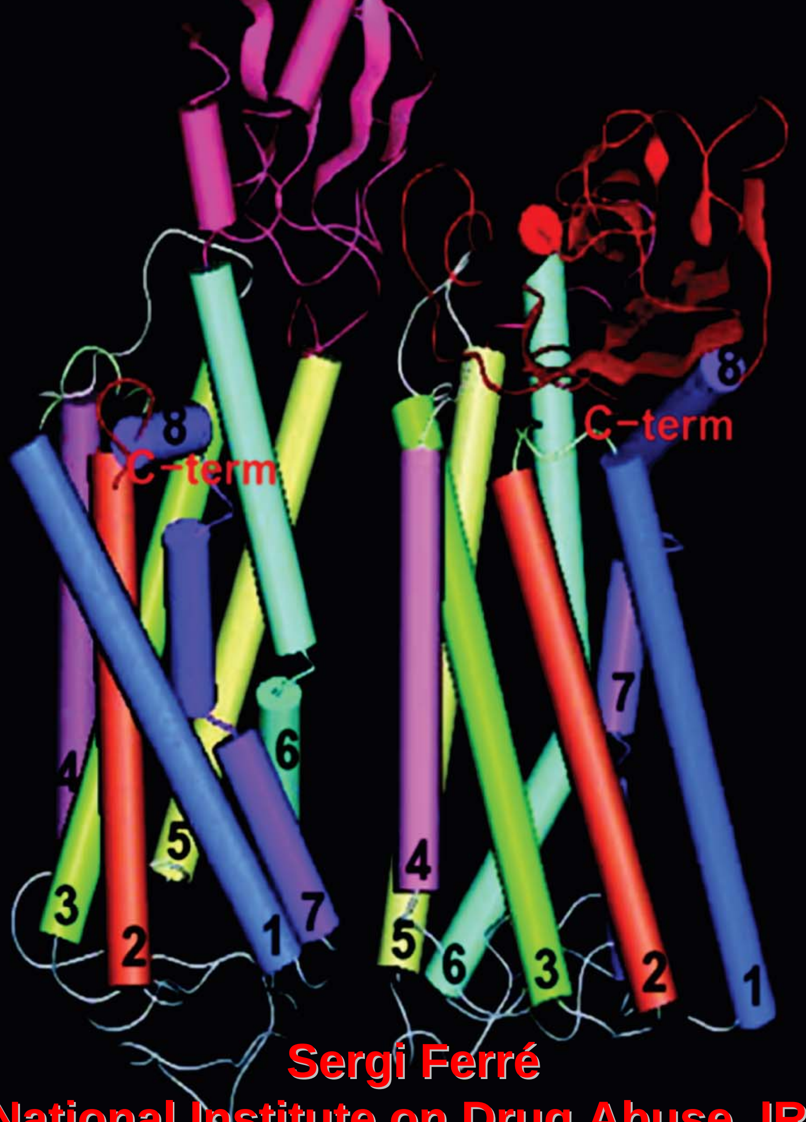
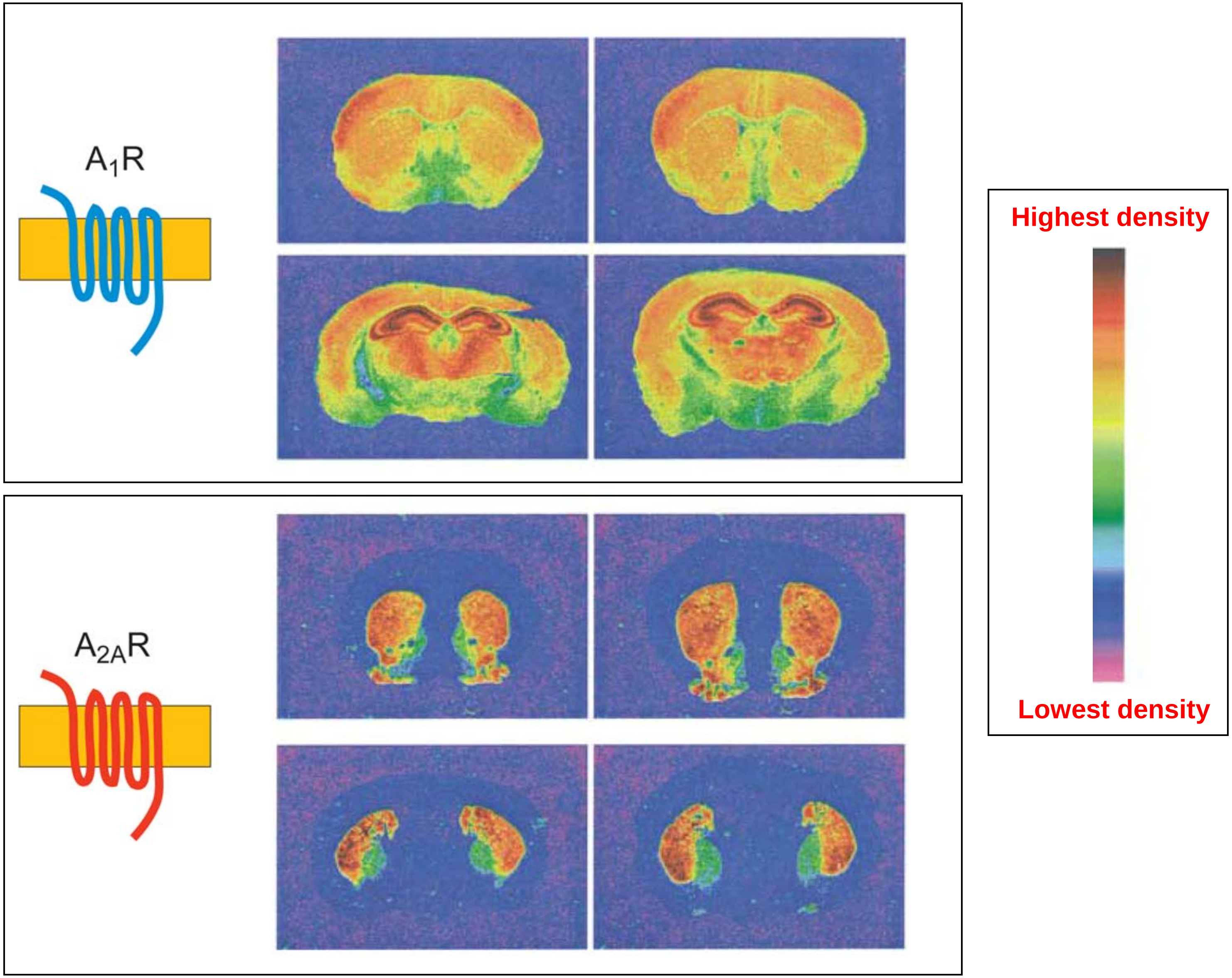
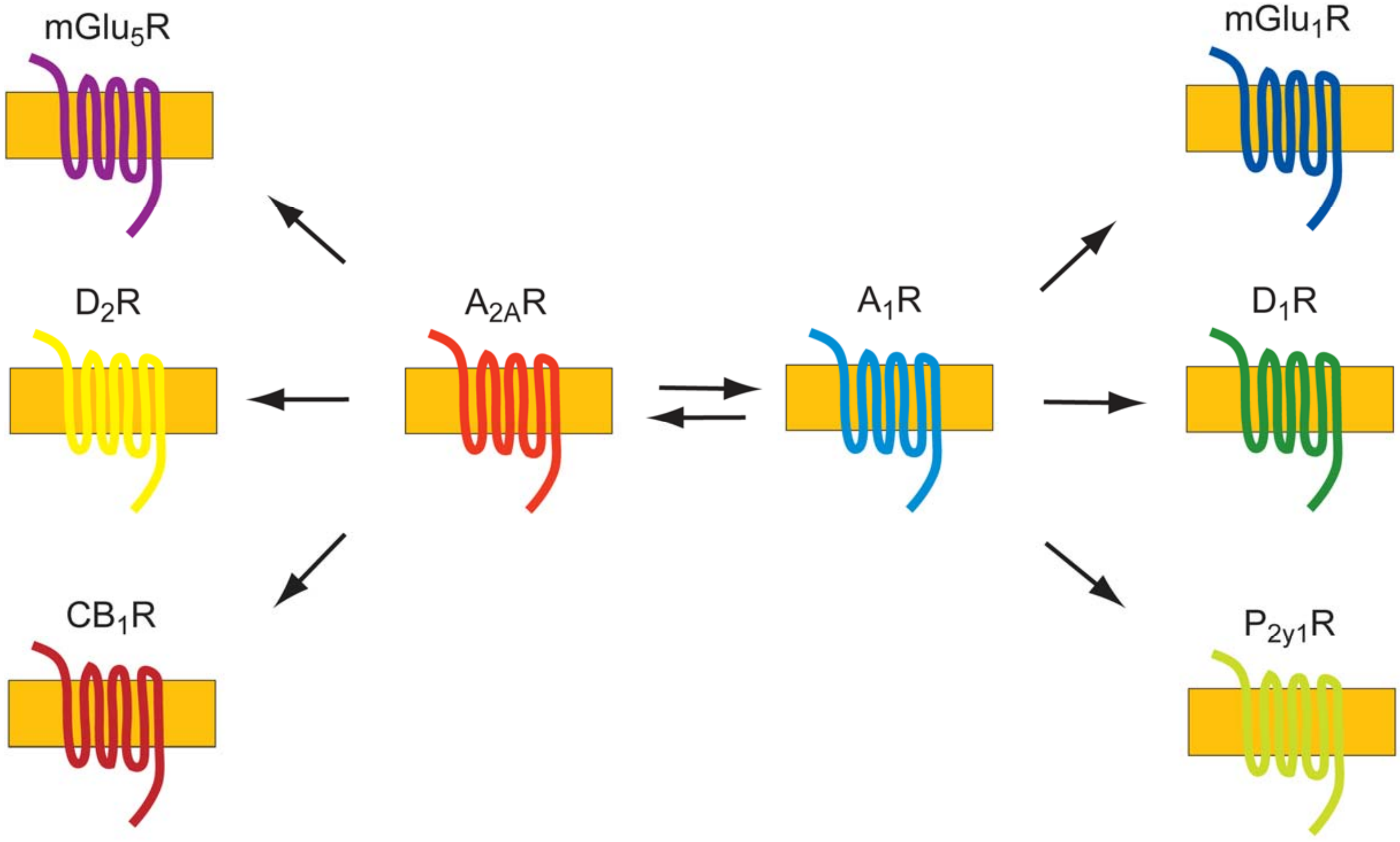
