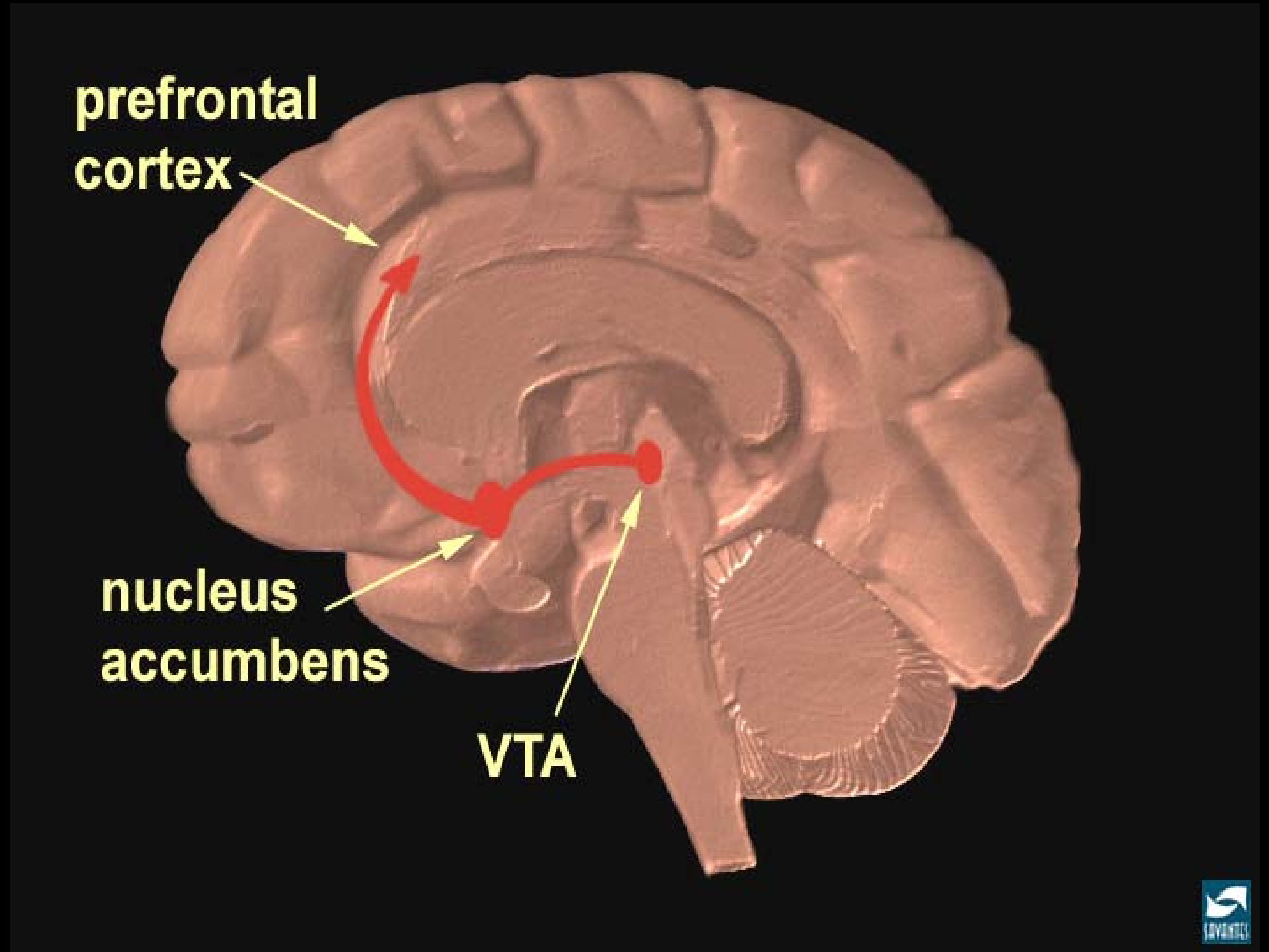

prefrontal
cortex
nucleus
accumbens
VTA

Overview of the striatum

dorsal

ventral

- Dorsal striatum important for motor planning and adaptive behaviors. Main inputs arise from motor cortex.
- Disorders involving dorsal striatum include Parkinson's disease and Huntington's disease.
- Ventral striatum (nucleus accumbens) is important for reward. Main inputs arise from amygdala and prefrontal cortex.
- Drug addiction, depression are disorders involving the striatum.

Neurotransmission and neuromodulation:

- Adrenaline (ca. 1900-)
- Acetylcholine (ca. 1900-)
- Neuropeptides (1930-)
- Amino Acids (GABA and Glutamate) (1950-)
- Monoamines (5-HT and Dopamine) (1950-)
- Endogenous opioids (1975-)
- Endogenous cannabinoids (1992-)

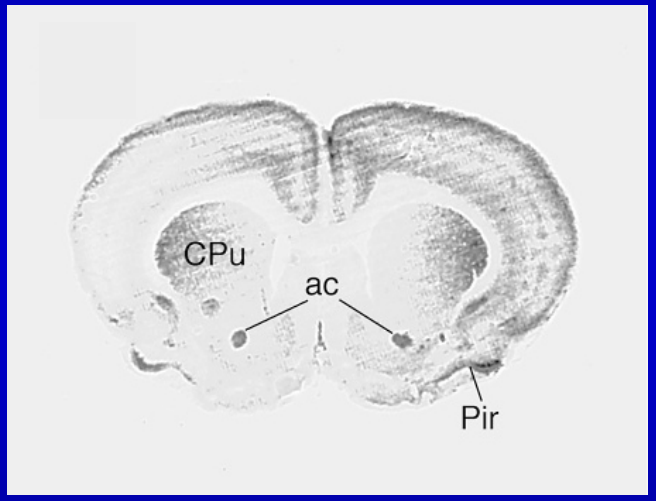
  -CB1 receptor cloned (1990)

  -discovery of endogenous endocannabinoids (1992)

  -modulation of synaptic function (2001)

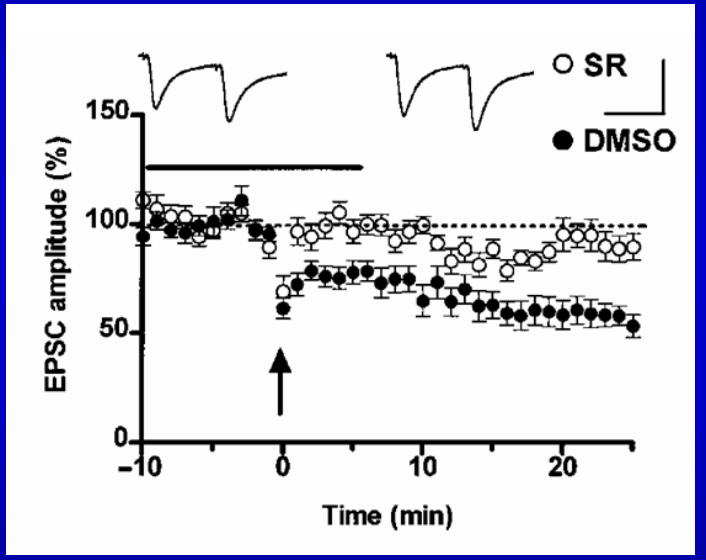
Endocannabinoid signaling in the striatum

CB1 immunoreactivity



Egertova and Elphick, **J Comp Neurology** (2000)

Corticostriatal LTD



Gerdeman et al., **Nat Neurosci** (2002)

Anatol Kreitzer

Sheela Singla

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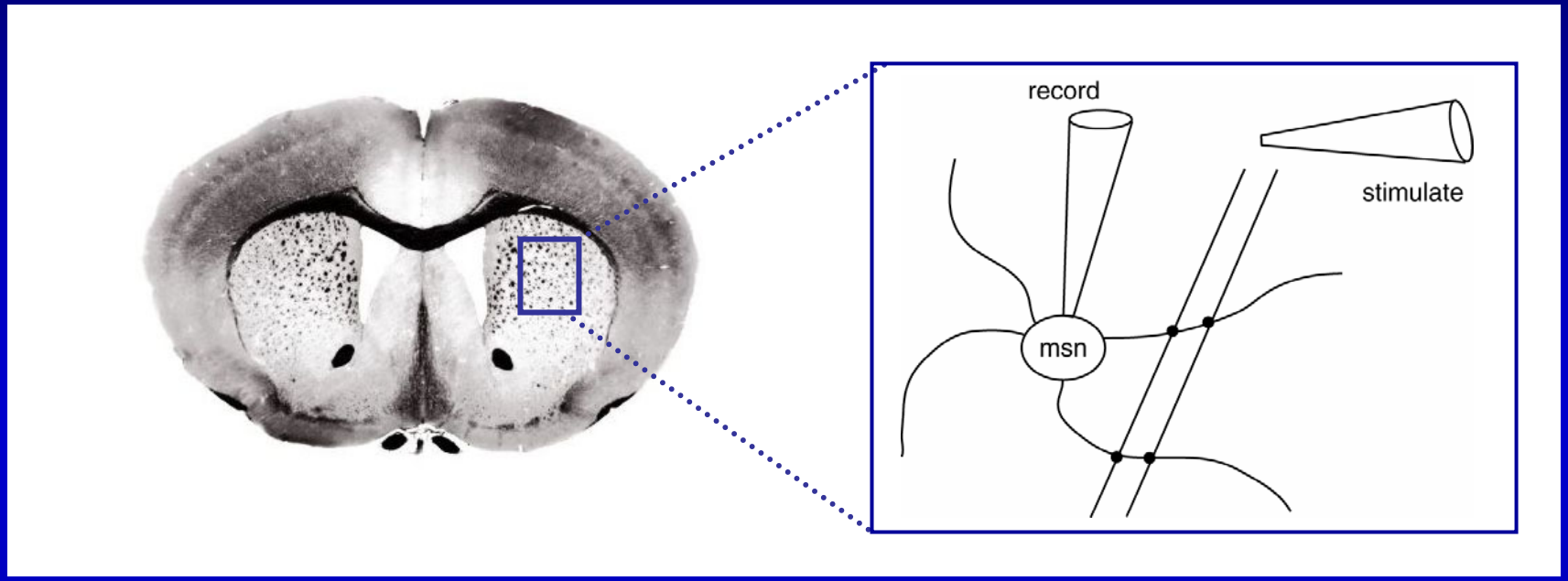
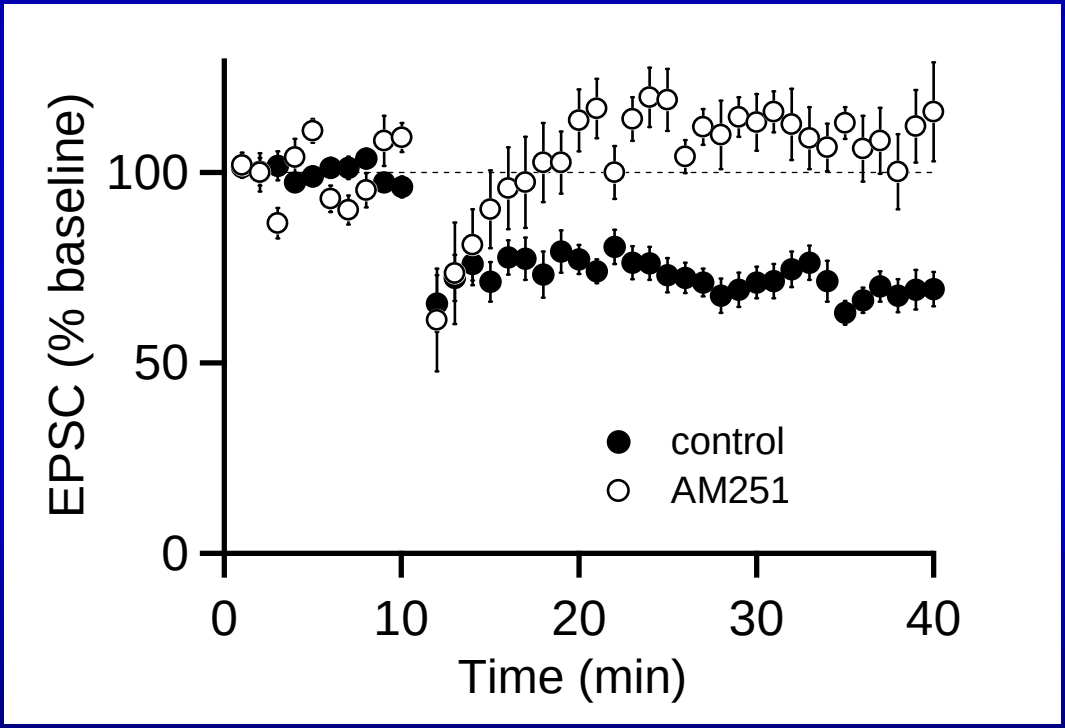
Percy Luu

Experimental Methods

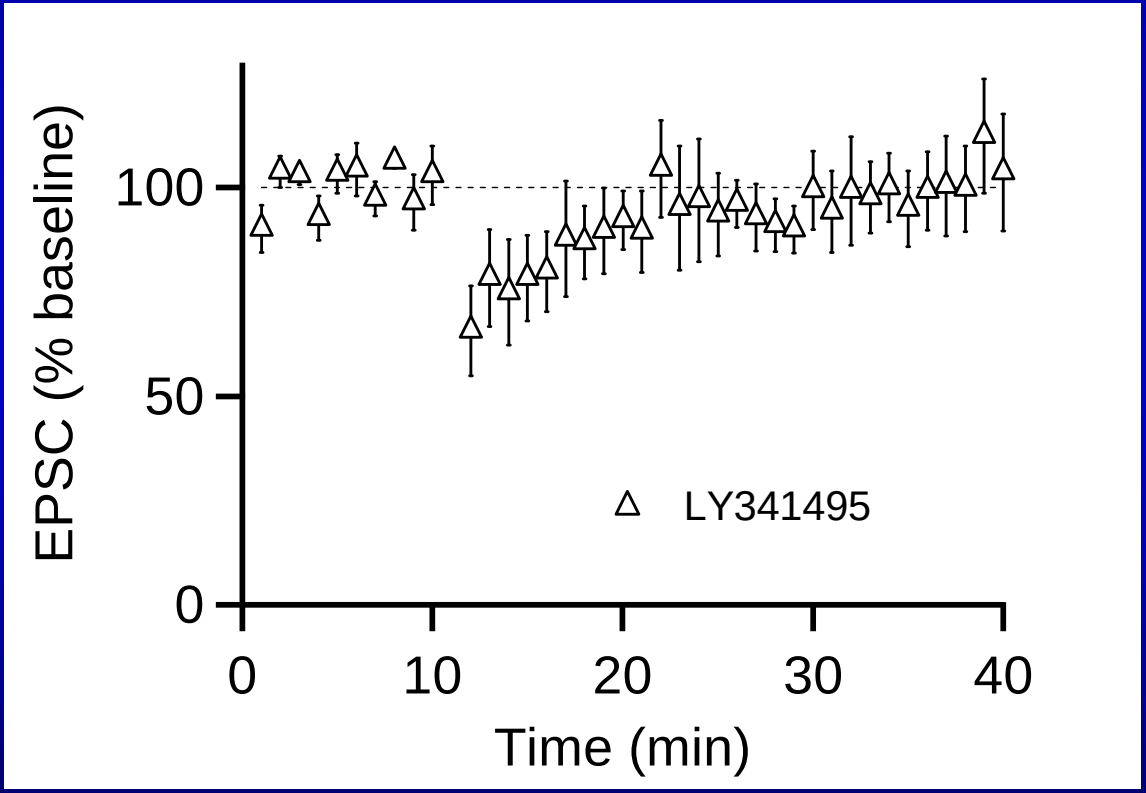


- Acute coronal brain slices – recordings performed from medium spiny neurons (MSNs) in **dorsolateral** striatum of 3- to 4-week-old rats and mice
- $CsMeSO_3$ based-internal solution, 0.2 mM EGTA, QX-314 to block Na currents
- External saline: 2 mM Ca, 1 mM Mg. Picrotoxin (50 μM) present to block $GABA_A$-mediated currents.
- Experiments performed at room temperature (RT) and 30-32 °C

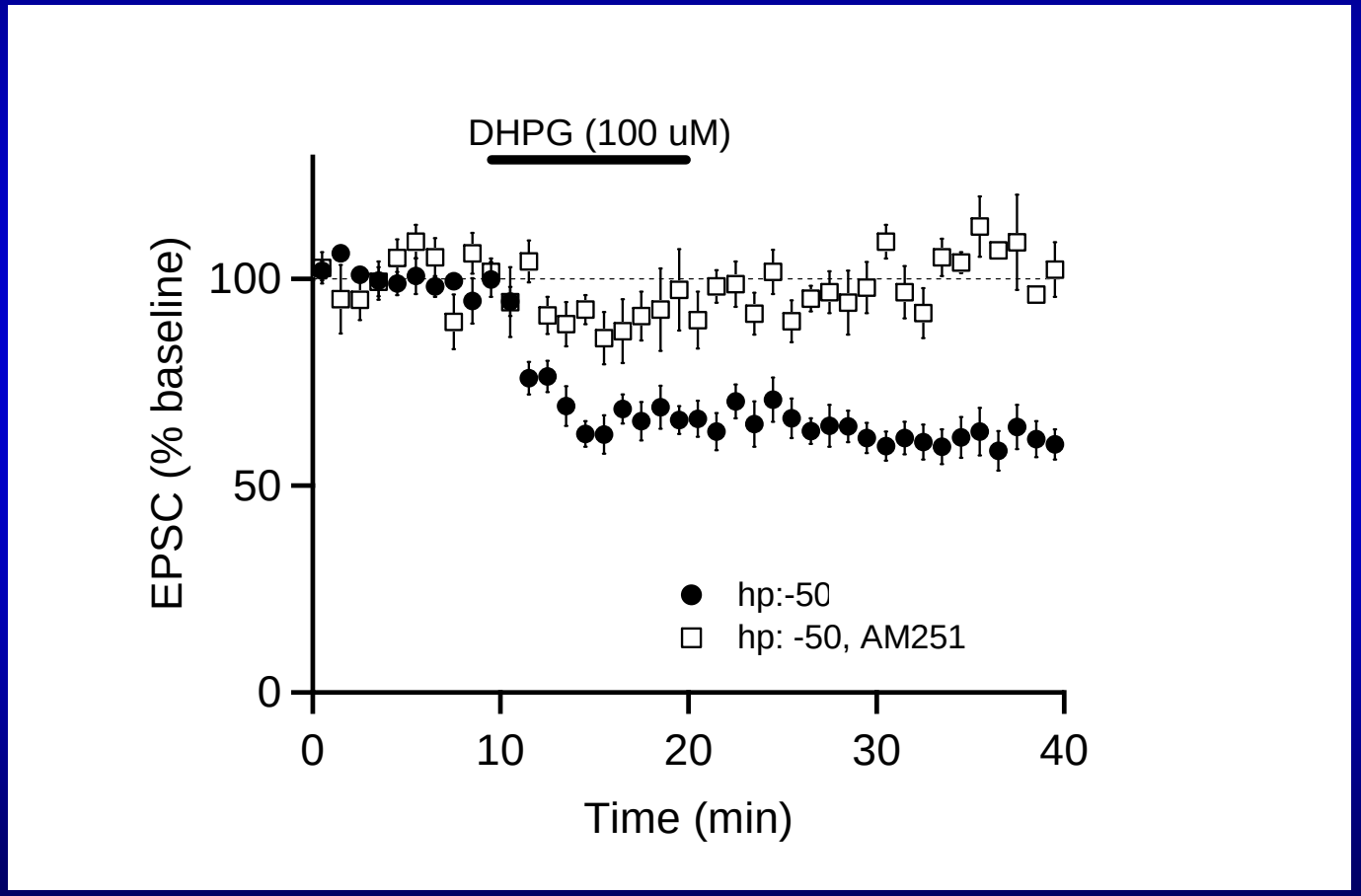
Tetanus induces endocannabinoid-mediated LTD (eCB-LTD)



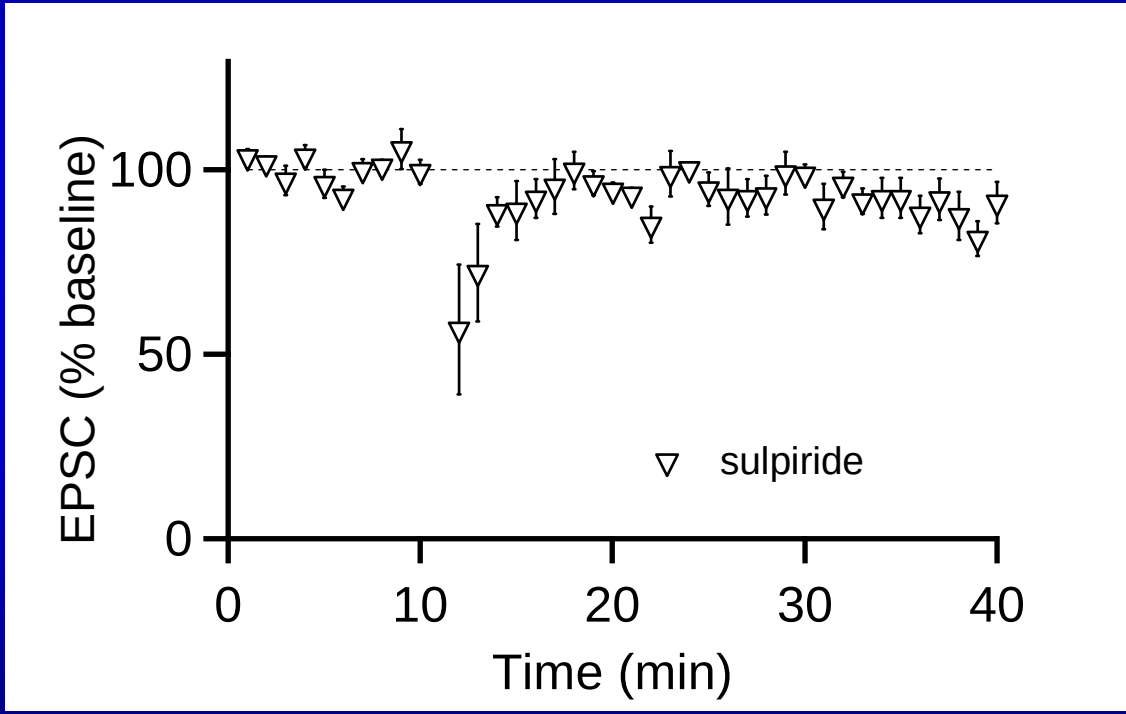
eCB-LTD requires mGluRs



Endocannabinoids are released by activation of postsynaptic mGluRs

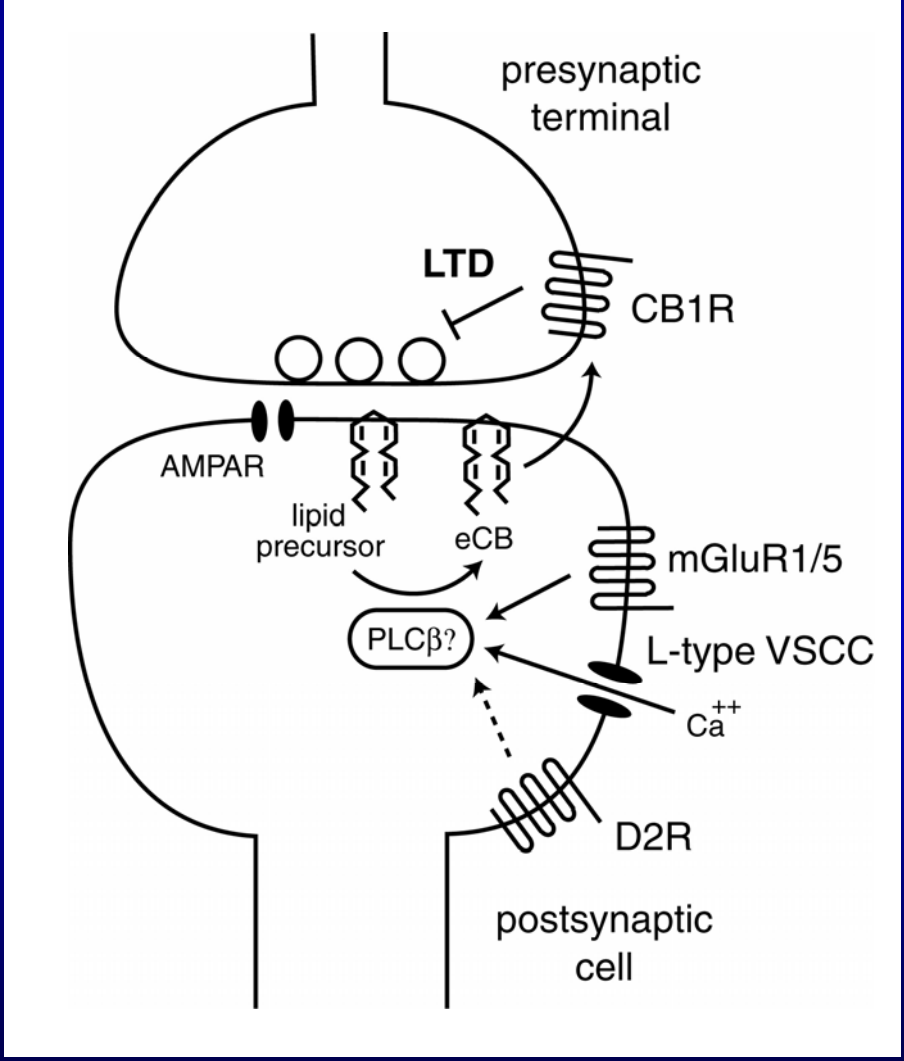


eCB-LTD requires D2 receptors



sulpiride=D2 antagonist

Model of endocannabinoid release and LTD in the striatum



1. mGluR activation, combined with subthreshold depolarization, leads to endocannabinoid (eCB) synthesis and release

