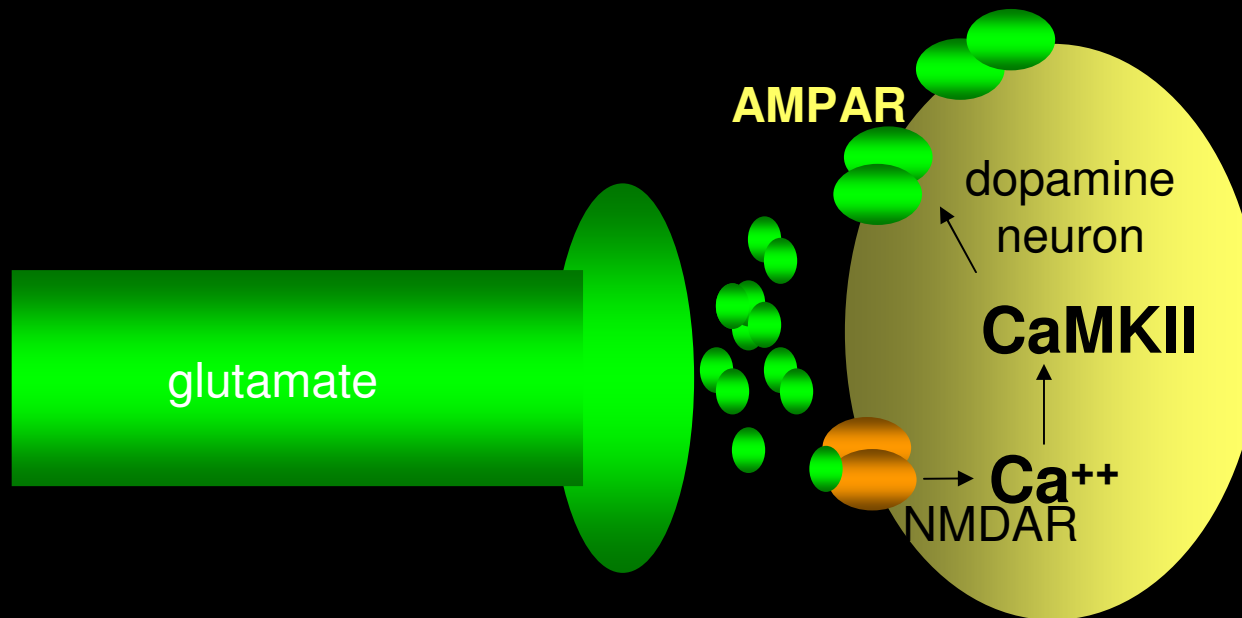
A fundamental cellular model of learning and memory: long-term potentiation (LTP)



What is LTP?



What is LTP?

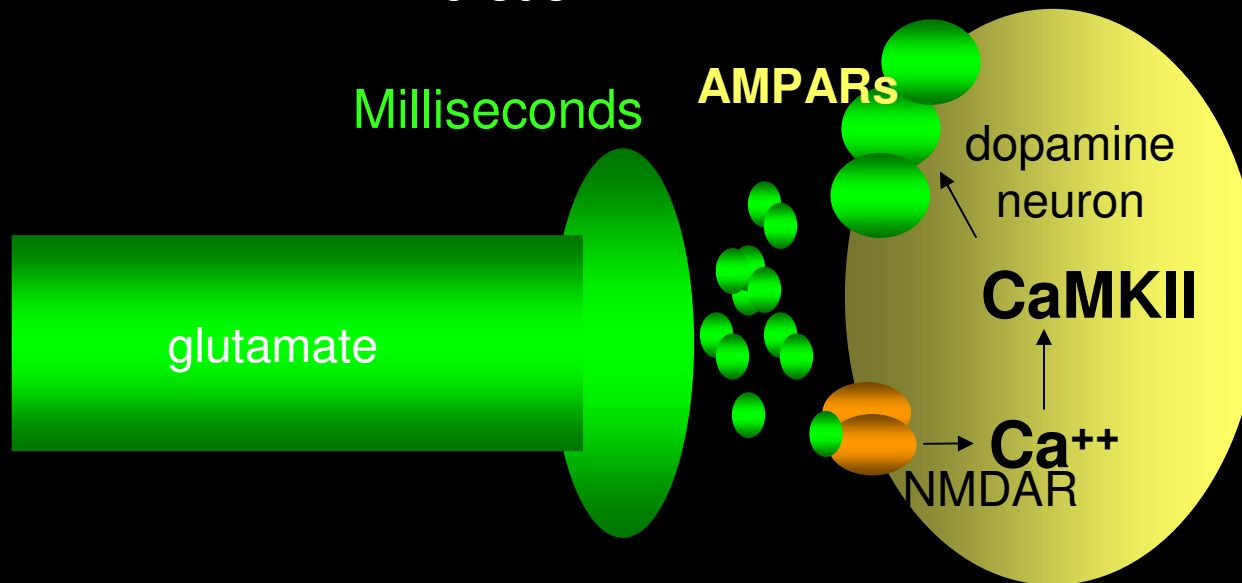


Why LTP?

Hours, days, months

versus

Milliseconds



Ungless et al., *Nature* (2001)

Ungless et al., *Neuron* (2003)

Borgland et al., *J Neurosci* (2004)

Borgland et al., *Neuron* (2006)

Miquel et al., *Nature Neurosci* (2006)

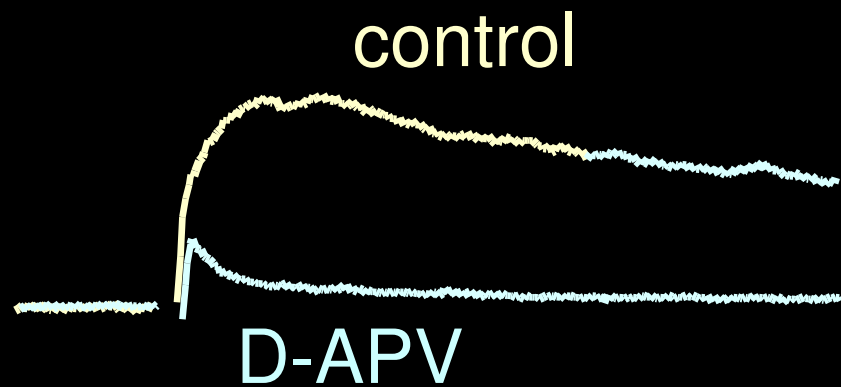
Schilstrom et al., *J Neurosci* (2006)

Sarti et al., *EJN* (2007)

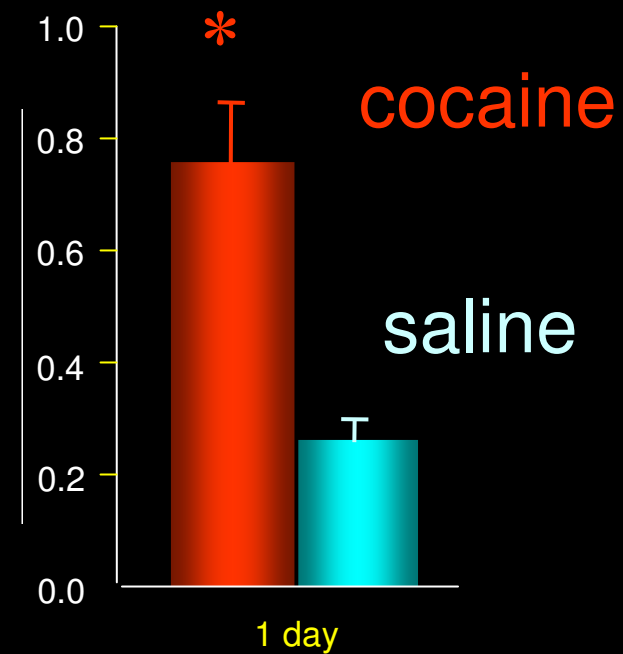
Are drugs of abuse capable of producing LTP?



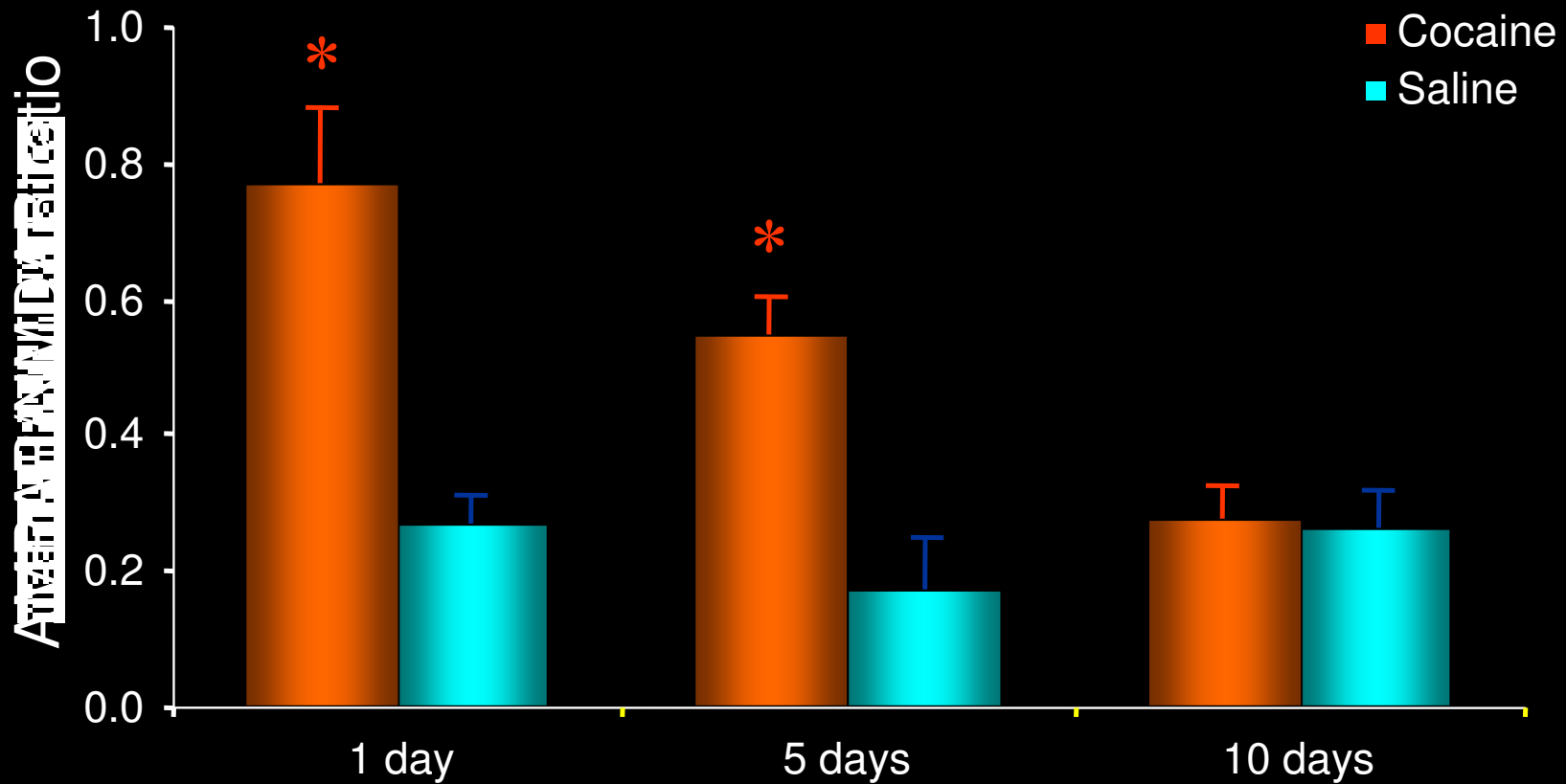
A single injection of cocaine
increases the AMPAR/NMDAR ratio and produces
LTP of AMPARs



