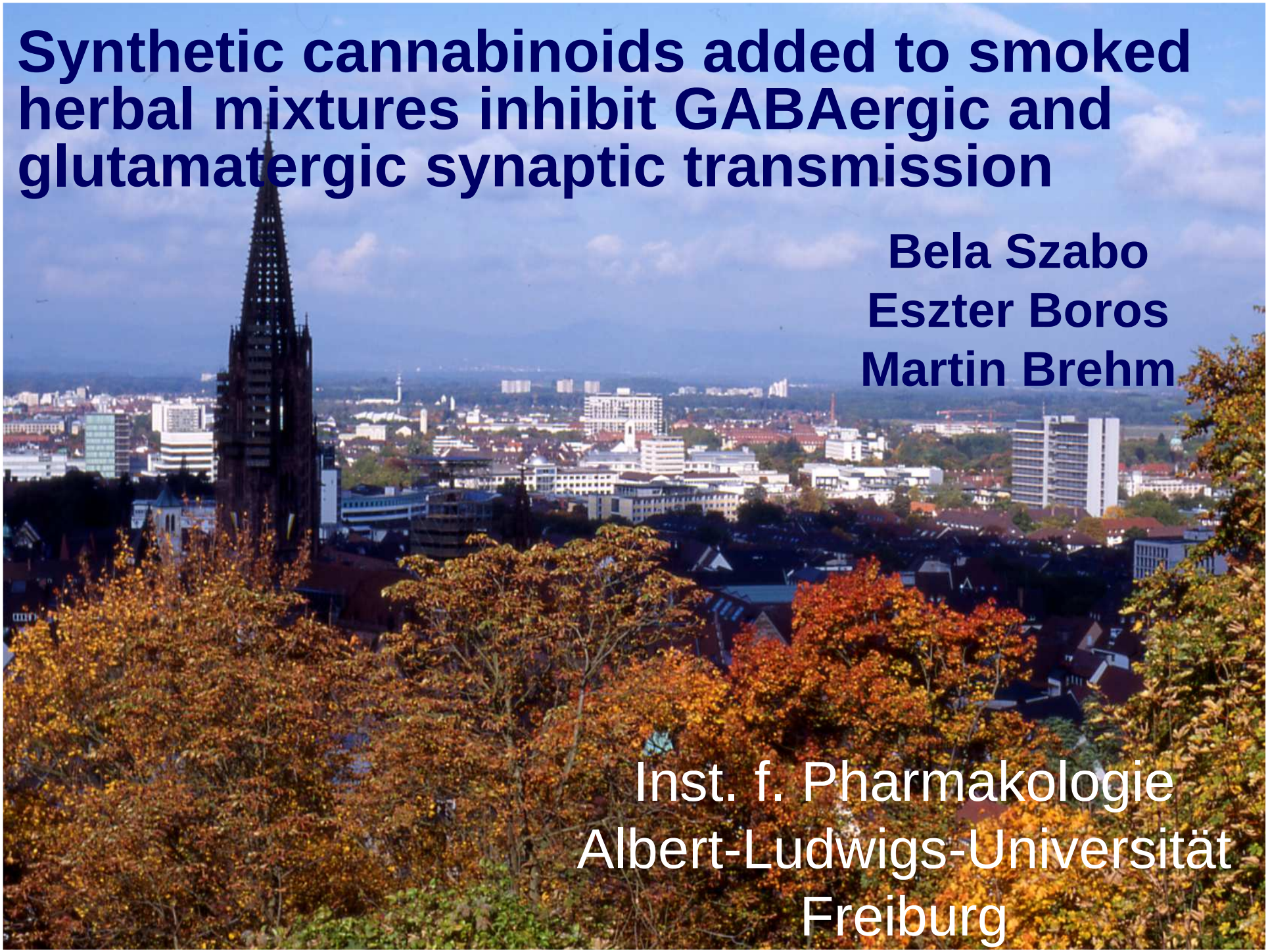
Synthetic cannabinoids added to smoked herbal mixtures inhibit GABAergic and glutamatergic synaptic transmission

Bela Szabo
Eszter Boros
Martin Brehm



Inst. f. Pharmakologie
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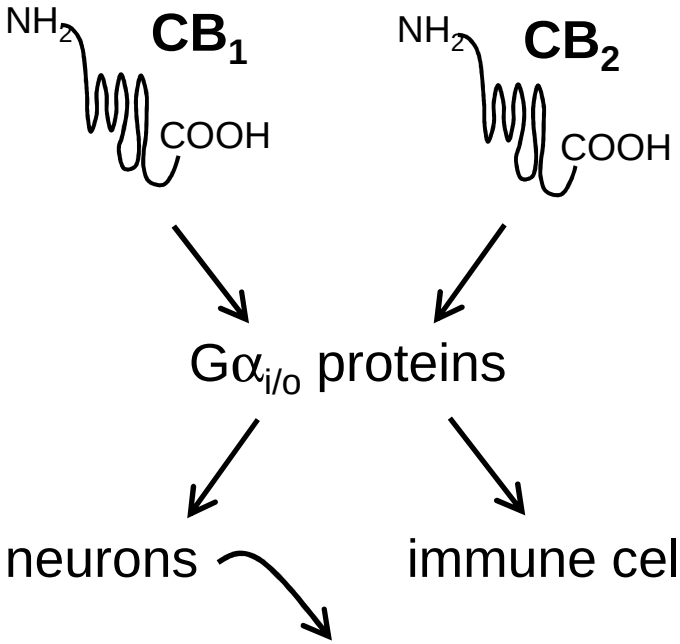
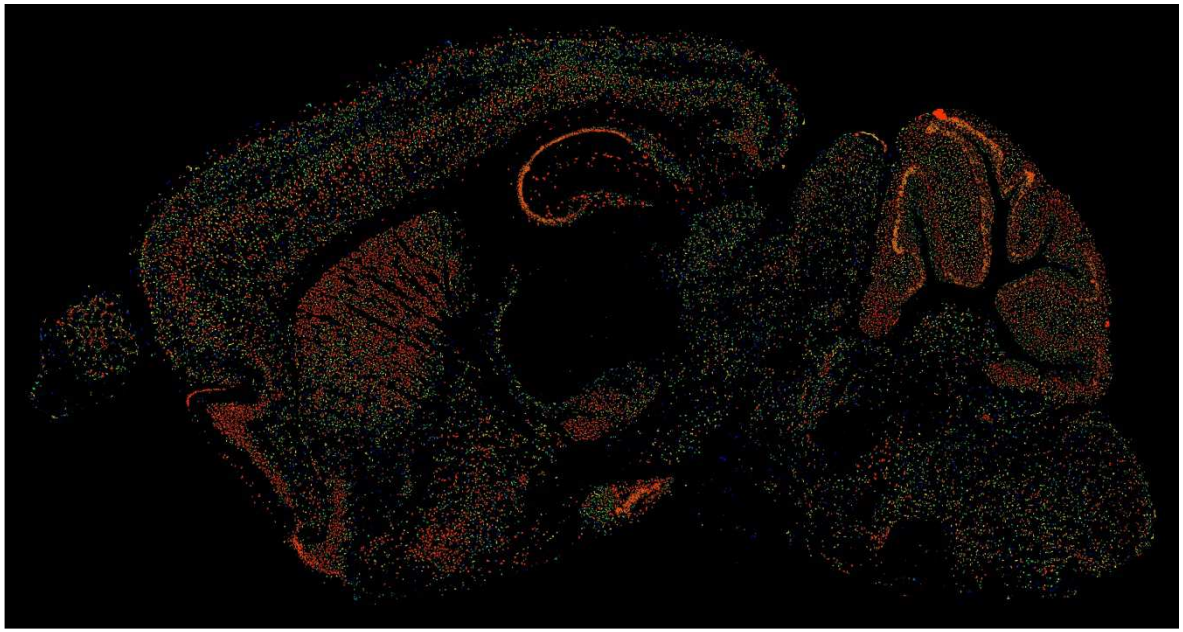
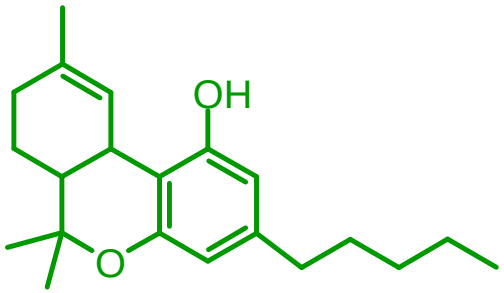
Freiburg

Cannabinoid receptors



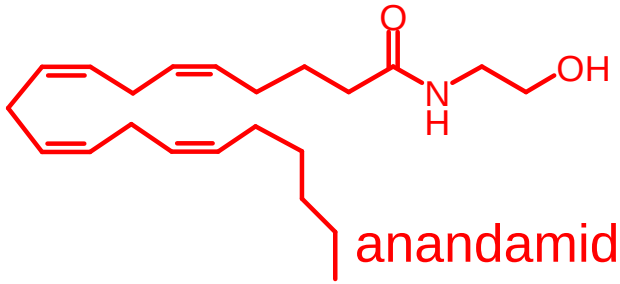


NATURAL

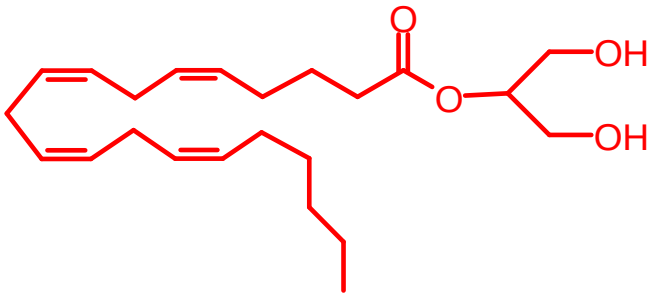


Δ^9-tetrahydrocannabinol

ENDOGENOUS



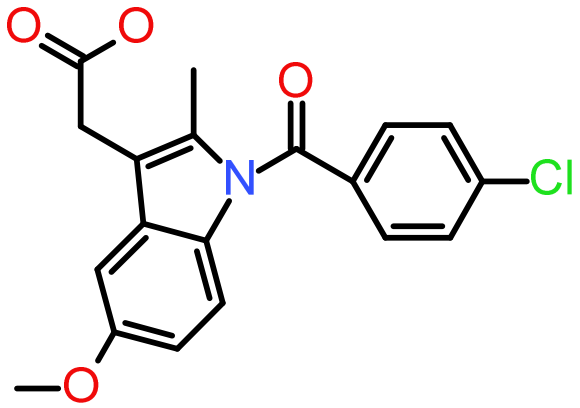
anandamide



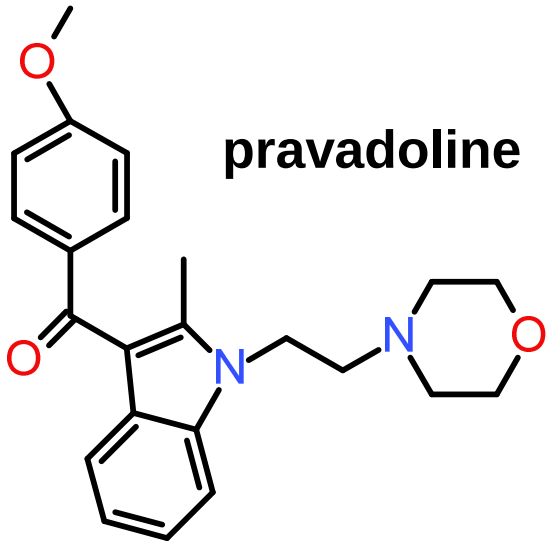
2-arachidonoylglycerol

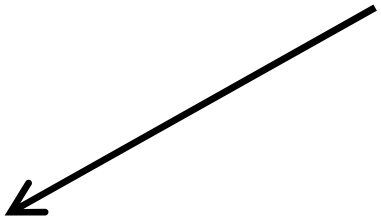
Synthetic cannabinoids from Sterling Winthrop

indomethacin

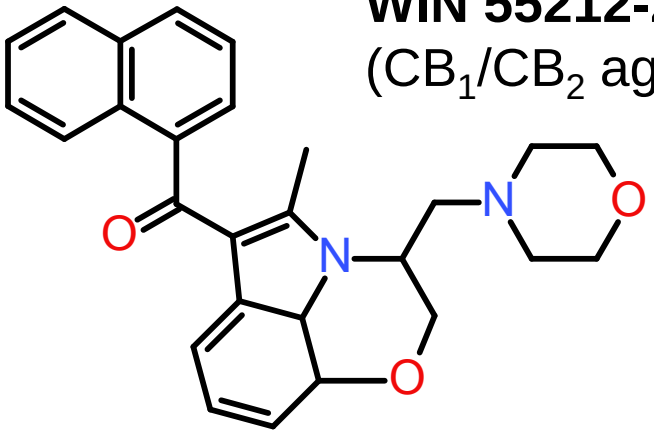


pravadoline



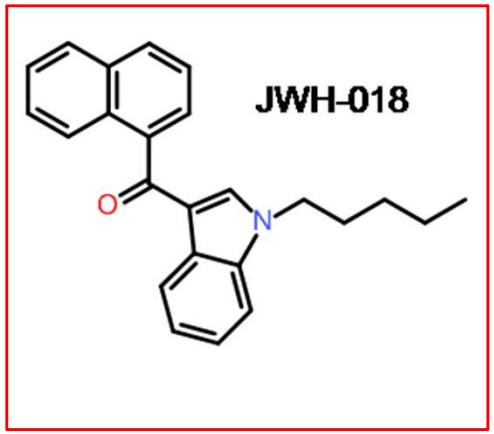


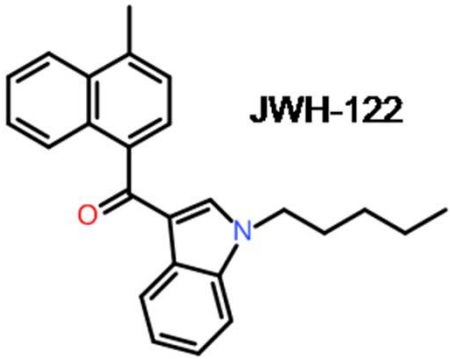
WIN 55212-2
(CB_1/CB_2 agonist)

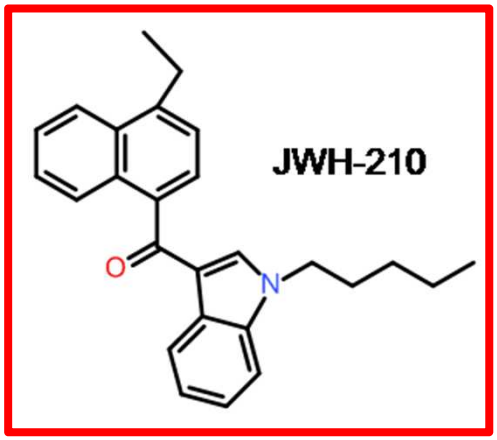


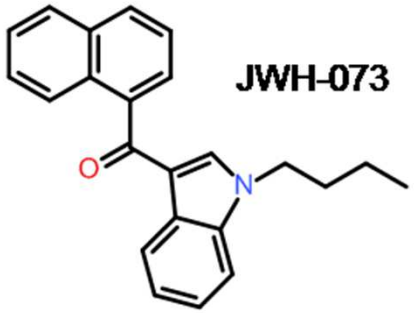
Ward et al., J Pharmacol Exp Ther 255: 1230-1239, 1990
Haubrich et al., J Pharmacol Exp Ther 255: 511-522, 1990
Kuster et al., J Pharmacol Exp Ther 264: 1352-1363, 1993

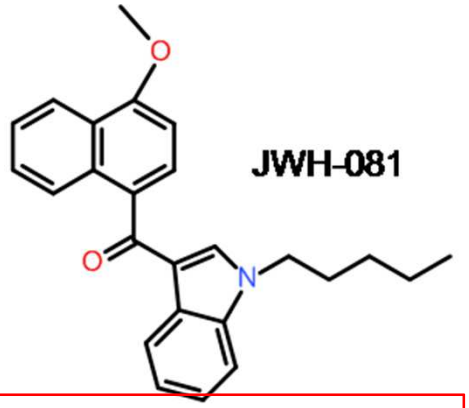
Cannabinoids synthesized by John William Huffman: JWH-compounds