Adenosine Receptor Heteromers and their Integrative Role in Striatal Function

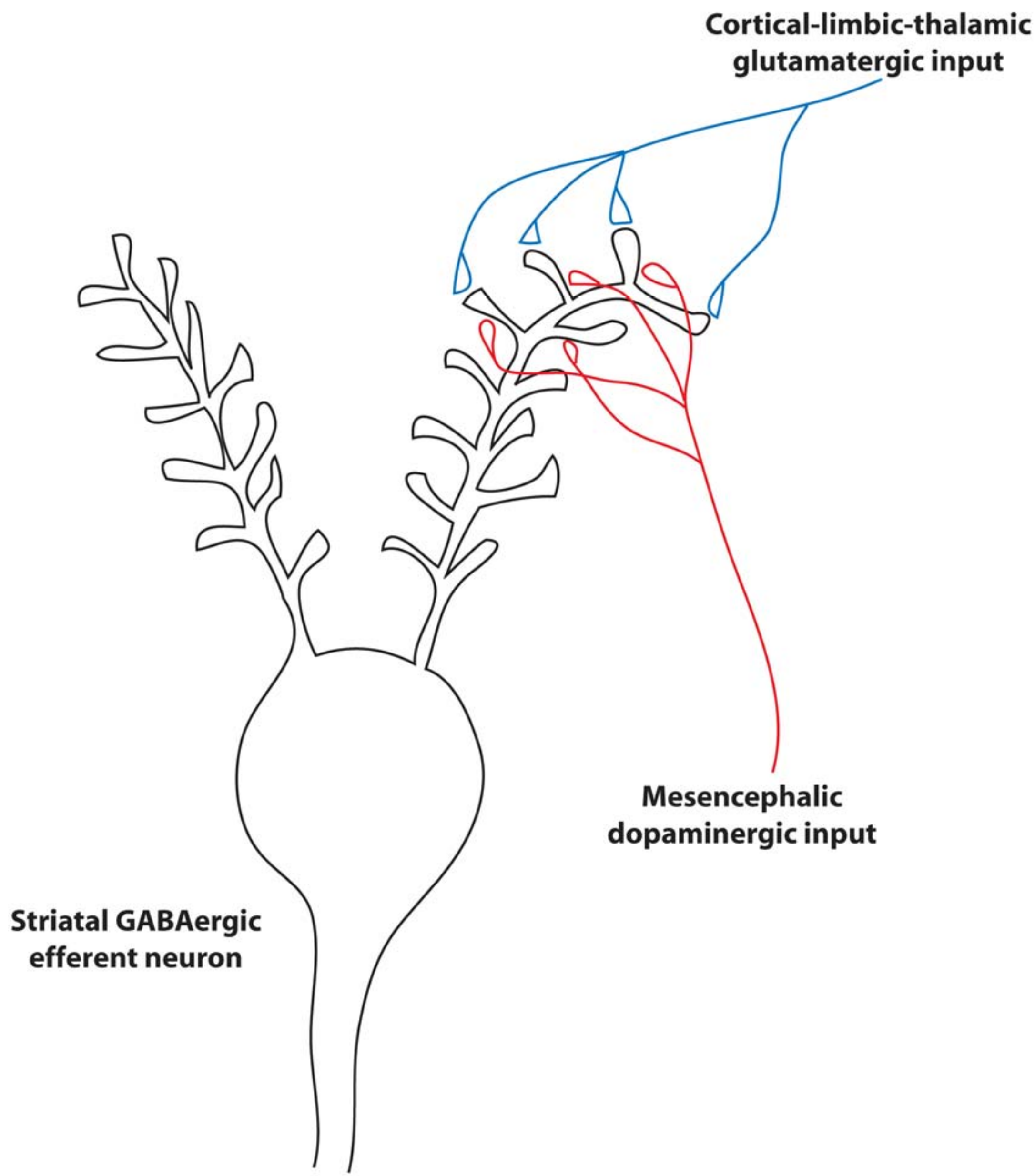