2. Dopamine D2 receptor activation enhances eCB synthesis, while D2 inhibition reduces eCB synthesis

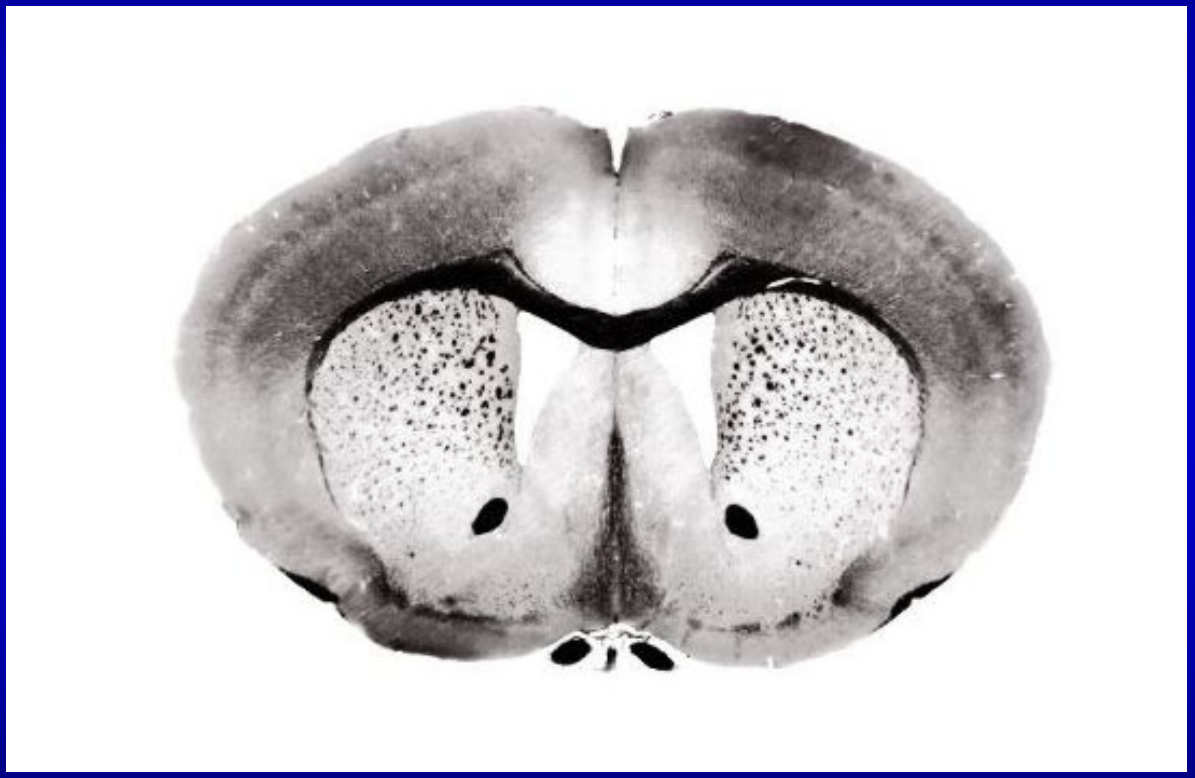
3. Released eCBs bind to presynaptic CB1 receptors and induce presynaptic LTD

4. Neurotransmitter release is reduced for tens of minutes or more

(Kreitzer and Malenka, 2005)

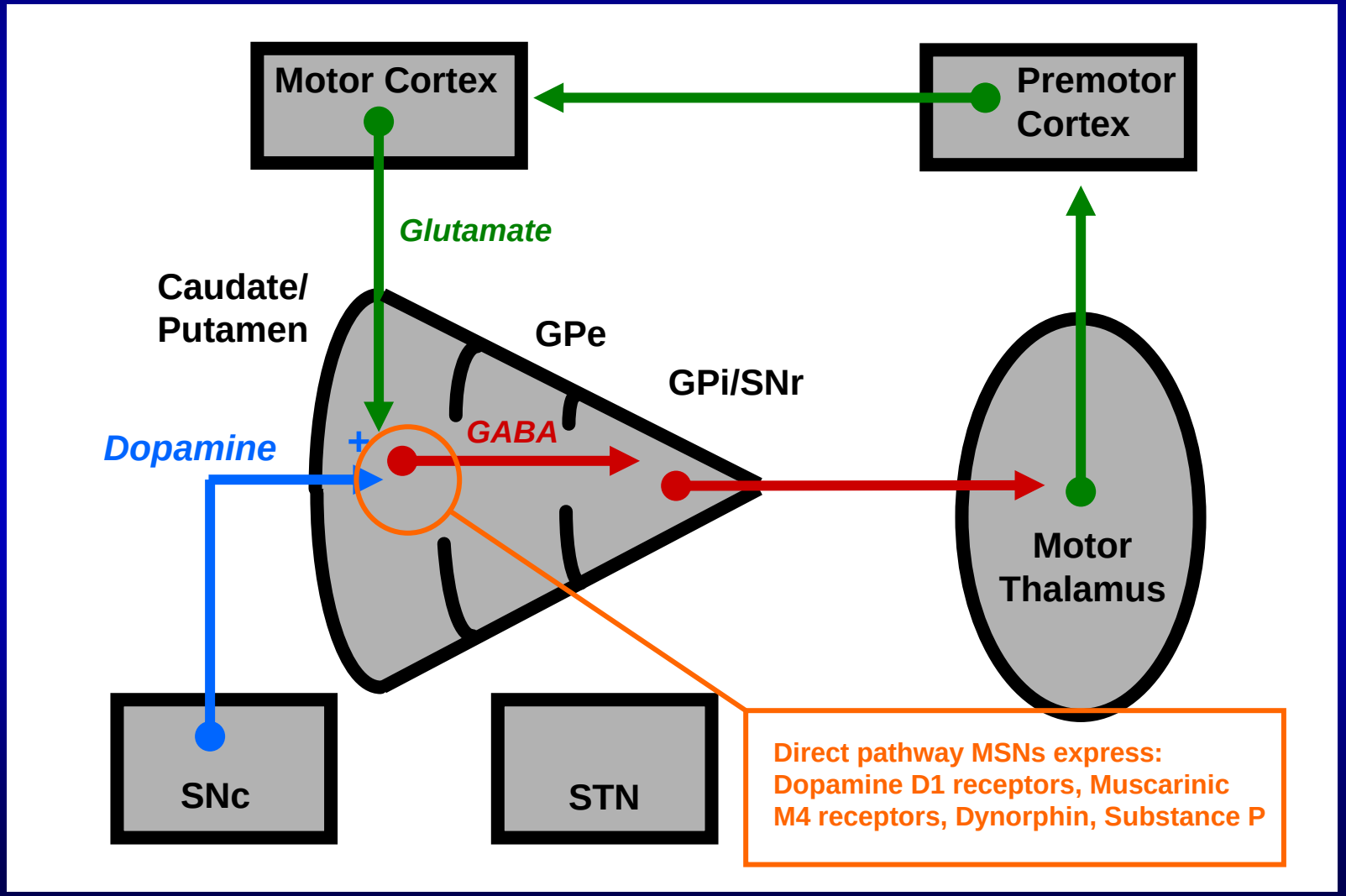
The striatum is not homogeneous (2 populations of medium spiny neurons)

dorsal

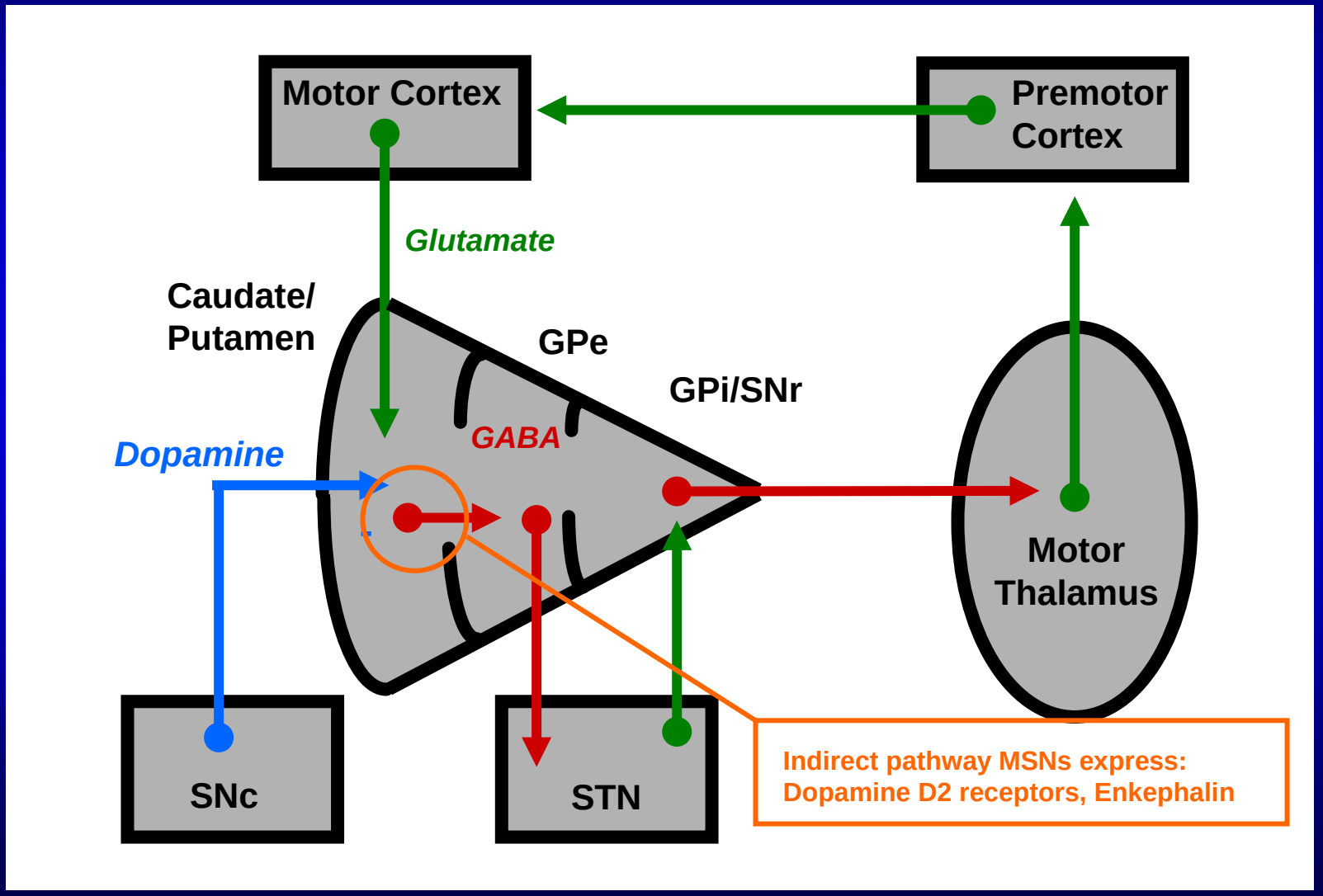


ventral

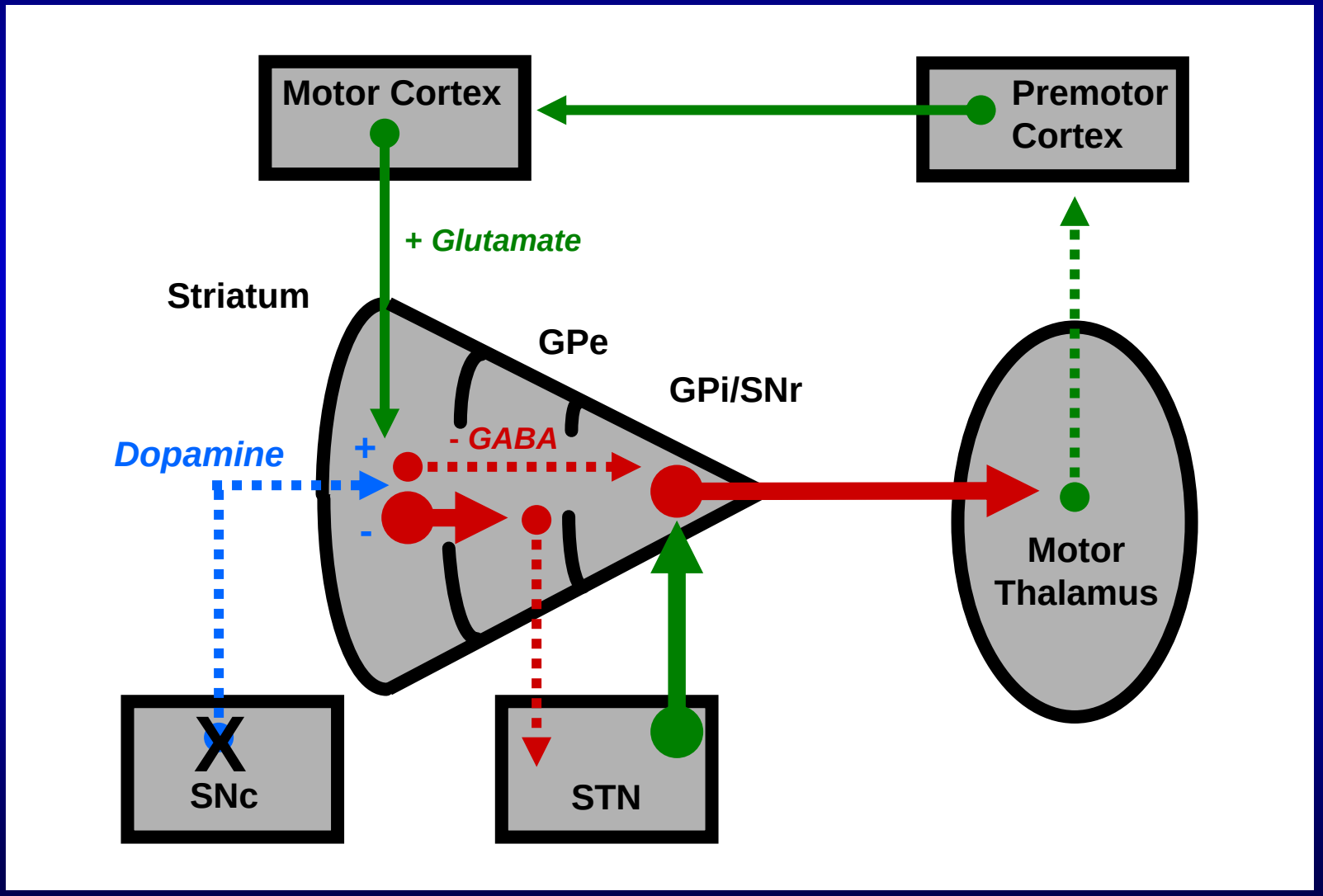
Basal ganglia motor circuit: direct pathway



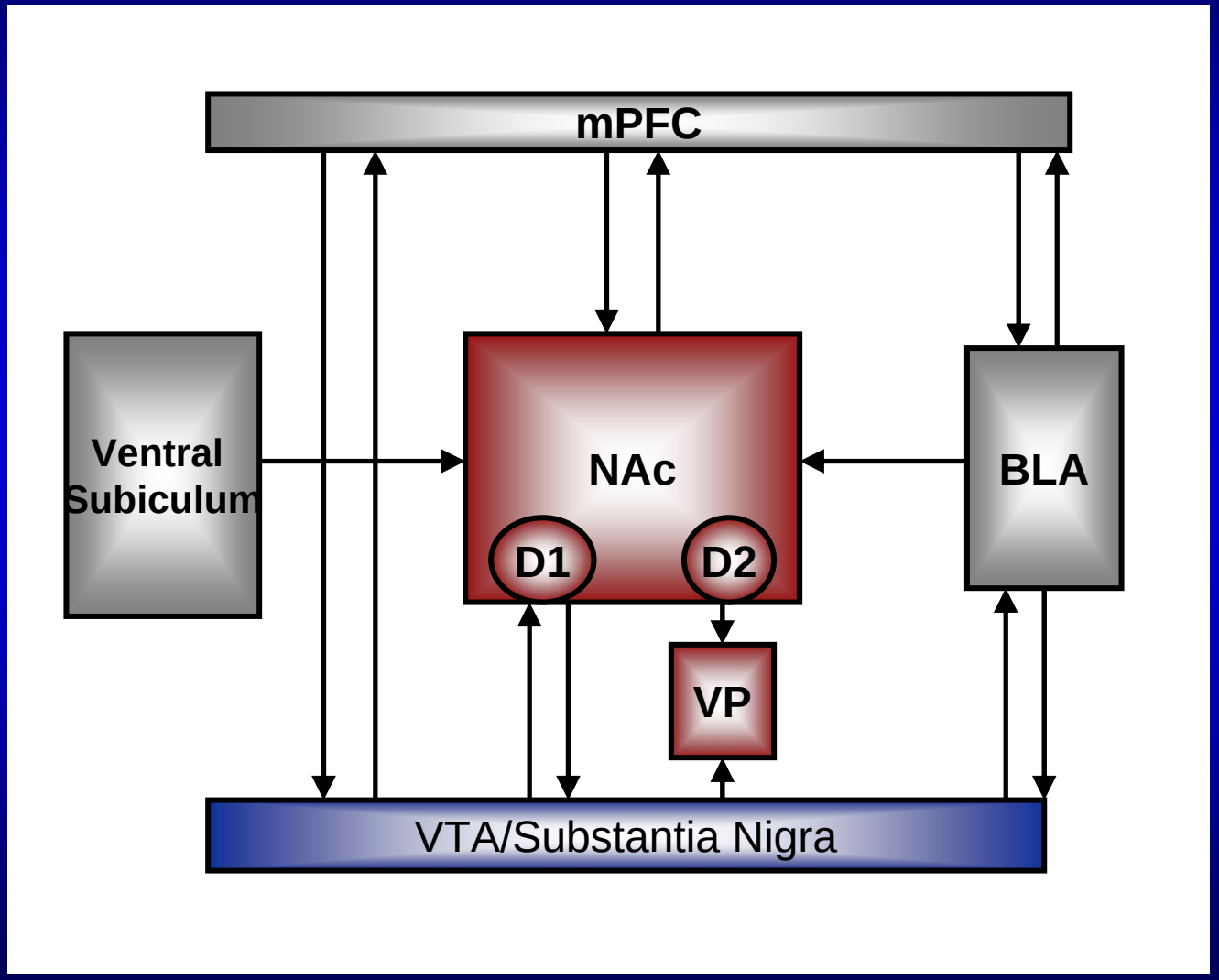
Basal ganglia motor circuit: indirect pathway



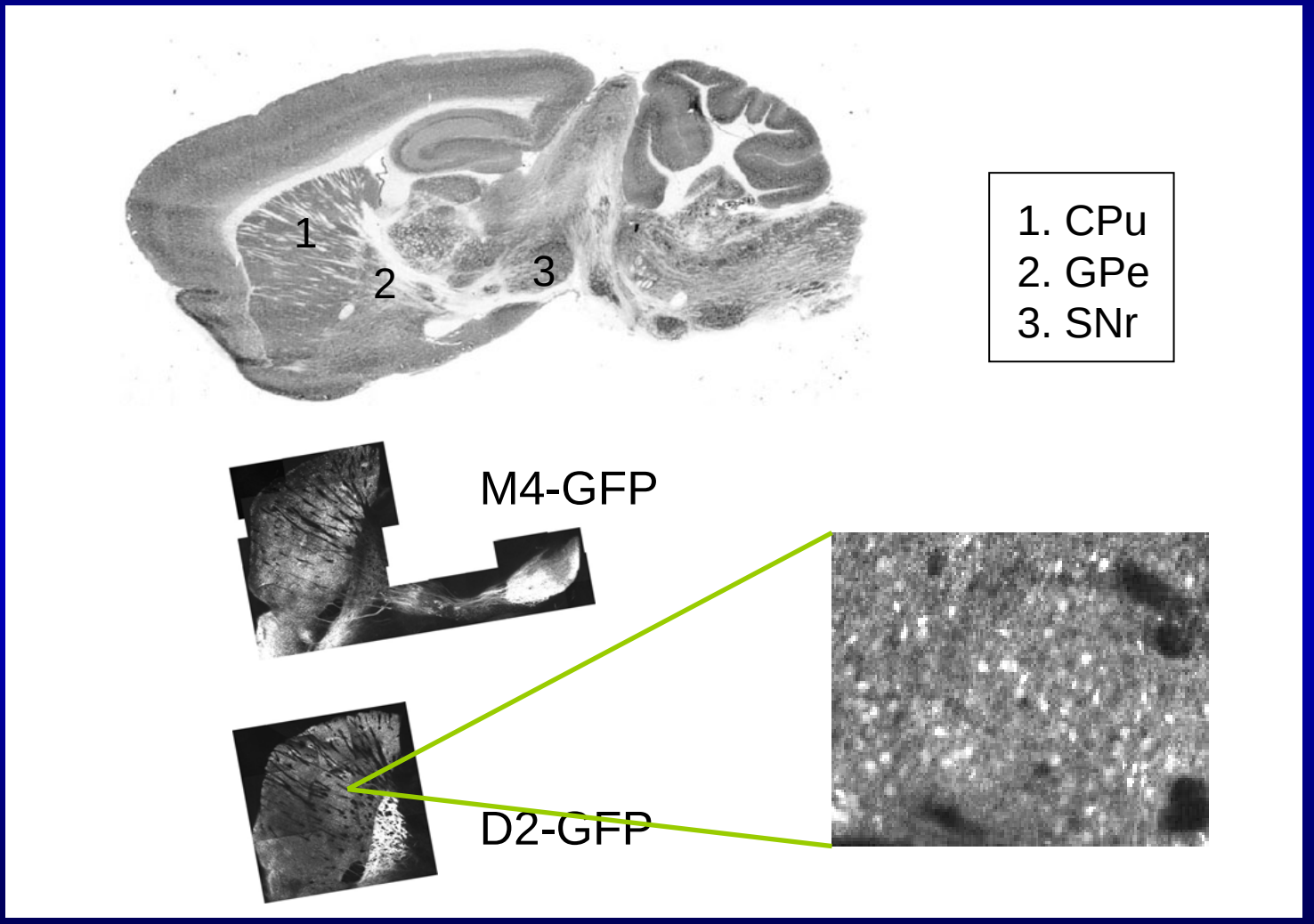
Basal ganglia motor circuit: Parkinson disease



Nucleus accumbens direct and indirect pathways?