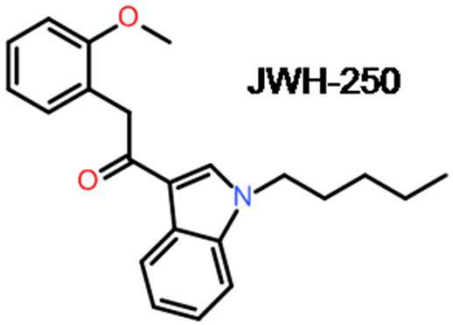


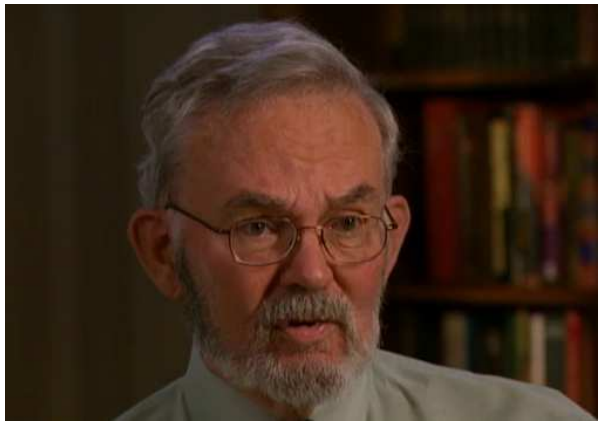


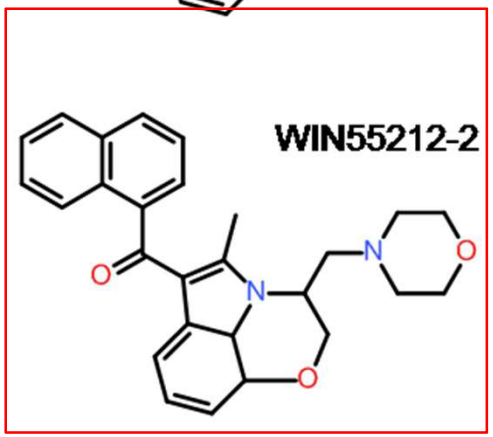


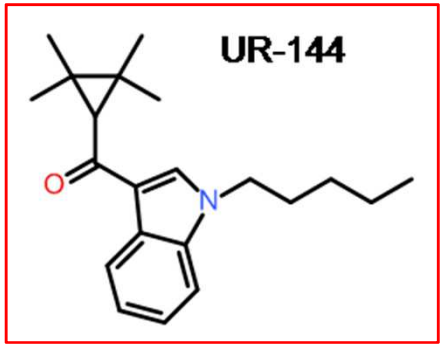






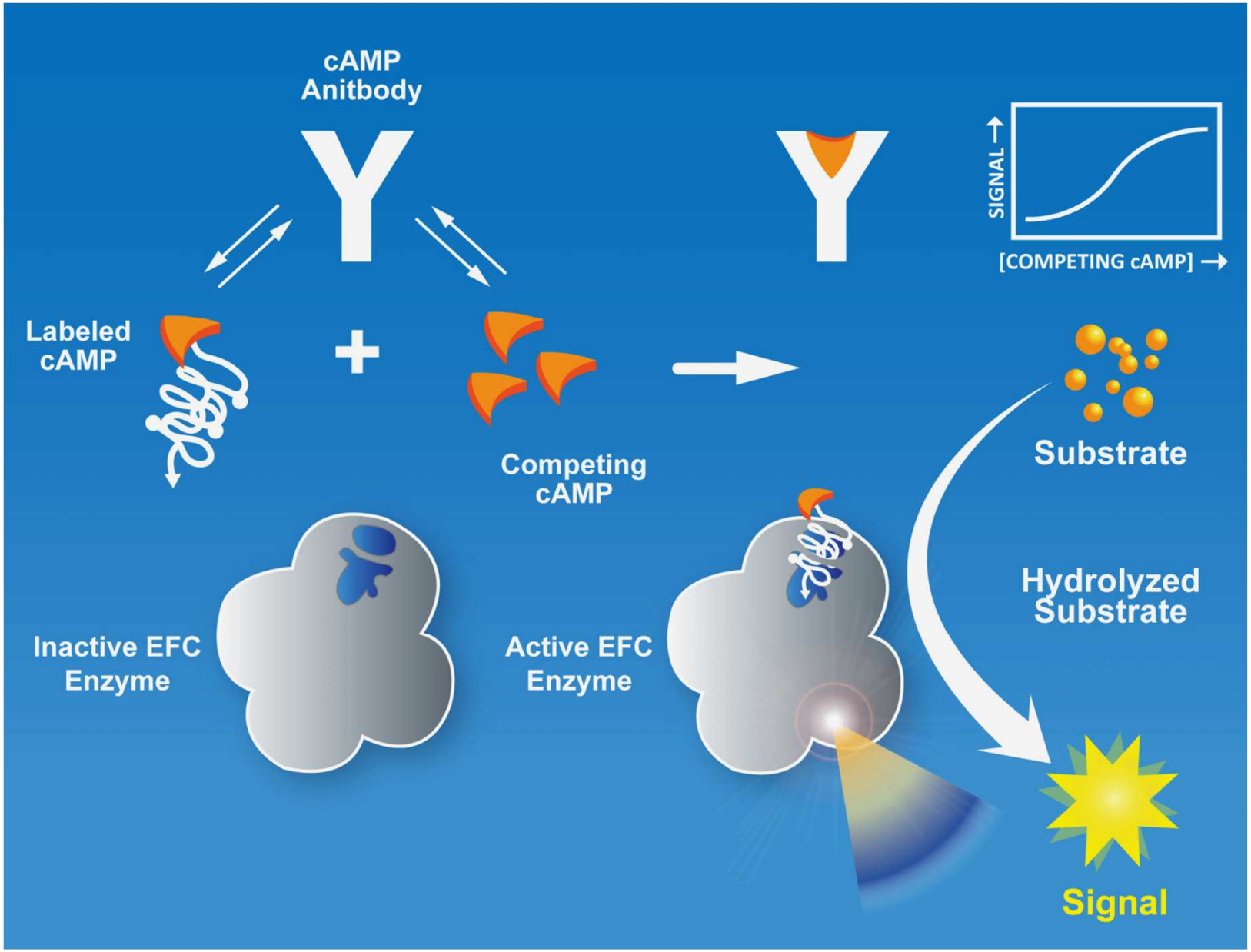






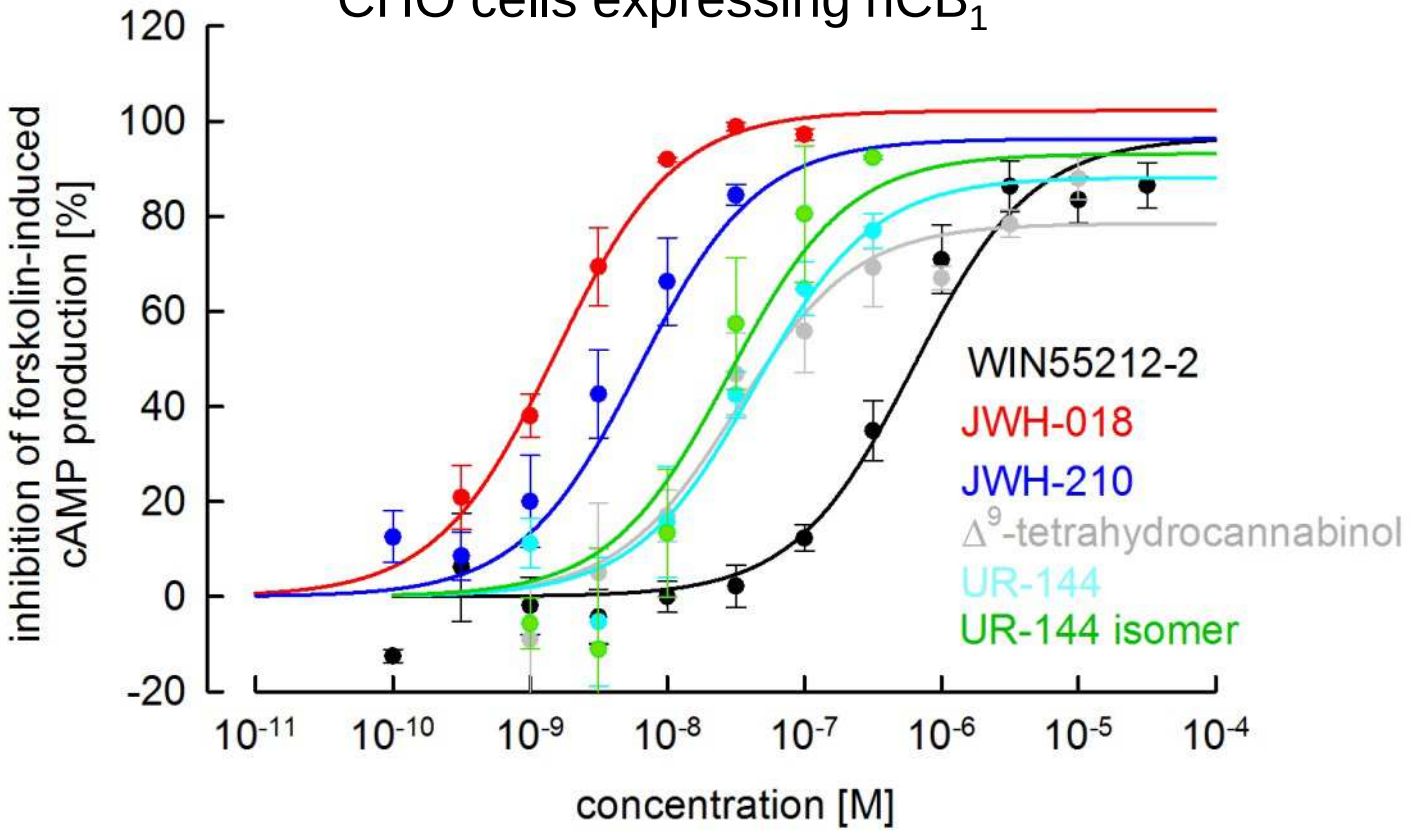
Huffman et al., Bioorg Med Chem 11: 539–549, 2003

Measurement of cAMP concentration: immunoassay + enzyme fragment complementation technology



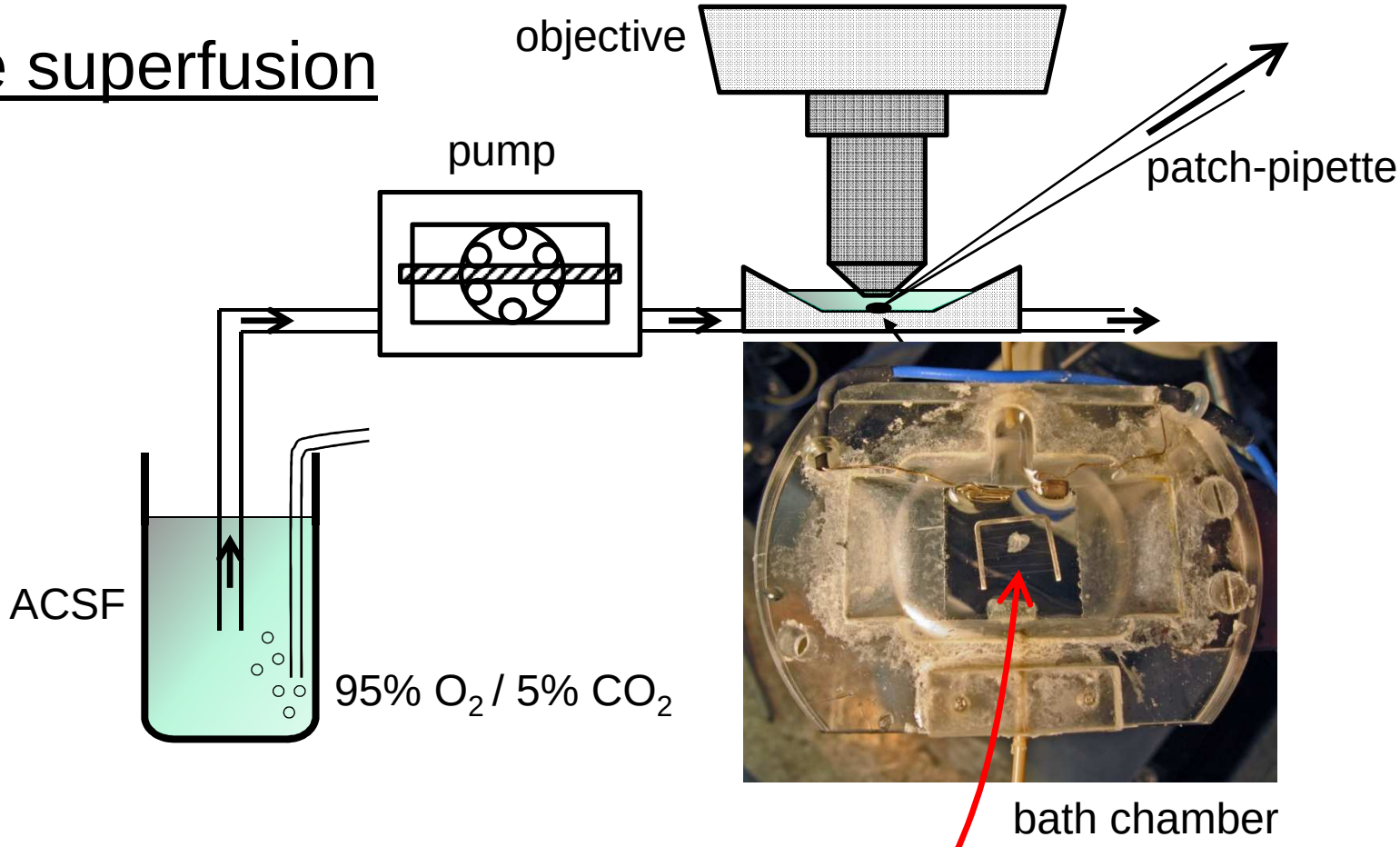
Inhibition of adenylyl cyclase by cannabinoids

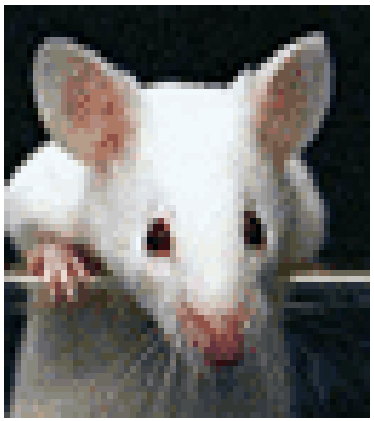
CHO cells expressing hCB_1

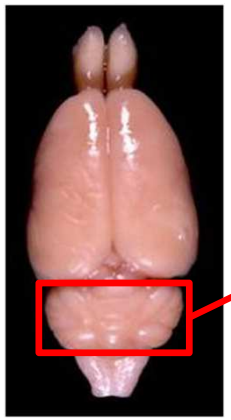


	IC_{50} [nM]	Imax [%]
Δ^9-tetrahydrocannabinol	32 ± 1.2	78 ± 4
WIN55212-2	594 ± 170	107 ± 7
JWH-210	6.2 ± 2.9	96 ± 4
JWH-018	1.5 ± 0.3	102 ± 2
UR-144	43 ± 18	88 ± 4
UR-144 isomer	39 ± 8.4	116 ± 3

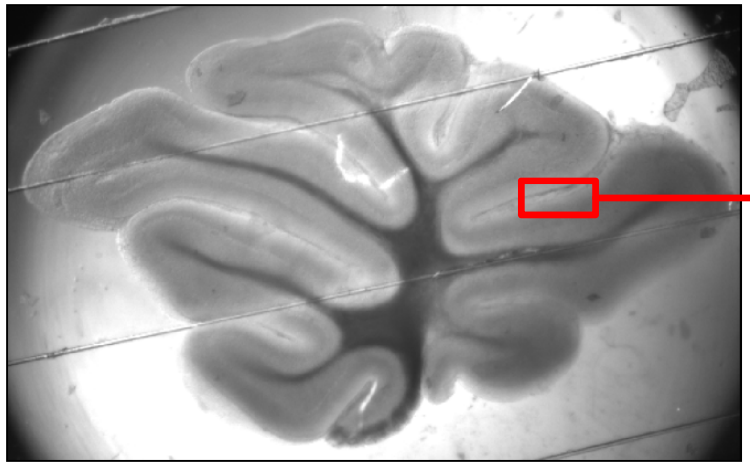
Brain slice superfusion



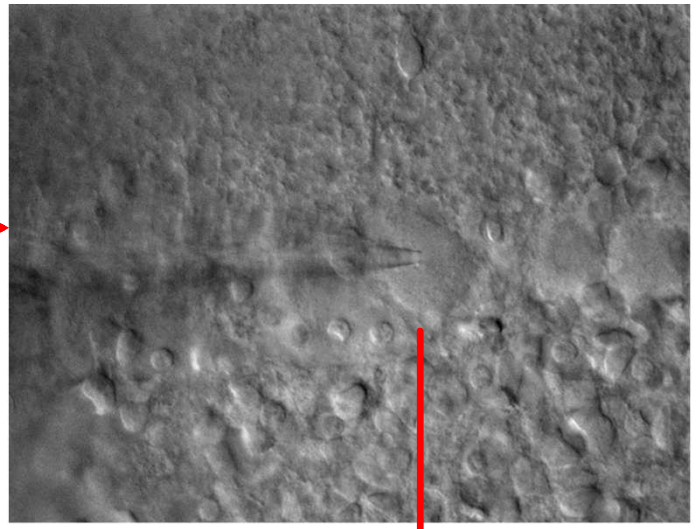


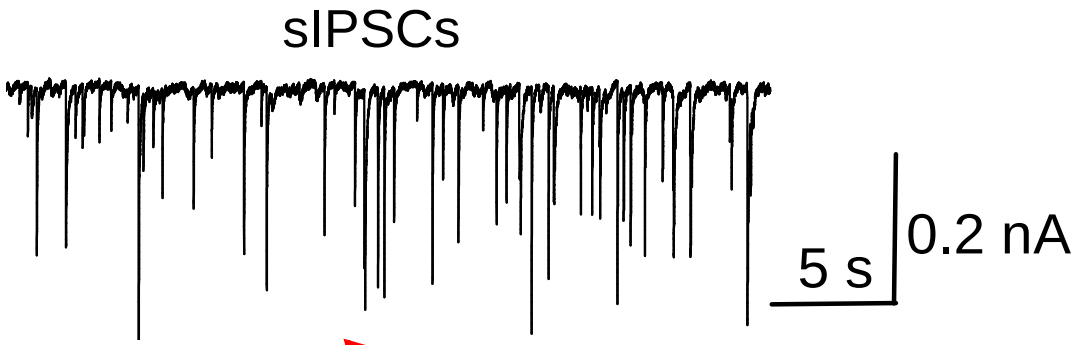


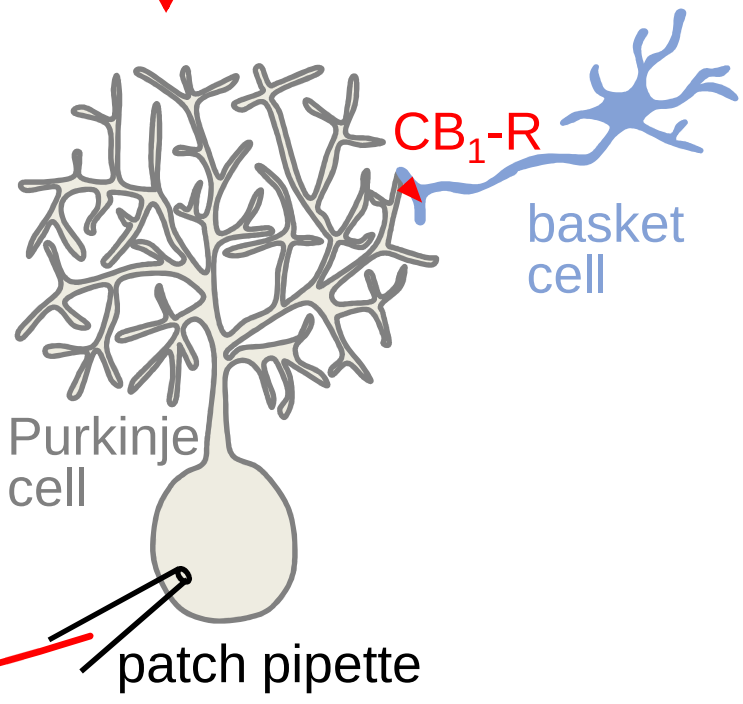
Patch-clamp recording in the cerebellar cortex