AMPA/NMDAR ratio



The increase in the AMPAR/NMDAR ratio is long-lasting



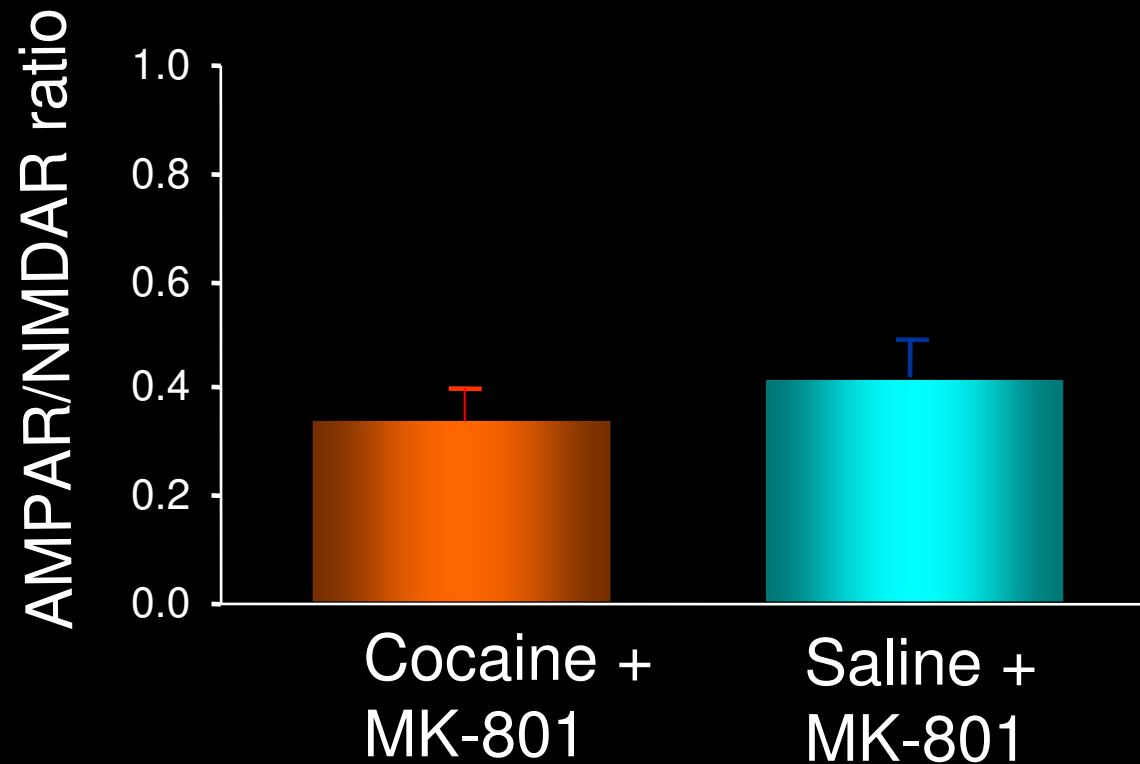
Ungless et al., Nature (2001)

Behavioral sensitization requires NMDAR activation
LTP requires NMDAR activation



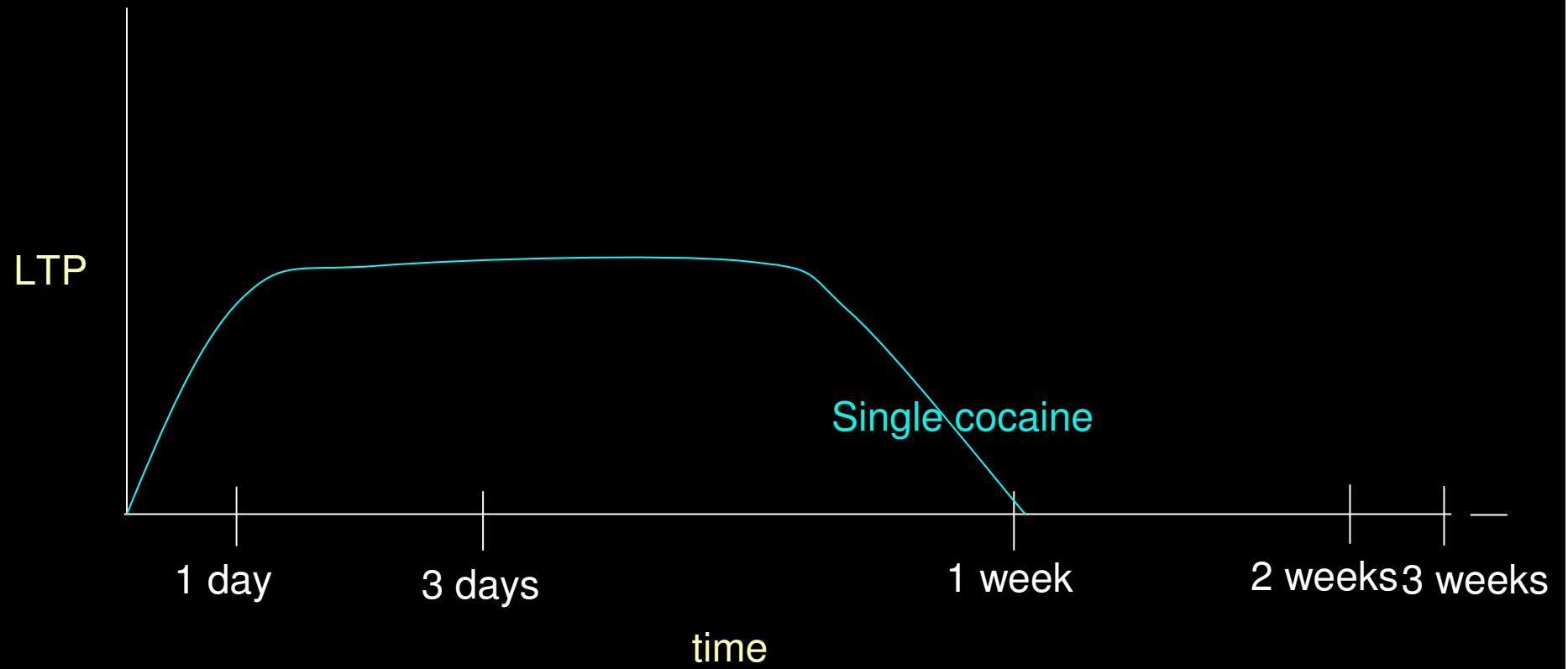
May be LTP underlies behavioral sensitization

Co-administration of cocaine + NMDAR antagonist blocks
increase of AMPAR/NMDAR ratio
and behavioral sensitization

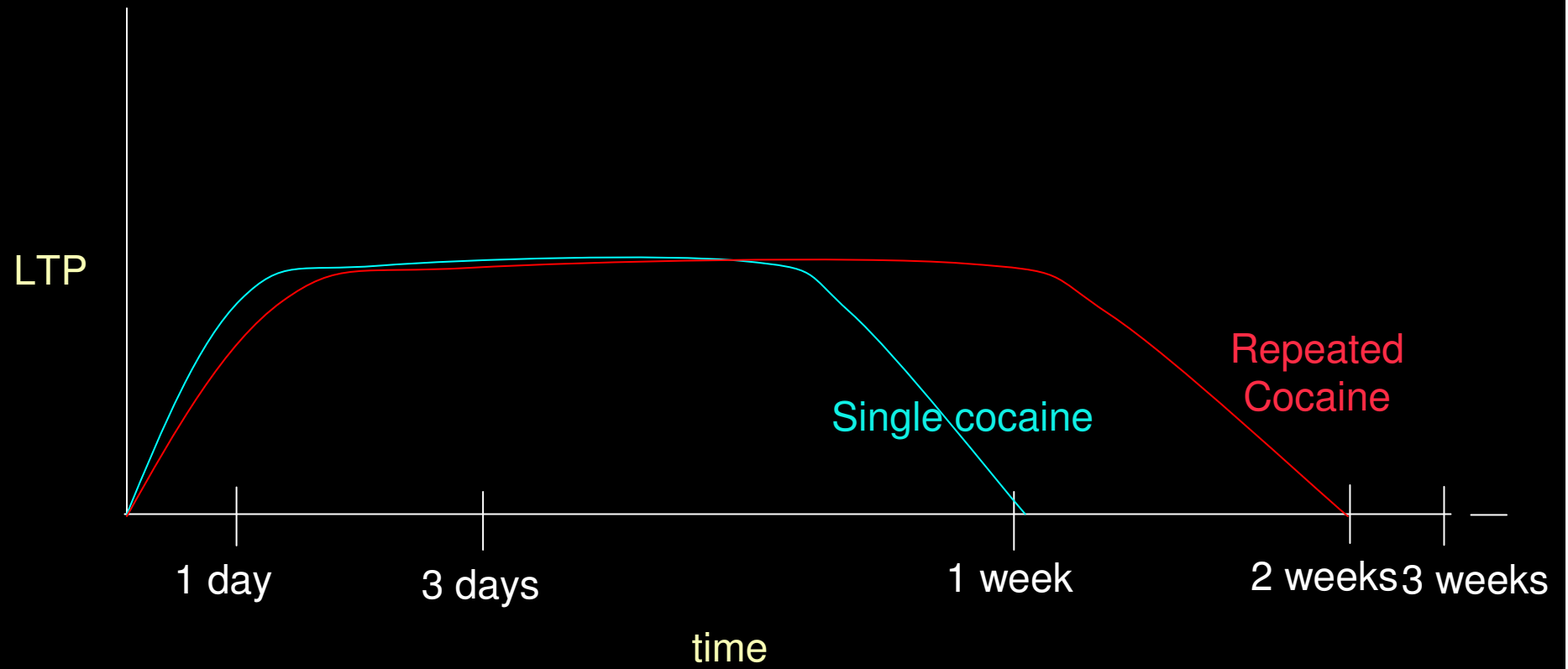


Ungless et al., Nature (2001)