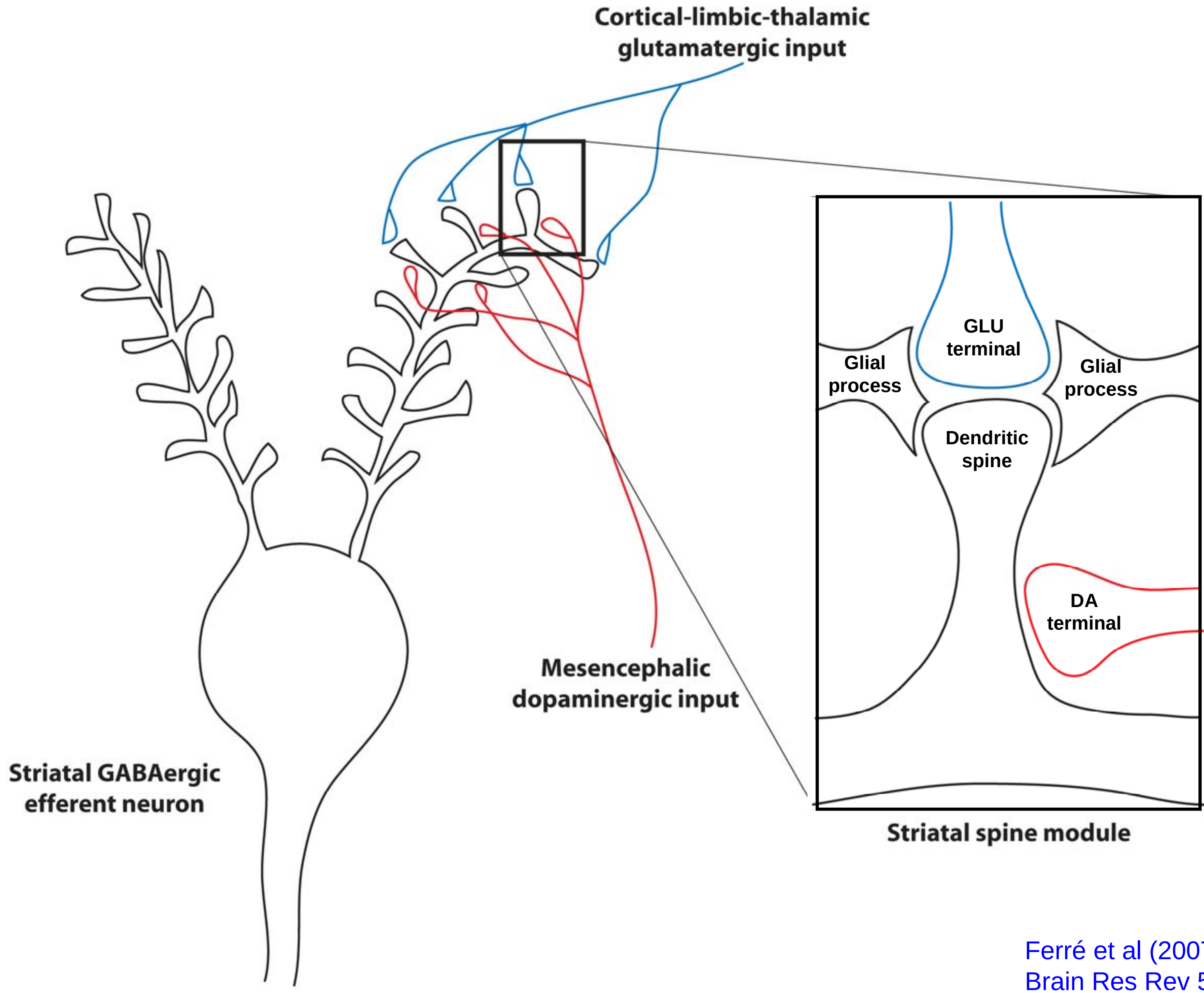
Sergi Ferré
National Institute on Drug Abuse, IRP
NIH, DHHS, Baltimore, MD, USA



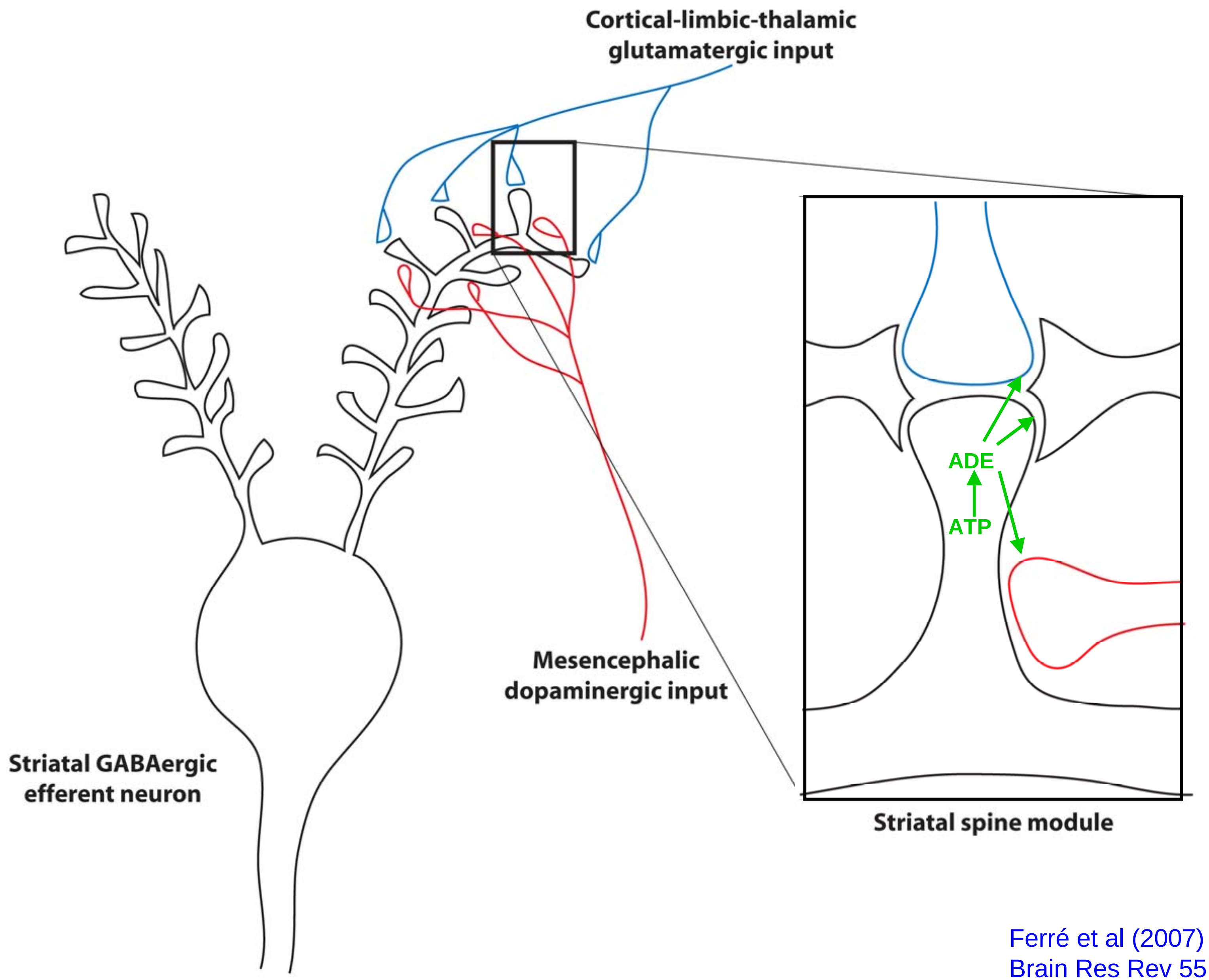