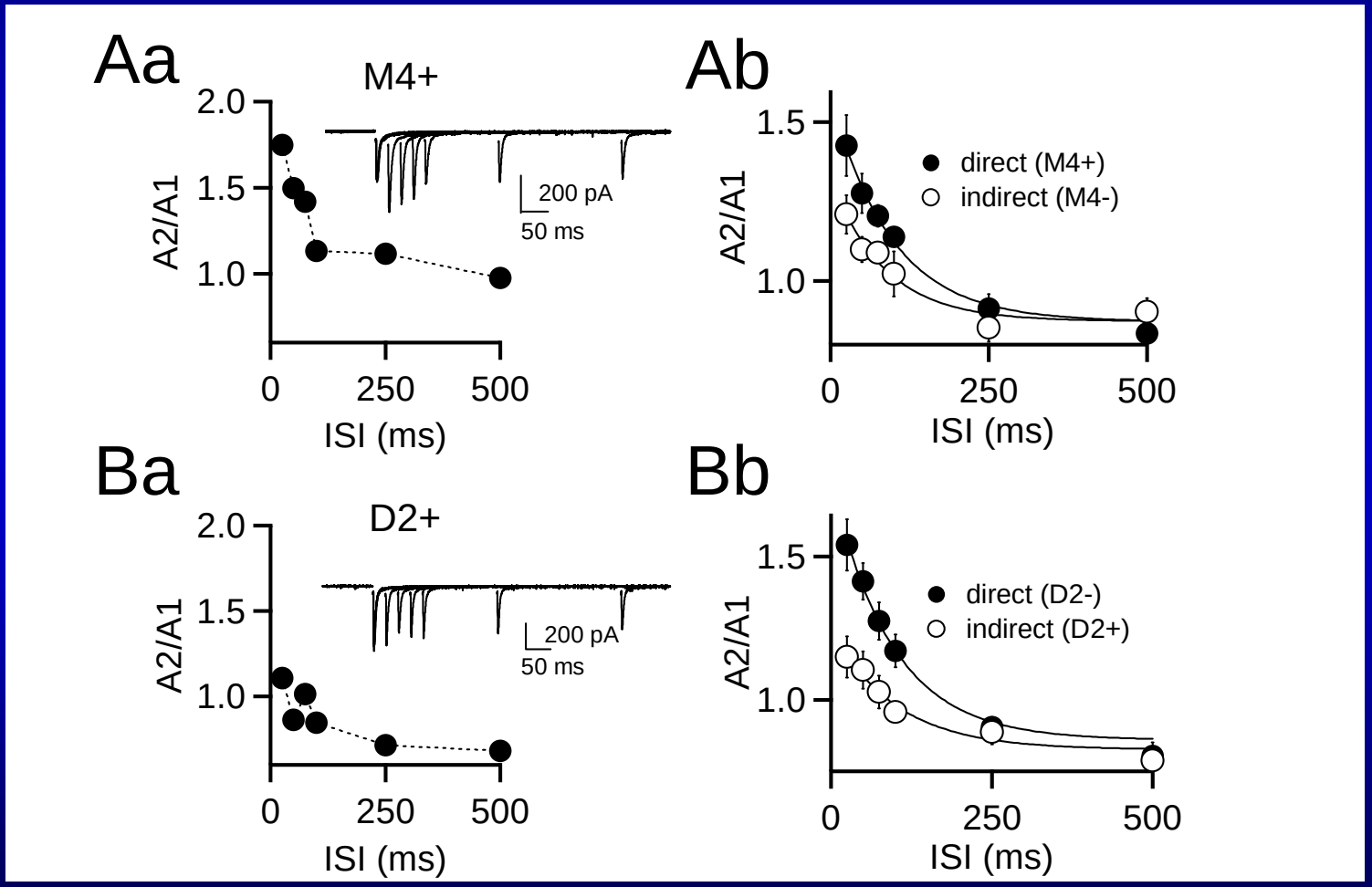


M4- and D2-GFP BAC-transgenic mice label direct and indirect pathway medium spiny neurons

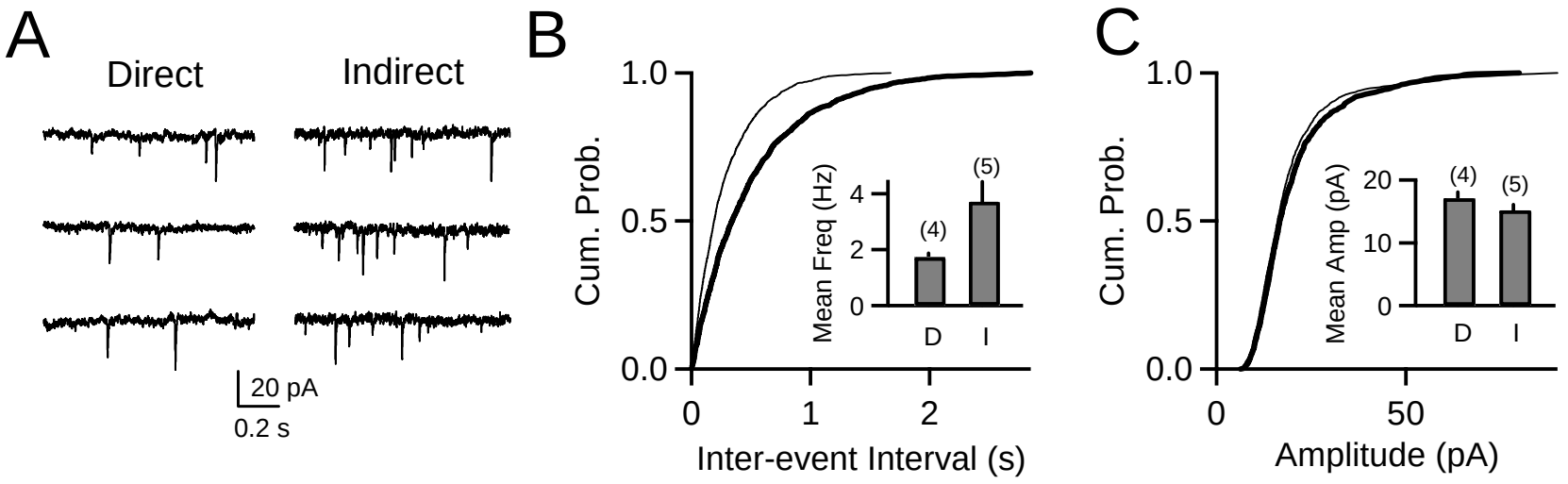


GENSAT Program (N. Heintz, M. Hatten, W. Yang)

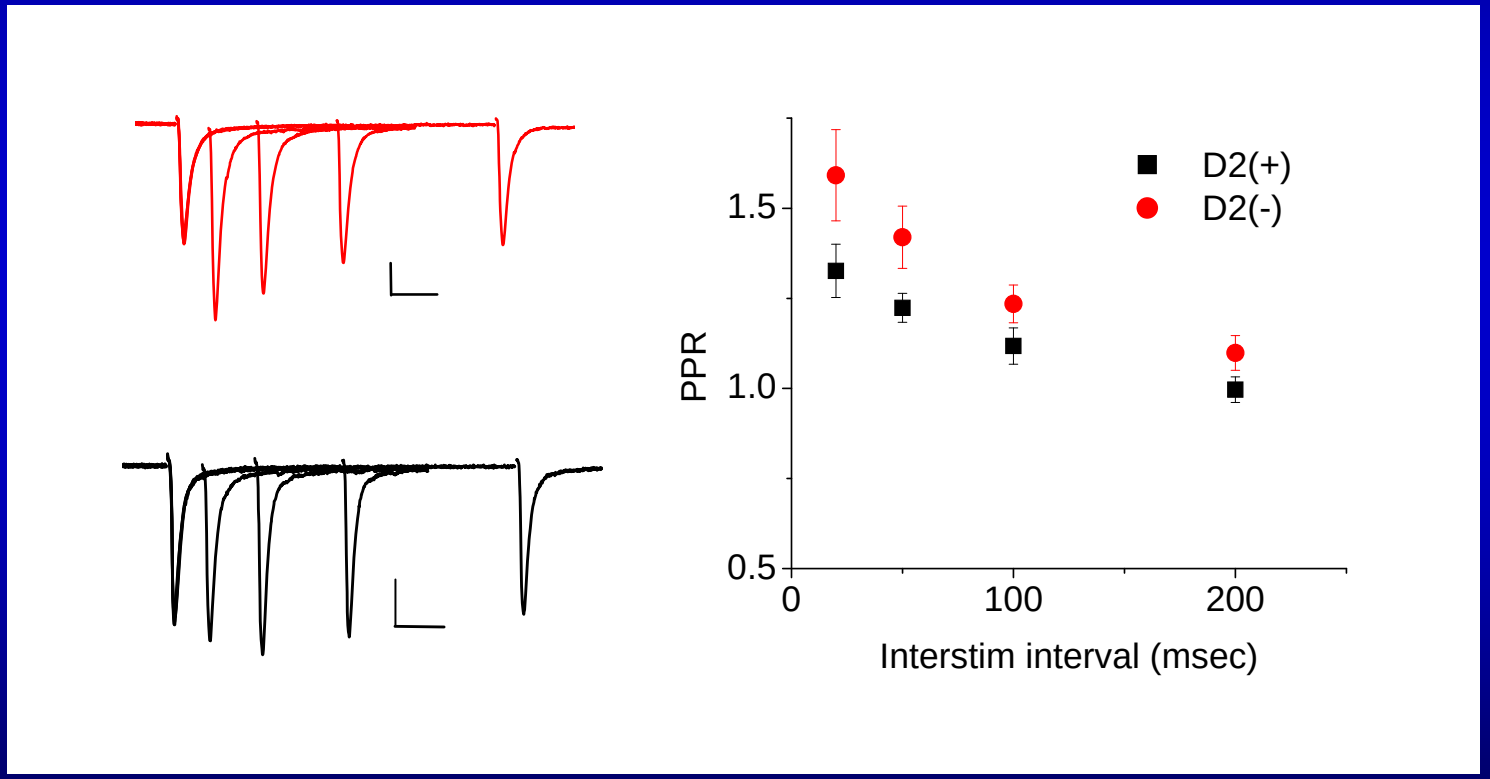
Direct and indirect pathway synapses display different paired-pulse ratios



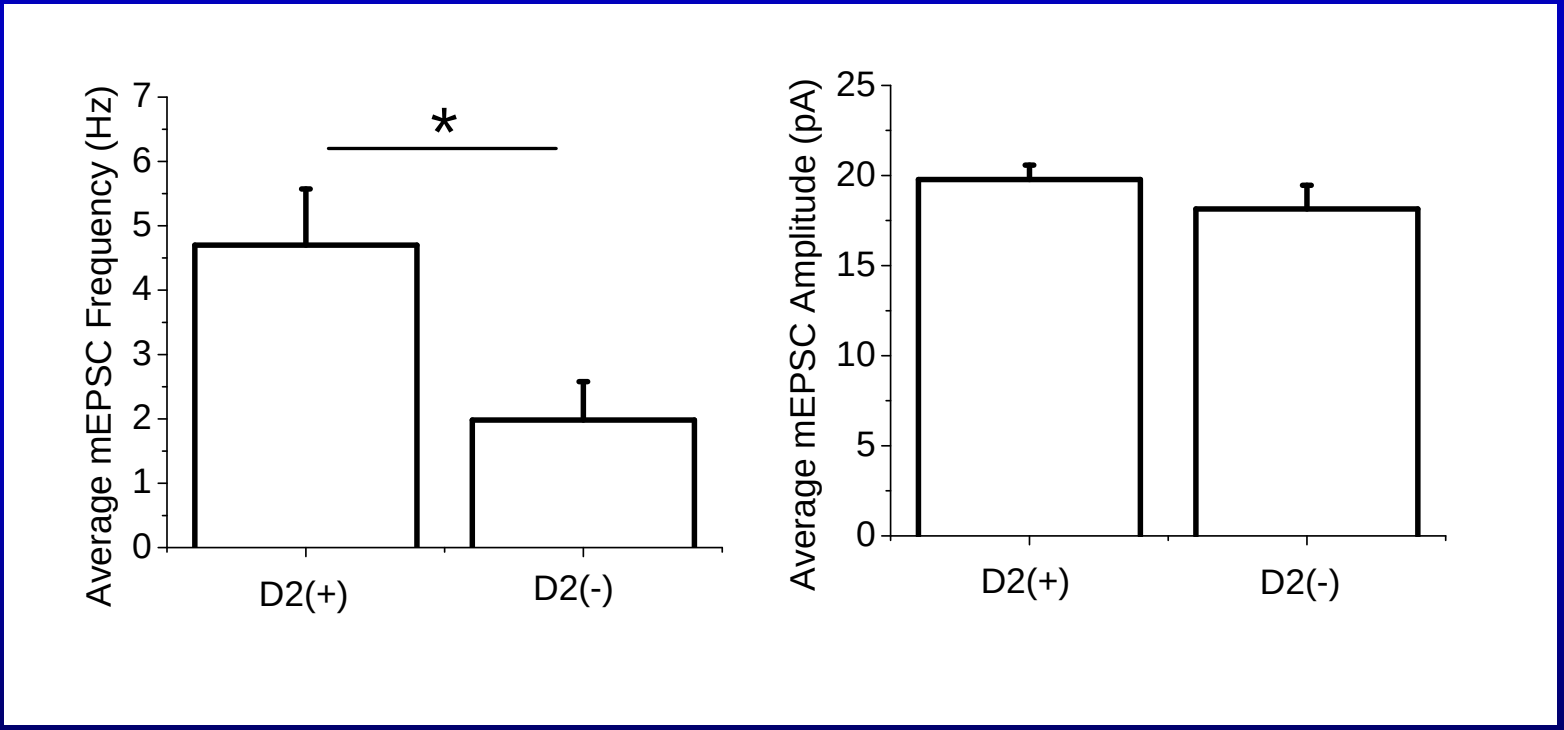
Indirect pathway synapses have a higher release probability



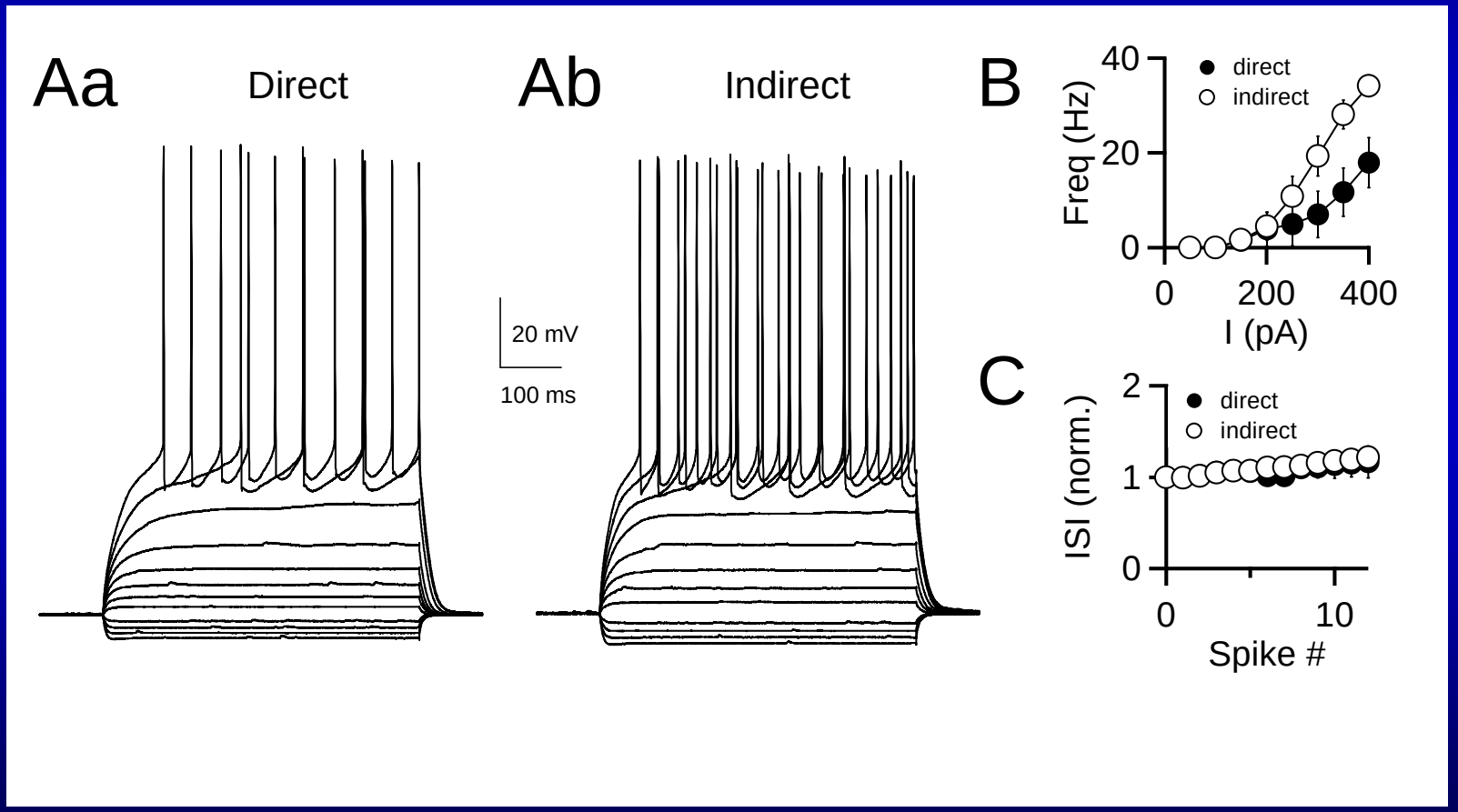
Direct and indirect pathway synapses display different paired-pulse ratios in nucleus accumbens



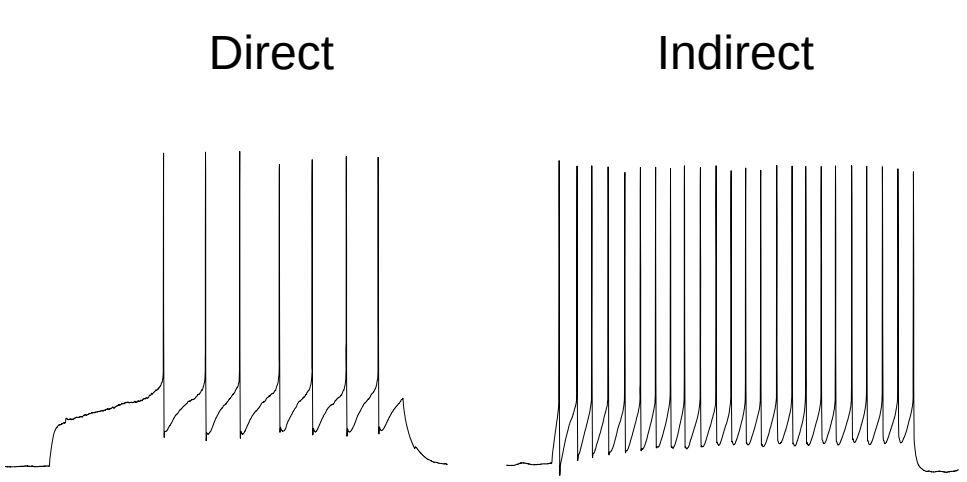
Indirect (D2+) pathway synapses have a higher release probability in nucleus accumbens?