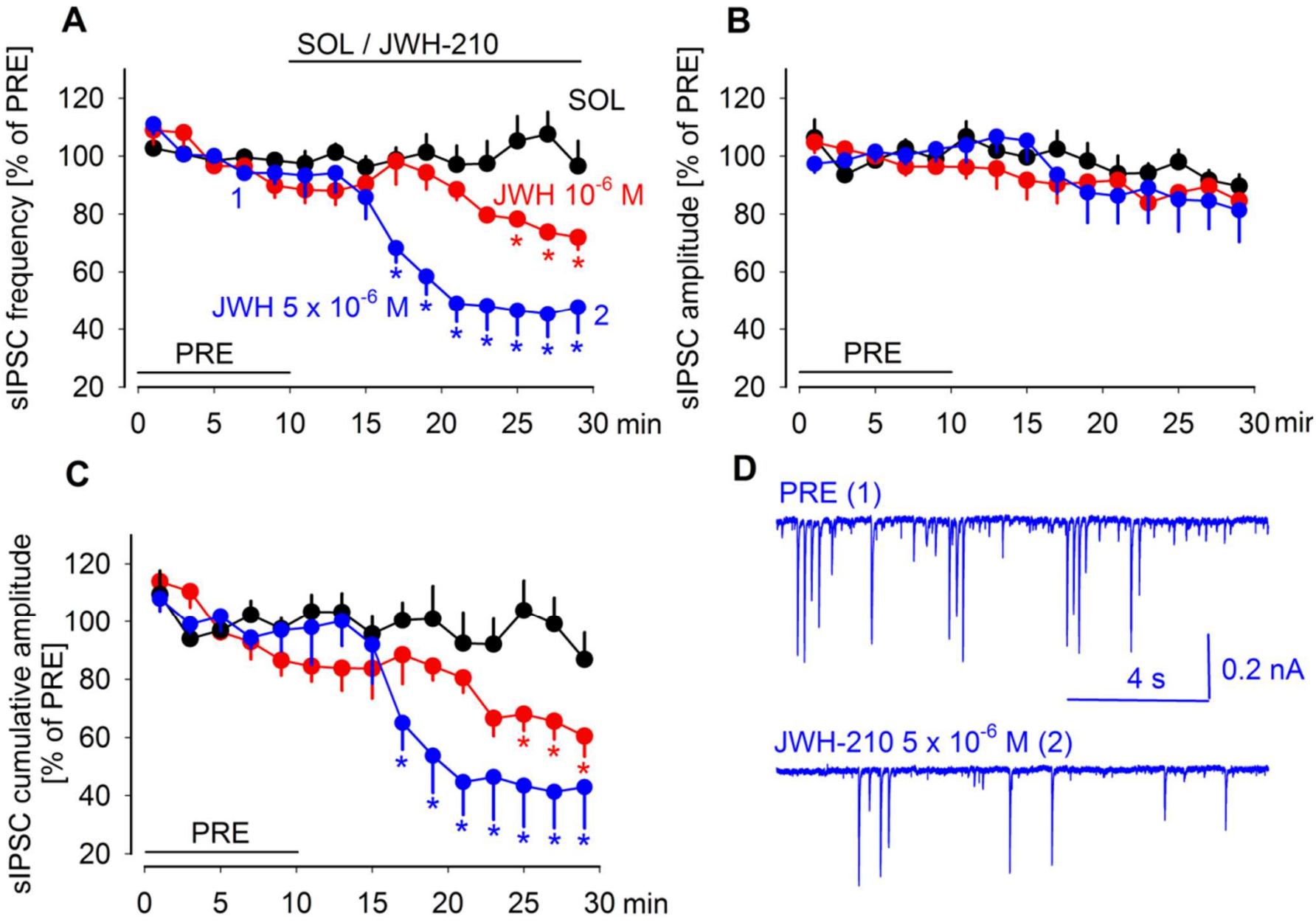
sagittal cerebellar slice



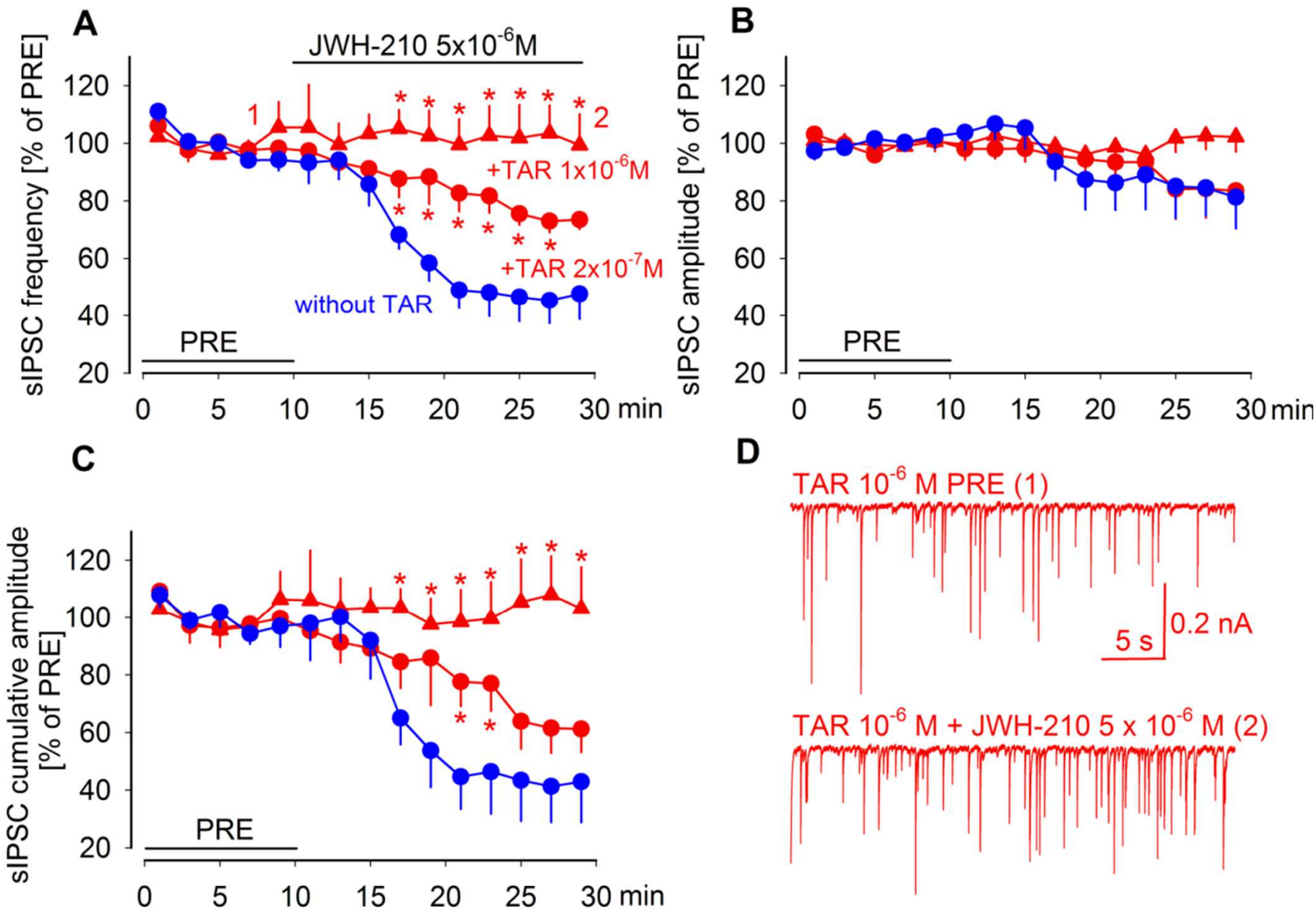




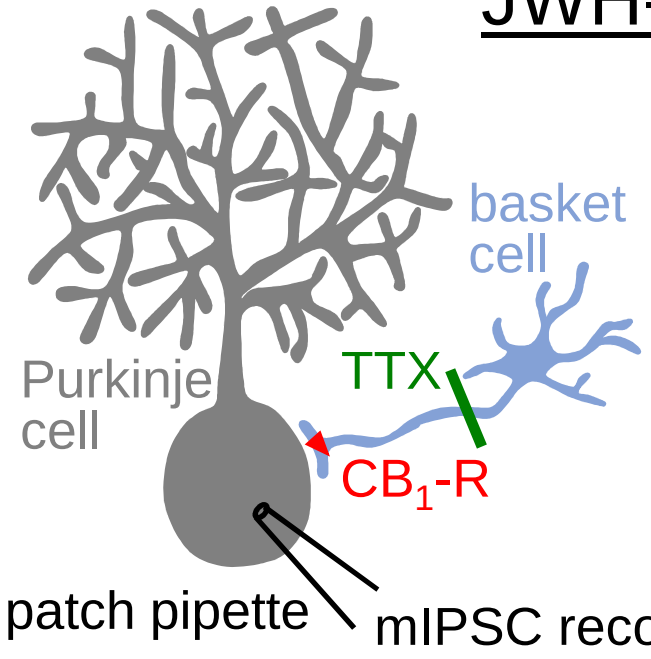
JWH-210 inhibits GABAergic synaptic transmission

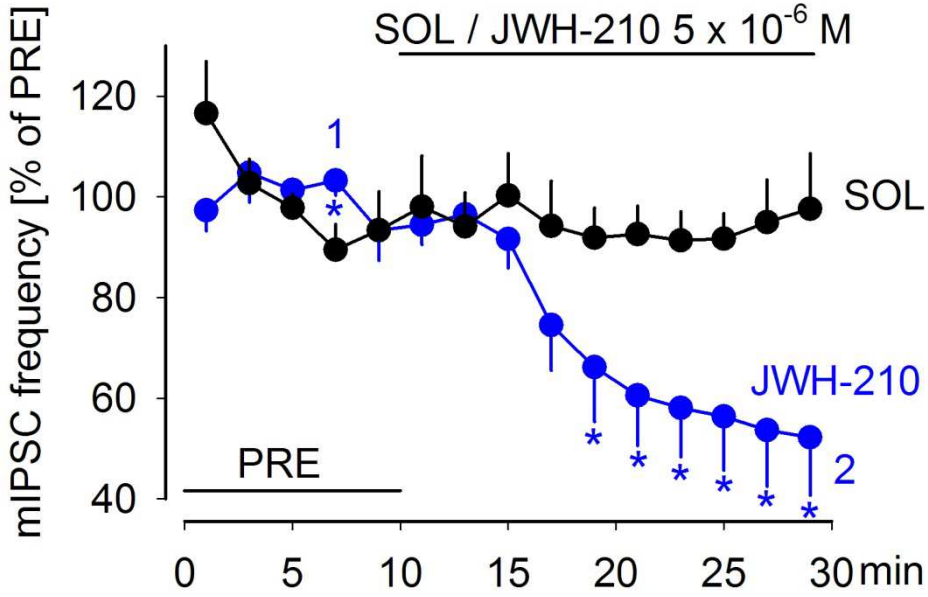


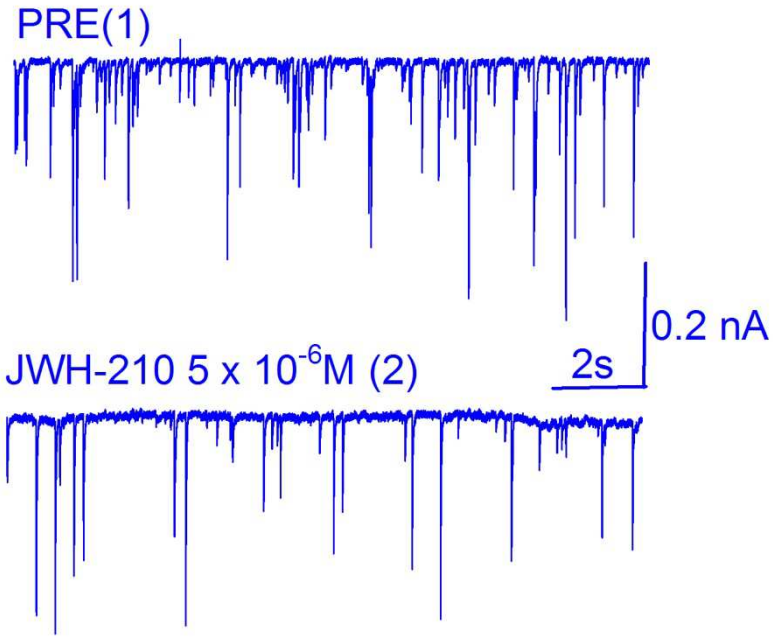
Taranabant antagonizes the effects of JWH-210