Bailey et al (2002)
Brain Res 94: 68-79


mGlu5R
D2R
CB1R
A2AR
A1R
mGlu1R
D1R
P2y1R

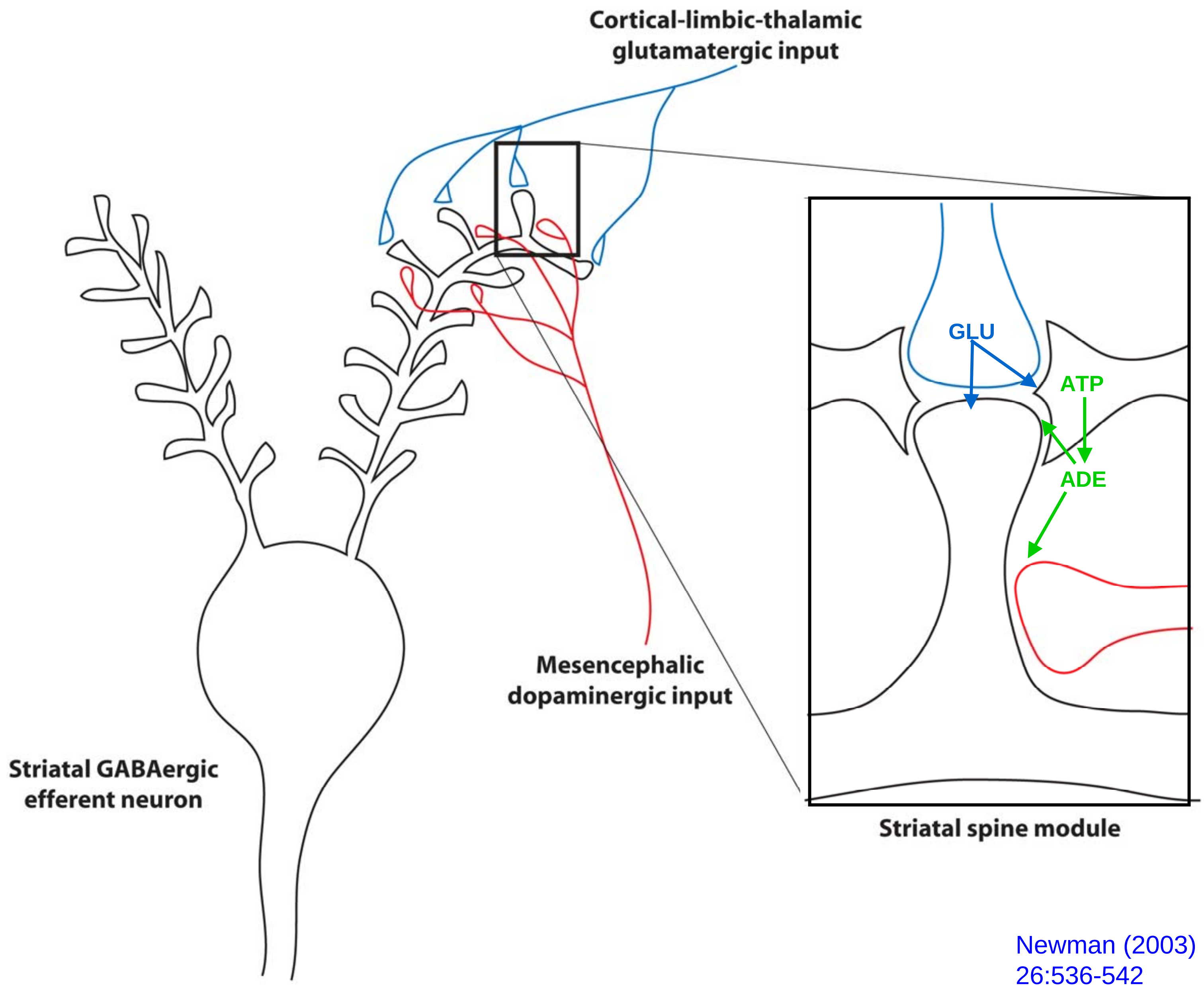