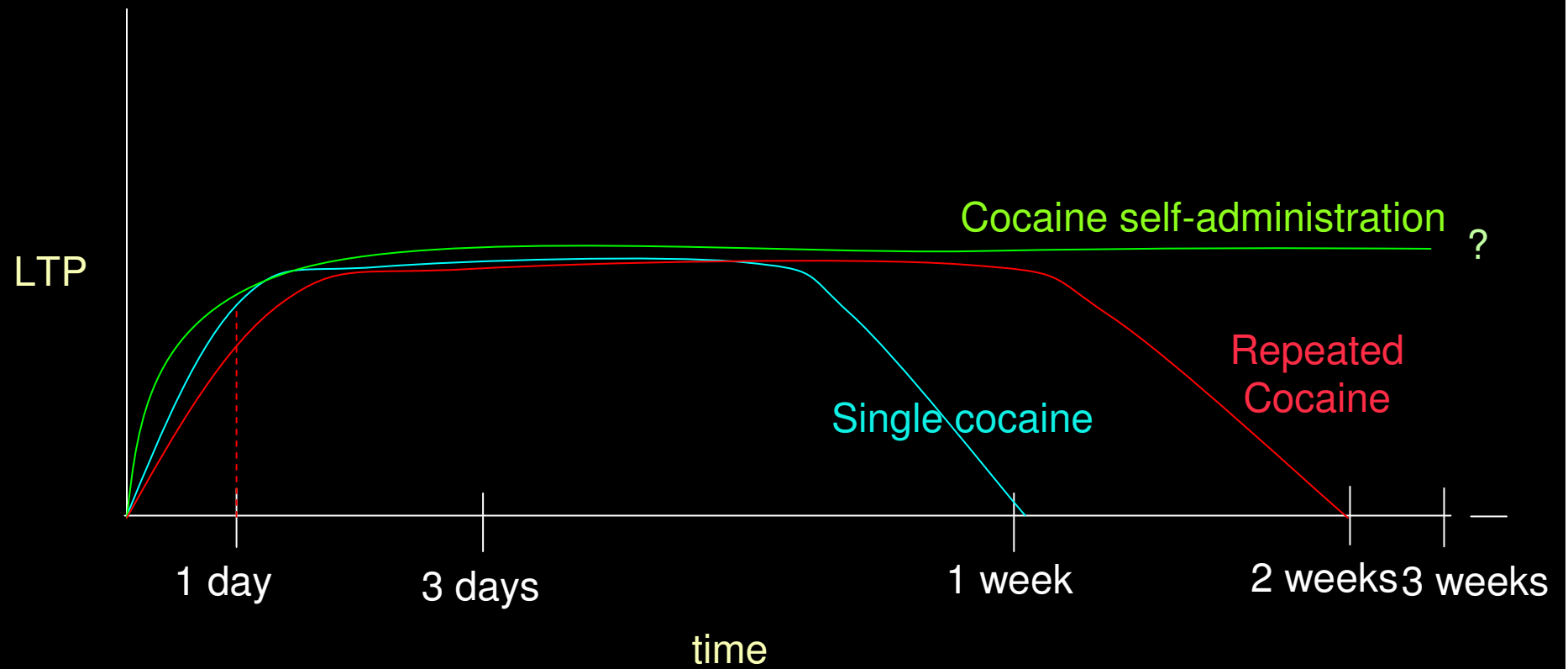
The time course of LTP



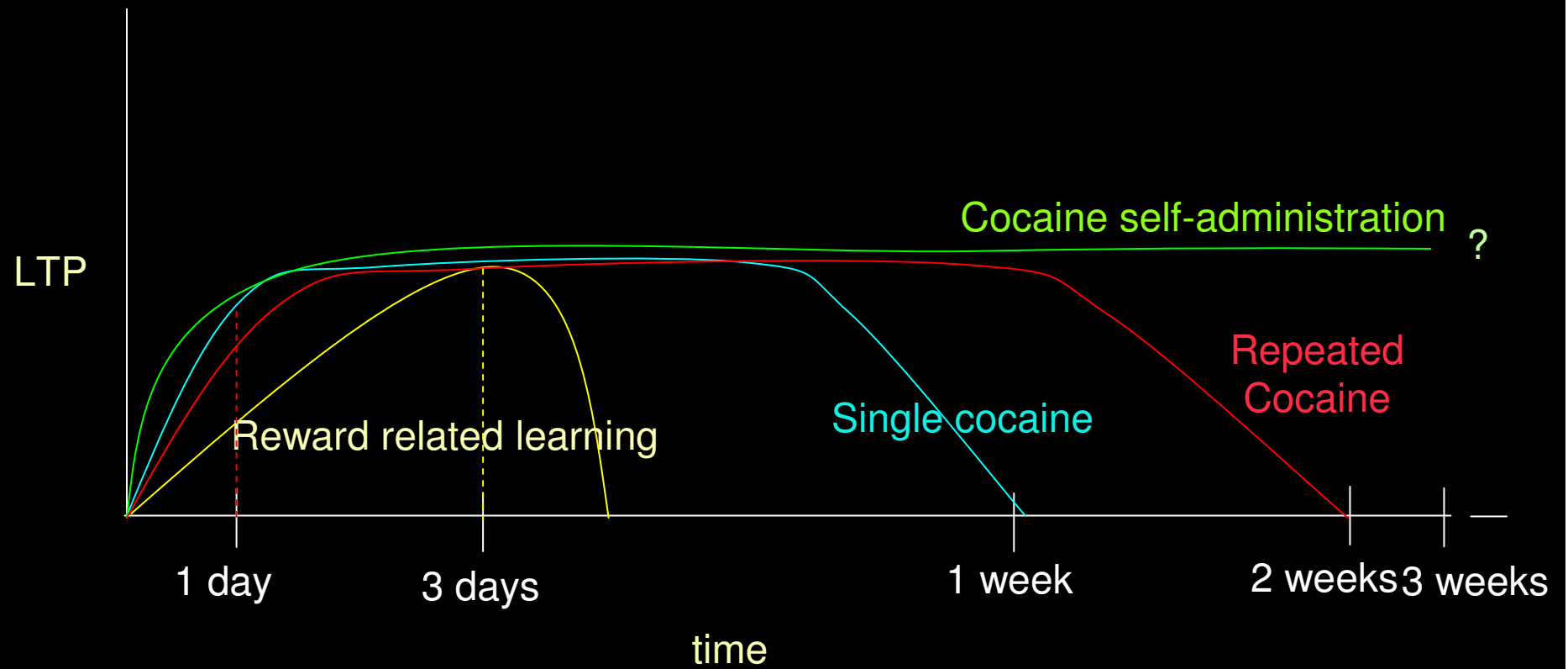
The time course of LTP



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The time course of LTP

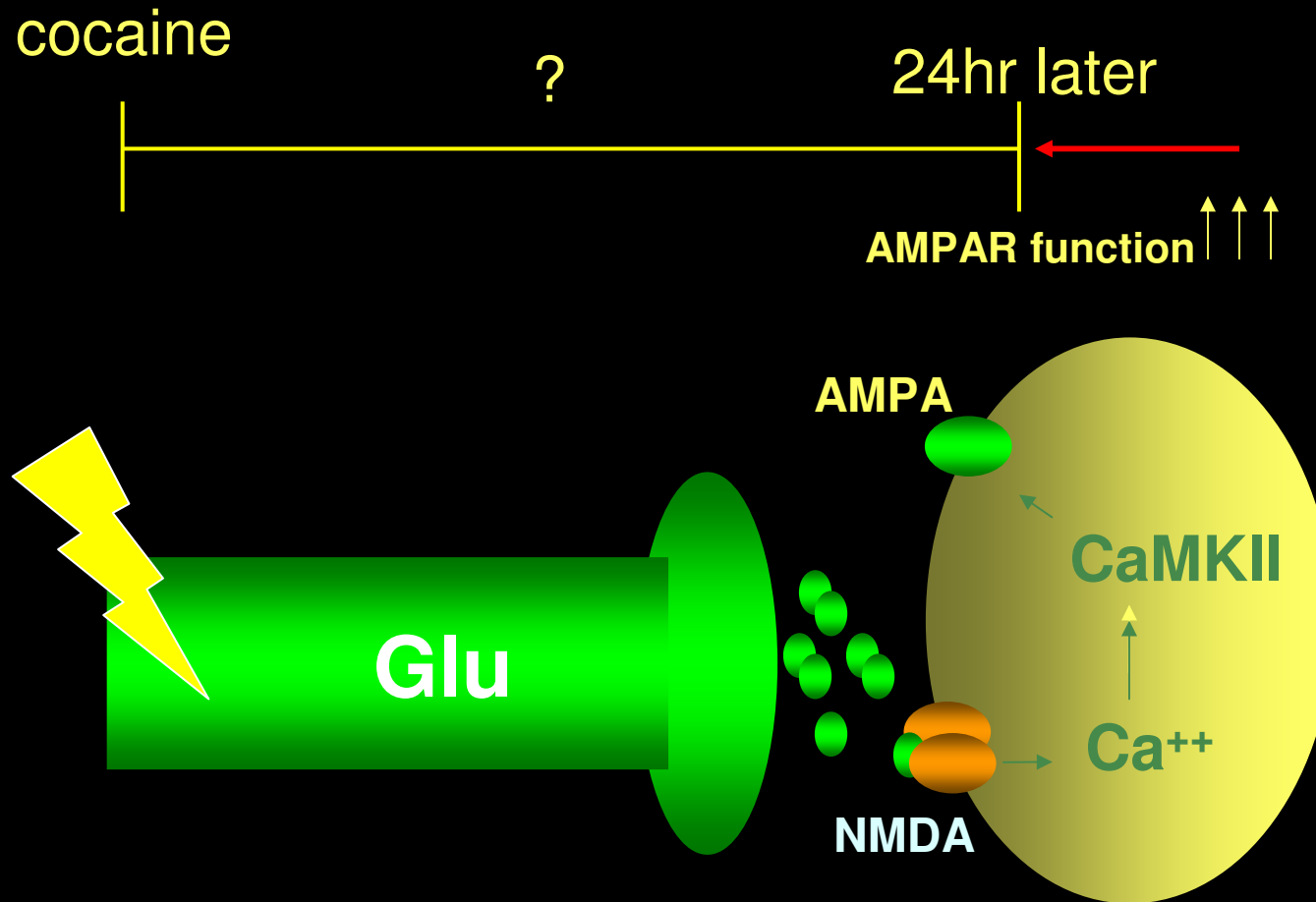


Conclusions

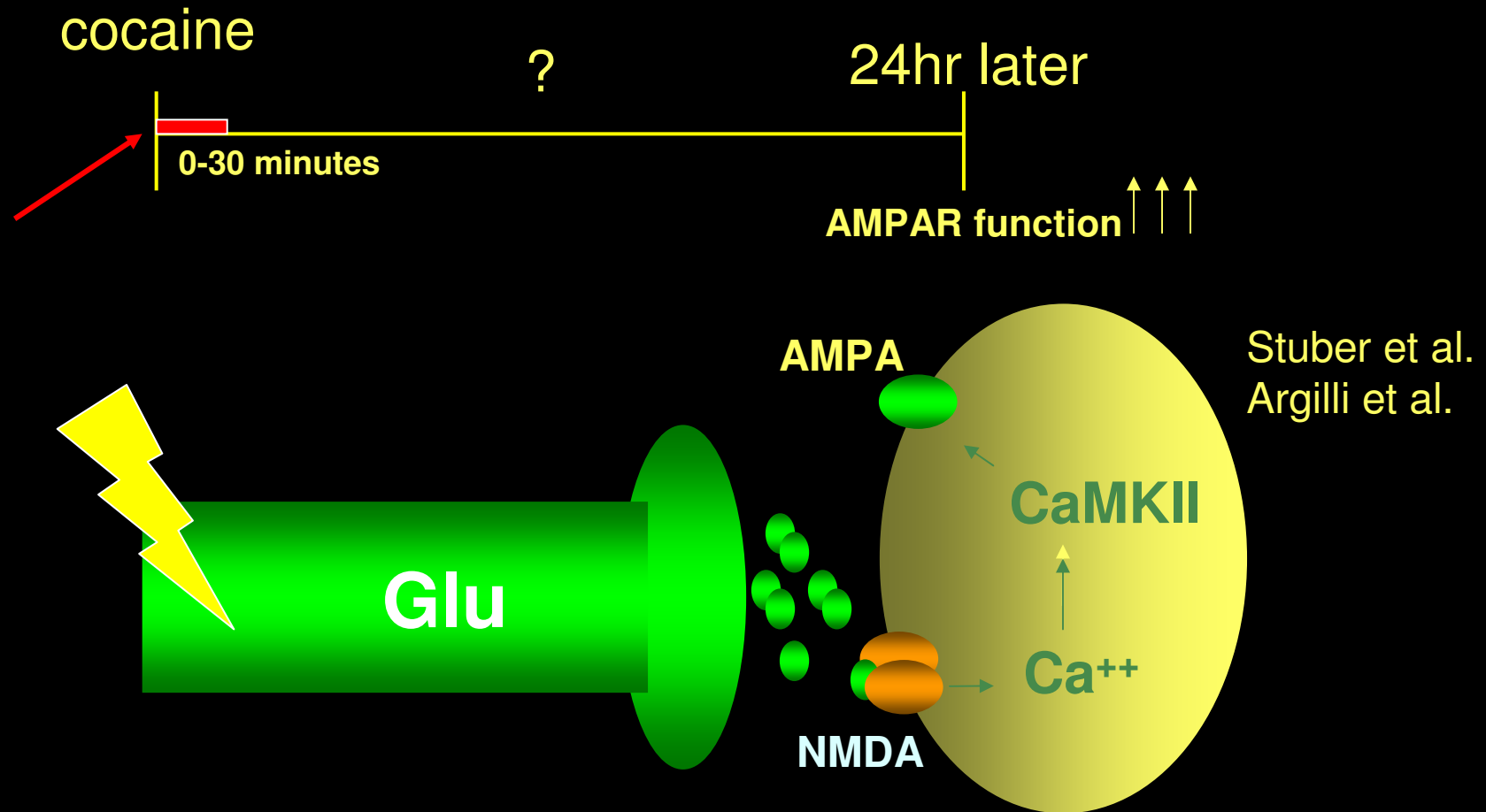
- Long-term potentiation (LTP) is a long-lasting increase in synaptic activity
- LTP represents a fundamental cellular phenomenon underlying normal learning and memory processes
- A single cocaine exposure produces LTP, lasting about a week
- Natural rewards (food, sucrose) produce short-lasting LTP (1-3 days)
- Cocaine self-administration produces persistent LTP in dopamine neurons (3 months)

What is the mechanism responsible for the induction of cocaine-dependent LTP?