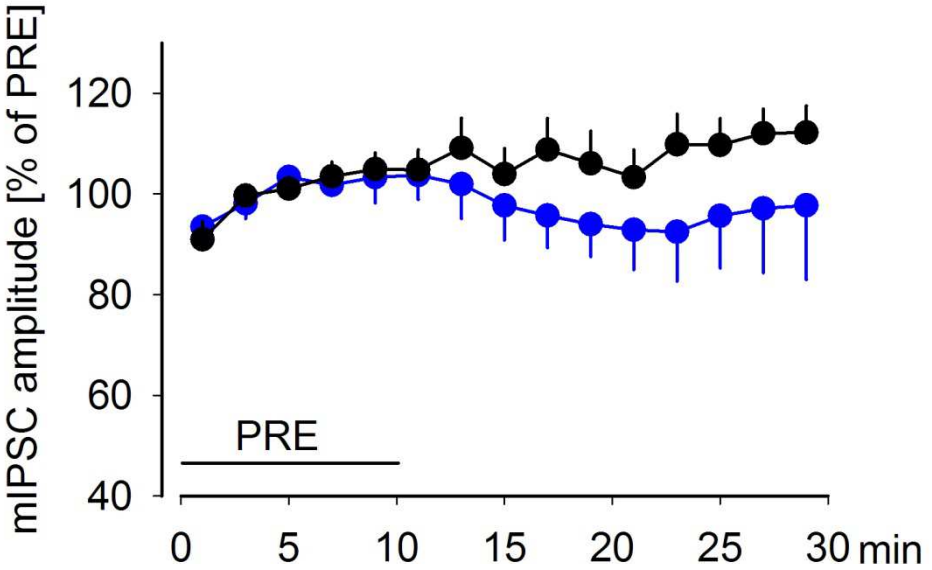


JWH-210 suppresses mIPSCs

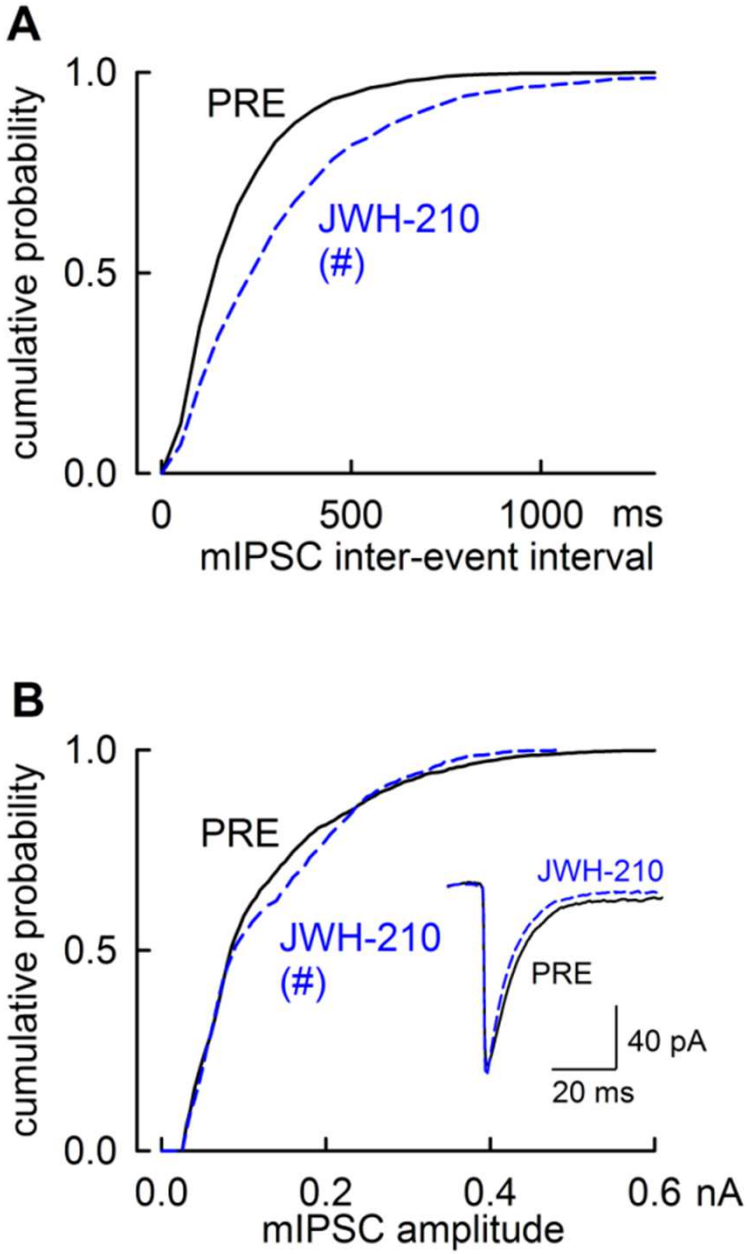




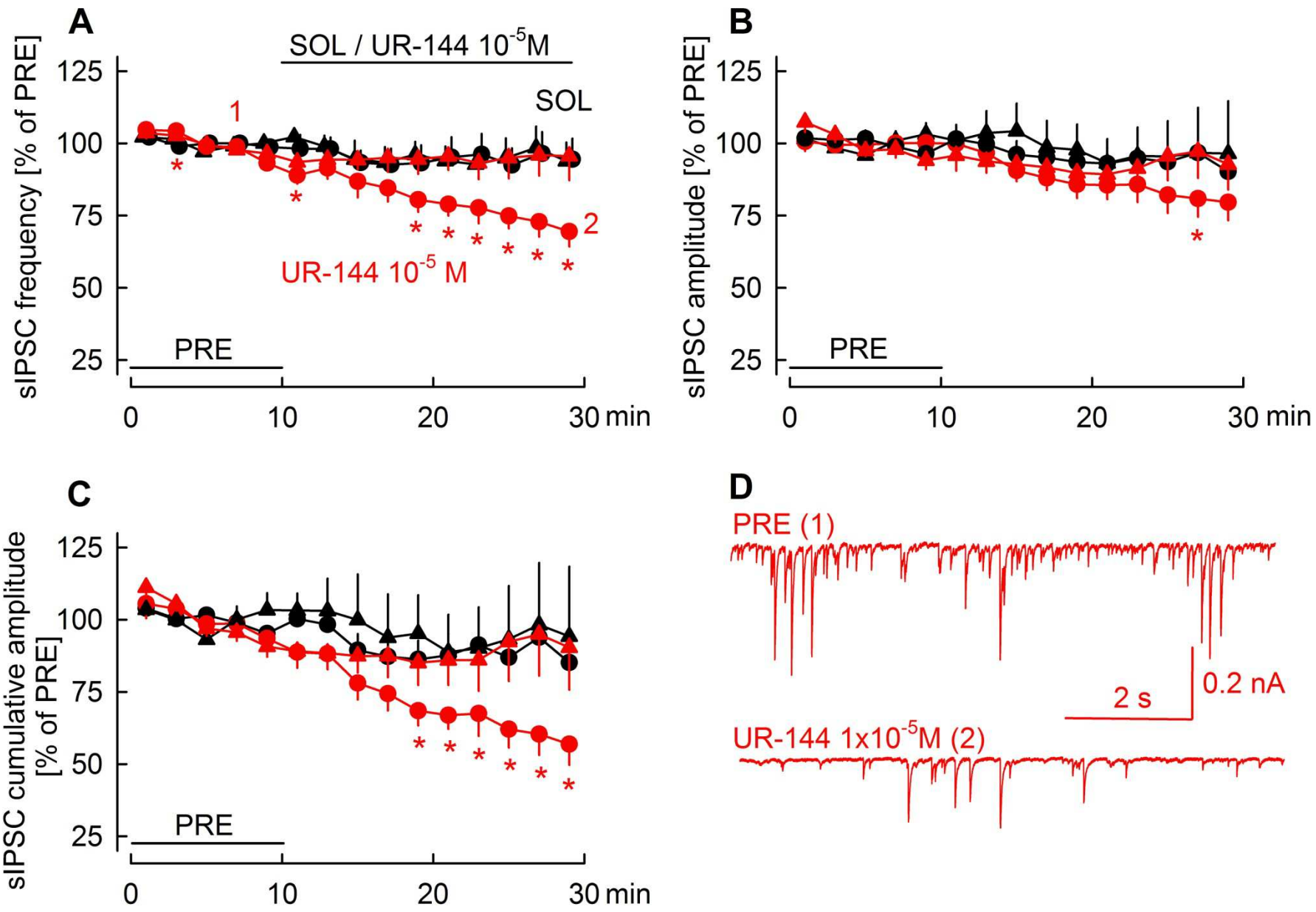




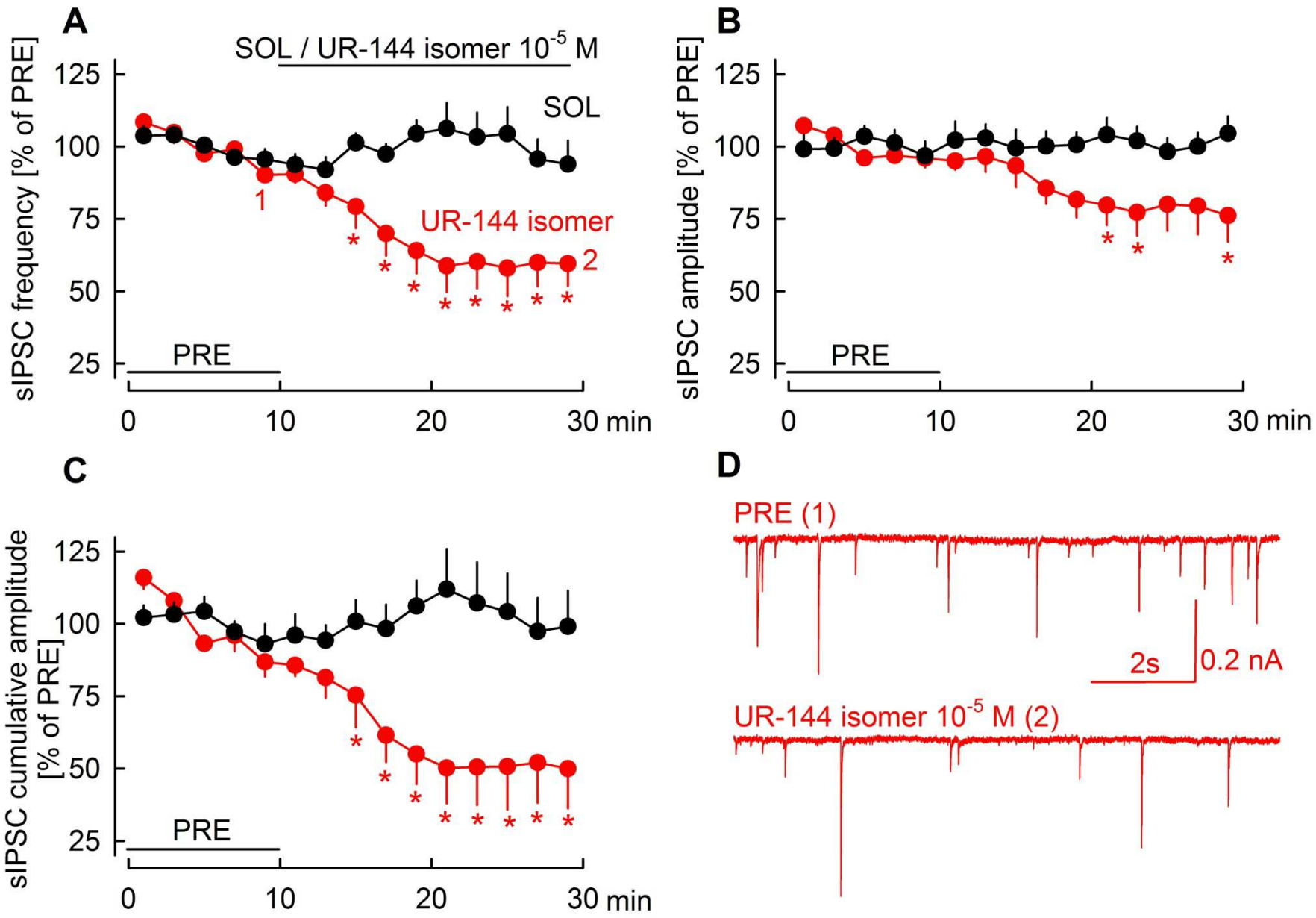
JWH-210 suppresses mIPSCs



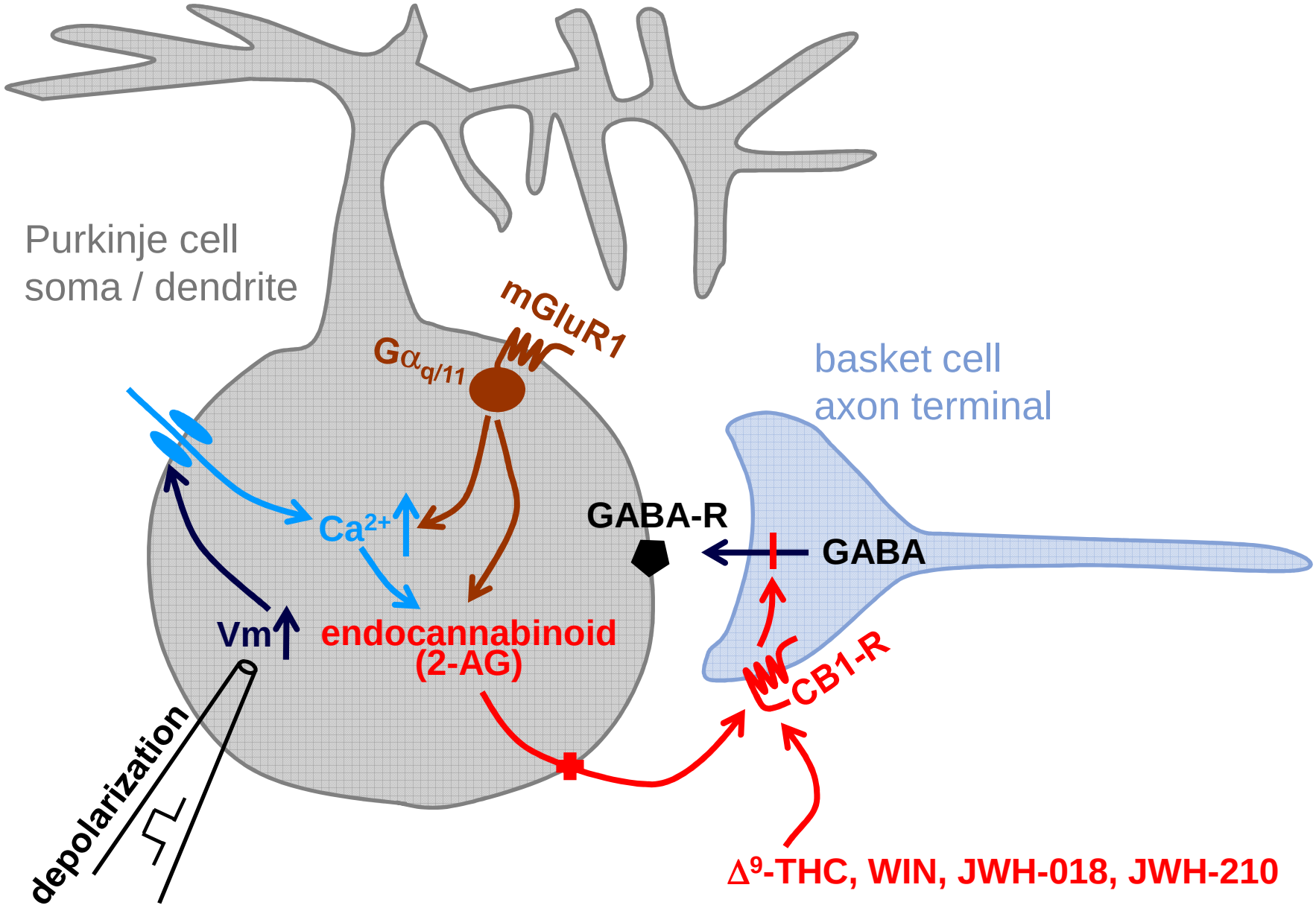
UR-144 inhibits GABAergic synaptic transmission



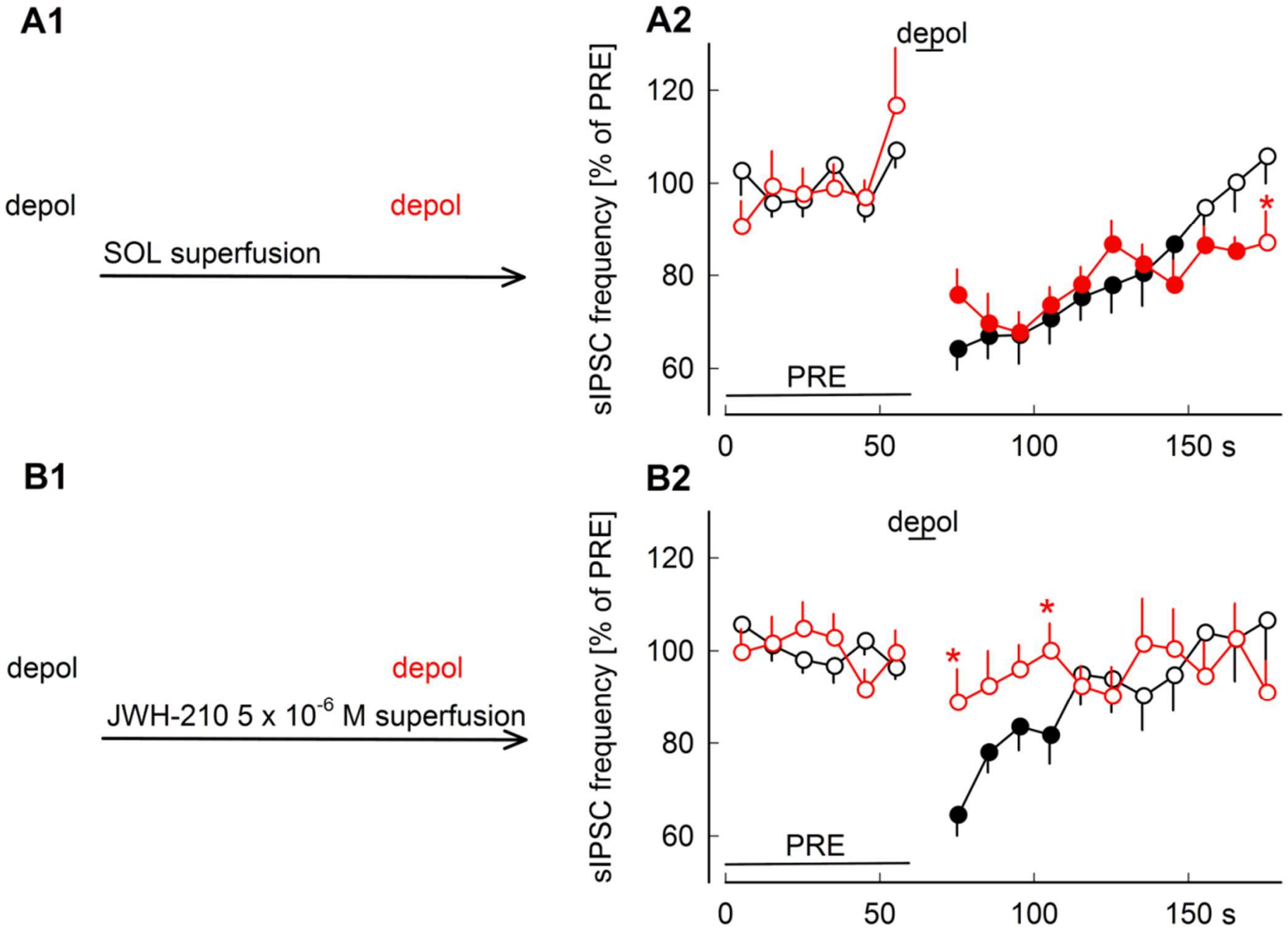
UR-144 isomer inhibits GABAergic synaptic transmission



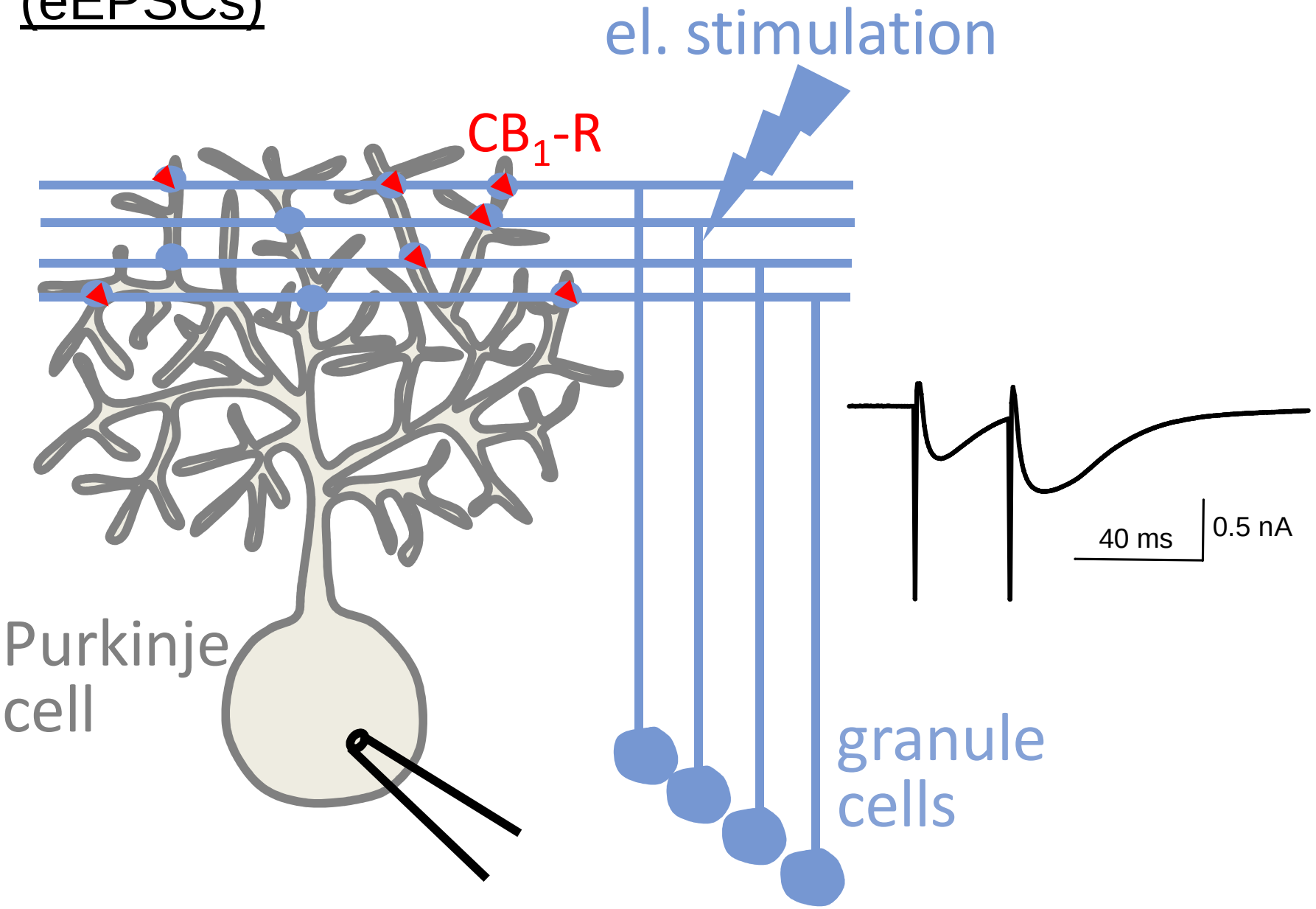
Retrograde signaling by endocannabinoids: depolarization-induced suppression of inhibition (DSI)



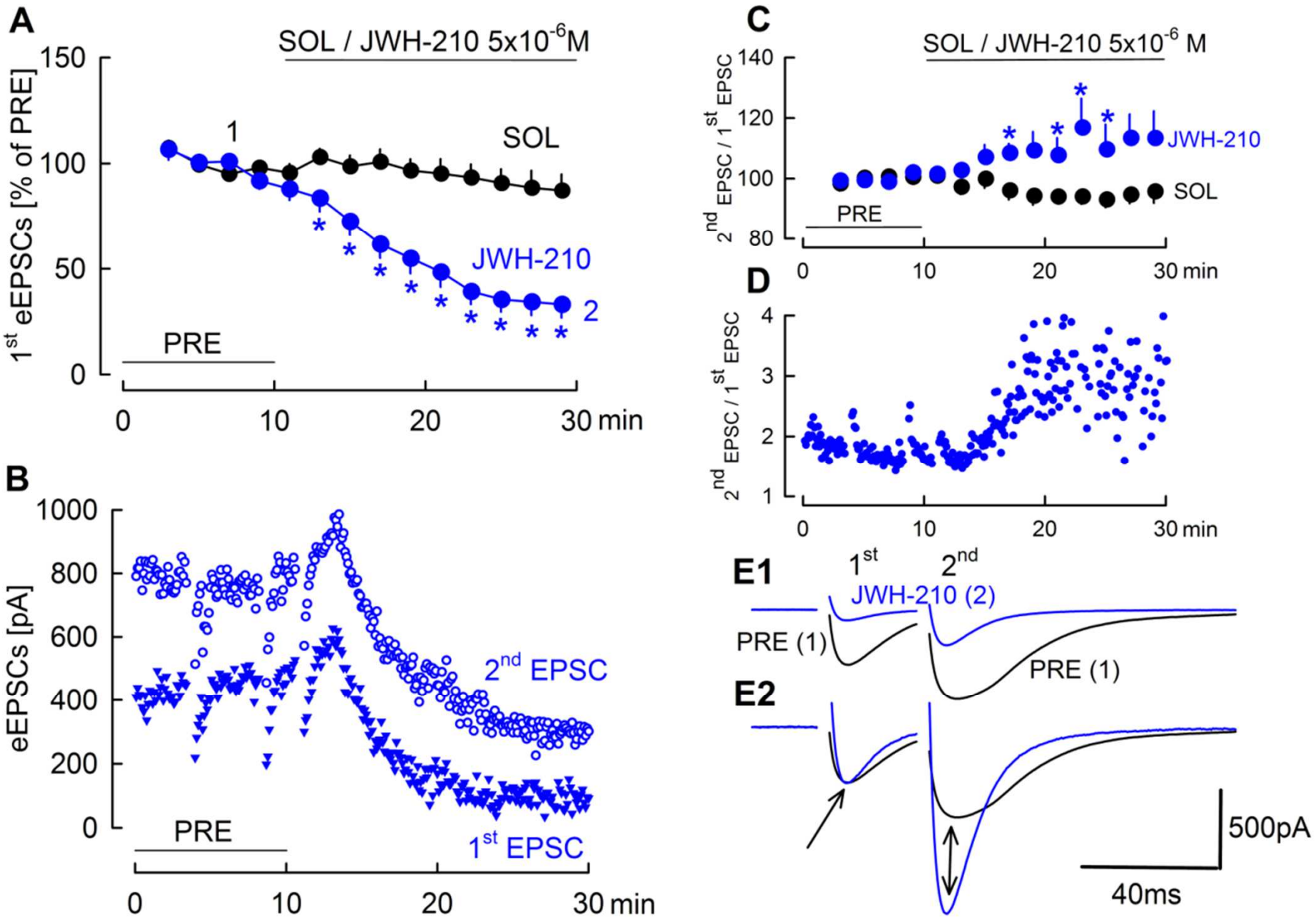
JWH-210 occludes DSI



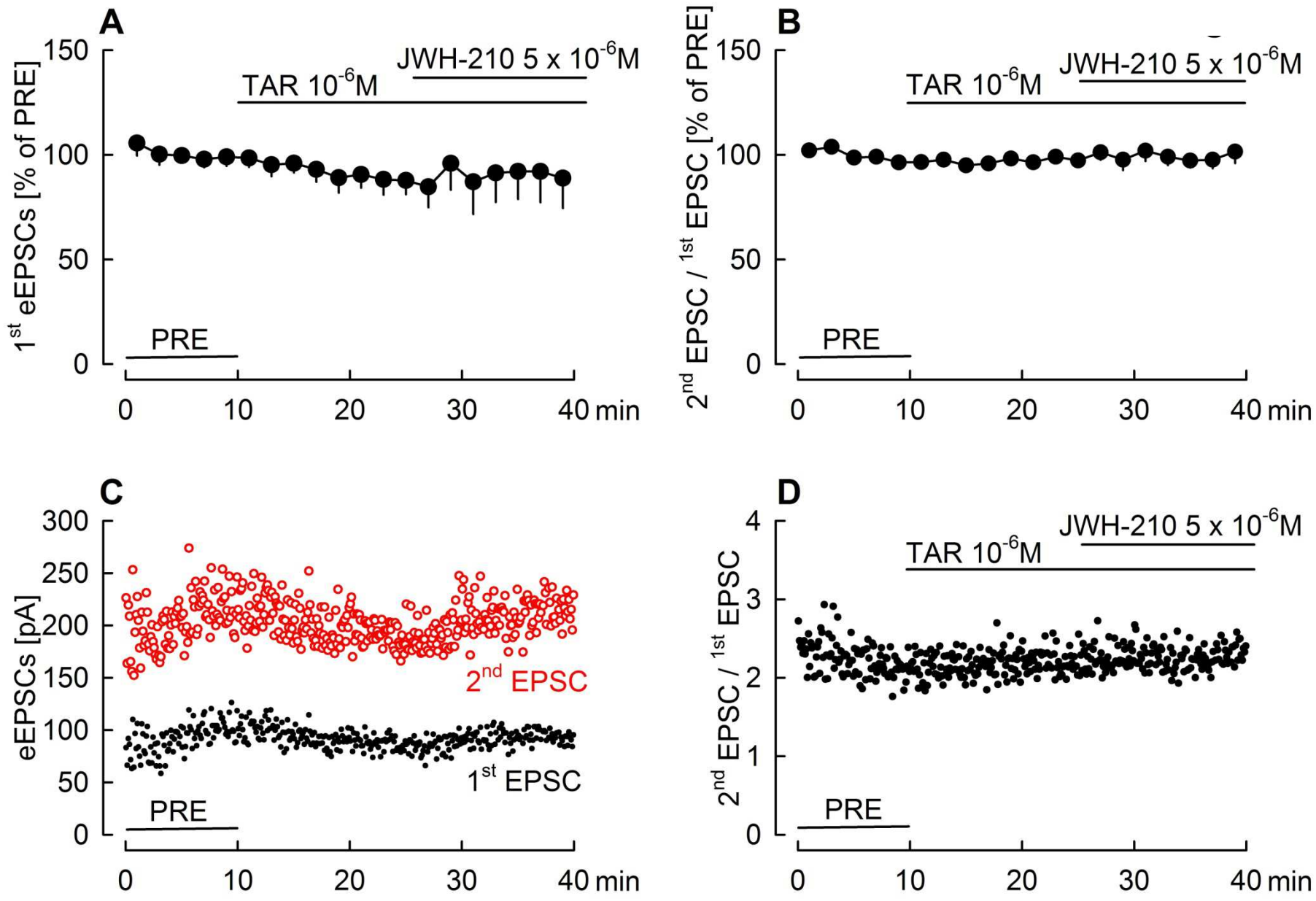
Recording of glutamatergic synaptic transmission (eEPSCs)