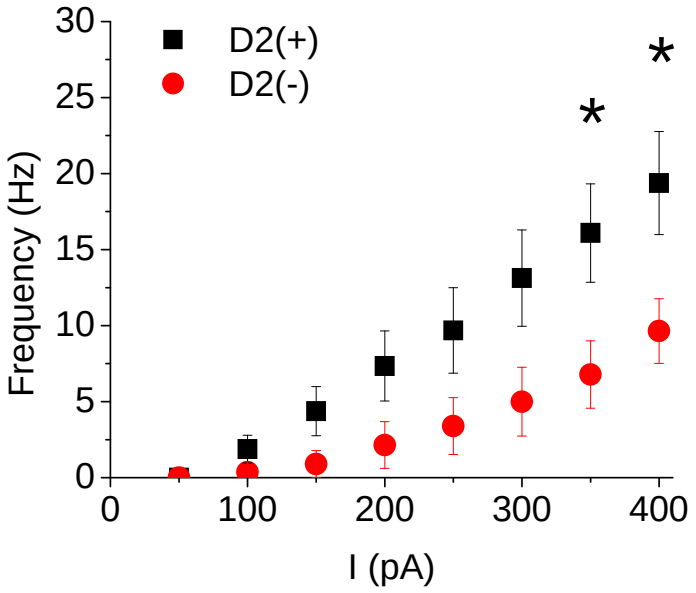


Indirect pathway medium spiny neurons are more excitable

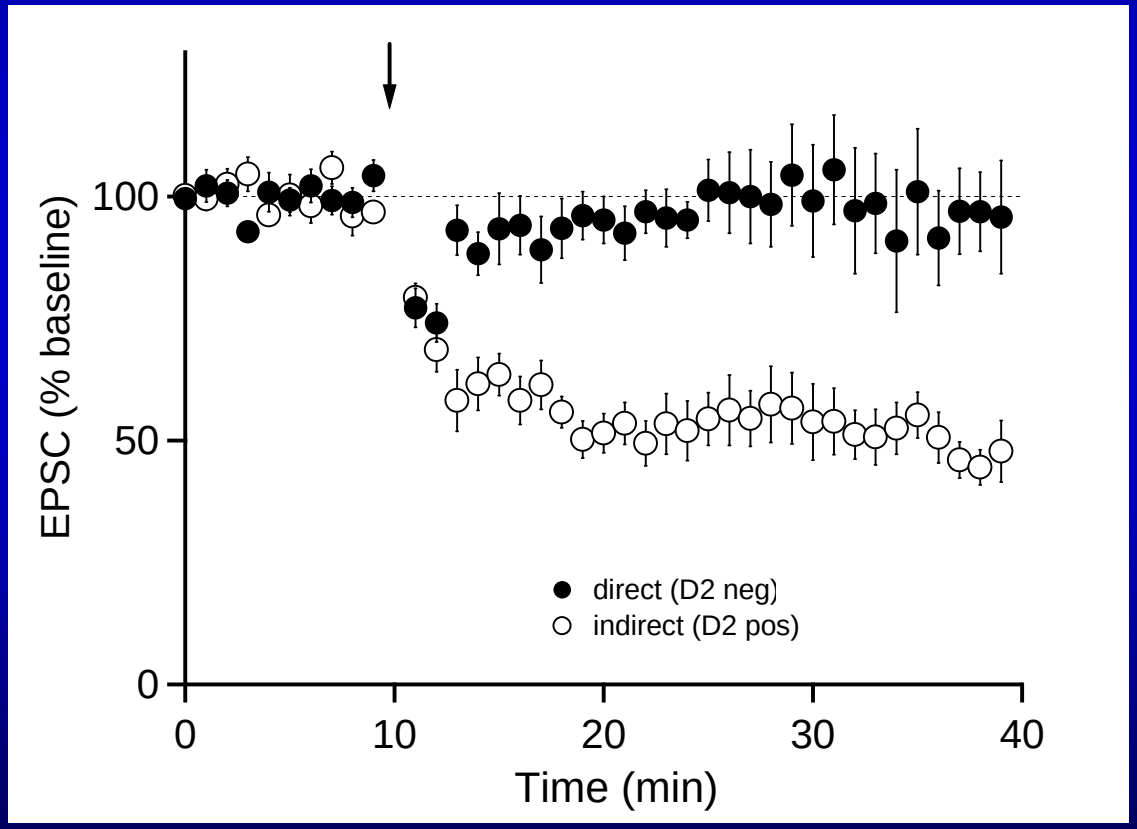


Indirect (D2+) pathway medium spiny neurons are more excitable in nucleus accumbens

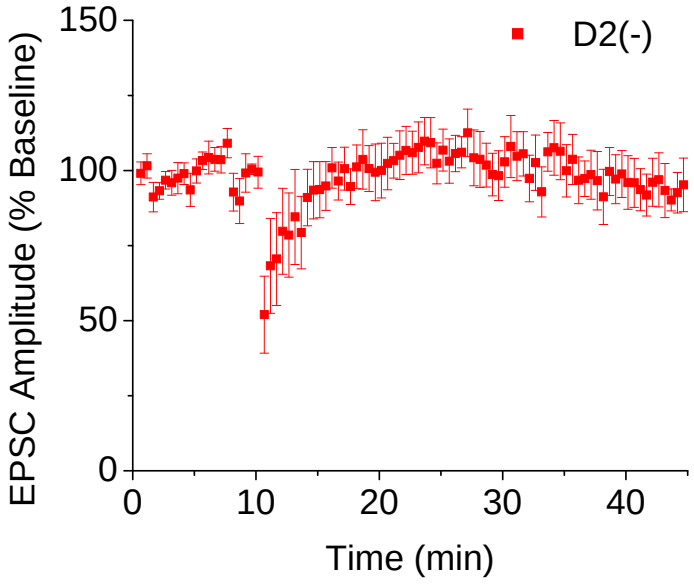


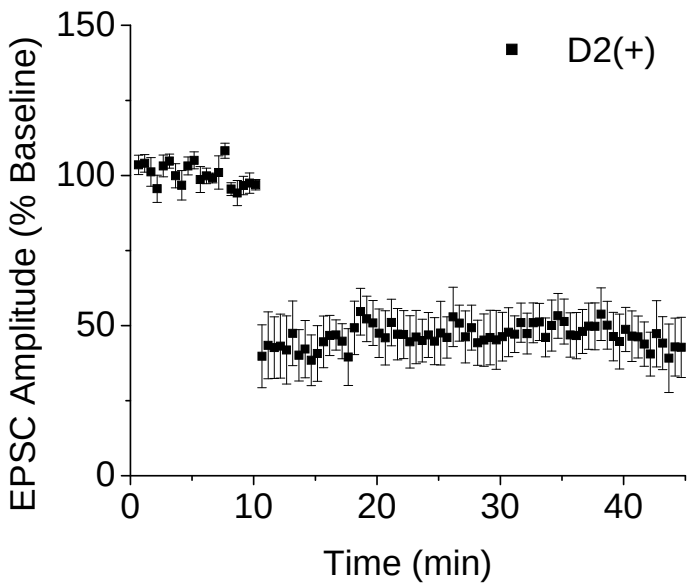


Endocannabinoid-mediated LTD occurs only at indirect pathway synapses

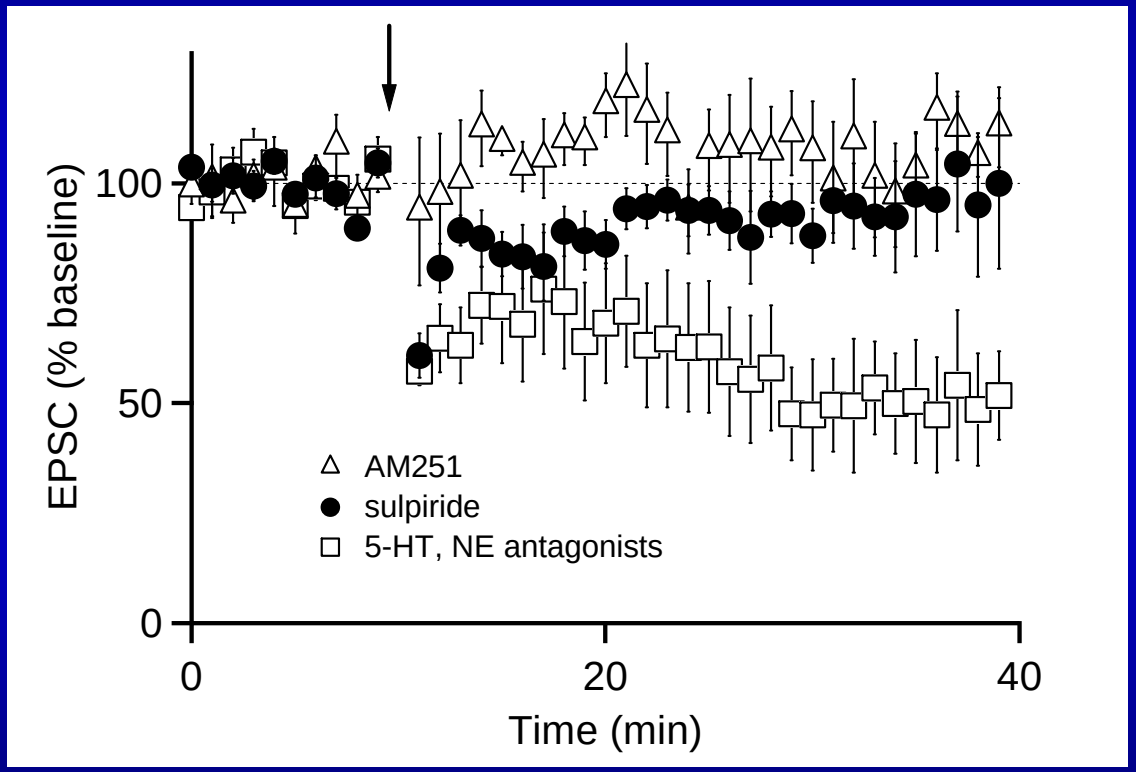


Endocannabinoid-mediated(?) LTD occurs only at indirect pathway synapses in nucleus accumbens



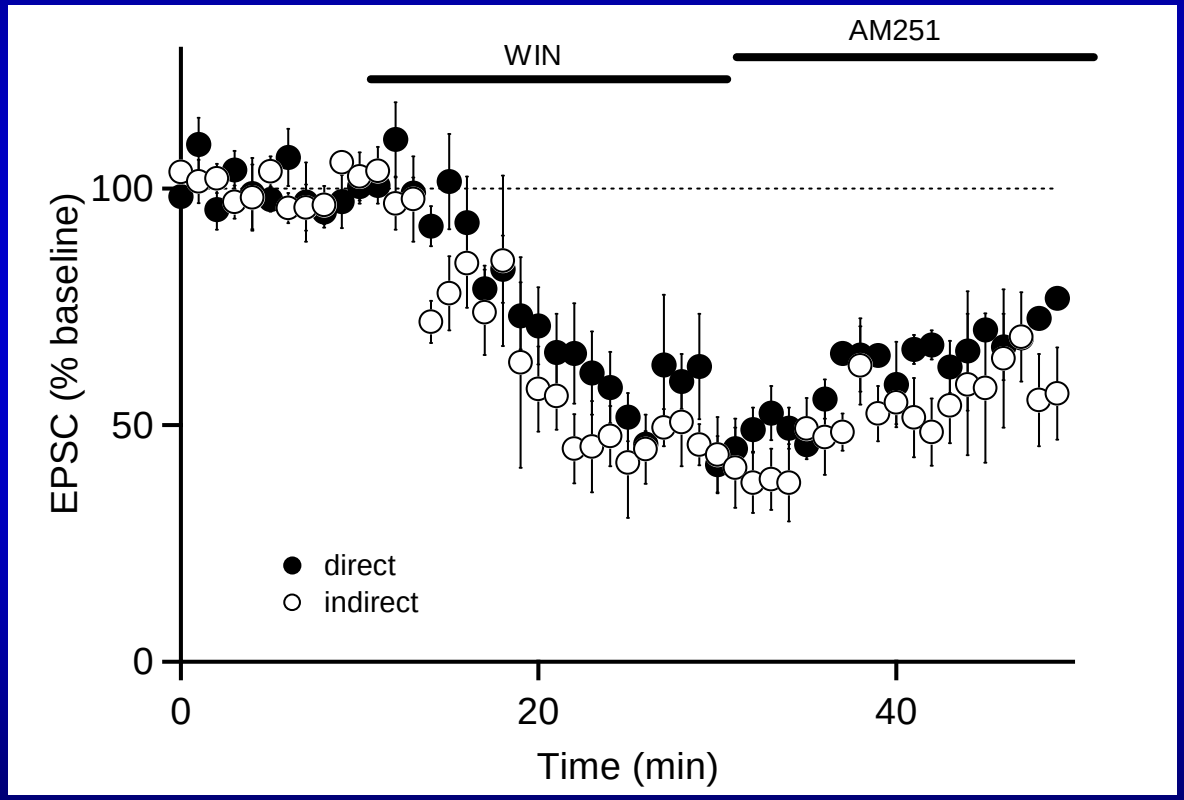


Indirect pathway eCB-LTD requires dopamine D2 receptor activation



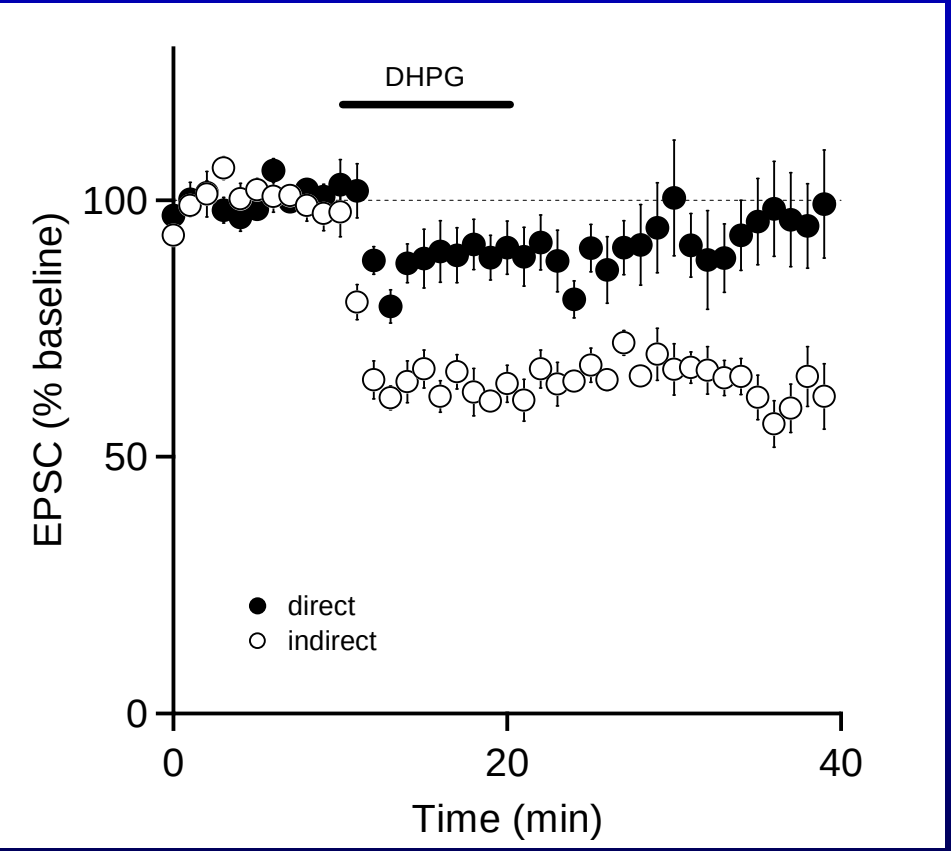
AM251: cannabinoid CB1 receptor antagonist
sulpiride: dopamine D2 receptor antagonist

CB1 receptor agonists inhibit transmitter release at both direct and indirect pathway synapses

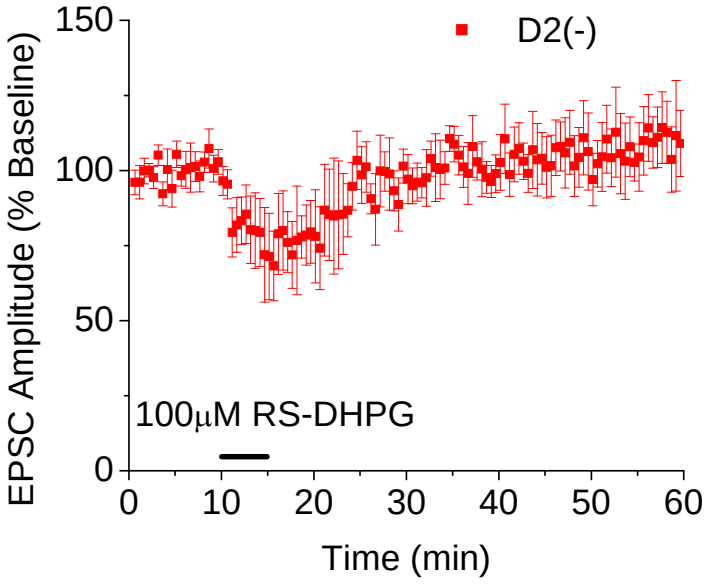


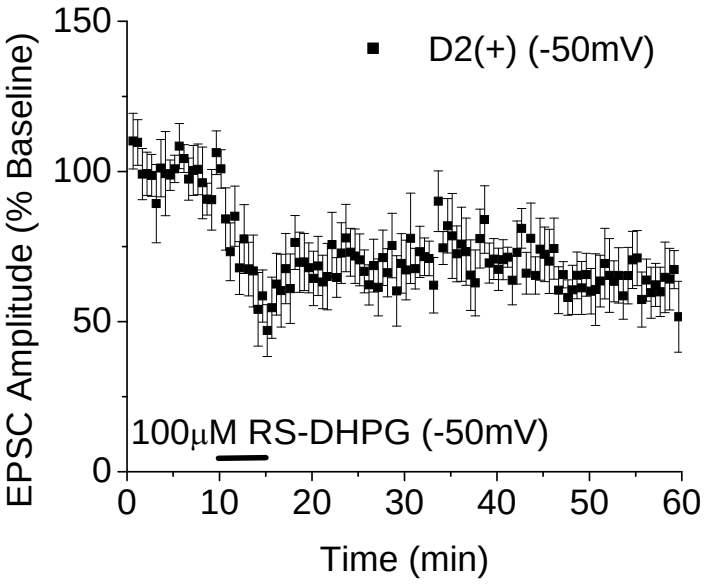
WIN55,212: cannabinoid CB1 receptor agonist
AM251: cannabinoid CB1 receptor antagonist

Postsynaptic mGluR-driven endocannabinoid release occurs primarily at indirect pathway synapses

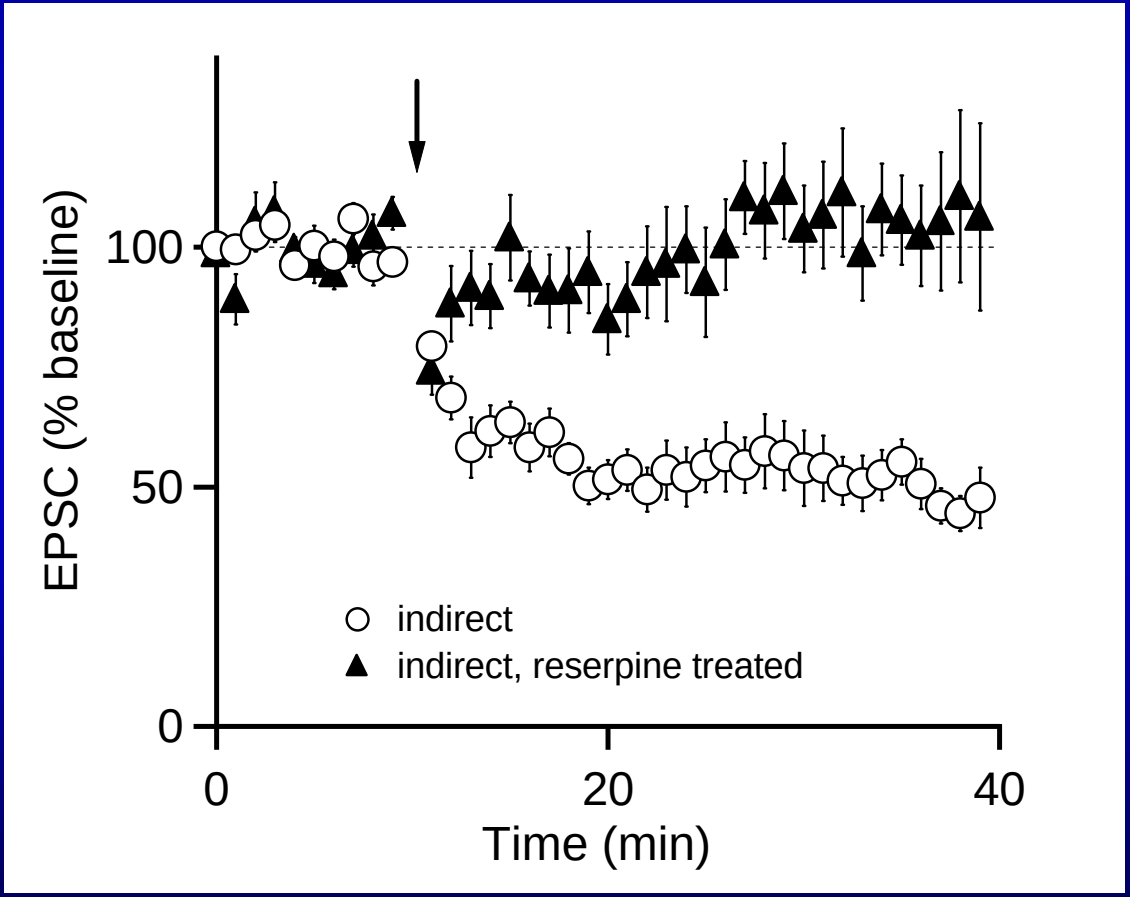


Postsynaptic mGluR-driven LTD occurs primarily at indirect pathway synapses in nucleus accumbens





Indirect pathway eCB-LTD is absent in an animal model of Parkinson disease



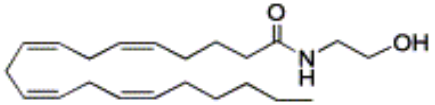
Endocannabinoid biosynthesis and inactivation

Phosphatidylethanolamine (PE)

N-Acyltransferase ← **Calcium**

N-arachidonoyl PE

NAPE-PLD ← **Calcium**



Anandamide (AEA)

FAAH (URB597)

Arachidonic acid + Ethanolamine

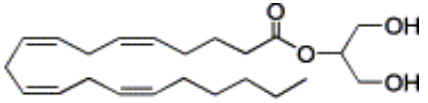
Phosphatidylinositol (PI)

Phospholipase Cβ ← **Receptor activation (mGluR or mAChR)**

Calcium

Diacylglycerol (DAG)

DAG Lipase

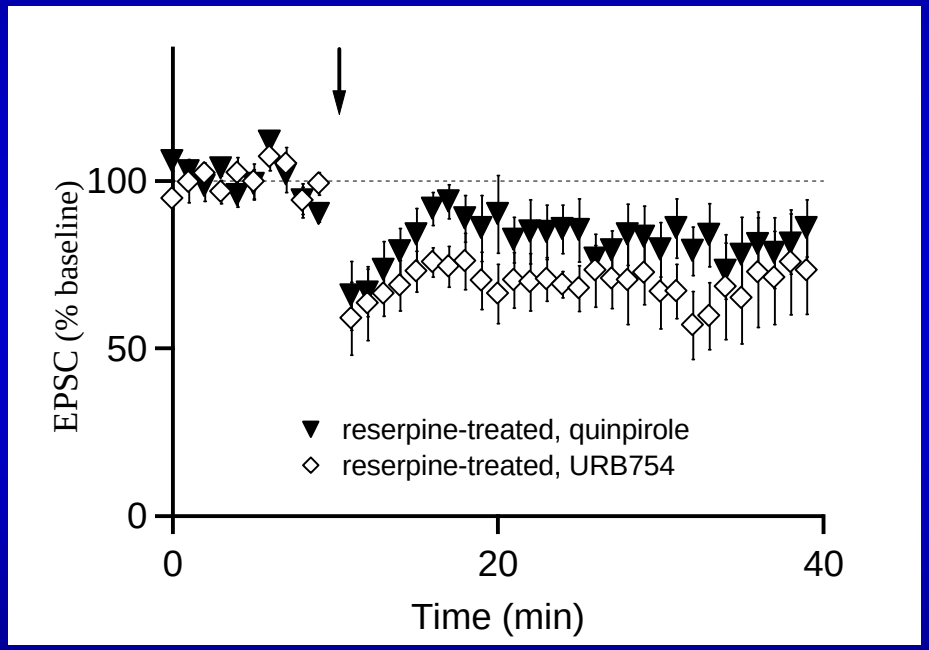


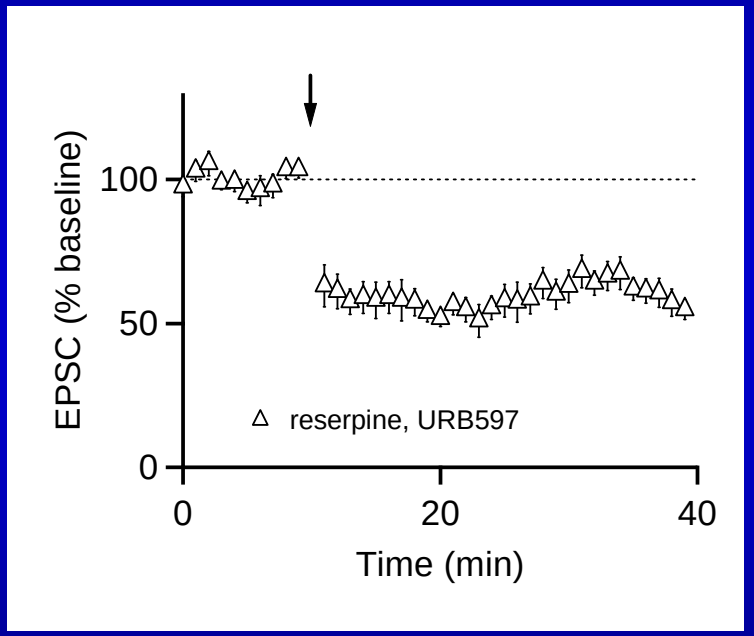
2-arachidonoylglycerol (2-AG)