Cortical-limbic-thalamic glutamatergic input
Mesencephalic dopaminergic input
Striatal GABAergic efferent neuron



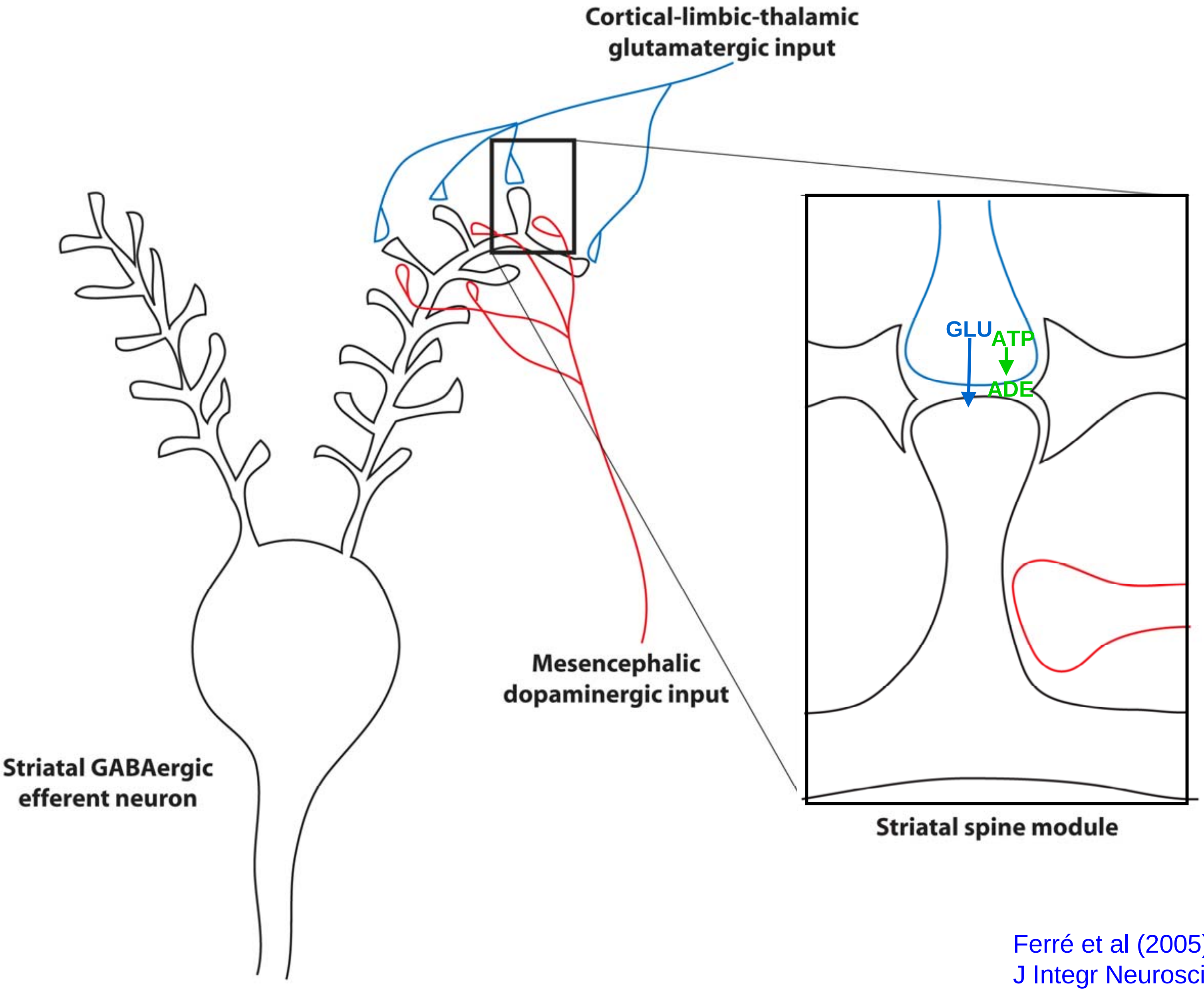
Ferré et al (2007)
Brain Res Rev 55:55-67



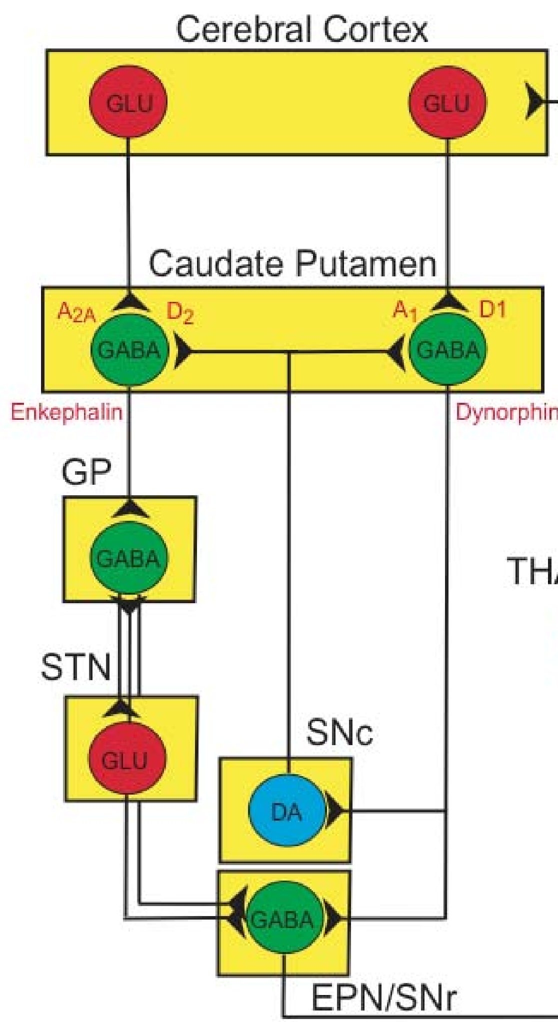