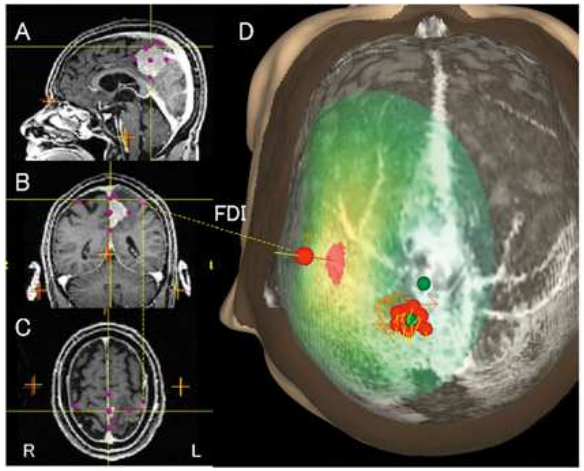
JWH-210 suppresses eEPSCs

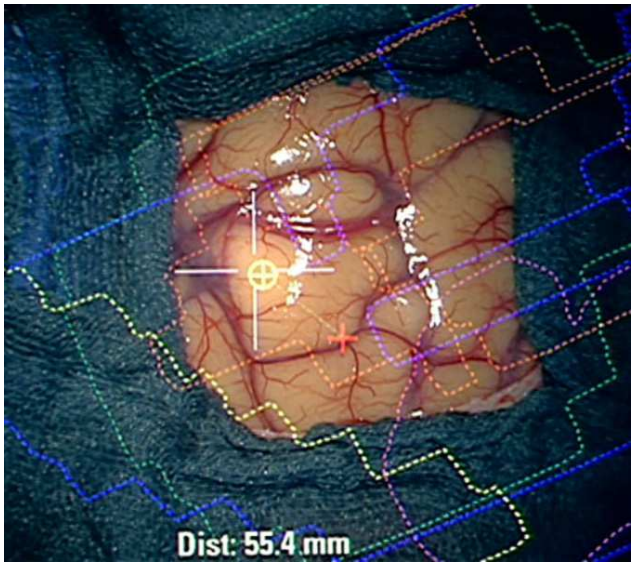


Taranabant antagonizes the effects of JWH-210 on eEPSCs

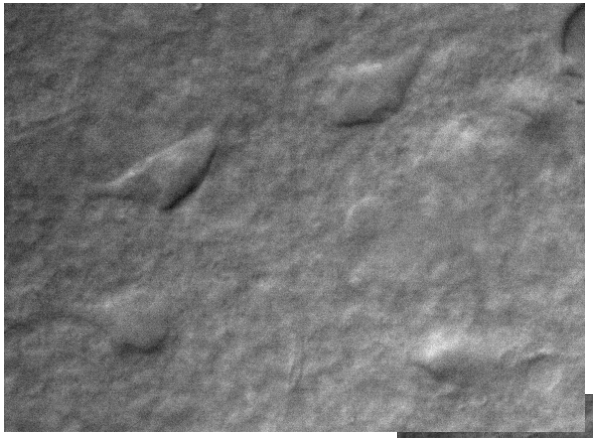


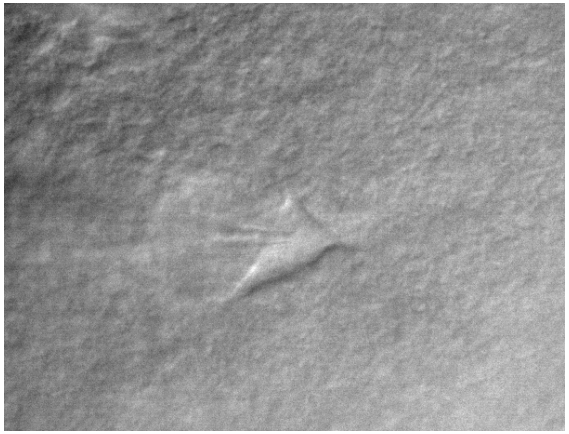
Synaptic transmission in the human neocortex

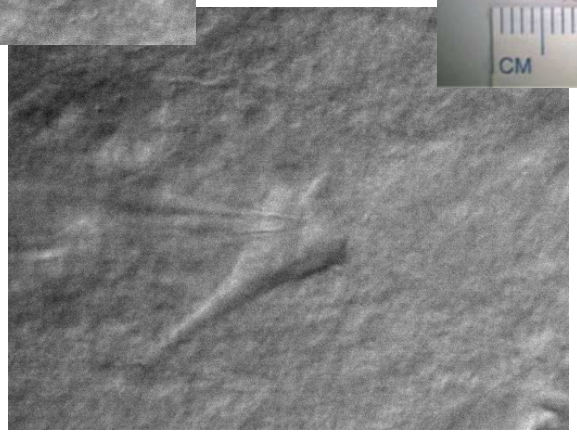




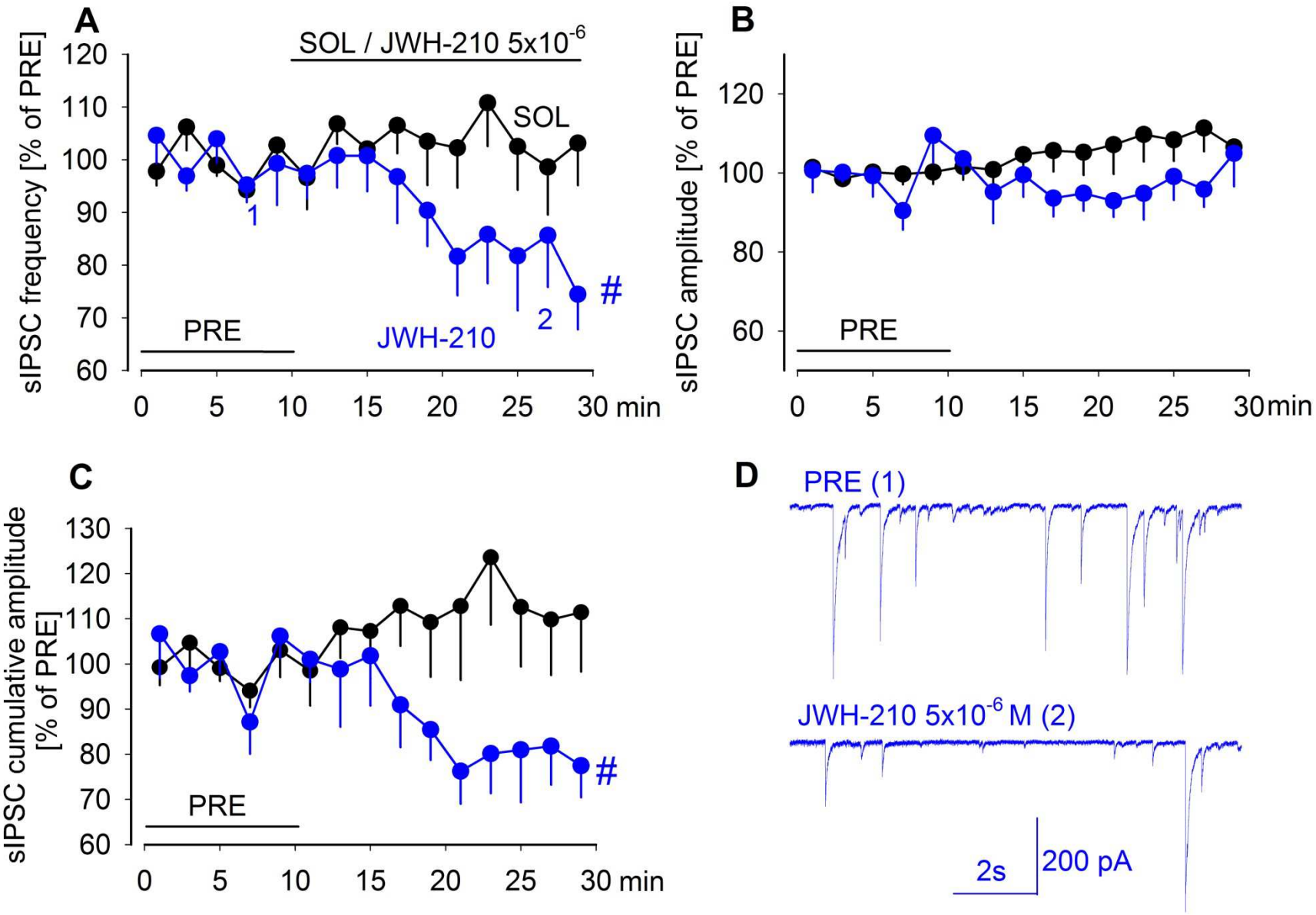
Catharina Donkels,
Prof. Thomas Feuerstein







Effects of JWH-210 on sIPSCs recorded in pyramidal cells in human neocortical slices



Pregnenolone Can Protect the Brain from Cannabis Intoxication

Monique Vallée,[1,2]† Sergio Vitiello,[1,2]* Luigi Bellocchio,[1,2]* Etienne Hébert-Chatelain,[1,2]* Stéphanie Monlezun,[3]* Elena Martin-Garcia,[4] Fernando Kasanetz,[1,2] Gemma L. Baillie,[5,7] Francesca Panin,[1,2] Adeline Cathala,[1,2] Valérie Roullot-Lacarrière,[1,2] Sandy Fabre,[3] Dow P. Hurst,[6] Diane L. Lynch,[6] Derek M. Shore,[6] Véronique Deroche-Gamonet,[1,2] Umberto Spampinato,[1,2] Jean-Michel Revest,[1,2] Rafael Maldonado,[4] Patricia H. Reggio,[6] Ruth A. Ross,[5,7] Giovanni Marsicano,[1,2] Pier Vincenzo Piazza[1,2]†‡

[1]INSERM, Neurocentre Magendie, Physiopathologie de la Plasticité Neuronale, U862, F-33000 Bordeaux, France. [2]Université de Bordeaux, Neurocentre Magendie, Physiopathologie de la Plasticité