MGL (URB754)

Arachidonic acid + glycerol

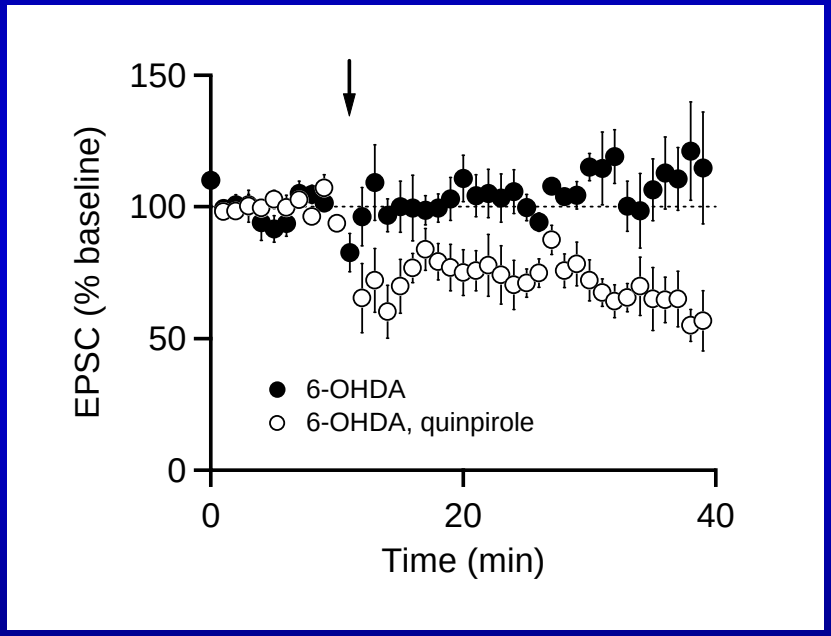
Rescue of indirect pathway LTD in a Parkinson's disease model (reserpine)

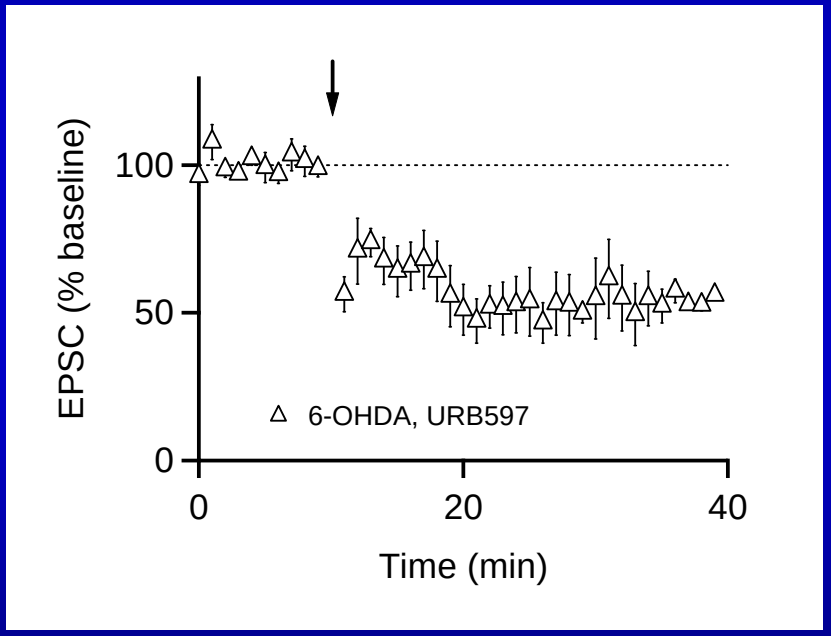




quinpirole: dopamine D2 receptor agonist
URB754: monoacylglycerol lipase (MGL) inhibitor
URB597: FAAH inhibitor

Rescue of indirect pathway LTD in a Parkinson's disease model (6-OHDA)

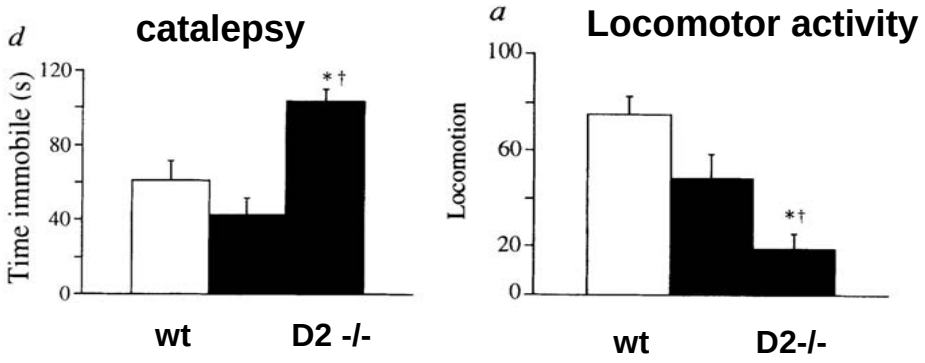




quinpirole: dopamine D2 receptor agonist
URB597: FAAH inhibitor

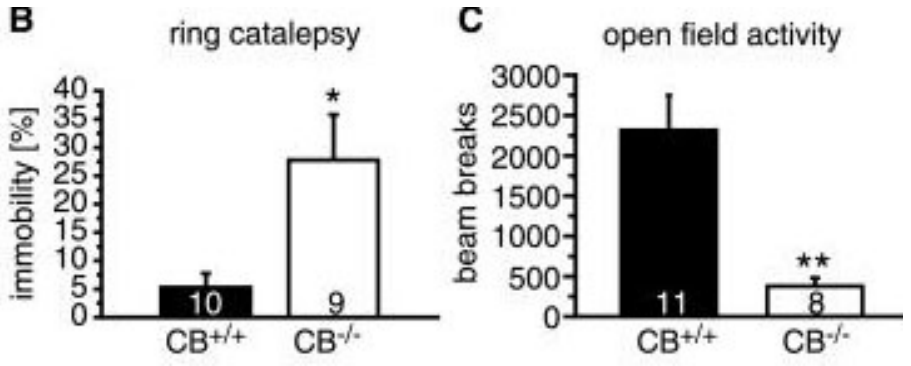
An important role for dopamine D2 receptors and cannabinoid CB1 receptors in movement

D2 -/- mouse



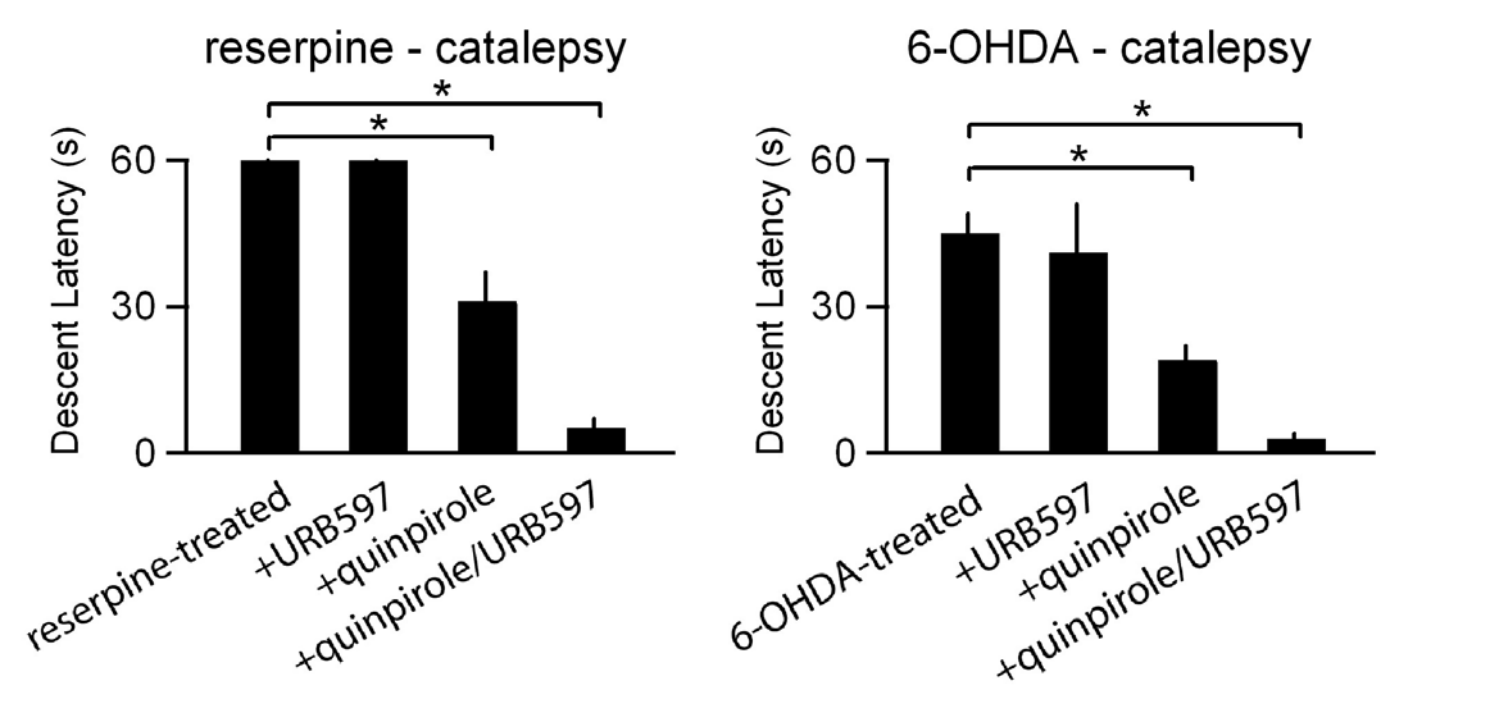
Baik et al. (1995), Nature

CB1 -/- mouse

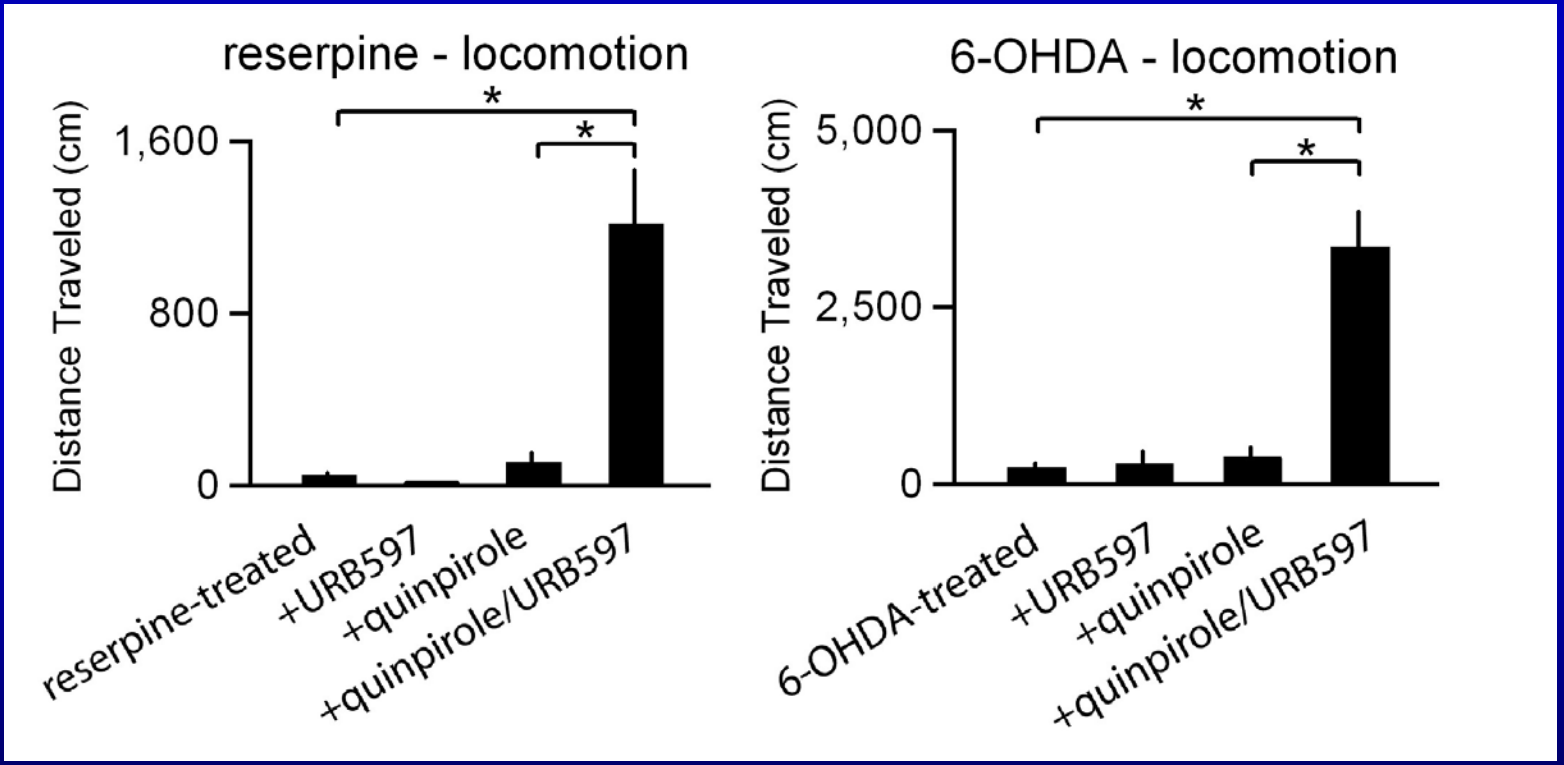


Zimmer et al. (1999), PNAS

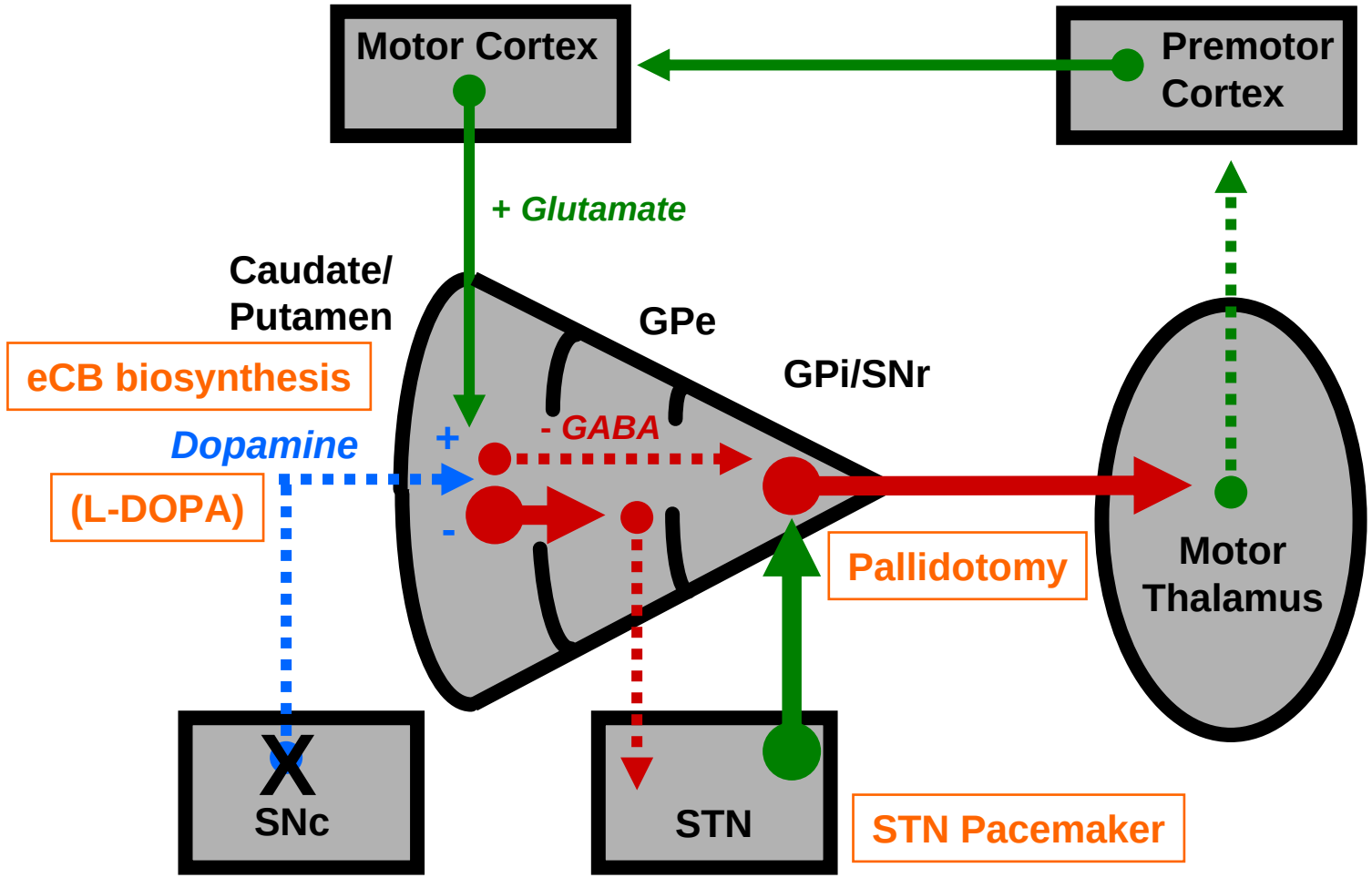
Inhibition of eCB degradation enhances D2-receptor-mediated recovery from catalepsy in animal models of Parkinson disease



Inhibition of eCB degradation enhances D2-receptor-mediated recovery of locomotor activity in animal models of Parkinson disease



Basal ganglia motor circuit: Parkinson's disease treatments



Conclusions

- eCB-LTD in the striatum is restricted to indirect pathway cells
- it is synapse specific because it requires presynaptic activity in addition to CB1 receptor activation
- eCB-LTD is prevented by dopamine depletion but can be rescued by a D2 agonist and an inhibitor of eCB degradation
- inhibition of eCB degradation improves motor performace in animals models of Parkinson disease
- D2(+) and D2(-) cells in the accumbens also have different synaptic properties

Anatol Kreitzer

Sheela Singla

Brad Grueter

Percy Luu

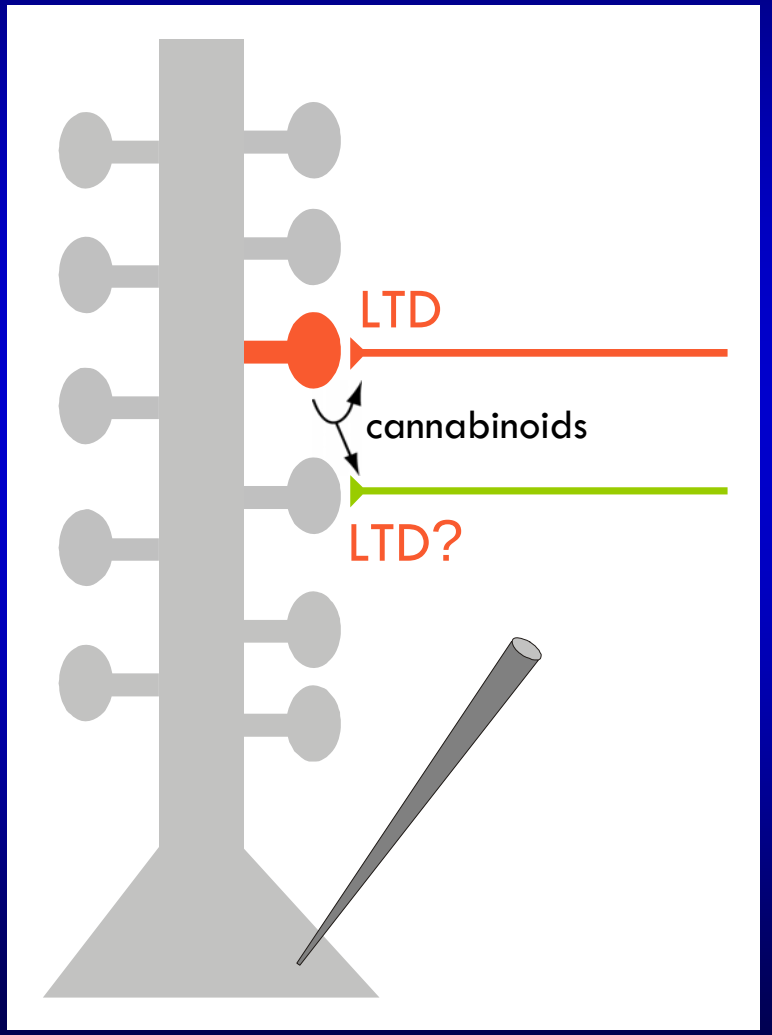
Nathaniel Heintz (Rockefeller)

X. William Yang (UCLA)

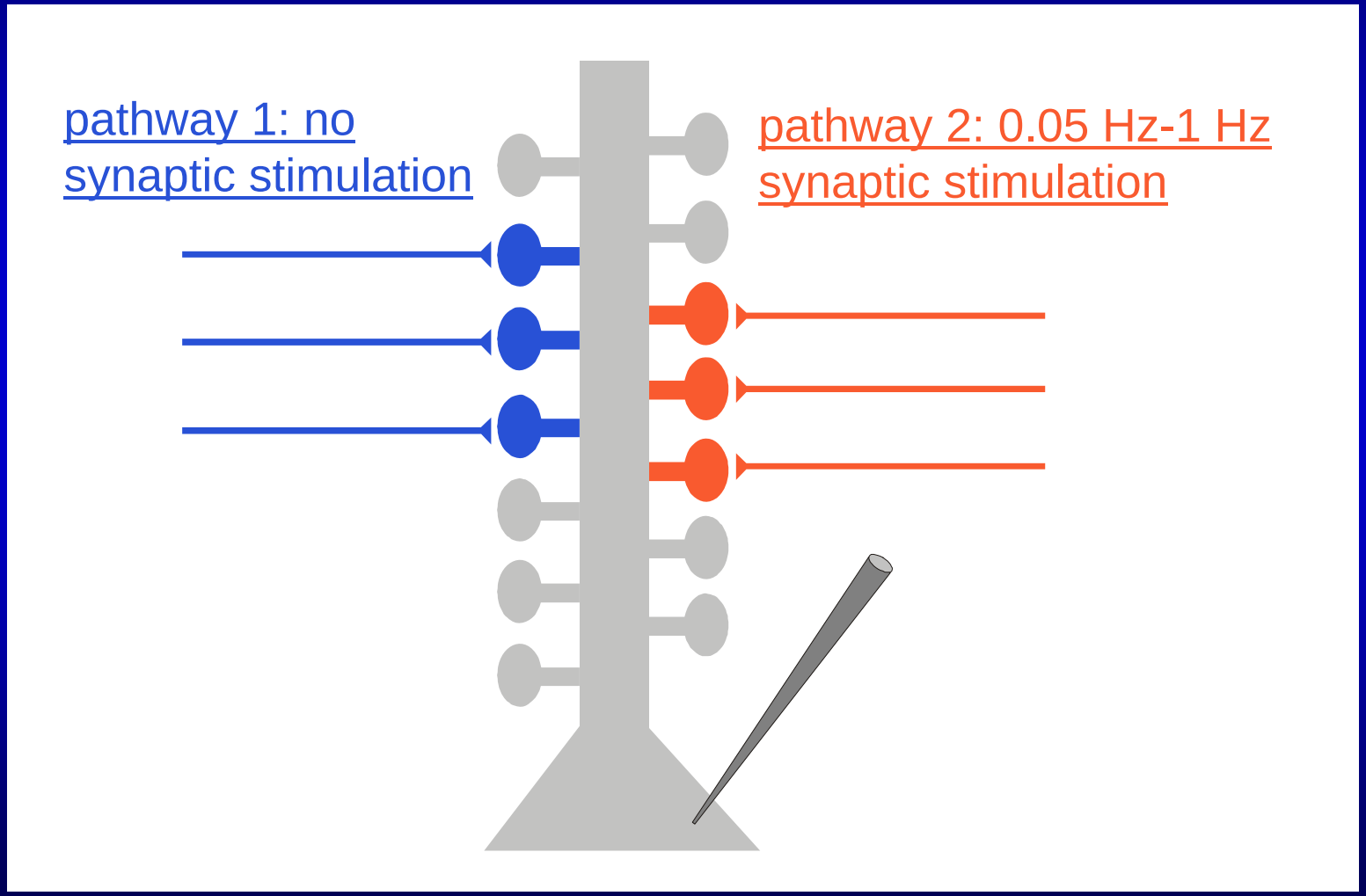
Is presynaptic eCB-LTD activity-dependent?