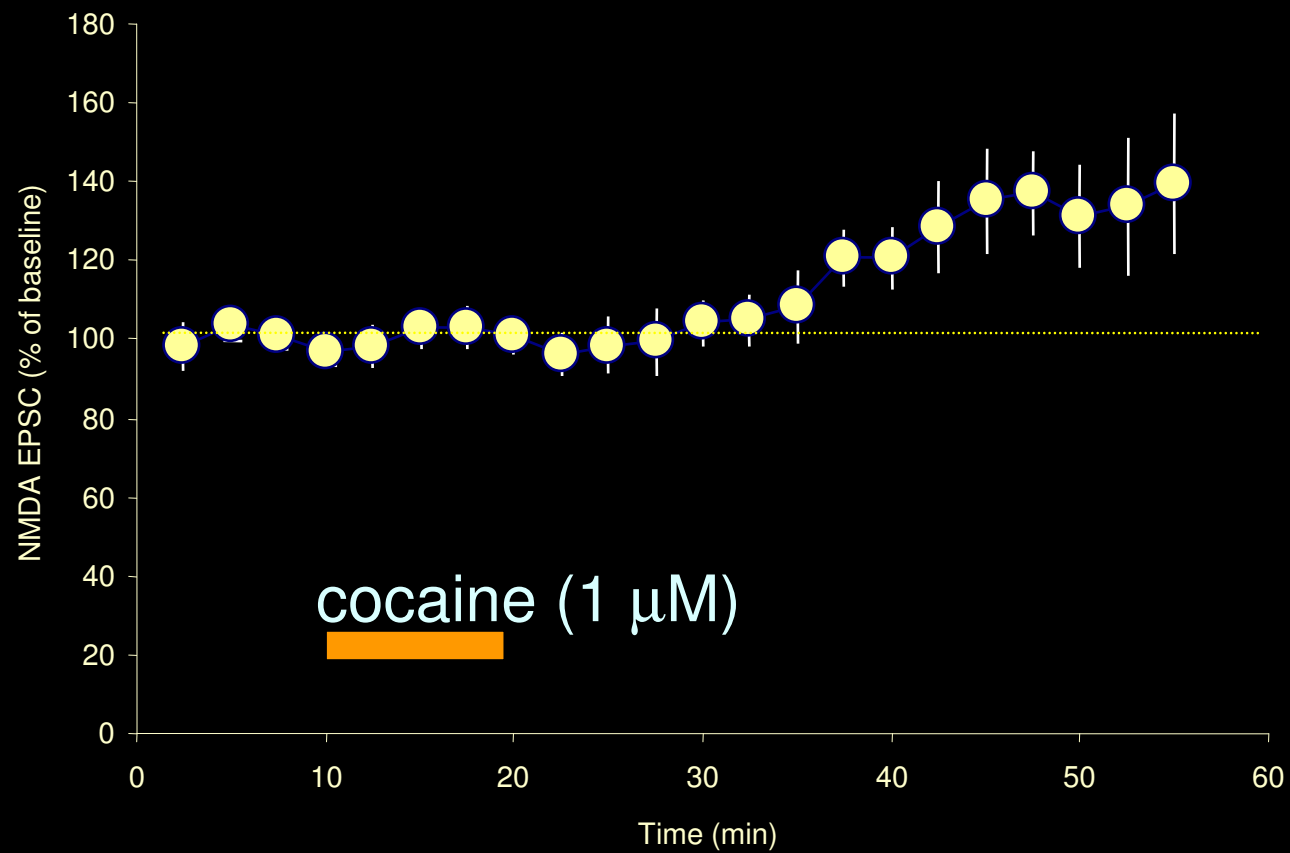
VTA long-term potentiation



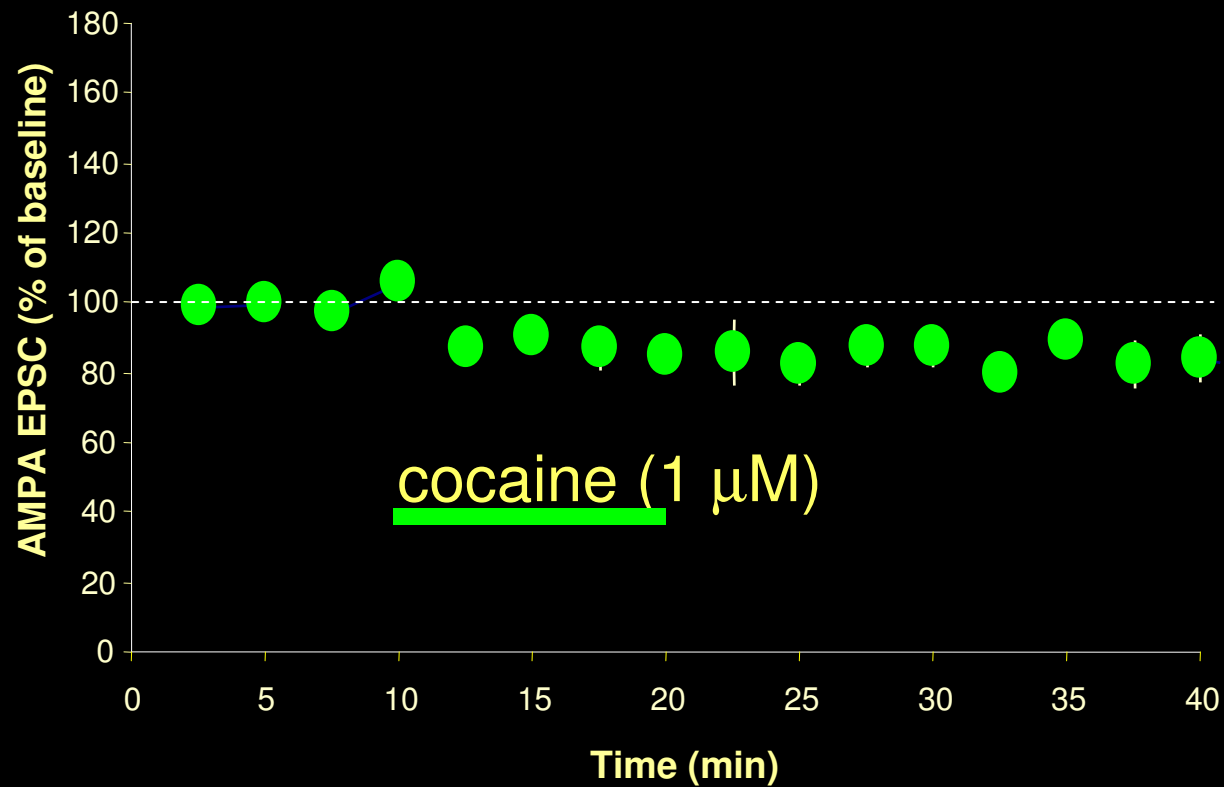
VTA long-term potentiation



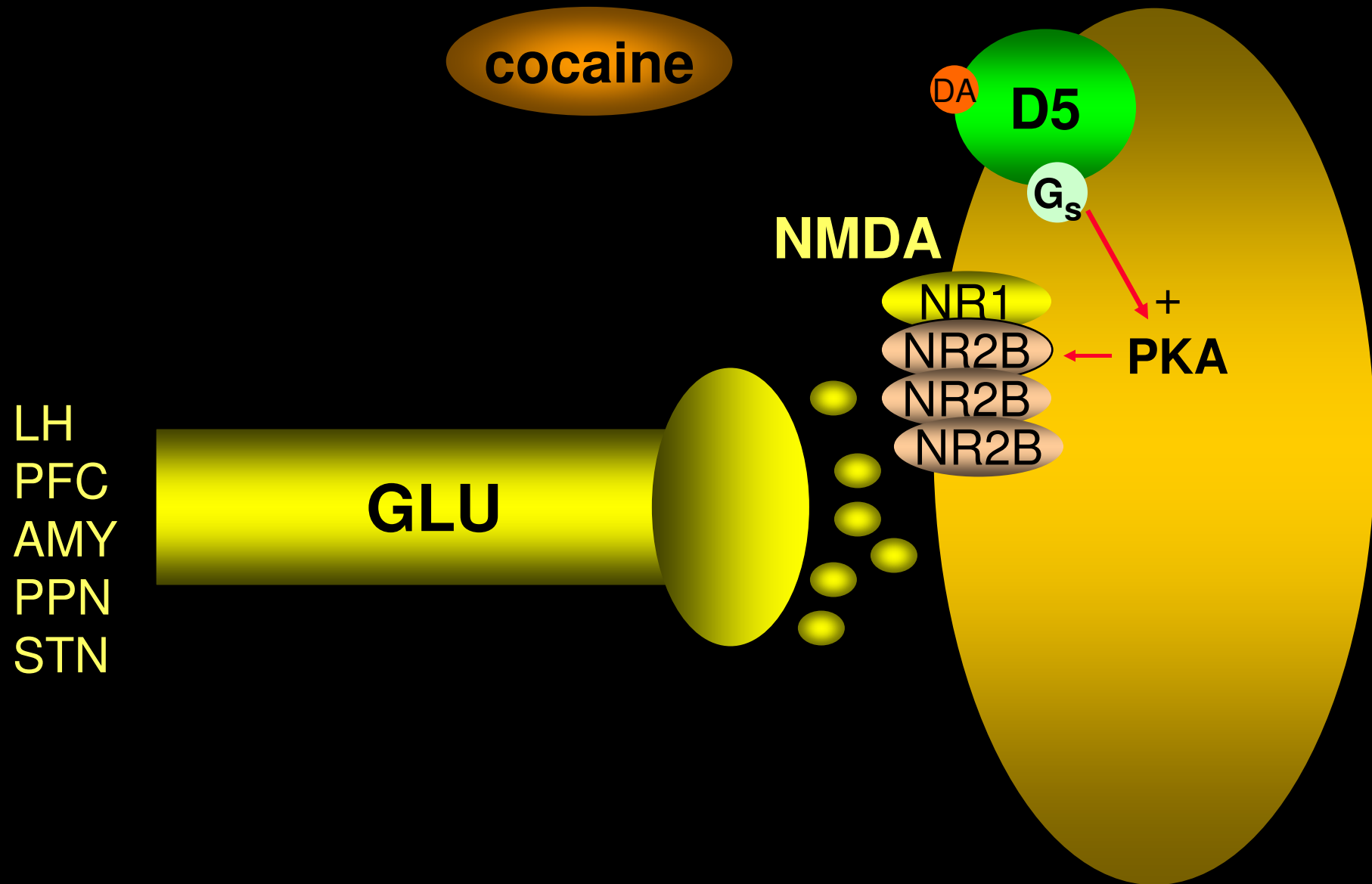
Acute superfusion of cocaine produces a delayed increase of NMDA currents