Ferré et al (2007)
Brain Res Rev 55:55-67



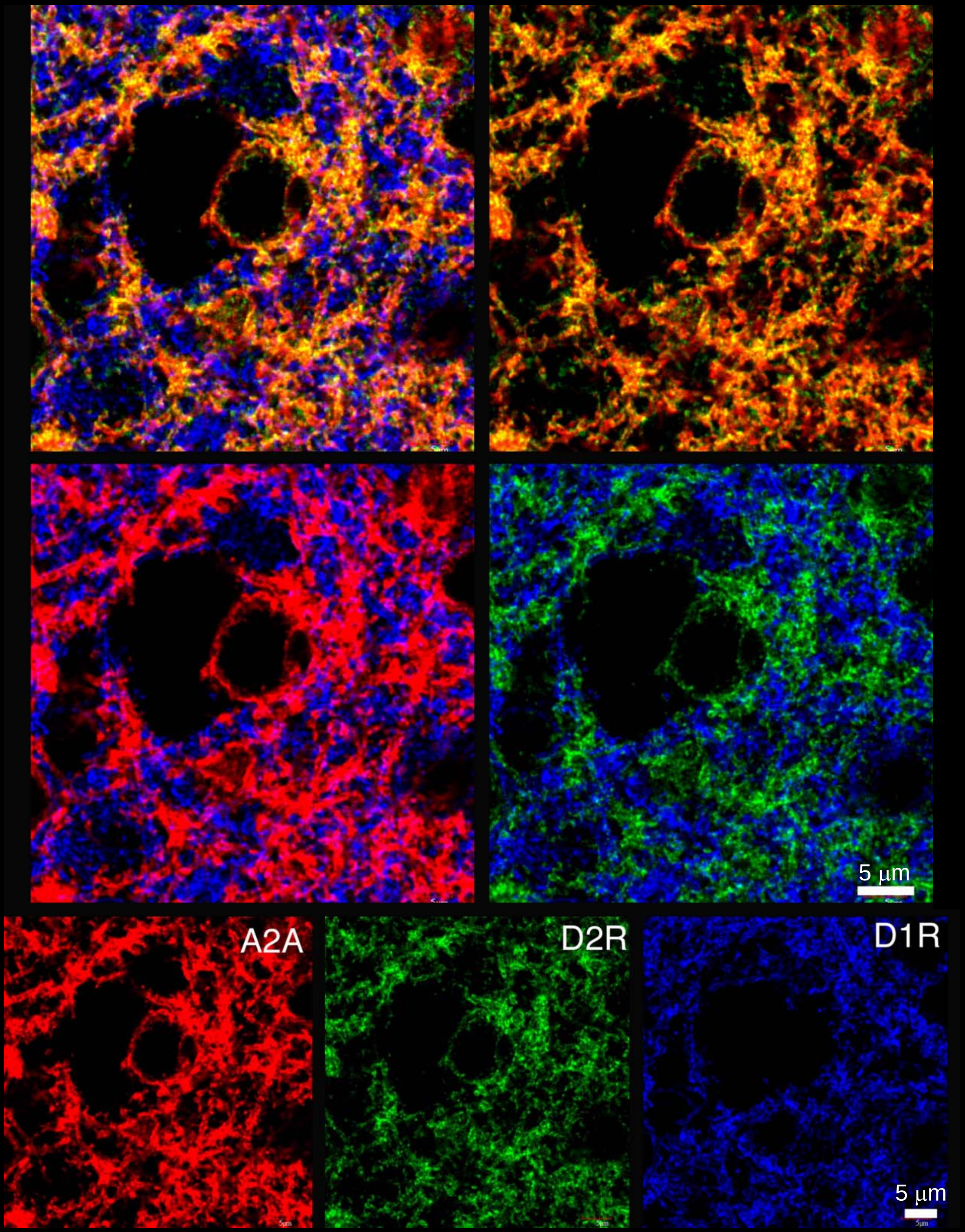
Newman (2003) Trends Neurosci 26:536-542