-Spillover onto synapses that did not participate in depolarizing the postsynaptic cell could cause LTD.

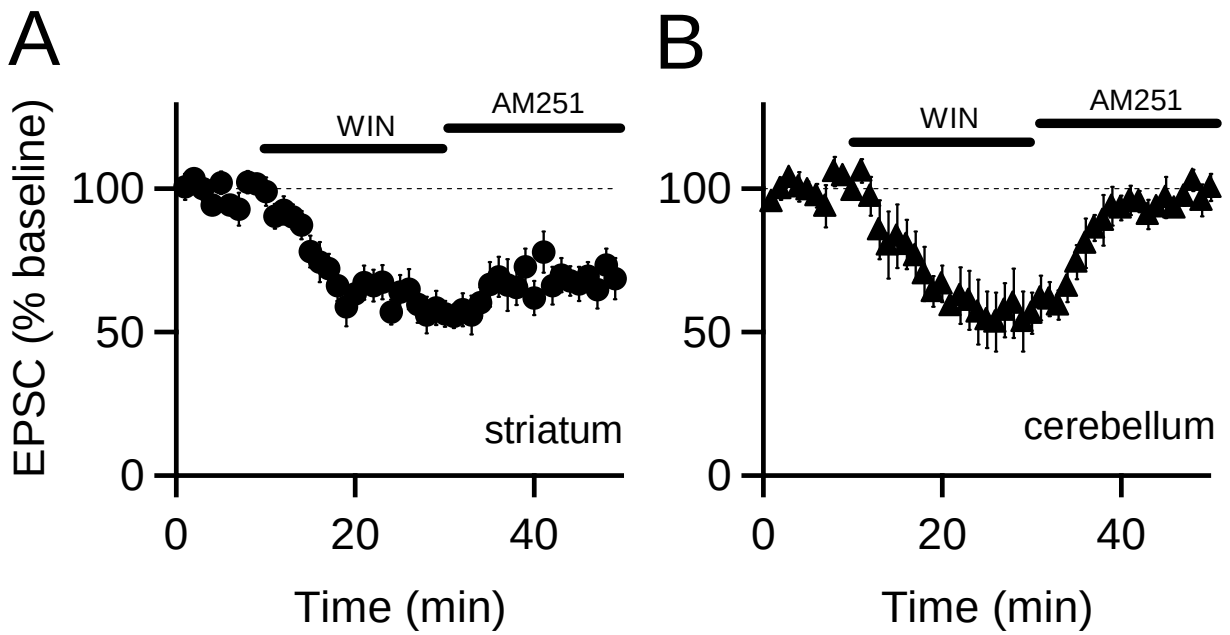
-Synapse specificity may be achieved if LTD depended on presynaptic activity and not just receptor activation.



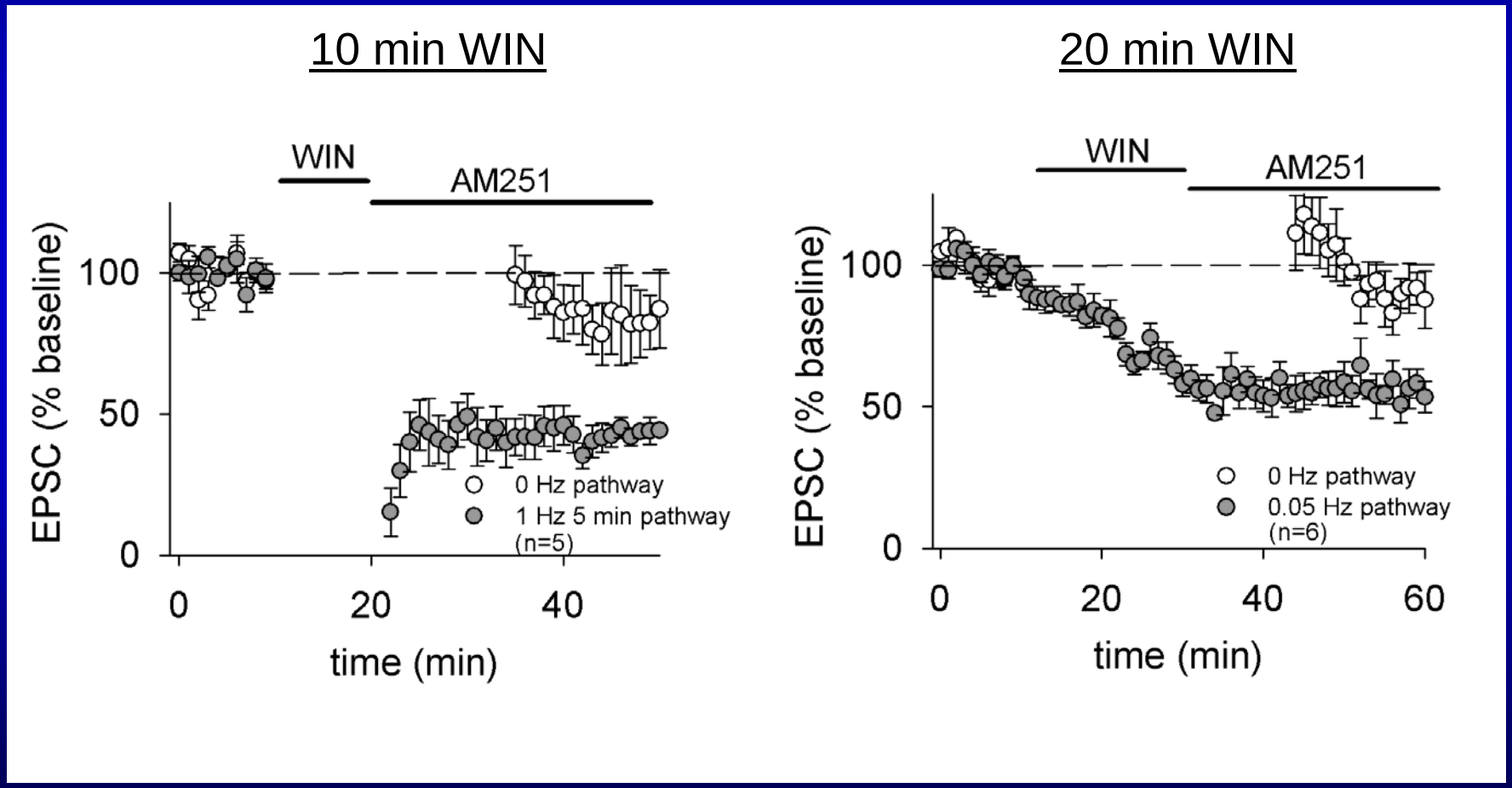
Testing the effect of synaptic activity on LTD



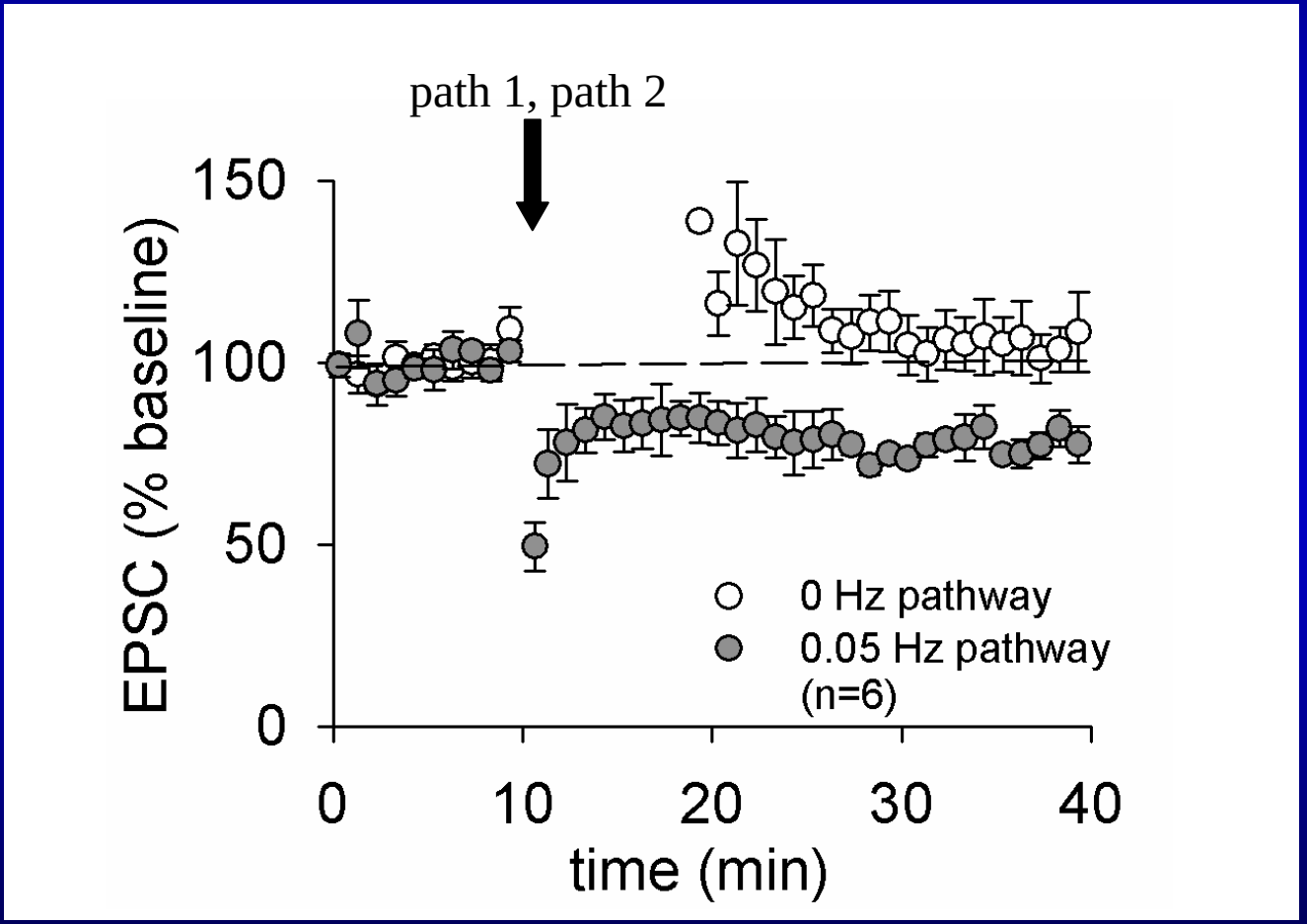
A CB1 agonist is sufficient to induce LTD in the striatum, but not the cerebellum



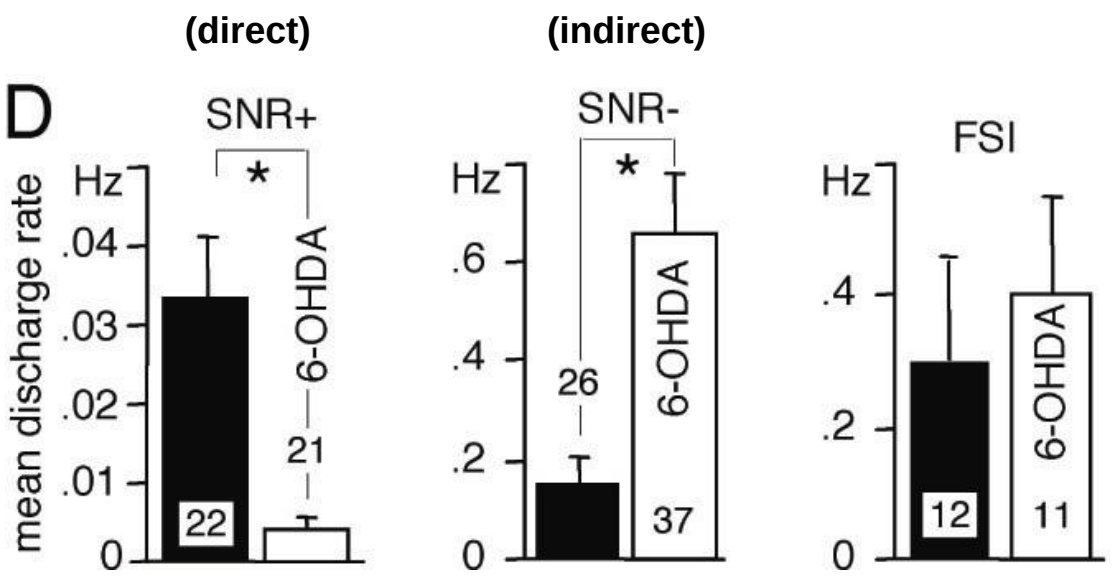
WIN-induced LTD is activity-dependent



eCB-LTD is activity-dependent

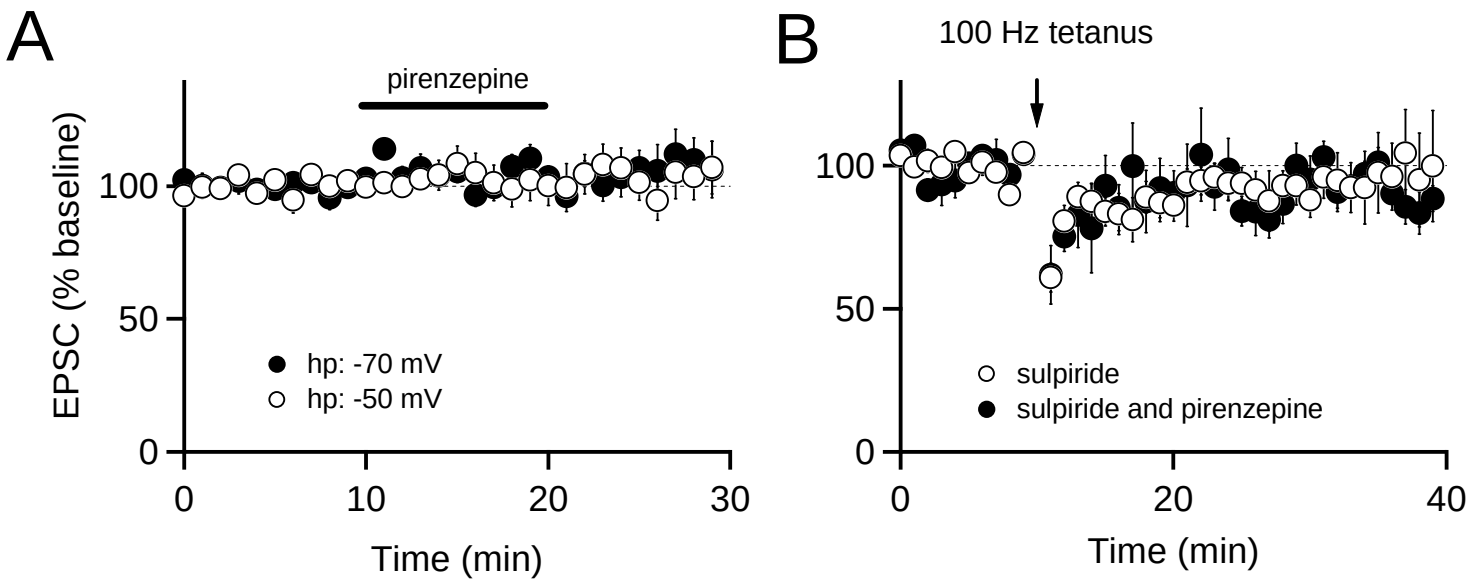


Imbalanced activity in striatal motor circuits *in vivo* in a Parkinson disease model



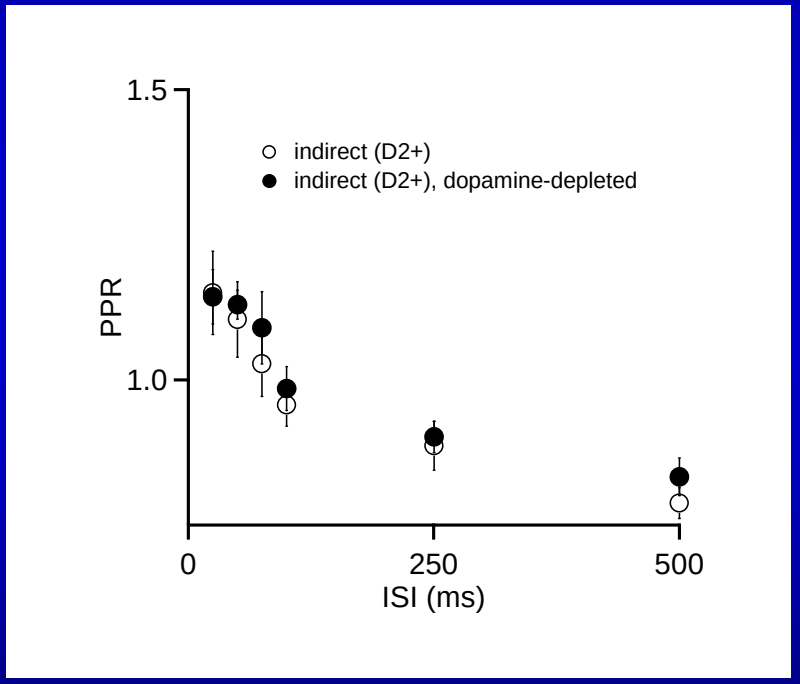
Mallet et al (2006) **J Neurosci**

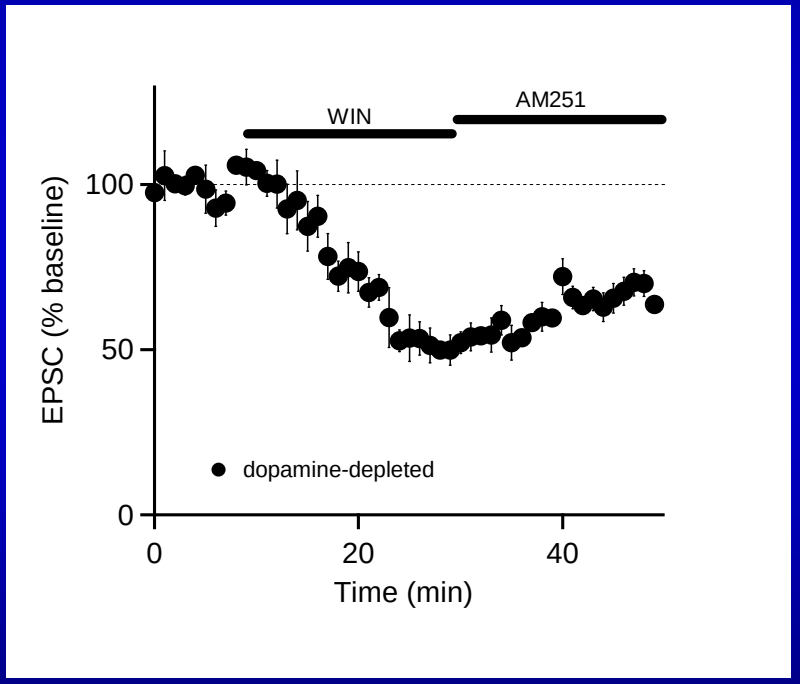
Muscarinic M1 receptors do not regulate striatal endocannabinoid release or eCB-LTD