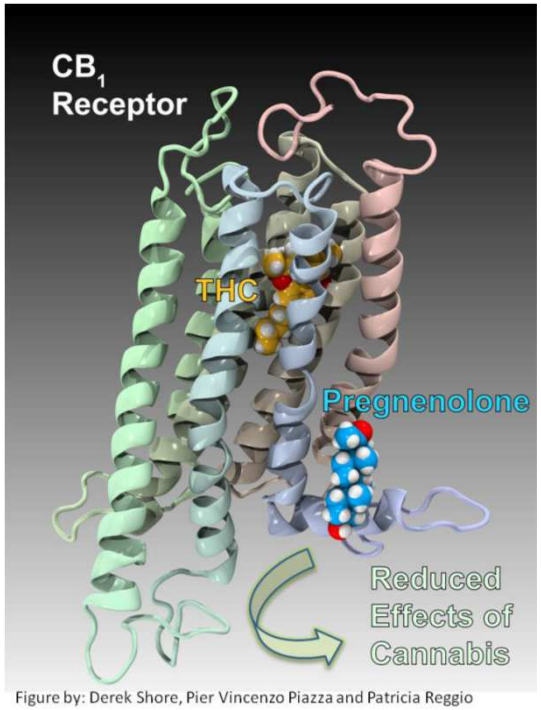


Figure by: Derek Shore, Pier Vincenzo Piazza and Patricia Reggio

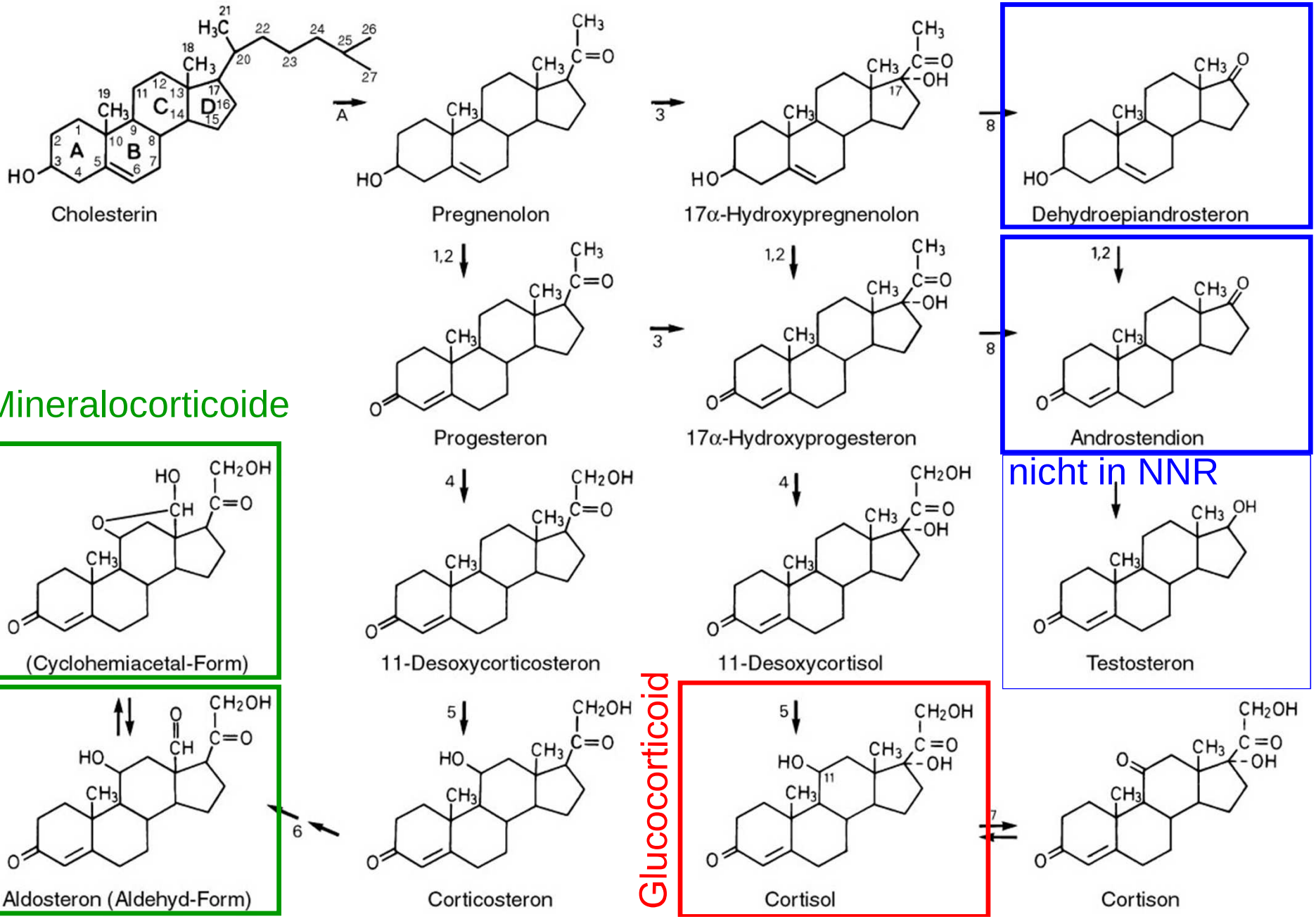
Science 343: 94-98, 2014

Corticosteroide: 3 Gruppen

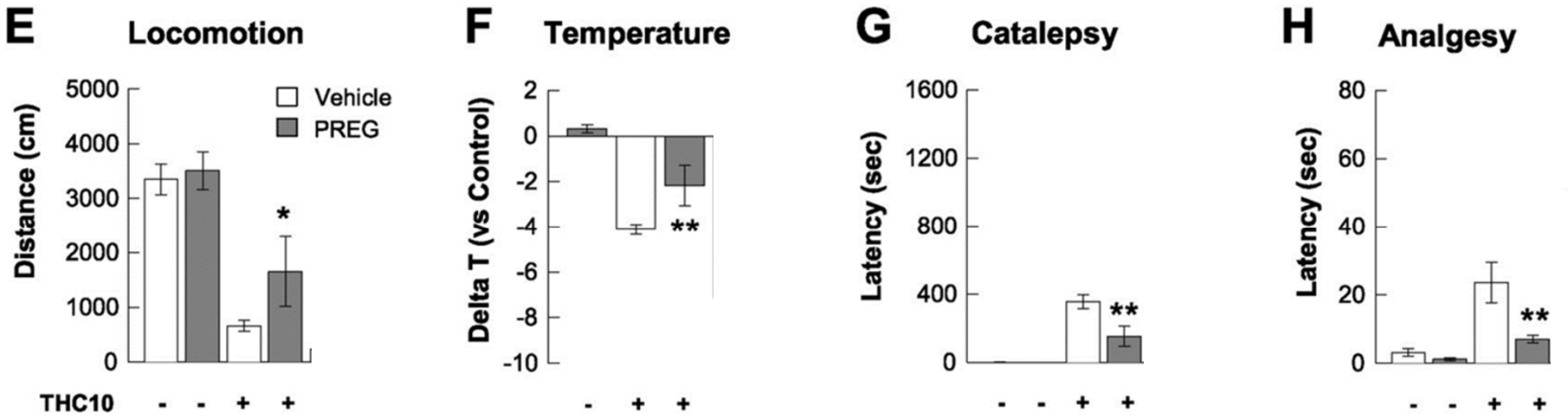
Androgene

Mineralocorticoide

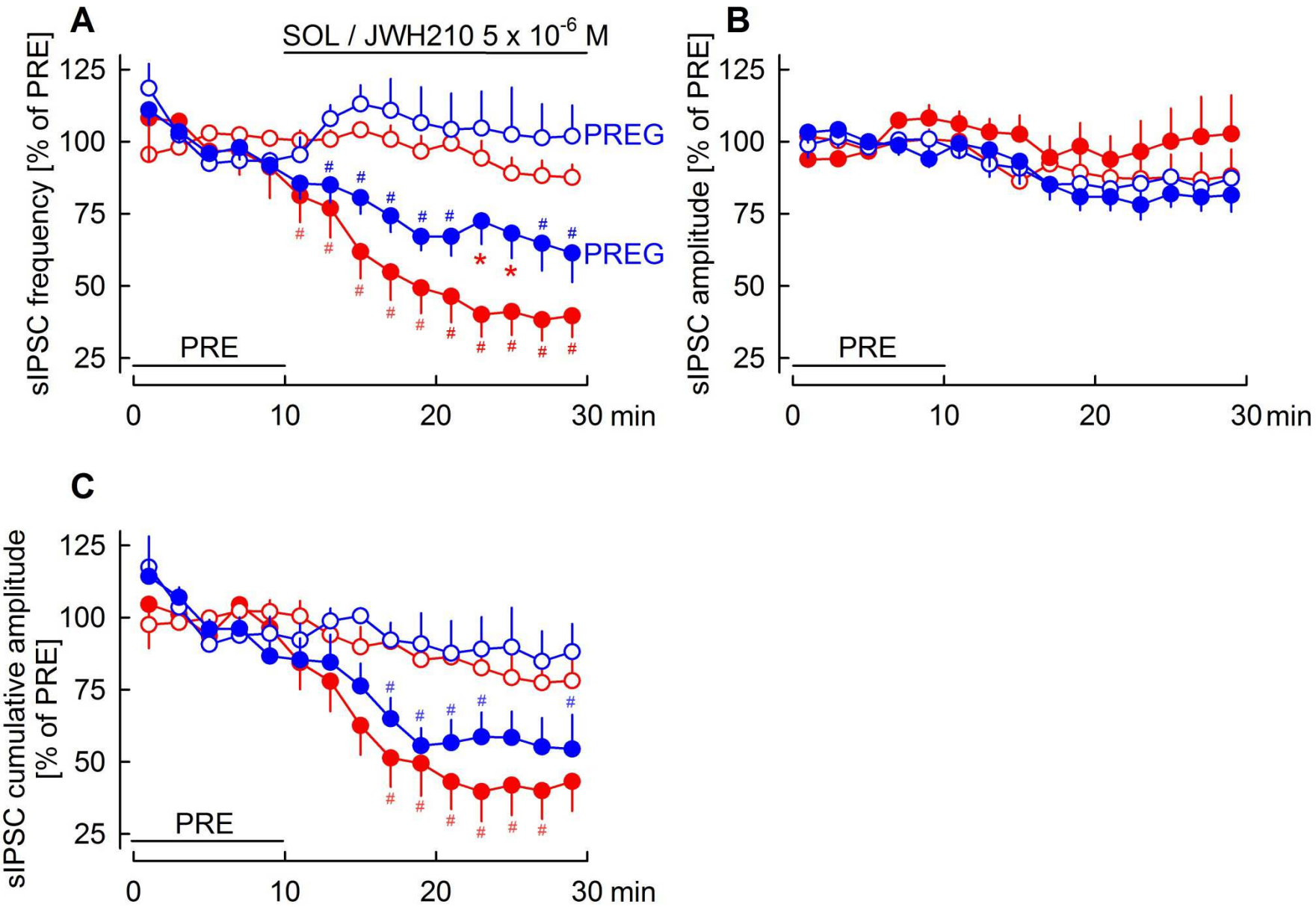
Glucocorticoid



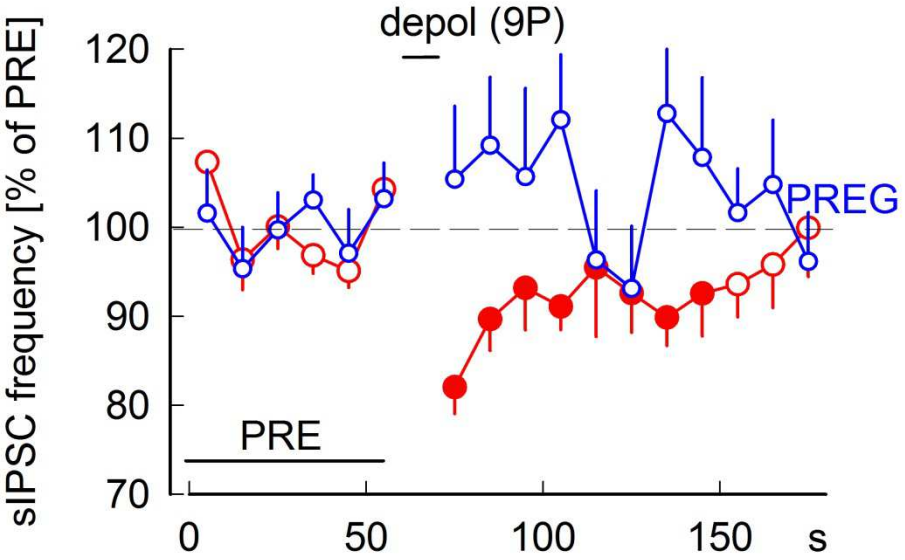
Pregnenolone attenuates Δ^9-THC effects

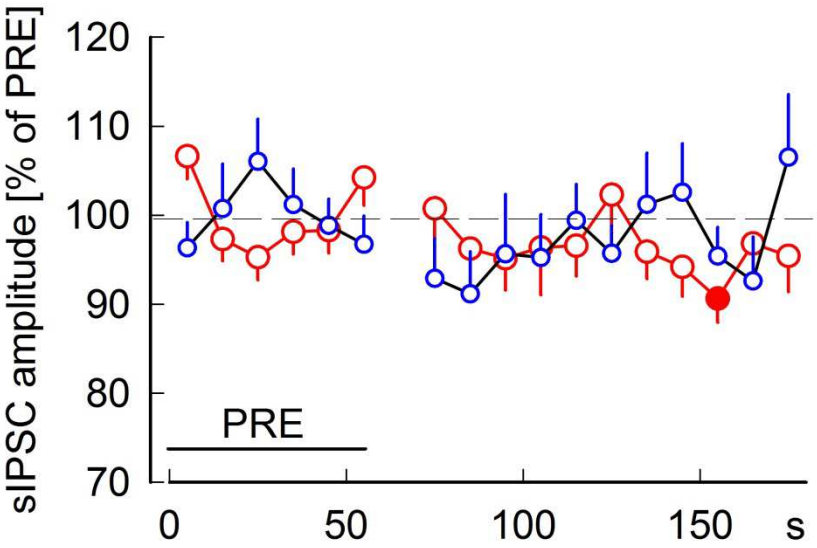


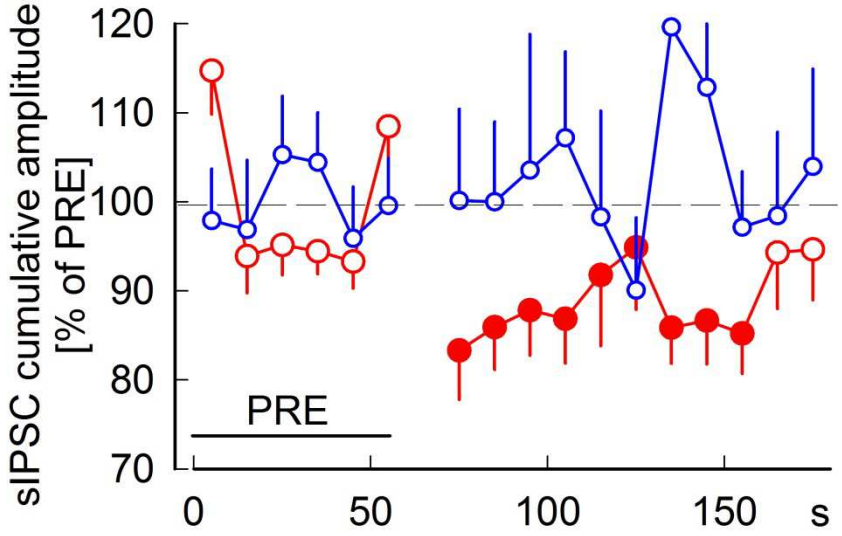
Pregnenolone attenuates the effects of JWH-210 on synaptic transmission



Pregnenolone attenuates depolarization-induced suppression of inhibition (DSI)







Summary

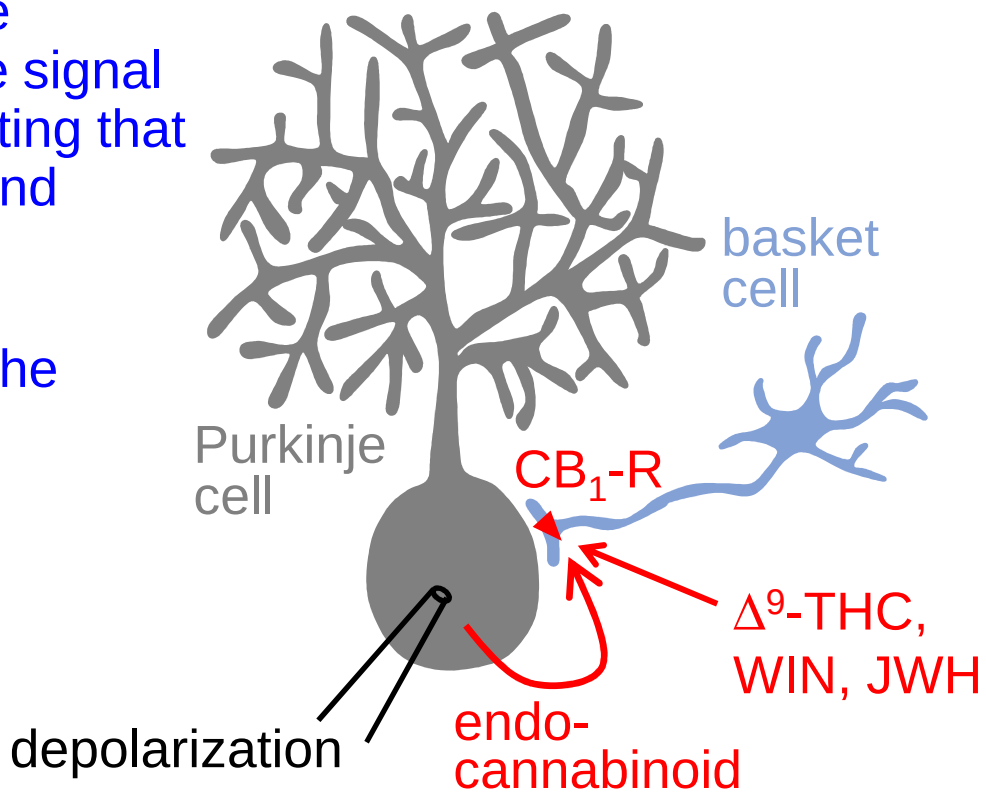
1) The synthetic aminoalkylindole cannabinoid JWH-210 (and JWH-018, UR-144, WIN-55212-2) inhibits GABAergic and glutamatergic synaptic transmission in the cerebellar cortex

2) The basis of the suppression is inhibition of GABA and glutamate release from the presynaptic axon terminals via CB_1 receptors

3) The synthetic cannabinoids occlude endocannabinoid-mediated retrograde signal transmission between neurons, indicating that they interfere with synaptic plasticity and memory

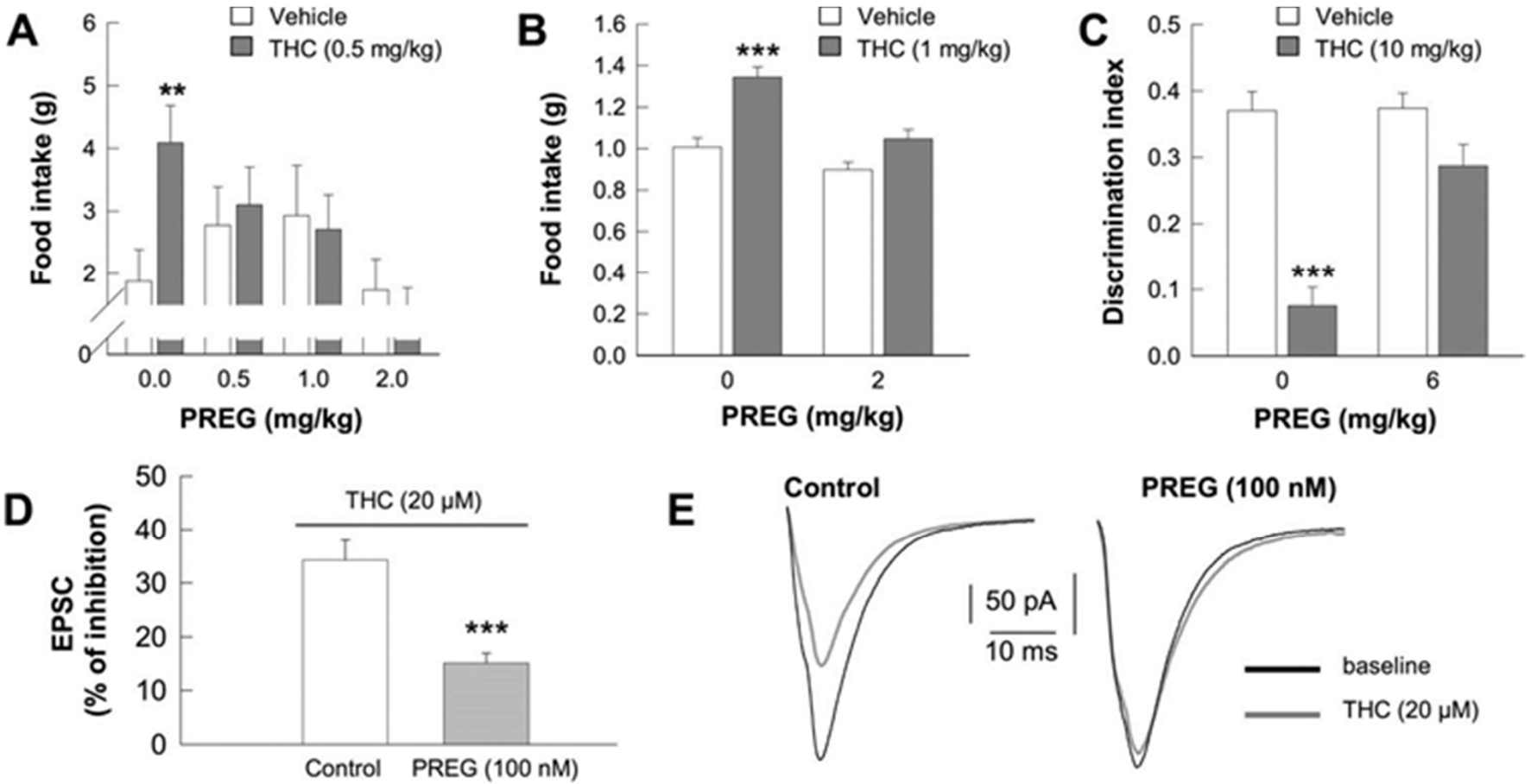
4) Synthetic cannabinoids act also in the human brain cortex

5) Pregnenolone may attenuate the effects of synthetic cannnabinoids




Thank you for
your attention!

Pregnenolone attenuates Δ^9-THC effects



Human CB_1 receptor differs from rodent CB_1 receptor: Species-specific functionality of CB_1 receptors ?

BJP British Journal of Pharmacology

Themed Section: Cannabinoids in Biology and Medicine, Part II

RESEARCH PAPER

Differential signalling in human cannabinoid CB_1 receptors and their splice variants in autaptic hippocampal neurones

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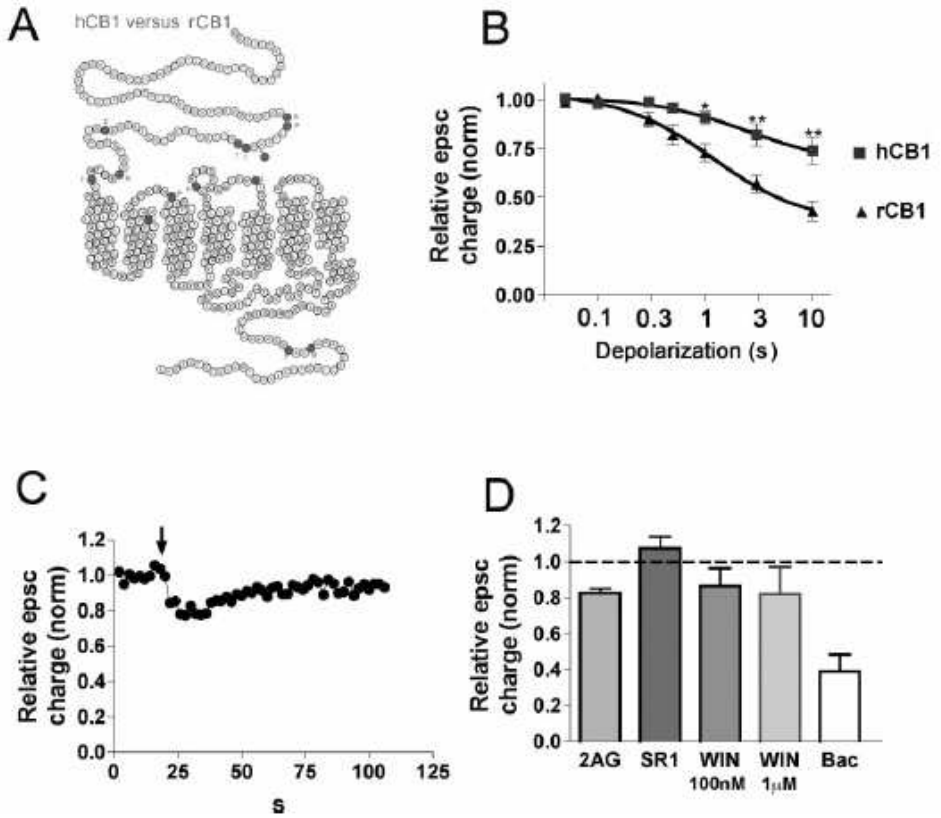


Figure 4

hCB_1 receptors signal less robustly than rCB_1 receptors. (A) Helixnet diagram shows the structure of the hCB_1 receptor, with residues different from rCB_1 receptors shown in darker symbols. (B) DSE depolarization–response curve, representing inhibition in response to increasing durations of depolarization (50 ms, 100 ms, 300 ms, 500 ms, 1 s, 3 s, 10 s) in cells transfected with rCB_1 receptors or with hCB_1 receptors. $^*P < 0.01$; $^{**}P < 0.001$, two-way ANOVA with Bonferroni *post hoc* test. (C) Typical DSE time course of an hCB_1 receptor-transfected neurone in response to a 3 s depolarization (arrow). (D) Bar graph shows responses to endocannabinoid 2-AG (5 μM), the CB_1 receptor antagonist SR1 (200 nM), the synthetic CB_1 agonist WIN (100 nM and 1 μM) and the $GABA_B$ receptor agonist baclofen (Bac; 25 μM) in hCB_1 receptor-transfected neurones.

Addiction
RESEARCH REPORT
doi:10.1111/j.1360-0443.2012.04078.x

Acute toxicity due to the confirmed consumption of synthetic cannabinoids: clinical and laboratory findings

Maren Hermanns-Clausen[1]*, Stefan Kneisel[2]*, Bela Szabo[3] & Volker Auwärter[2]

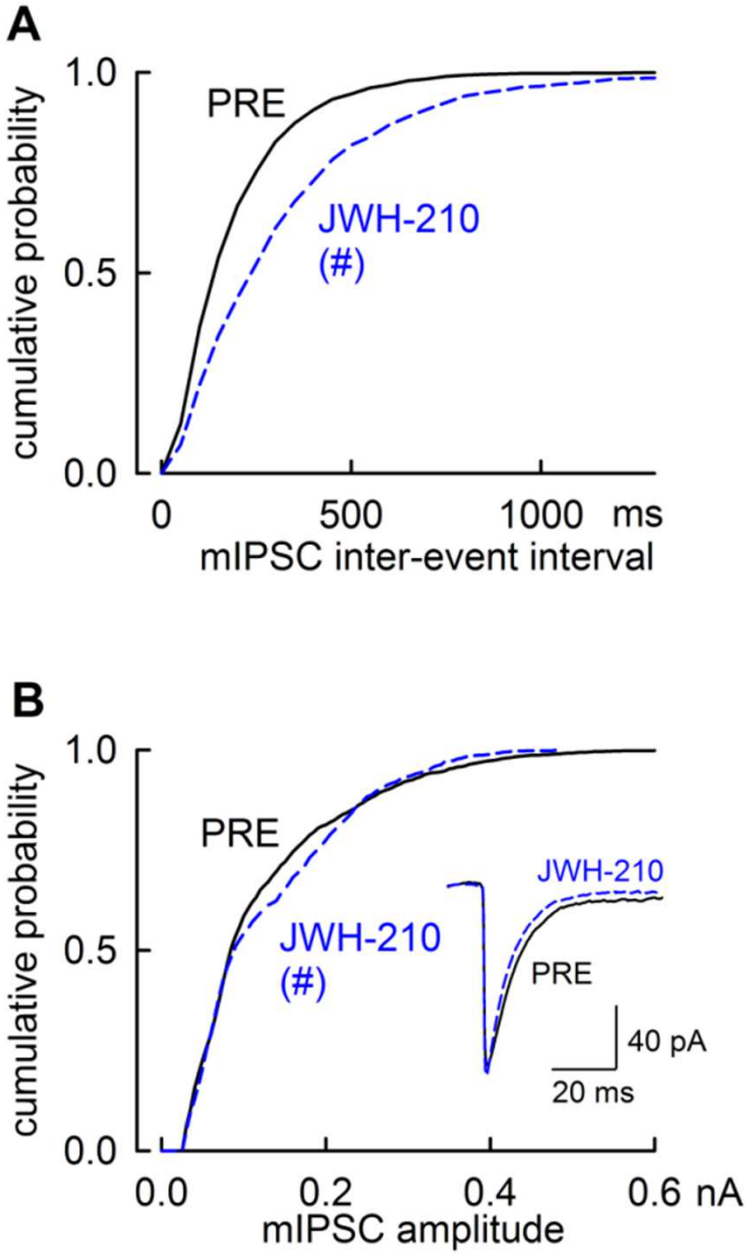
Poisons Information Center Freiburg, University Medical Center Freiburg, Freiburg, Germany,[1] Institute of Forensic Medicine, University Medical Center Freiburg, Freiburg, Germany[2] and Institute of Experimental and Clinical Pharmacology and Toxicology, University of Freiburg, Freiburg, Germany[3]

in all probability, higher than the percentage of first-time consumers within the complete user population and may indicate that first-time users are particularly vulnerable to the toxic effects of these compounds. A similar vulnerability may also be true for high-dose cannabis. This is suggested, for example, by reports on small children who developed pronounced adverse effects such as unconsciousness after accidental ingestion of Δ^9-THC [30,31]. In contrast to first-time consumers, regular consumers can have high concentrations of synthetic cannabinoids in their blood (up to 17 ng/ml of JWH-081 and 8 ng/ml of JWH-018) and are still devoid of toxic symptoms [64]. The lack of adverse effects in these patients suggests development of tolerance. Development of tolerance was also described in a patient after continued abuse of a product containing CP-47,497-C8 and JWH-018 [65]. Rapid and potent CB_1 receptor internalization was observed in *in-vitro* experiments with

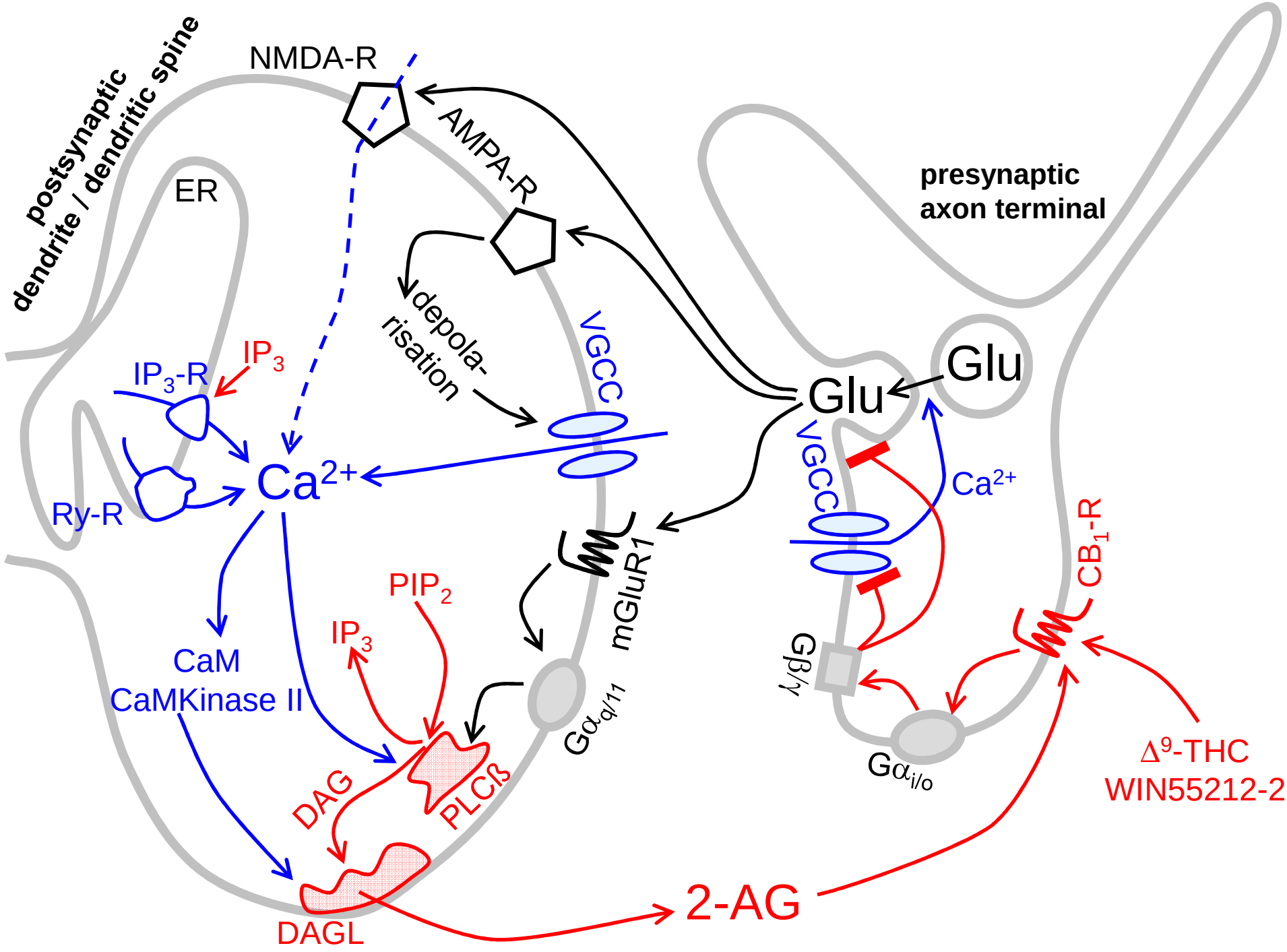
CONCLUSIONS

From 2008 to 2011 a shift to the extremely potent synthetic cannabinoids JWH-122 and JWH-210 occurred. One reason for this shift can be seen in changes in the legal control of these drugs, i.e. placing further substances under the German controlled substances legislation. In intoxications with herbal mixtures enriched with synthetic cannabinoids, symptoms were mostly similar to adverse effects after high-dose cannabis. However, agitation, seizures, hypertension, emesis and hypokalaemia also occurred—symptoms which are usually not seen even after high doses of cannabis. It is likely that these symptoms were due to strong stimulation of CB_1 receptors, because the synthetic cannabinoids are high-affinity and high-efficacy agonists of the CB_1 receptor. Our results suggest that the synthetic cannabinoids elicit more serious acute adverse effects than cannabis products.