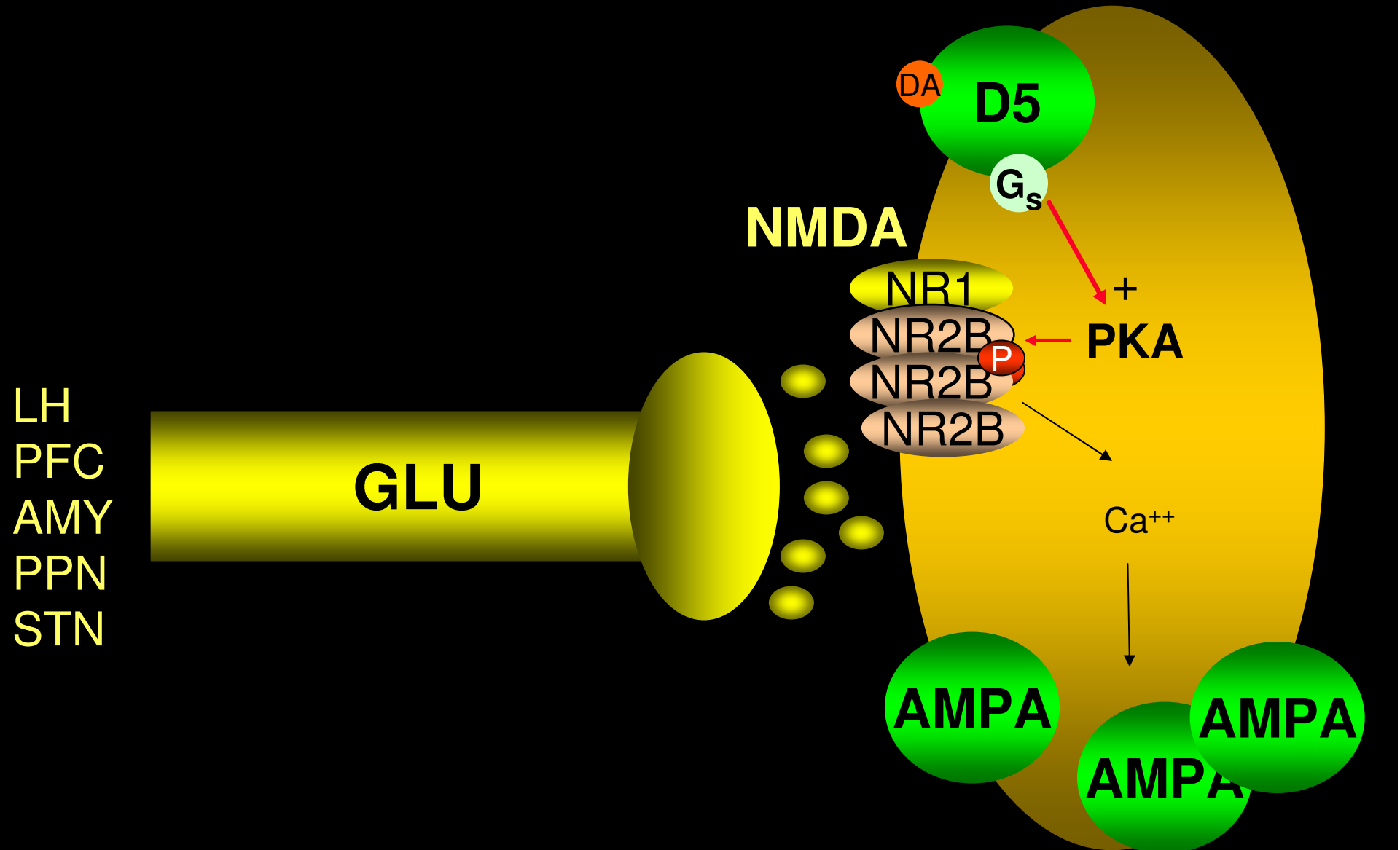
Acute cocaine does not increase AMPA currents



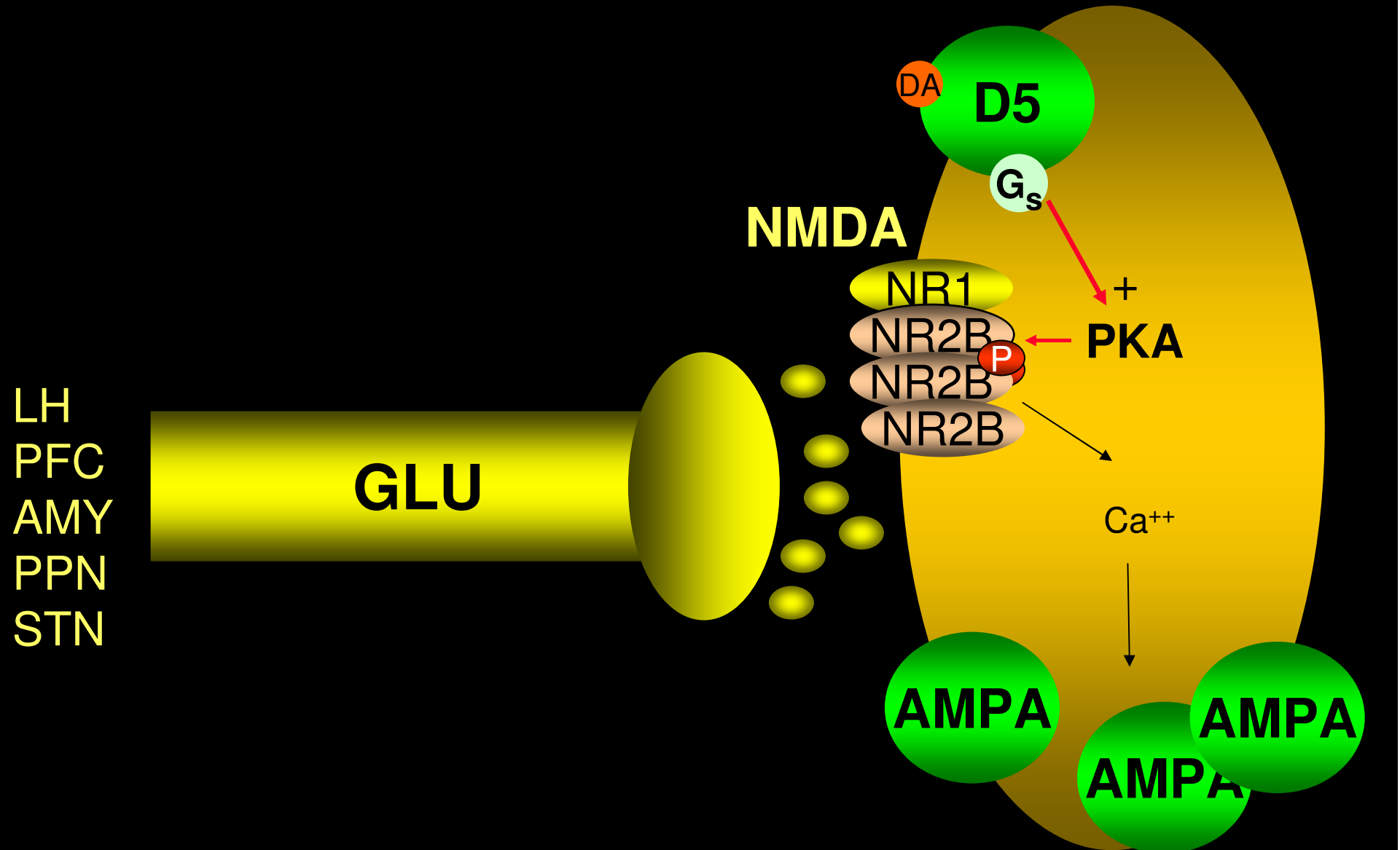
Cocaine acutely potentiates NMDARs via PKA, and D5 receptors