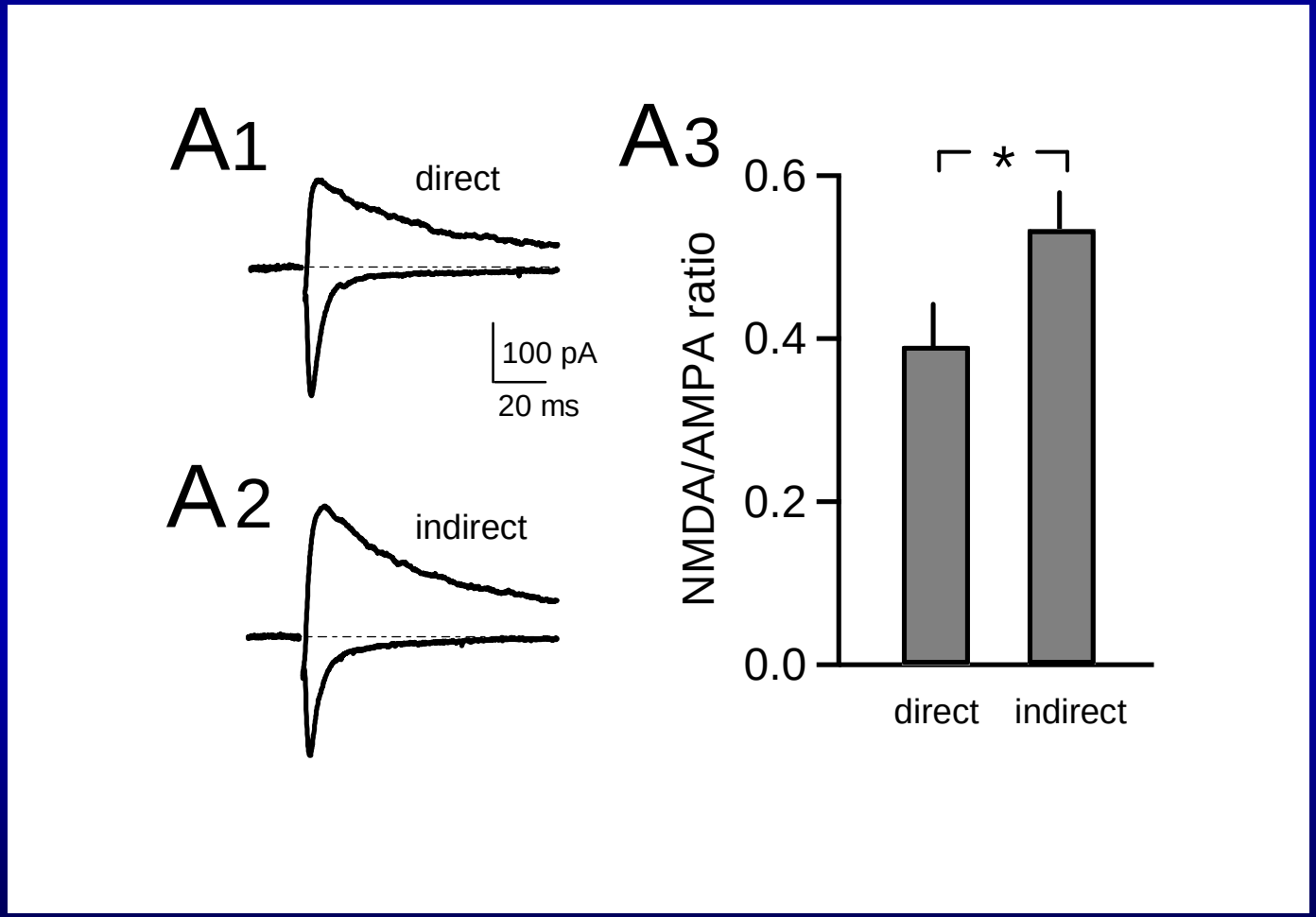
pirenzepine: muscarinic M1 receptor antagonist
sulpiride: dopamine D2 receptor antagonist

Dopamine-depleted mice do not have altered paired-pulse plasticity or sensitivity to cannabinoids

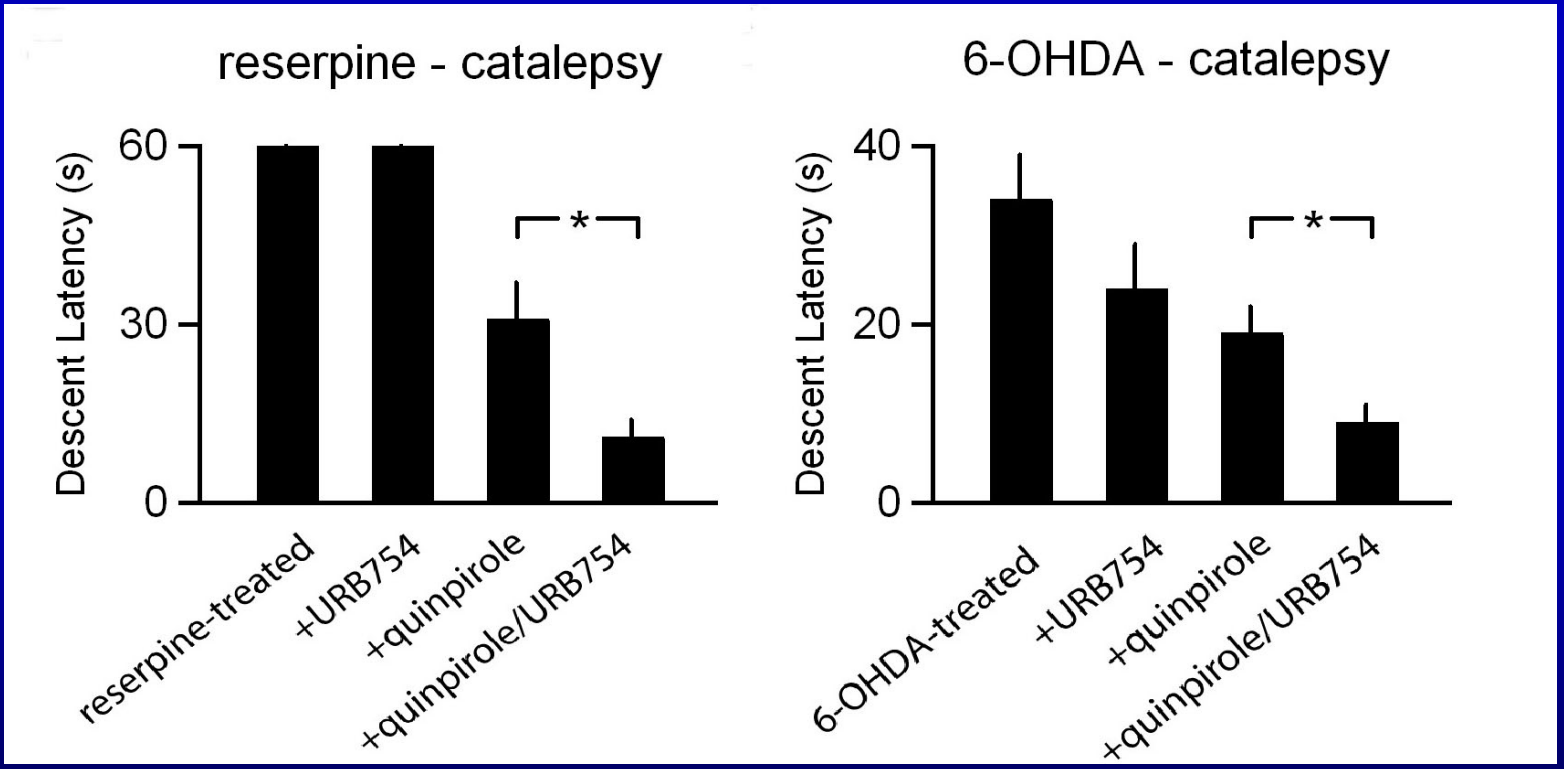




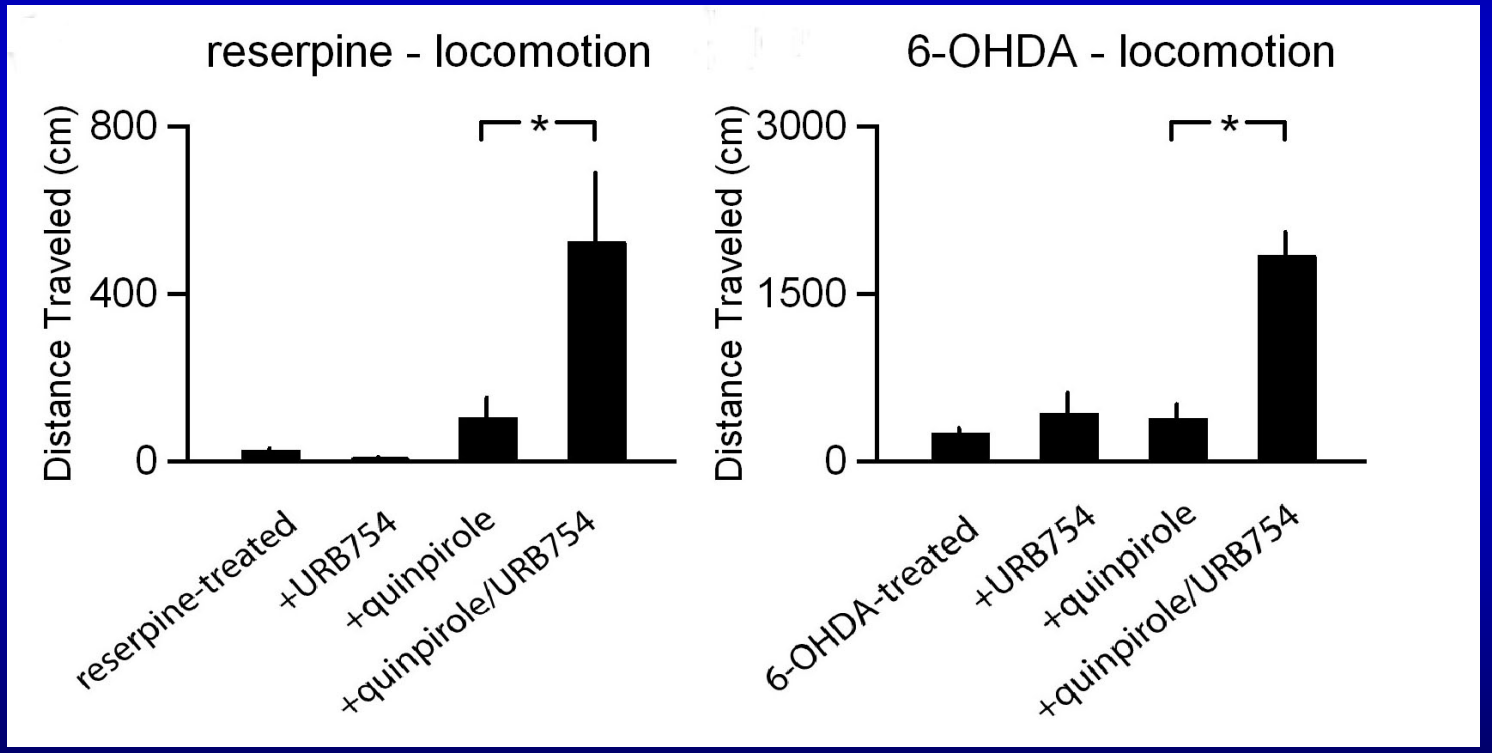
Indirect pathway synapses have larger NMDA/AMPA current ratios



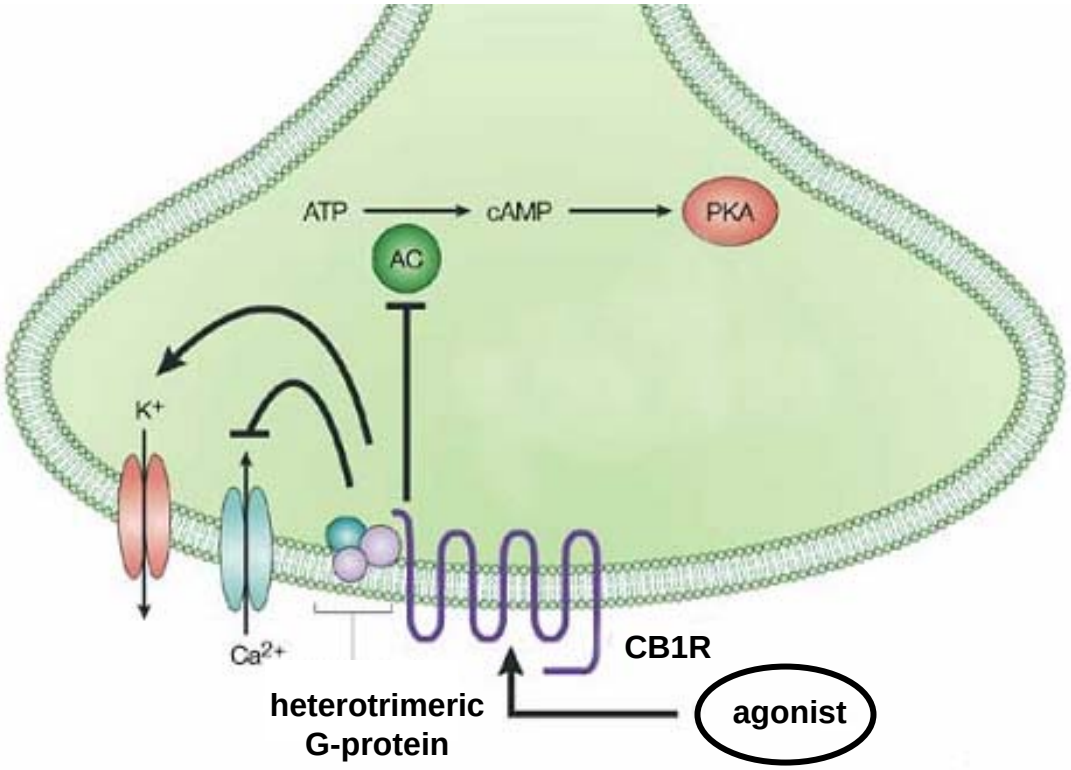
Inhibition of eCB degradation enhances D2-receptor-mediated recovery from catalepsy in animal models of Parkinson disease

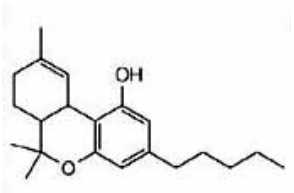


Inhibition of eCB degradation enhances D2-receptor-mediated recovery of locomotor activity in animal models of Parkinson disease

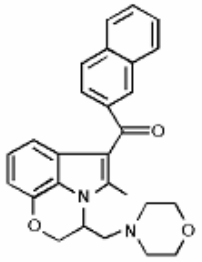


Signaling through CB1 receptors

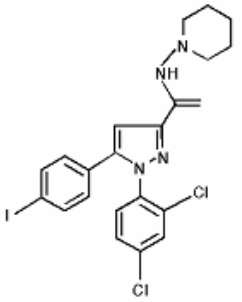




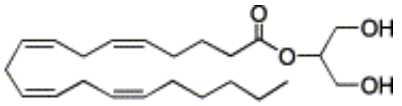
THC (partial agonist)



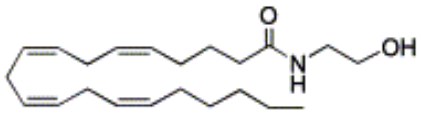
WIN 55,212-2 (agonist)



AM 251 (antagonist)



2-AG (endogenous agonist)



Anandamide (endogenous agonist)

Adapted from DiMarzo et al., **Nature Reviews Drug Discovery** (2004)

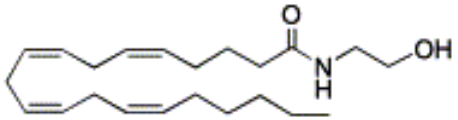
Endocannabinoid biosynthesis and inactivation

Phosphatidylethanolamine (PE)

N-Acyltransferase ← **Calcium**

N-arachidonoyl PE

NAPE-PLD ← **Calcium**



Anandamide (AEA)

FAAH

Arachidonic acid + Ethanolamine

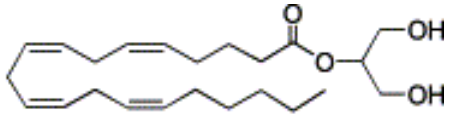
Phosphatidylinositol (PI)

Phospholipase Cβ ← **Receptor activation (mGluR or mAChR)**

Phospholipase Cβ ← **Calcium**

Diacylglycerol (DAG)

DAG Lipase

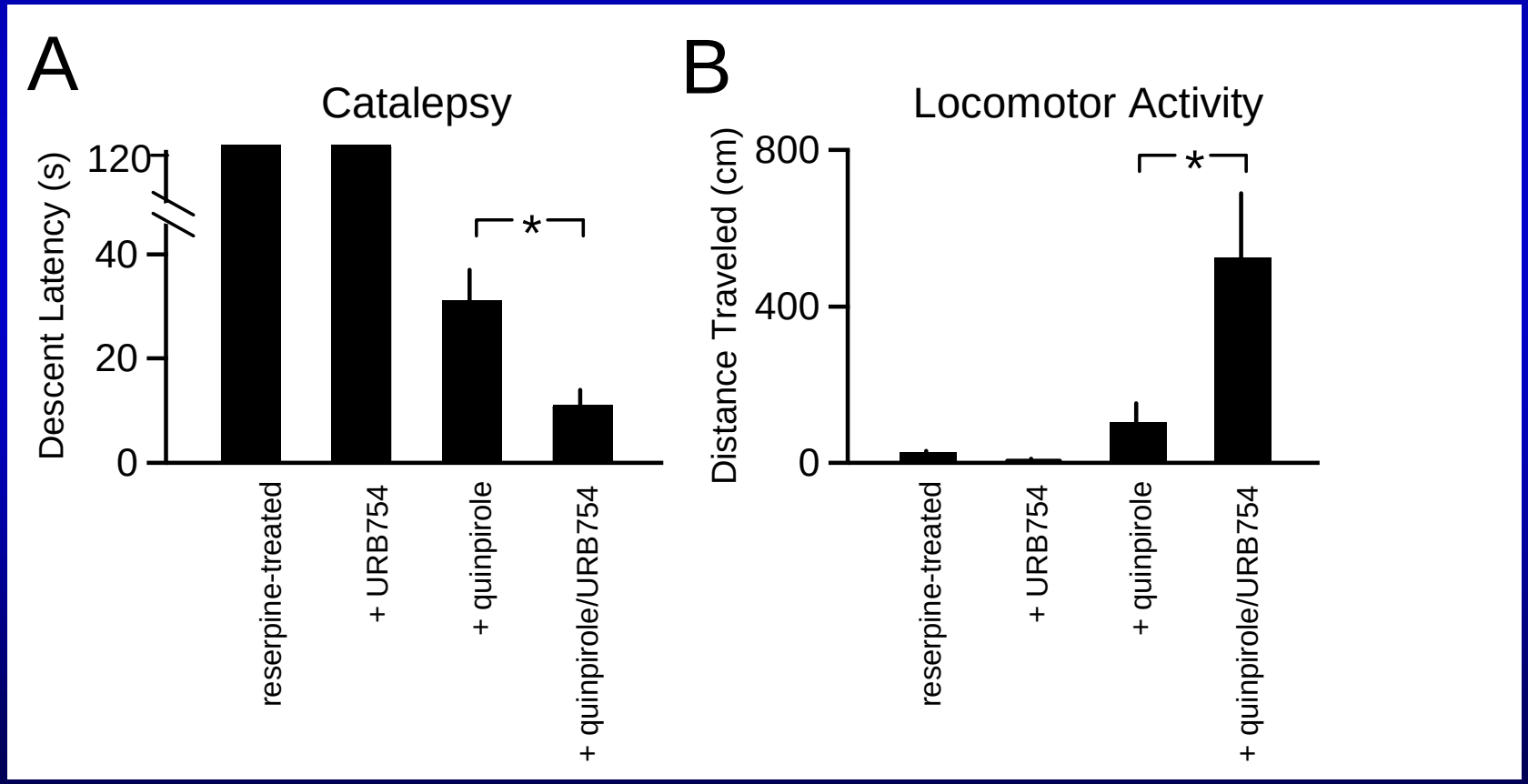


2-arachidonoylglycerol (2-AG)

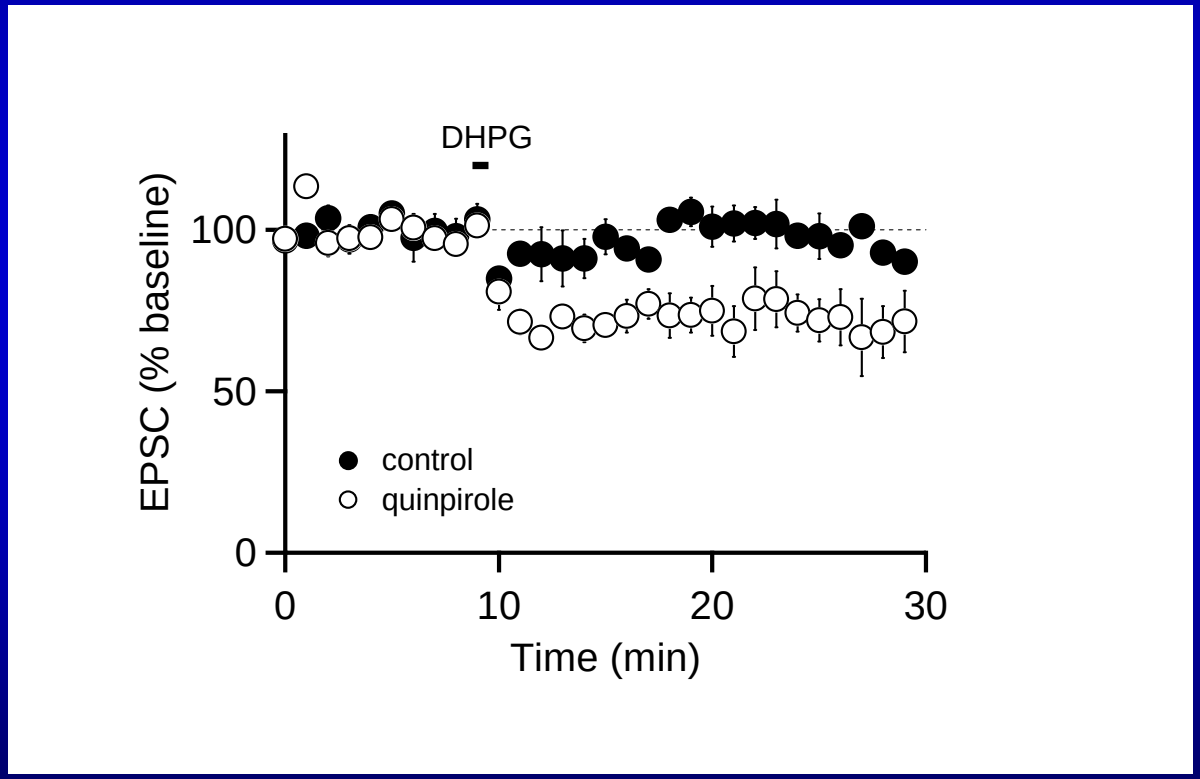
MGL

Arachidonic acid + glycerol

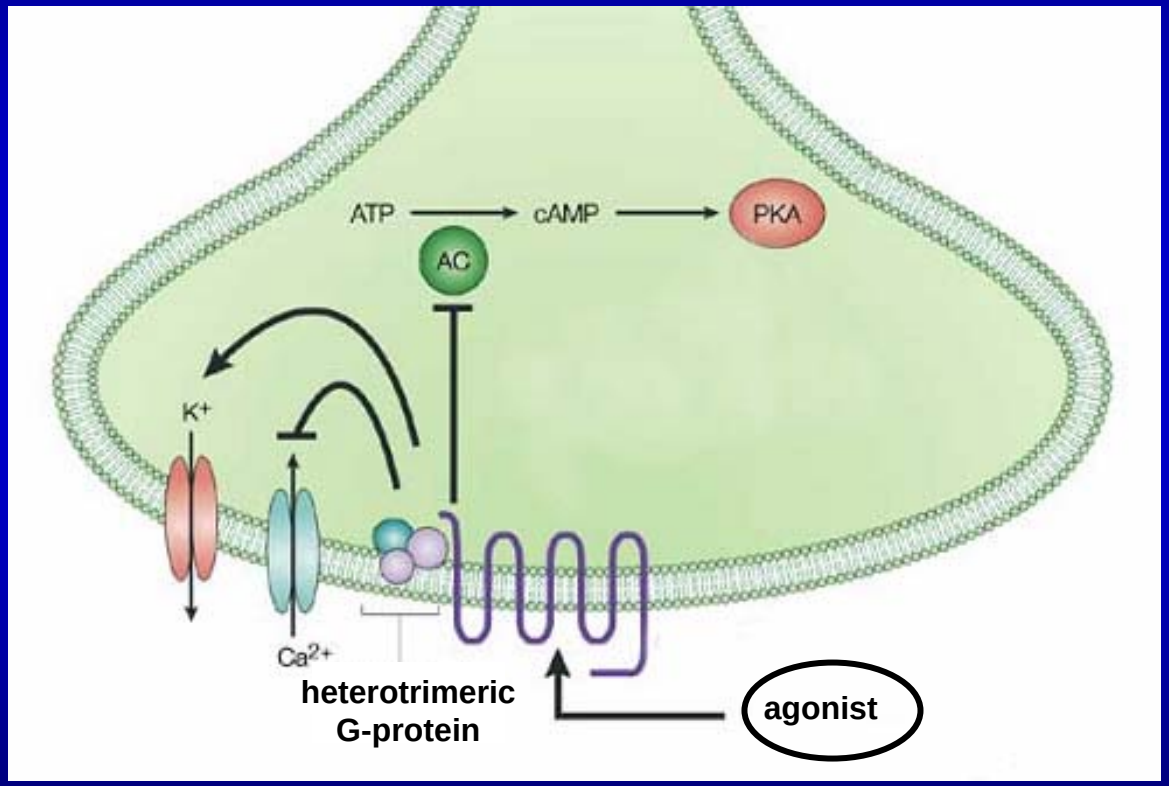
Inhibition of endocannabinoid degradation enhances D2-receptor-mediated recovery of movement in a Parkinson disease model