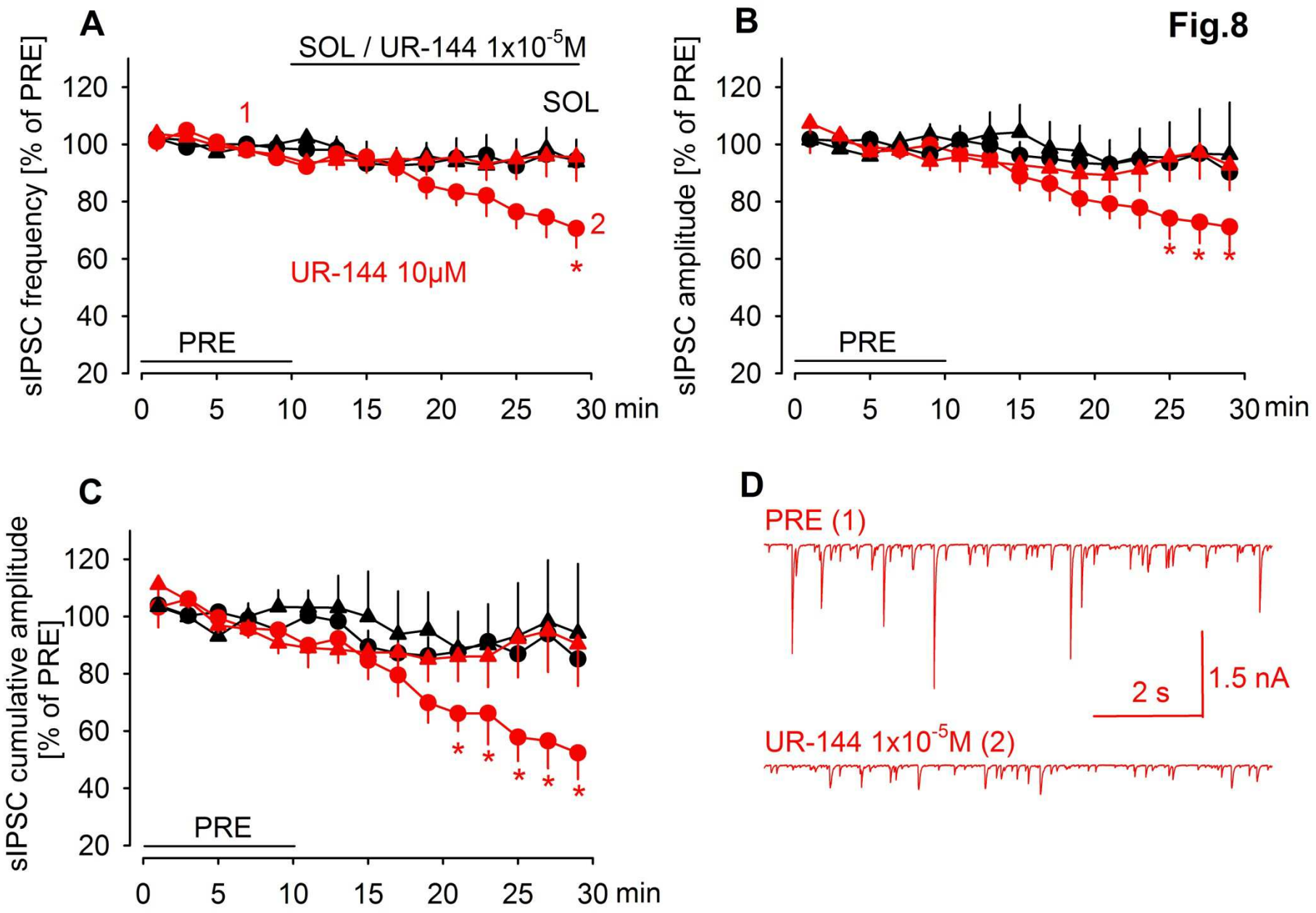
JWH-210 suppresses mIPSCs



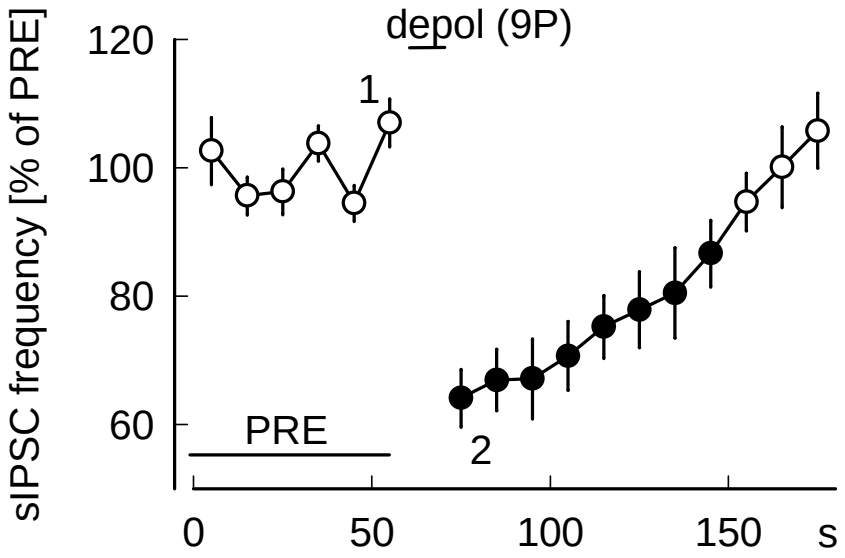
mIPSC = miniature inhibitory postsynaptic currents

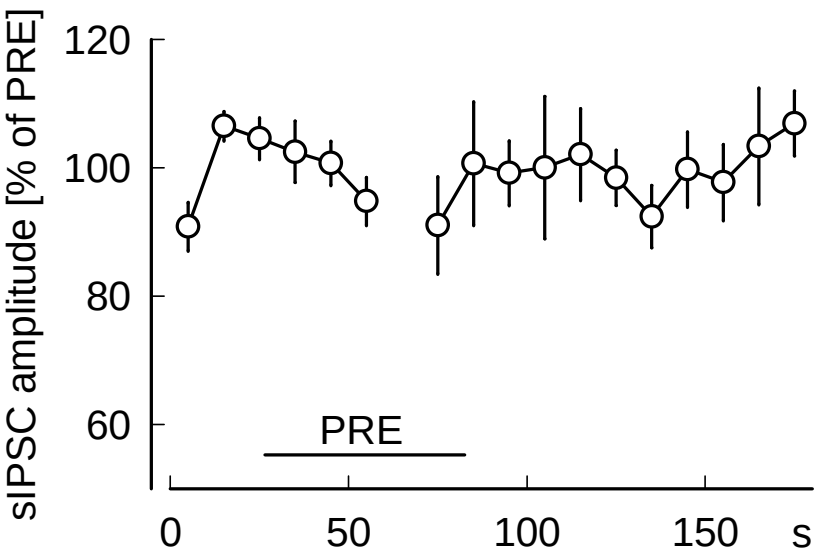

postsynaptic
dendrite / dendritic spine
NMDA-R
AMPA-R
ER
depola-
risation
VGCC
IP3-R
IP3
Ca2+
Ry-R
CaM
CaMKinase II
PIP2
IP3
DAG
PLCβ
DAGL
mGluR1
Gαq/11
presynaptic
axon terminal
Glu
Glu
VGCC
Ca2+
CB1-R
Gβ/γ
Gαi/o
Δ9-THC
WIN55212-2
2-AG

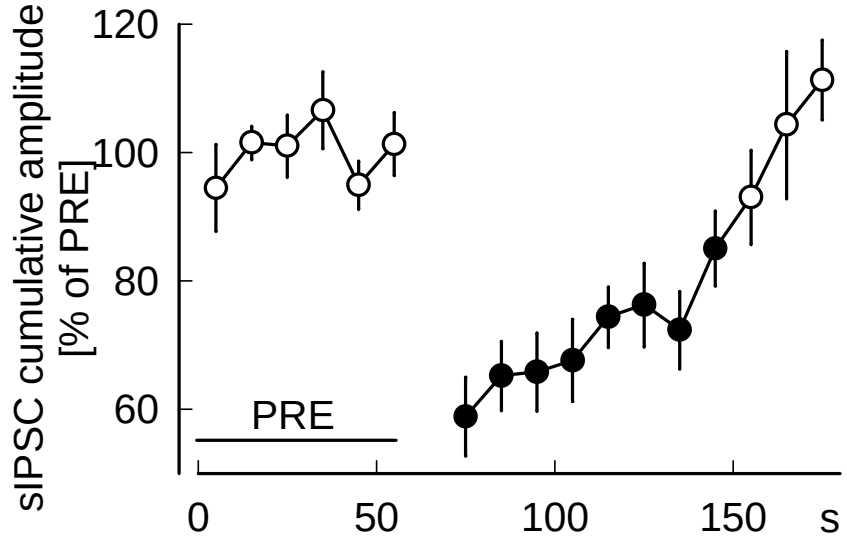
UR-144 inhibits GABAergic synaptic transmission

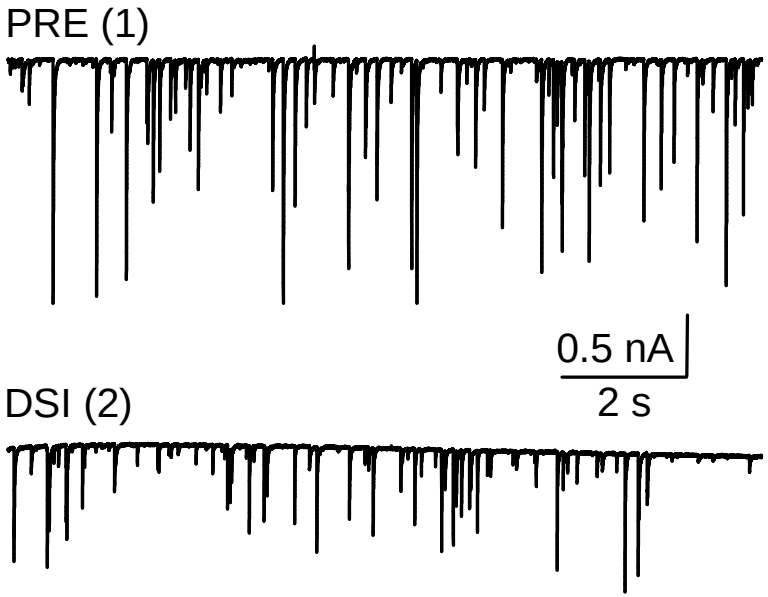


Depolarisation-induced suppression of inhibition (DSI)









Synthetic cannabinoids from John William Huffman: JWH-compounds

Pergamon

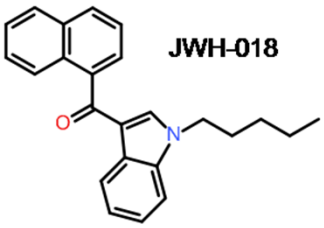
SCIENCE DIRECT®

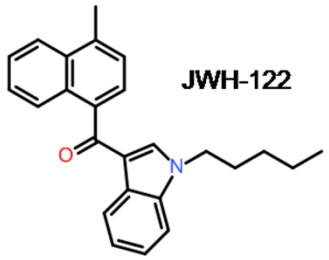
Bioorganic & Medicinal Chemistry 11 (2003) 539–549

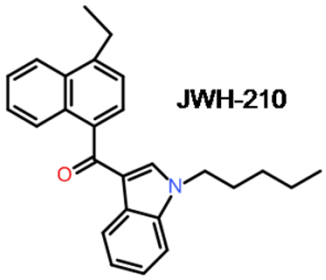
BIOORGANIC & MEDICINAL CHEMISTRY

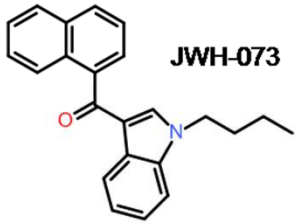
3-Indolyl-1-naphthylmethanes: New Cannabimimetic Indoles Provide Evidence for Aromatic Stacking Interactions with the CB_1 Cannabinoid Receptor

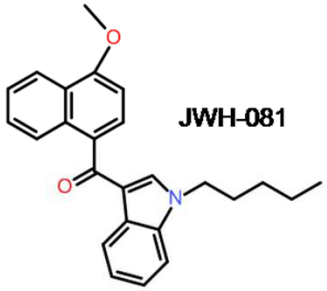
John W. Huffman,[a,*] Ross Mabon,[a] Ming-Jung Wu,[a] Jianzhong Lu,[a] Richard Hart,[b] Dow P. Hurst,[b] Patricia H. Reggio,[b] Jenny L. Wiley[c] and Billy R. Martin[c]

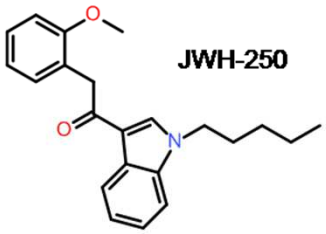


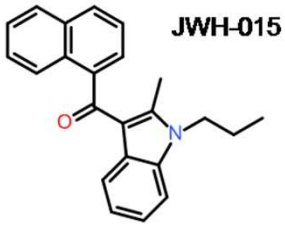


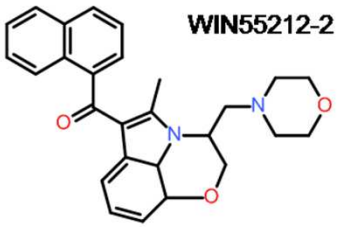


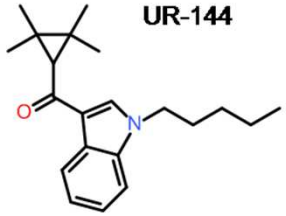


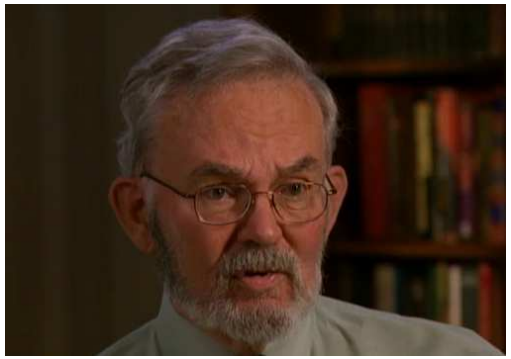




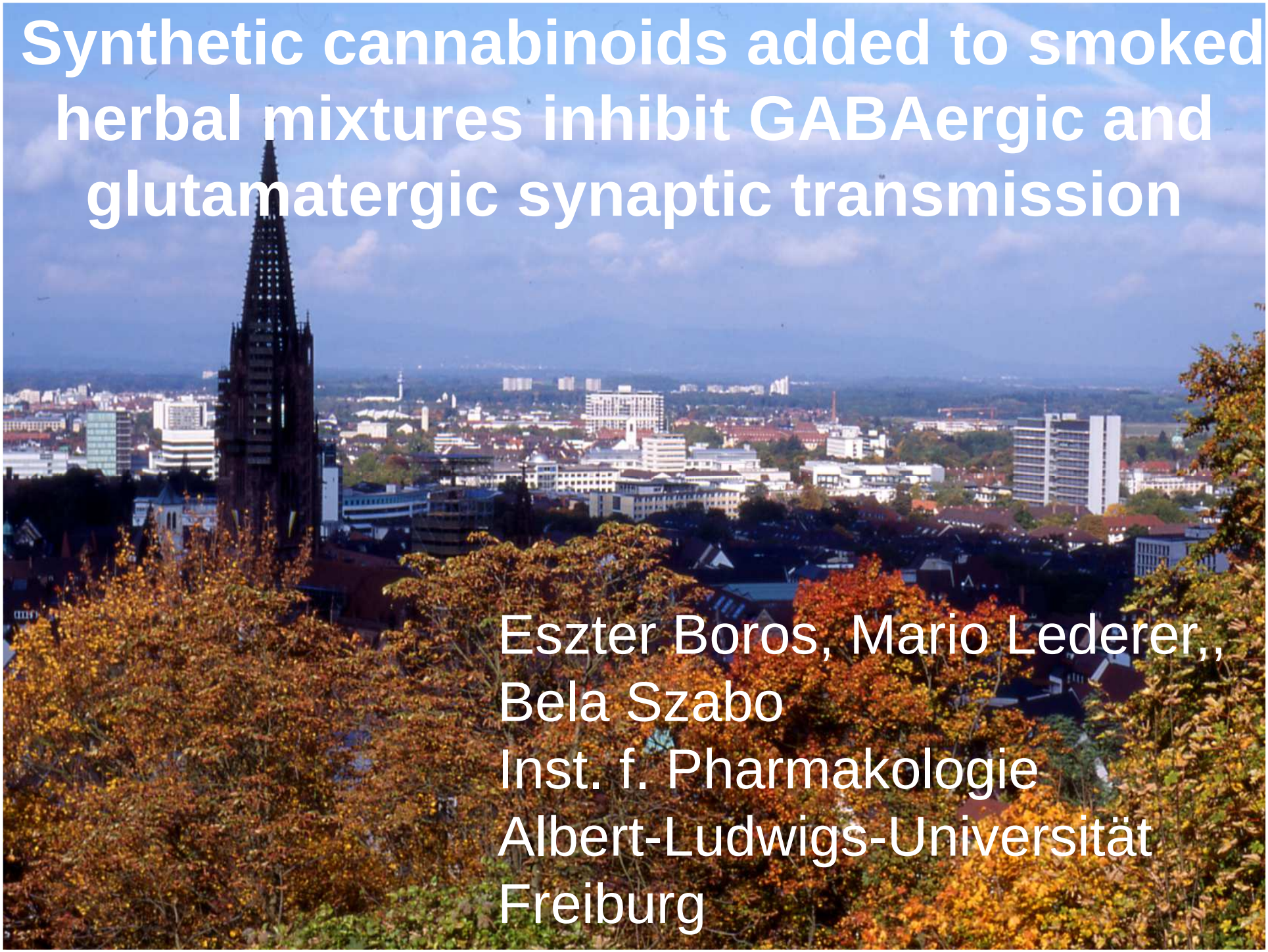








Synthetic cannabinoids added to smoked herbal mixtures inhibit GABAergic and glutamatergic synaptic transmission