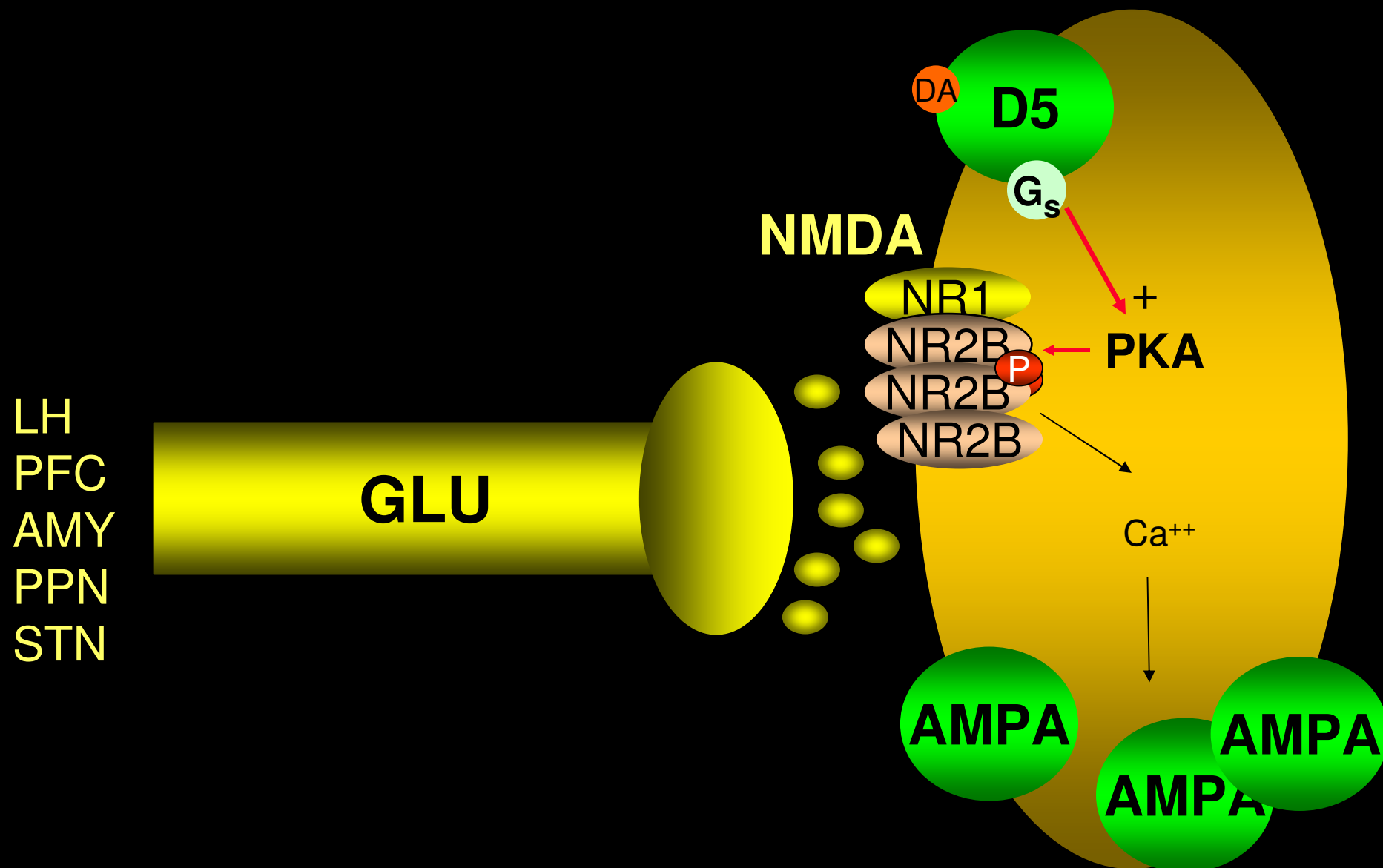
Cocaine acutely potentiates NMDARs via PKA, and D5 receptors



First possibility for therapeutic intervention: blocking NMDARs or D5Rs

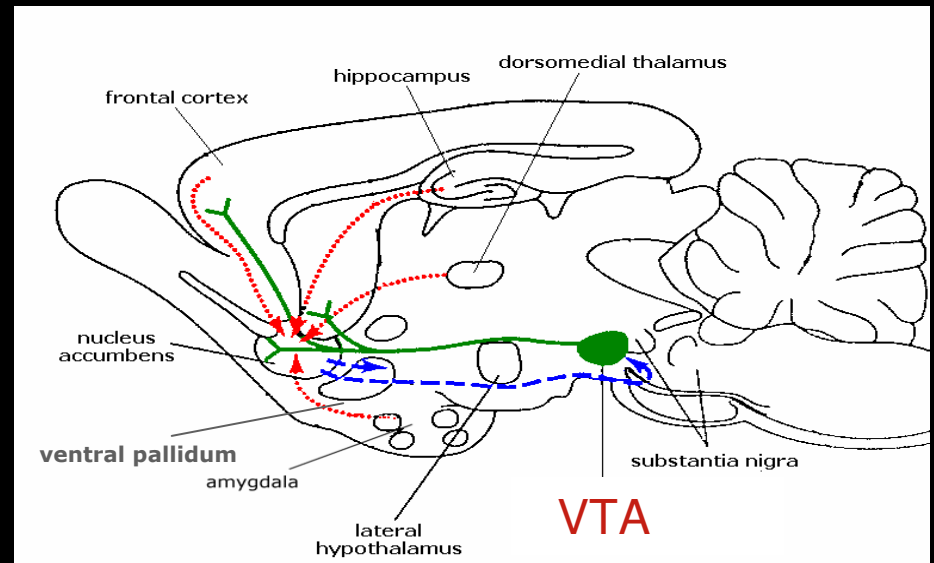


At high doses, methadone is an NMDAR antagonist



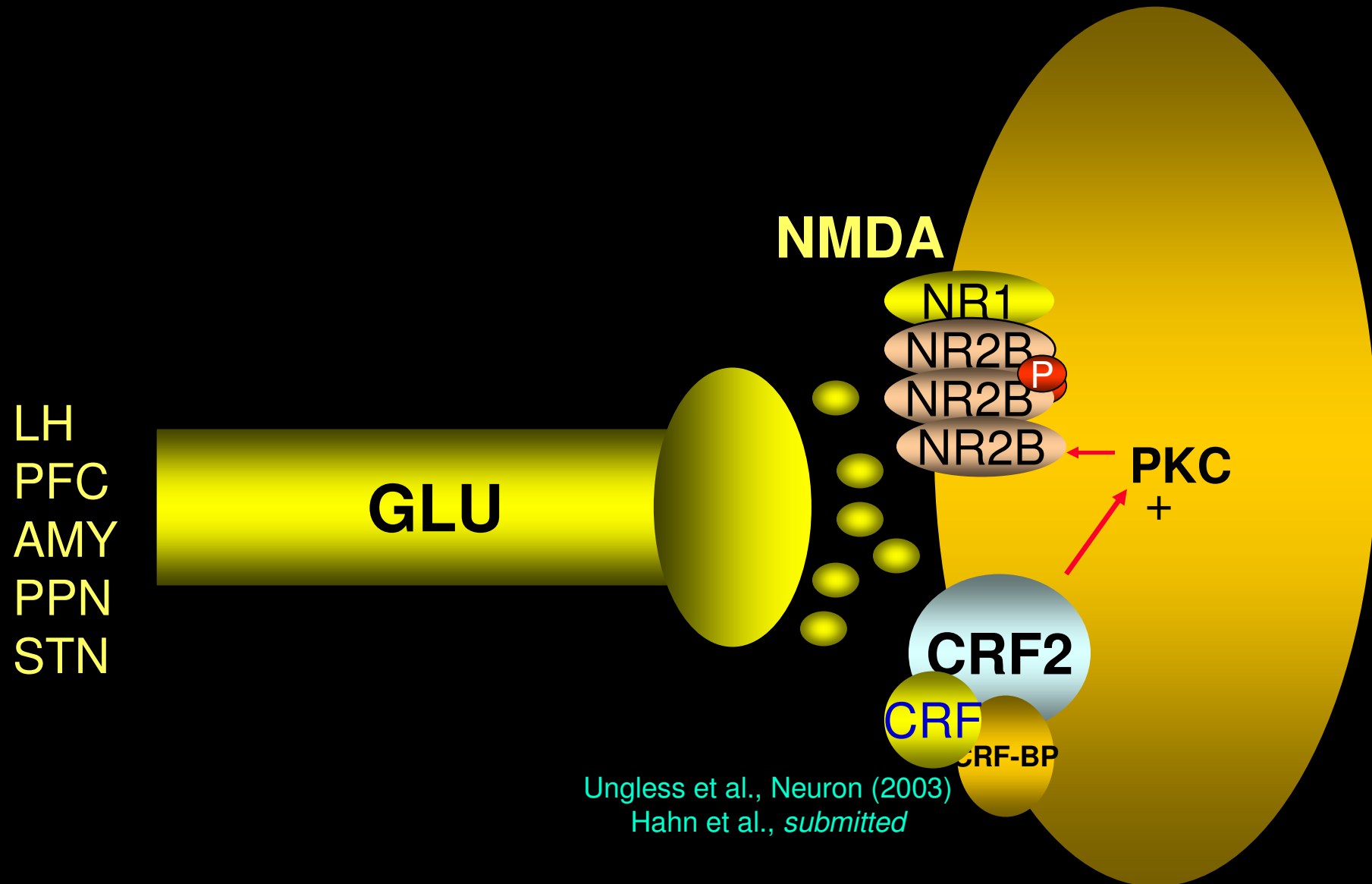
Stress and dopamine neurons

- Stress selectively activates VTA DA neurons (Redmond et al., 2002).
- Intra-VTA CRF increase locomotor activity and DA metabolism in the prefrontal cortex (Kalivas et al., 1987).
- Intra-VTA CRF reinstates cocaine-seeking (Wang et al., 2005).