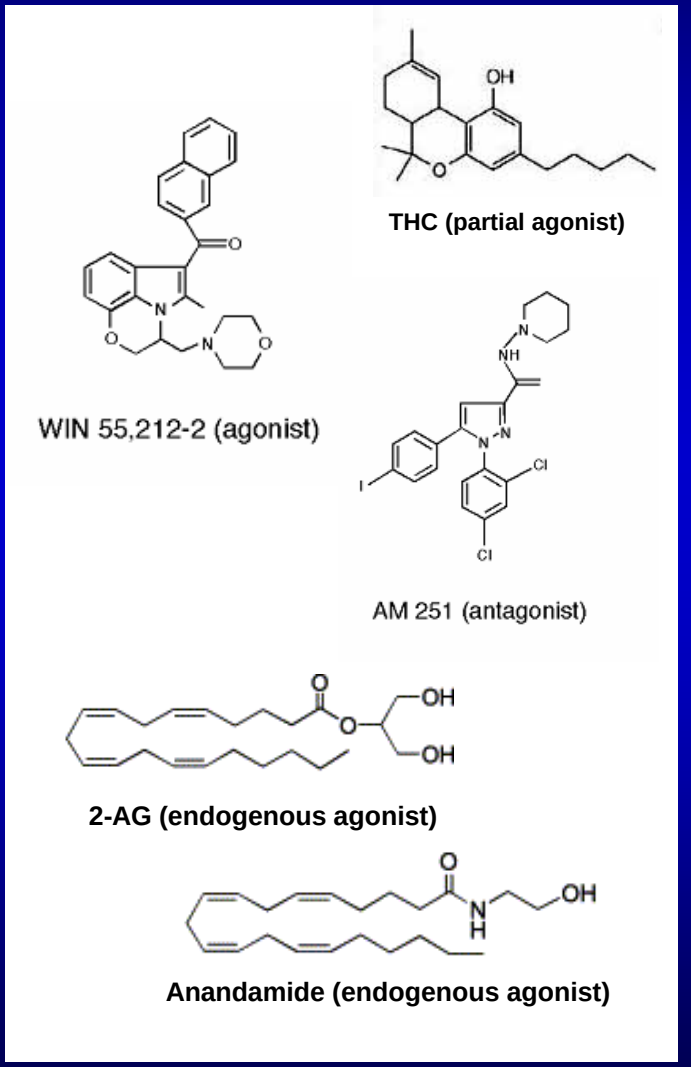


D2 receptor activation enhances endocannabinoid release in response to brief mGluR activation



Signaling through CB1 receptors





Adapted from DiMarzo et al., **Nature Reviews Drug Discovery** (2004)

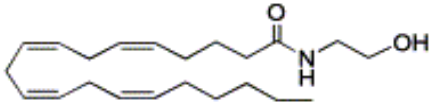
Endocannabinoid biosynthesis and inactivation

Phosphatidylethanolamine (PE)

N-Acyltransferase ← **Calcium**

N-arachidonoyl PE

NAPE-PLD ← **Calcium**



Anandamide (AEA)

FAAH (URB597)

Arachidonic acid + Ethanolamine

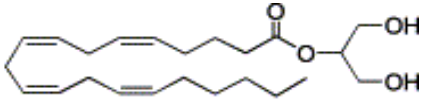
Phosphatidylinositol (PI)

Phospholipase Cβ ← **Receptor activation (mGluR or mAChR)**

Phospholipase Cβ ← **Calcium**

Diacylglycerol (DAG)

DAG Lipase

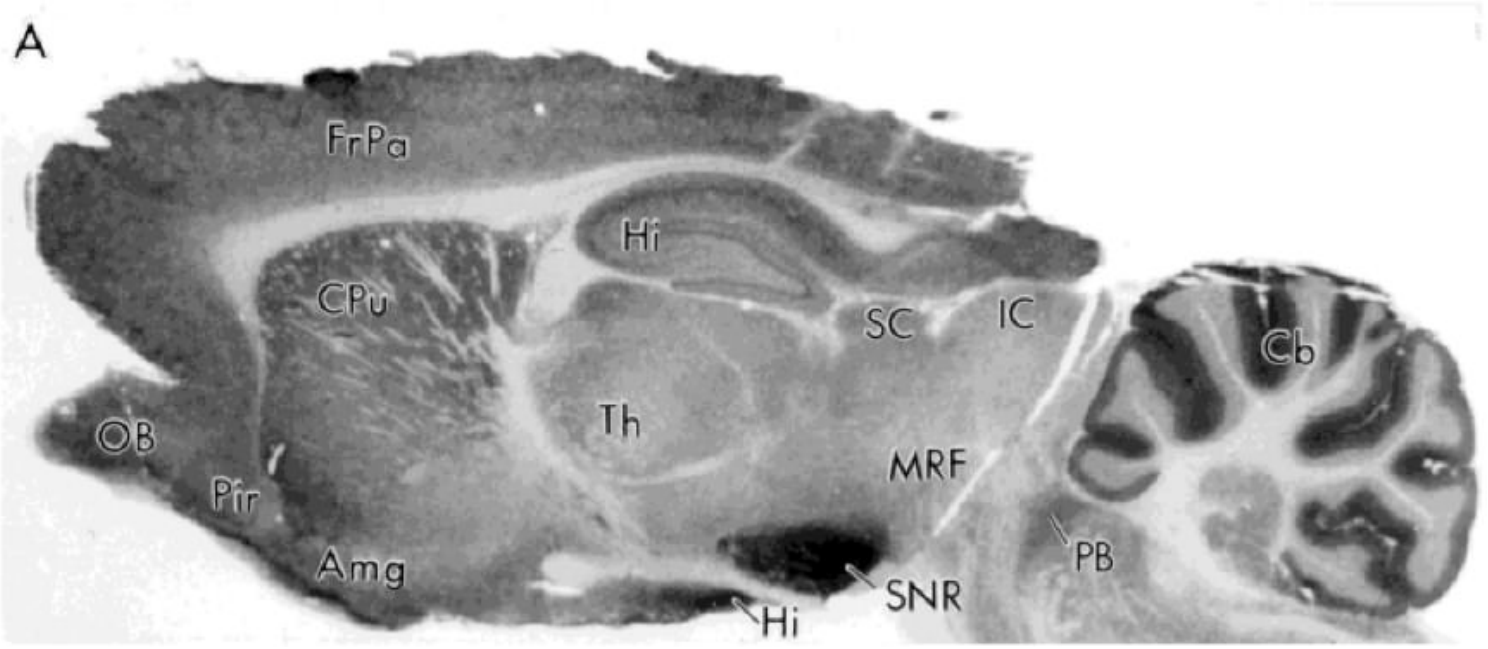


2-arachidonoylglycerol (2-AG)

MGL (URB754)

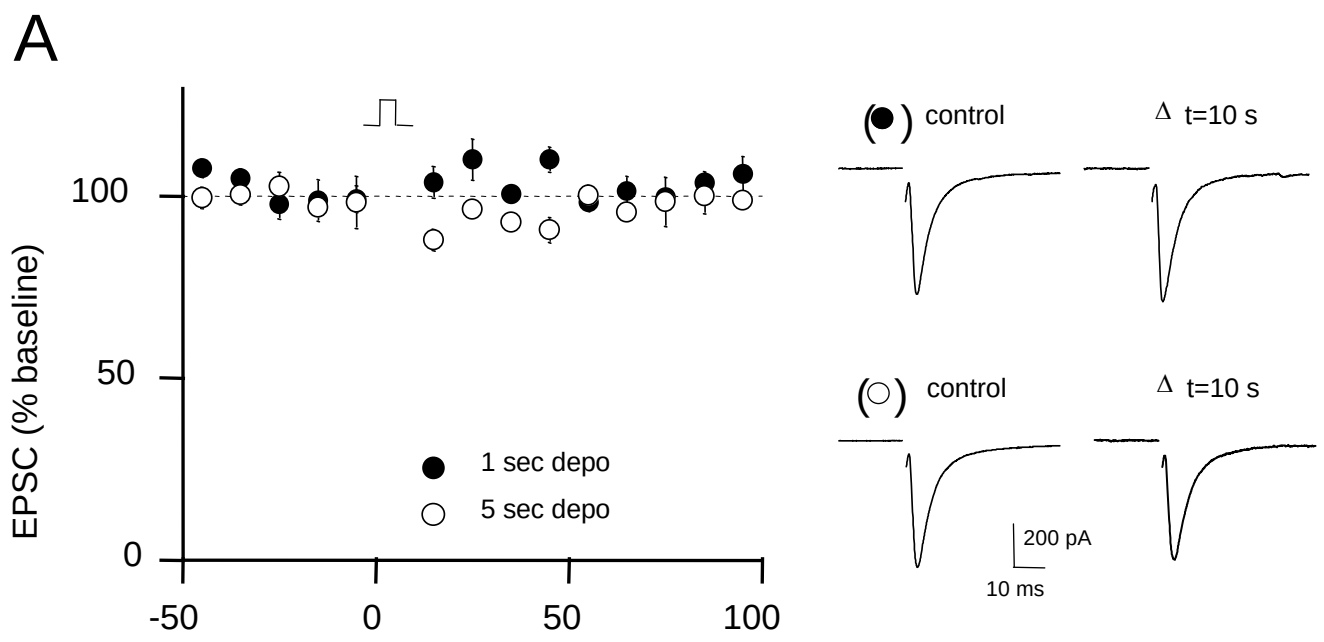
Arachidonic acid + glycerol

CB1 receptor distribution in rat brain

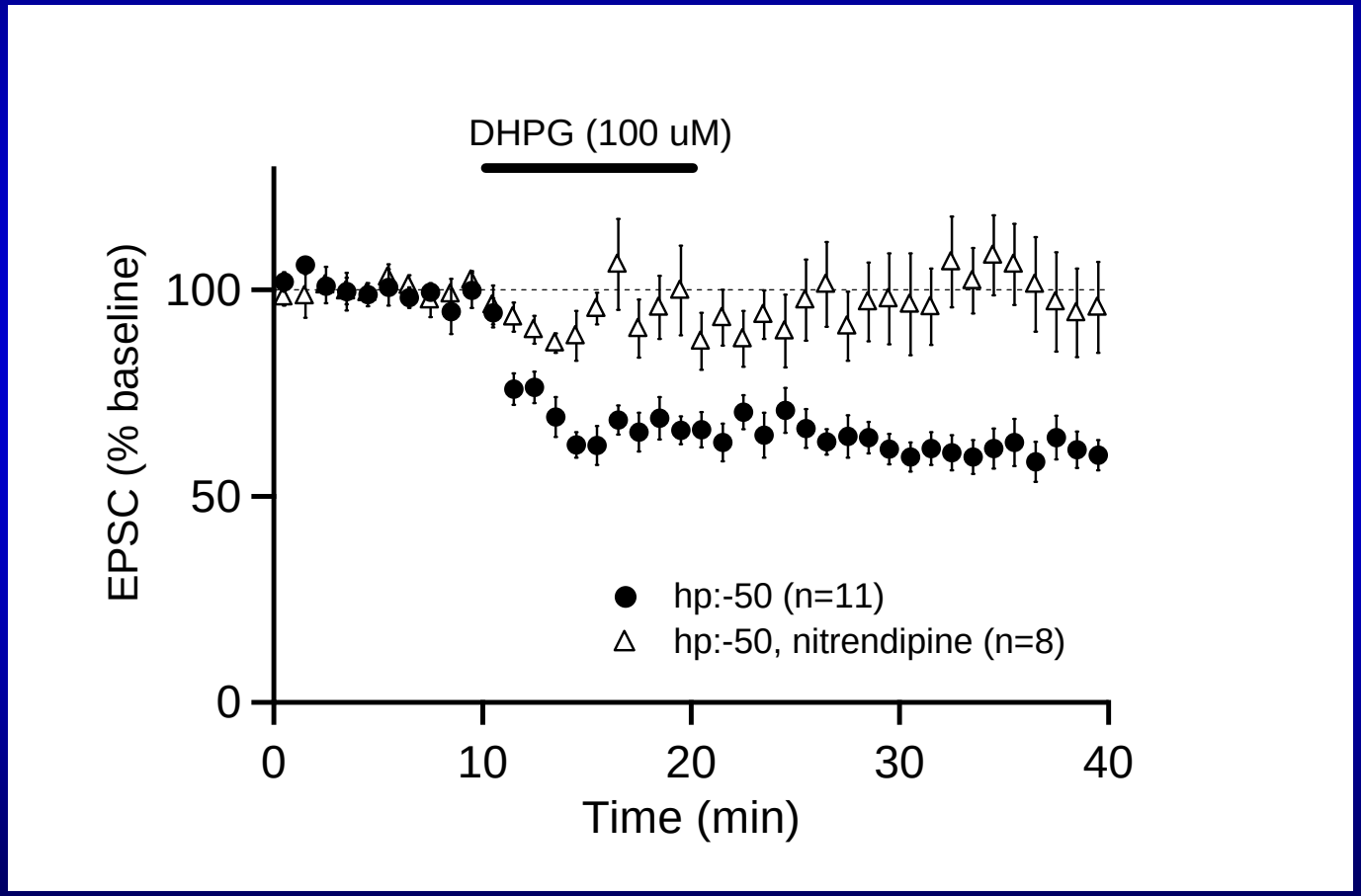


(from Pettit *et al.*, 1998)

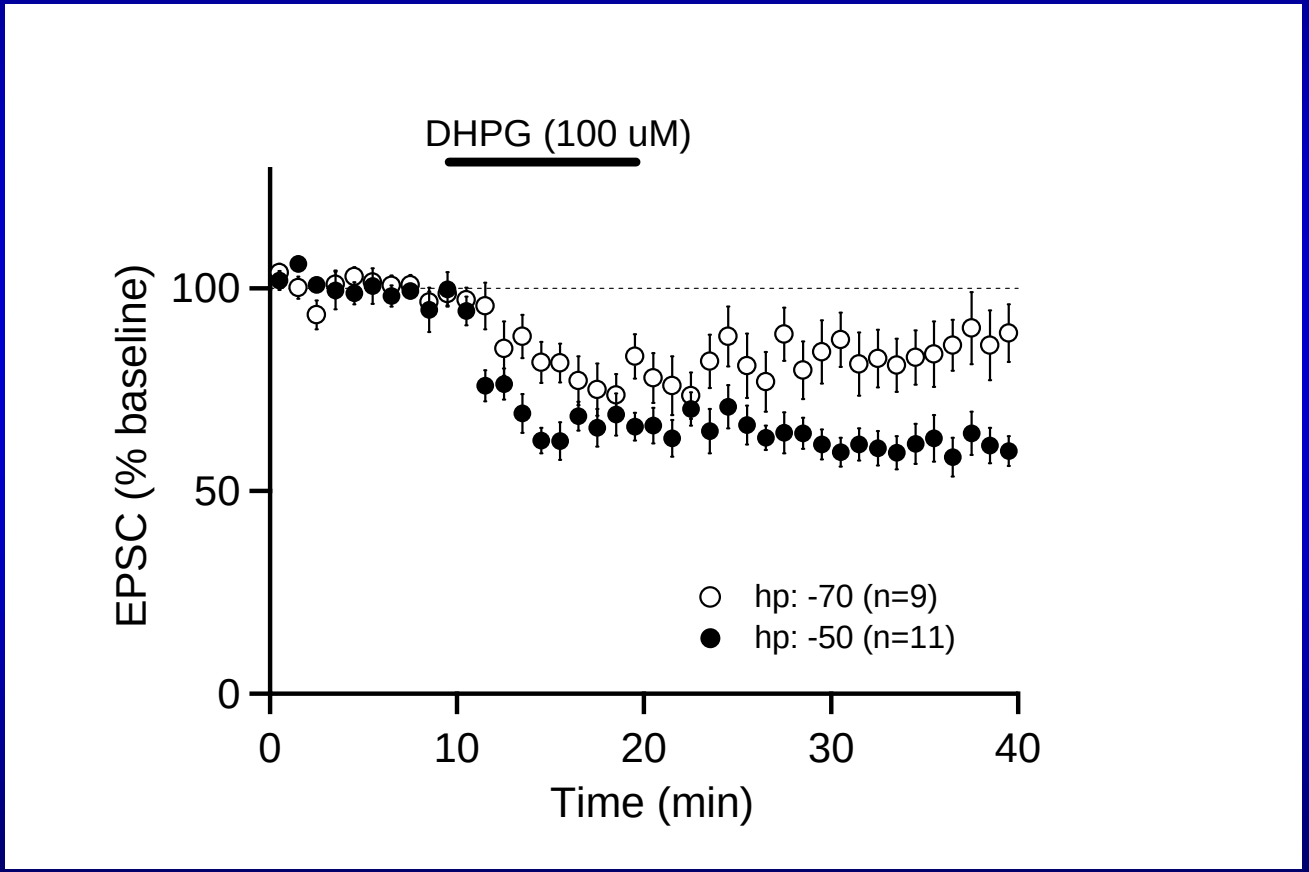
Endocannabinoids are not released by medium spiny neuron depolarization



mGluR-mediated endocannabinoid release requires L-type calcium channels



mGluR-mediated endocannabinoid release is enhanced by subthreshold depolarization



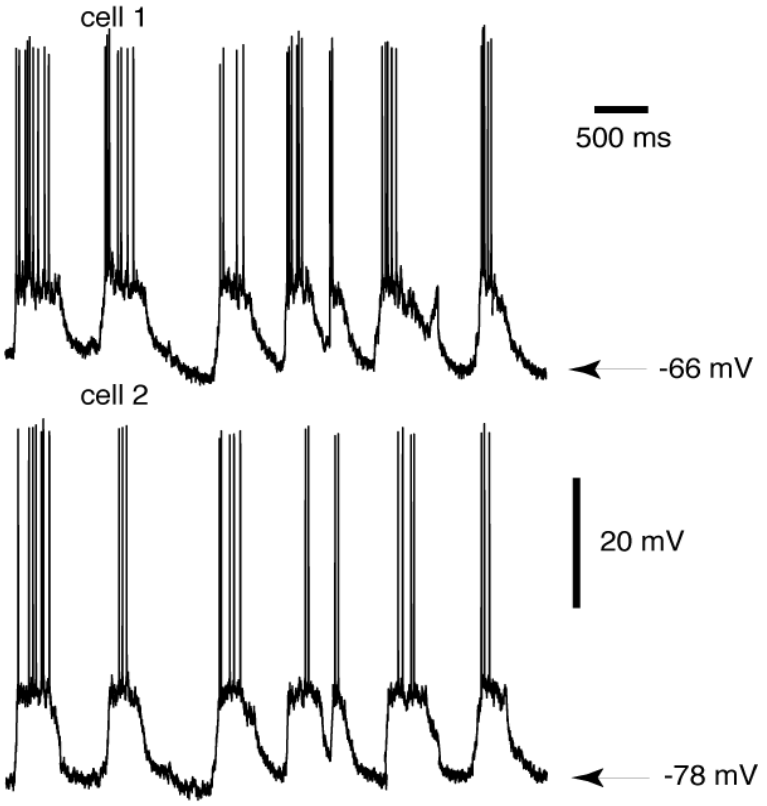
Medium spiny neurons: up and down states

Down state: -60 to –90 mV
calcium influx mediated by T- and R-type VSCCs

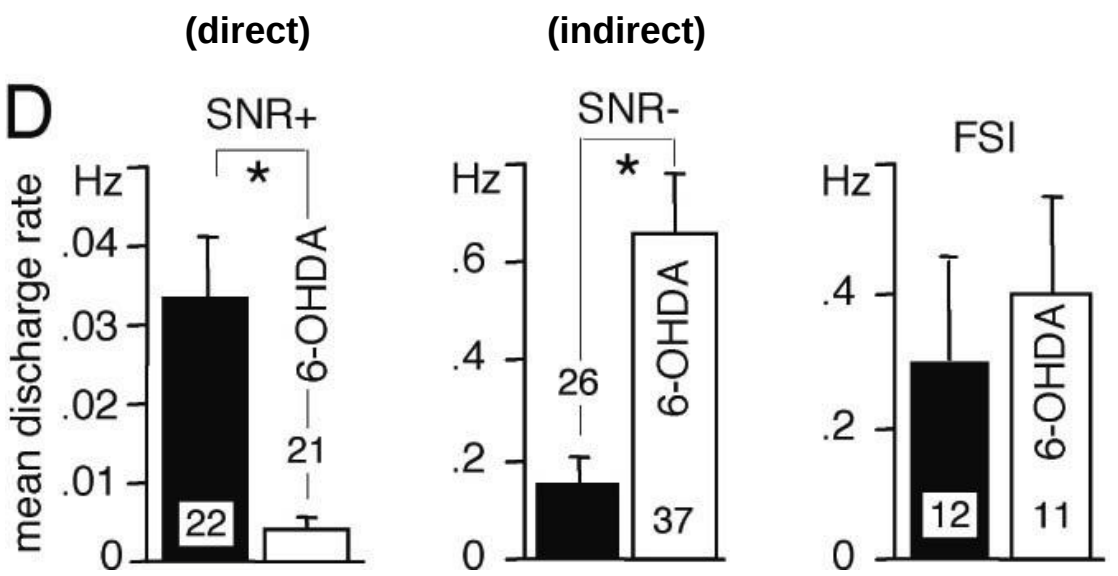
Up state: -40 to –70 mV,
calcium influx mediated by L- and R-type VSCCs

Wilson and Kawaguchi (1996), J Neurosci
Carter and Sabatini (2004), Neuron

Stern et al.(1998), Nature



Imbalanced activity in striatal motor circuits *in vivo* in a Parkinson disease model



Mallet et al (2006) **J Neurosci**