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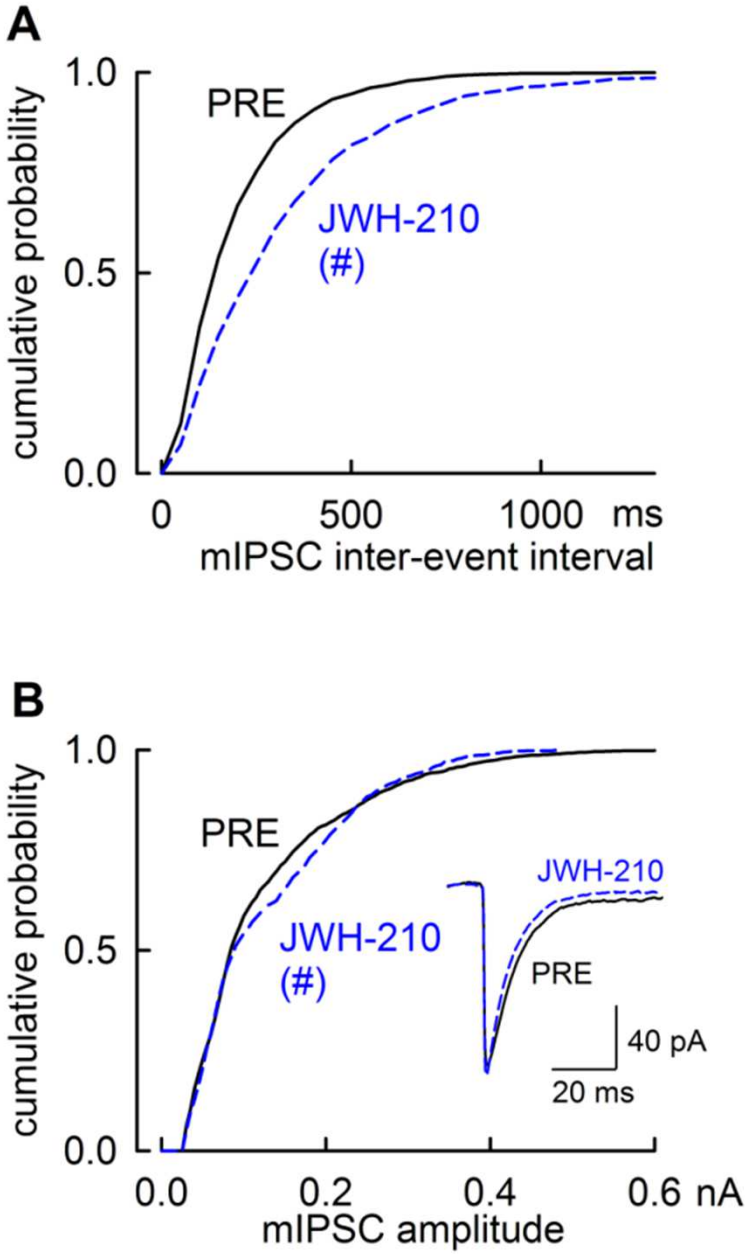
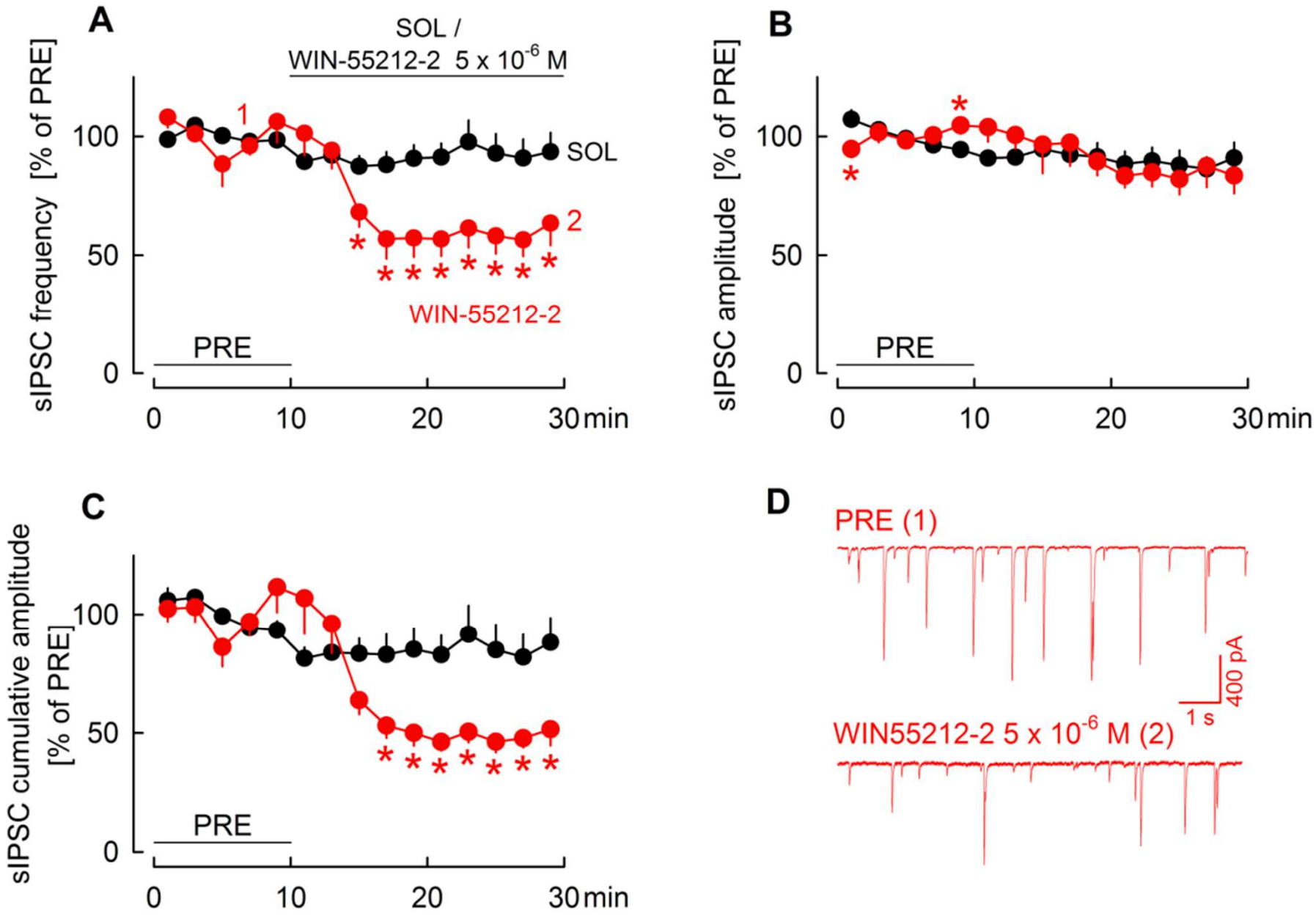
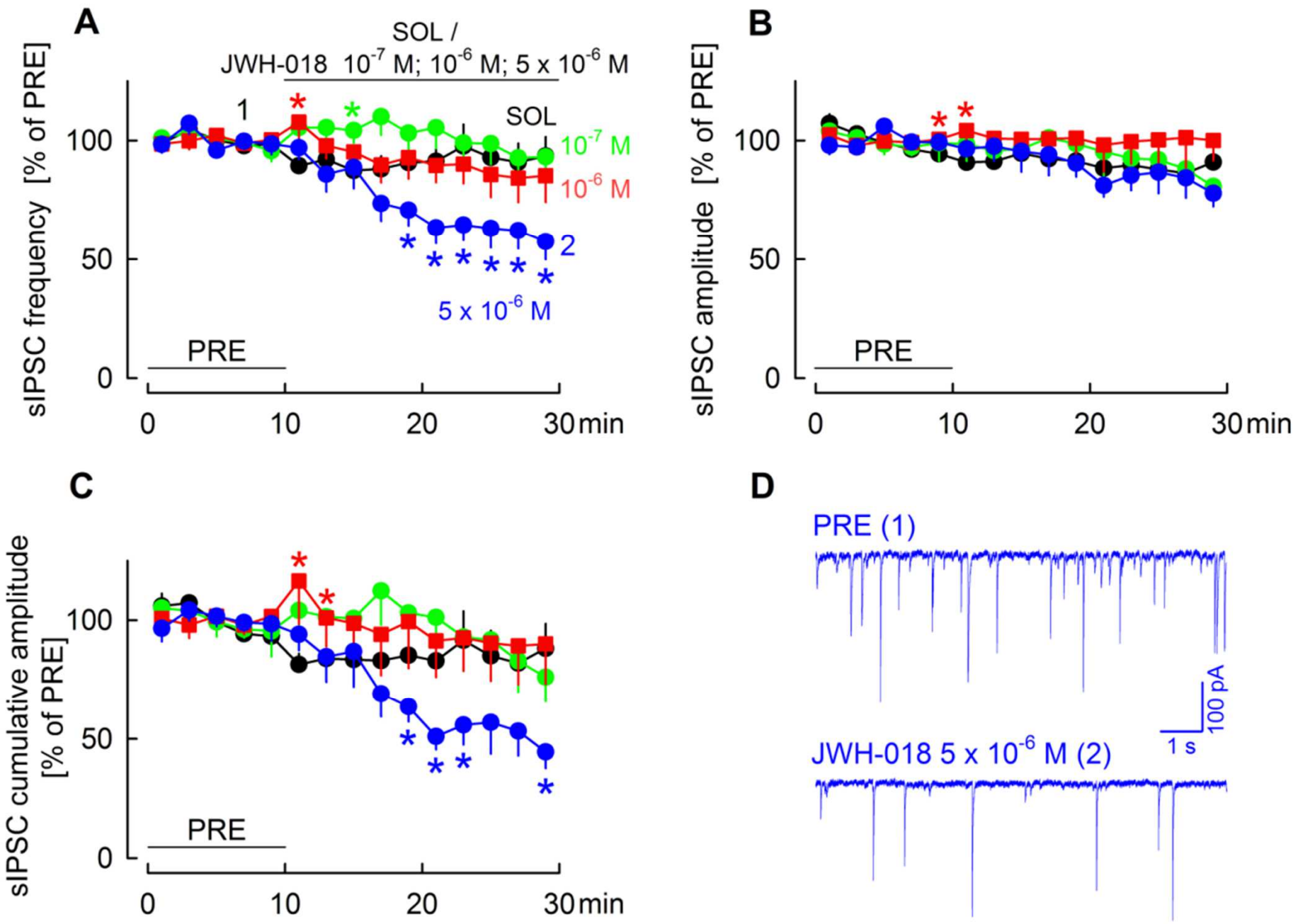
Freiburg

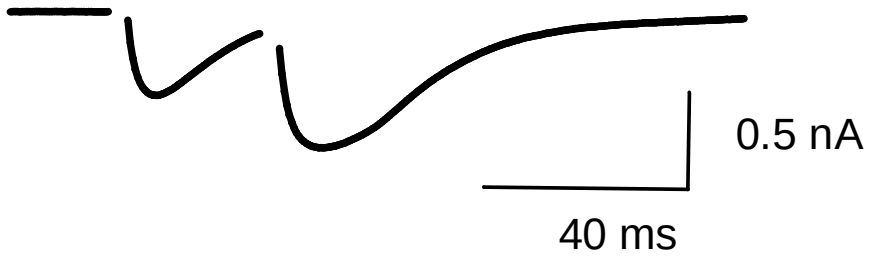
JWH-210 suppresses mIPSCs



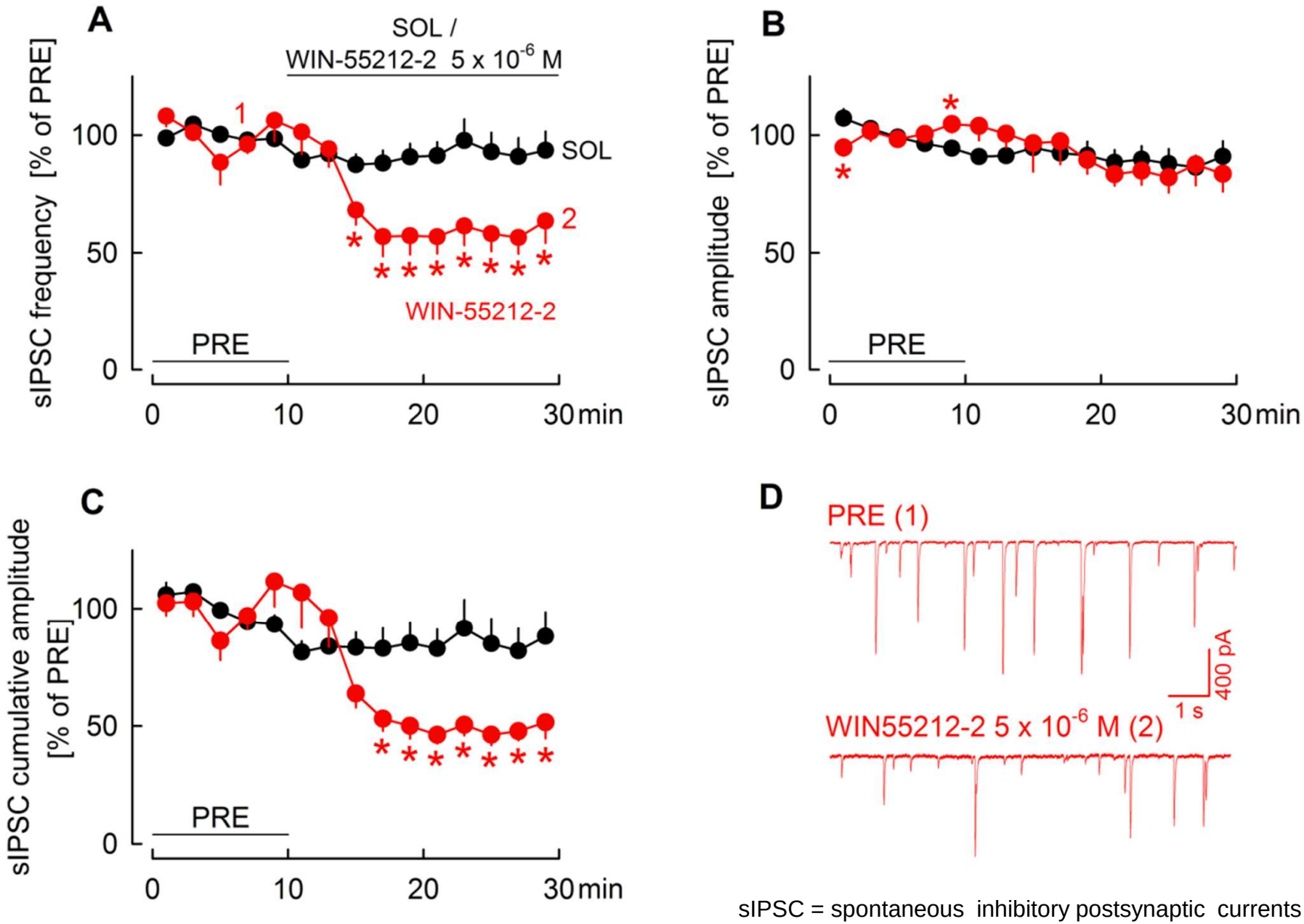
mIPSC = miniature inhibitory postsynaptic currents


A
SOL /
WIN-55212-2 5 x 10-6 M
sIPSC frequency [% of PRE]
100
50
0
1
2
SOL
WIN-55212-2
PRE
0
10
20
30 min
B
sIPSC amplitude [% of PRE]
100
50
0
PRE
0
10
20
30 min
C
sIPSC cumulative amplitude [% of PRE]
100
50
0
PRE
0
10
20
30 min
D
PRE (1)
400 pA
1 s
WIN55212-2 5 x 10-6 M (2)


A
SOL /
JWH-018 10-7 M; 10-6 M; 5 x 10-6 M
sIPSC frequency [% of PRE]
100
50
0
1
SOL
10-7 M
10-6 M
2
5 x 10-6 M
PRE
0
10
20
30 min
B
sIPSC amplitude [% of PRE]
100
50
0
PRE
0
10
20
30 min
C
sIPSC cumulative amplitude [% of PRE]
100
50
0
PRE
0
10
20
30 min
D
PRE (1)
100 pA
1 s
JWH-018 5 x 10-6 M (2)

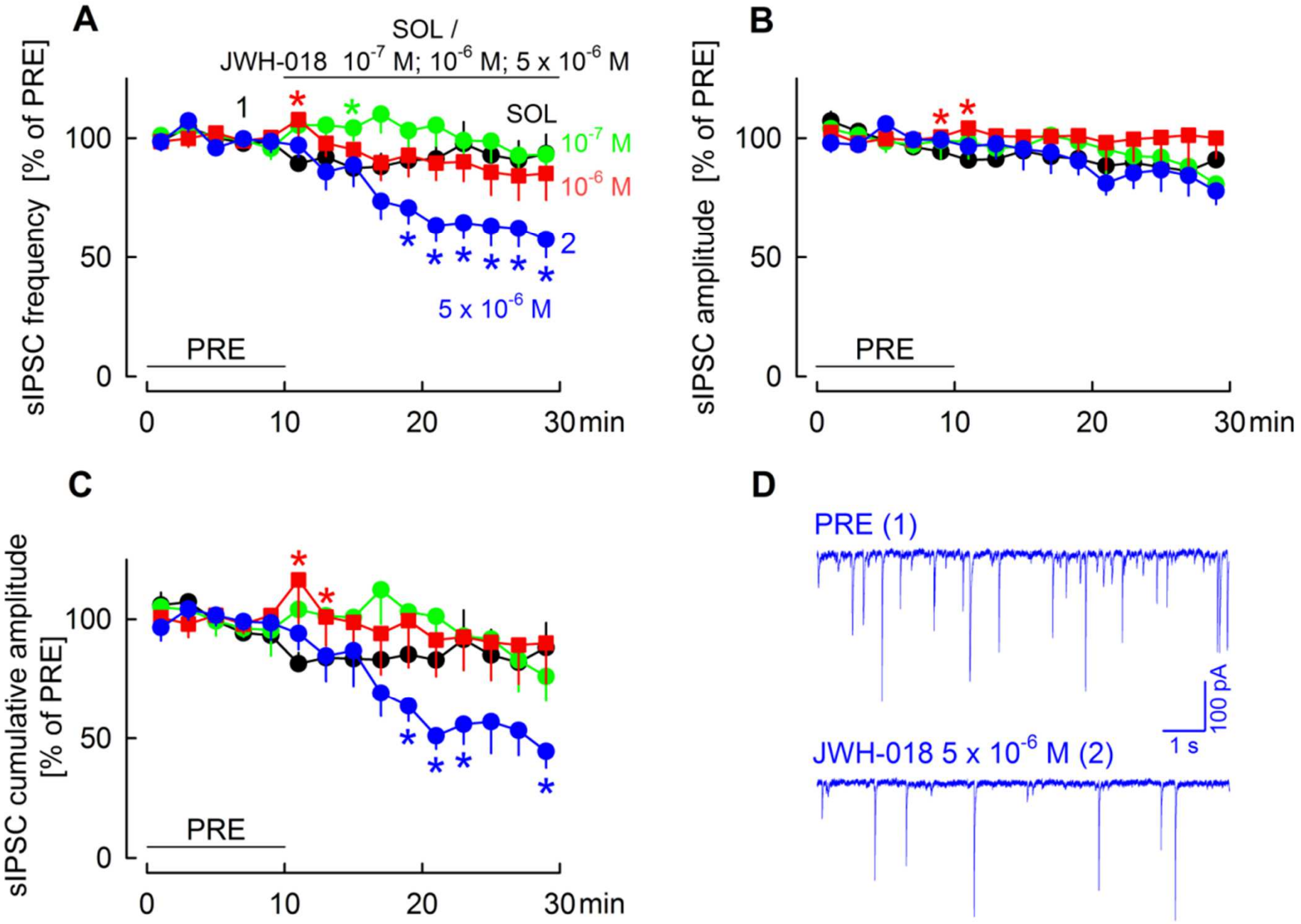

0.5 nA
40 ms

WIN55212-2 inhibits GABAergic synaptic transmission



sIPSC = spontaneous inhibitory postsynaptic currents

JWH-018 inhibits GABAergic synaptic transmission



Synthetic cannabinoids added to smoked herbal mixtures inhibit GABAergic and glutamatergic synaptic transmission

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Eszter Boros
Martin Brehm

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Aim of the study: characterization of the neuronal effect of synthetic cannabinoids