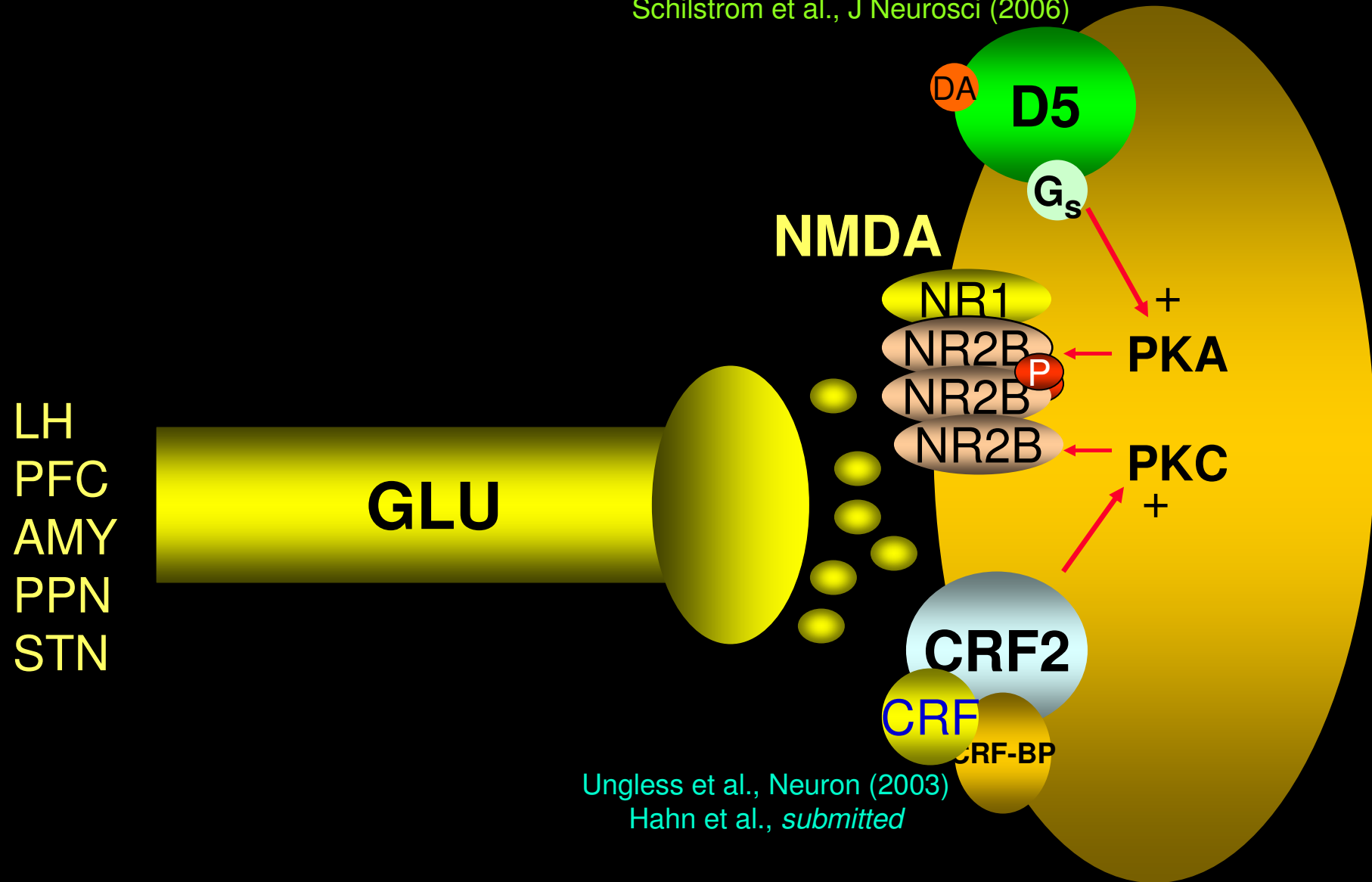
- projections of the mesolimbic dopamine system.
- - - efferents from the NAc
- - - limbic afferents to NAc

Like cocaine, CRF increases NMDARs in DA neurons



Second possibility for therapeutic intervention: blocking CRFR2

Schilstrom et al., J Neurosci (2006)



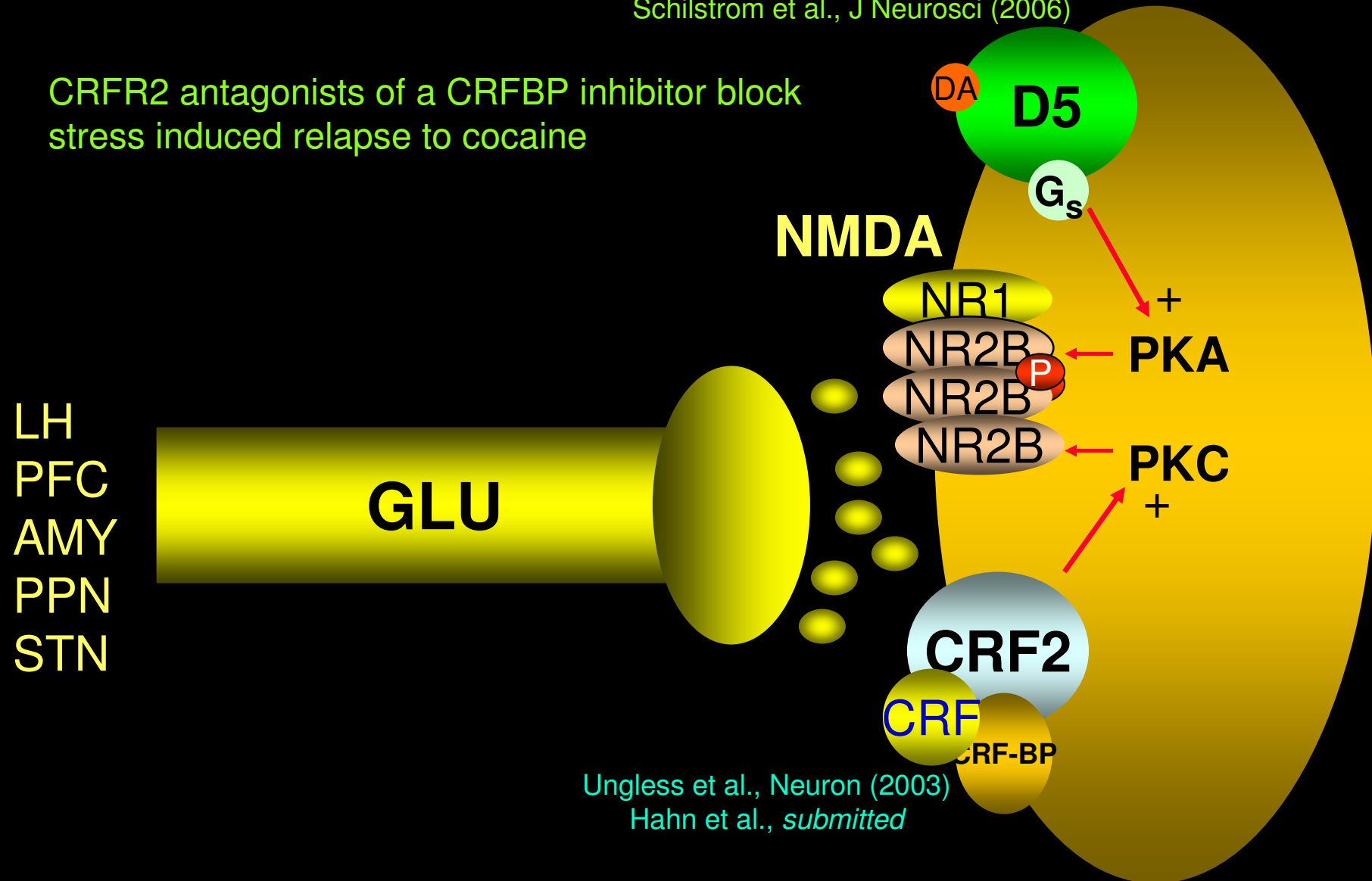
Ungless et al., Neuron (2003)

Hahn et al., *submitted*

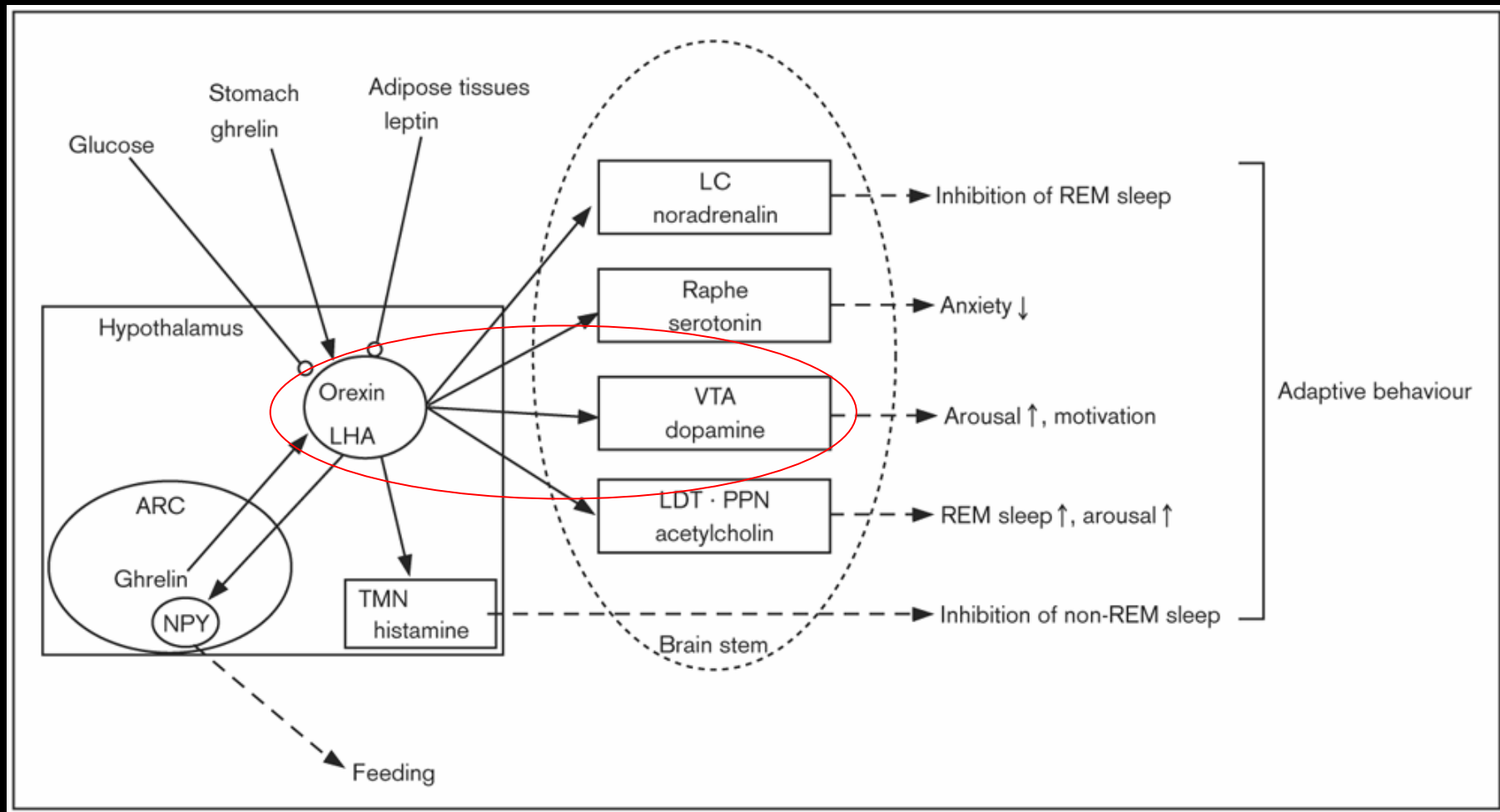
Second possibility for therapeutic intervention: blocking CRFR2

Schilstrom et al., J Neurosci (2006)

CRFR2 antagonists of a CRFBP inhibitor block stress induced relapse to cocaine



Orexin-releasing neurons from LH to the VTA are key mediators of motivated behaviors

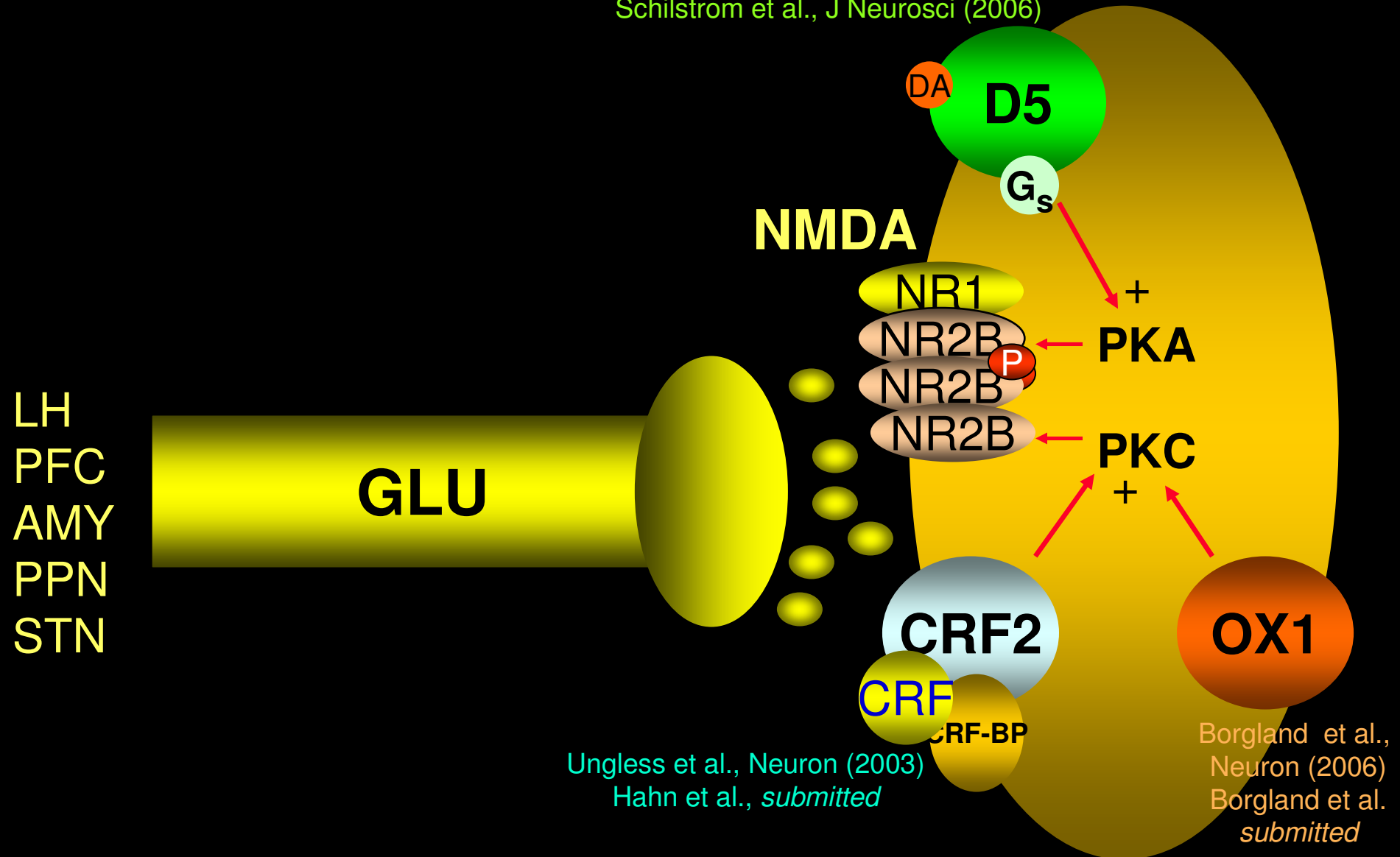


Another promising target: Orexin

- - A deficiency in the hypocretin/orexin system is related to narcolepsy. However, narcoleptic patients treated with amphetamine-like drugs rarely become addicted to these drugs.

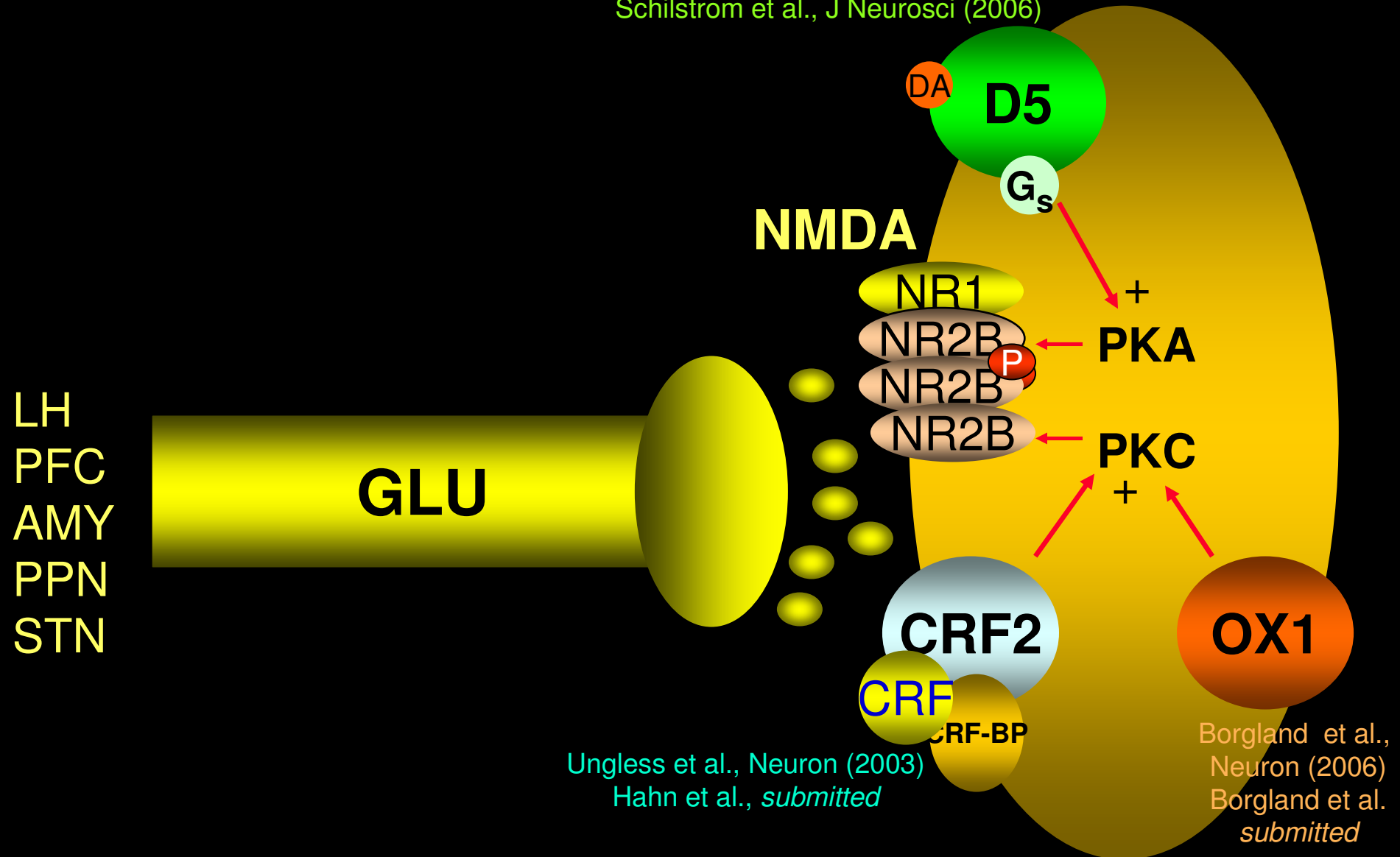
Orexin acutely potentiate NMDARs: A functional link between stress, motivation and substance abuse

Schilstrom et al., J Neurosci (2006)



Third therapeutic possibility: inhibition of orexin receptors

Schilstrom et al., J Neurosci (2006)



Summary and Conclusions

In vitro single cell studies represent a very powerful tool to create novel therapeutic targets against drug abuse

Convergence of actions on NMDARs by cocaine, CRF and Orexin in the induction of LTP

Our work has highlighted the role of three novel therapeutic targets in sustaining cocaine-dependent behaviors

Acknowledgements

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