Pascual et al (2005) Science 310:113-116



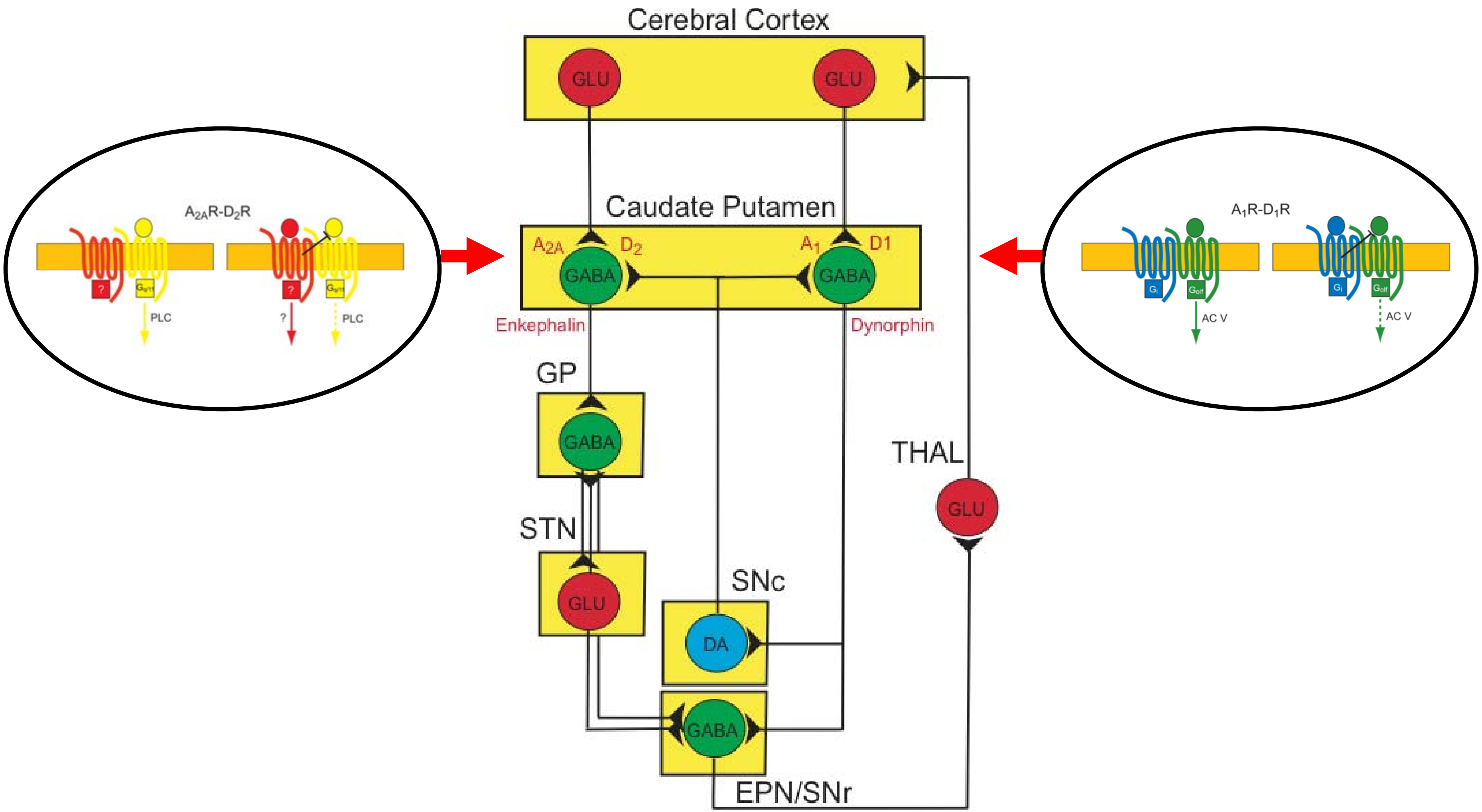
Ferré et al (2005)
J Integr Neurosci 4:445-464



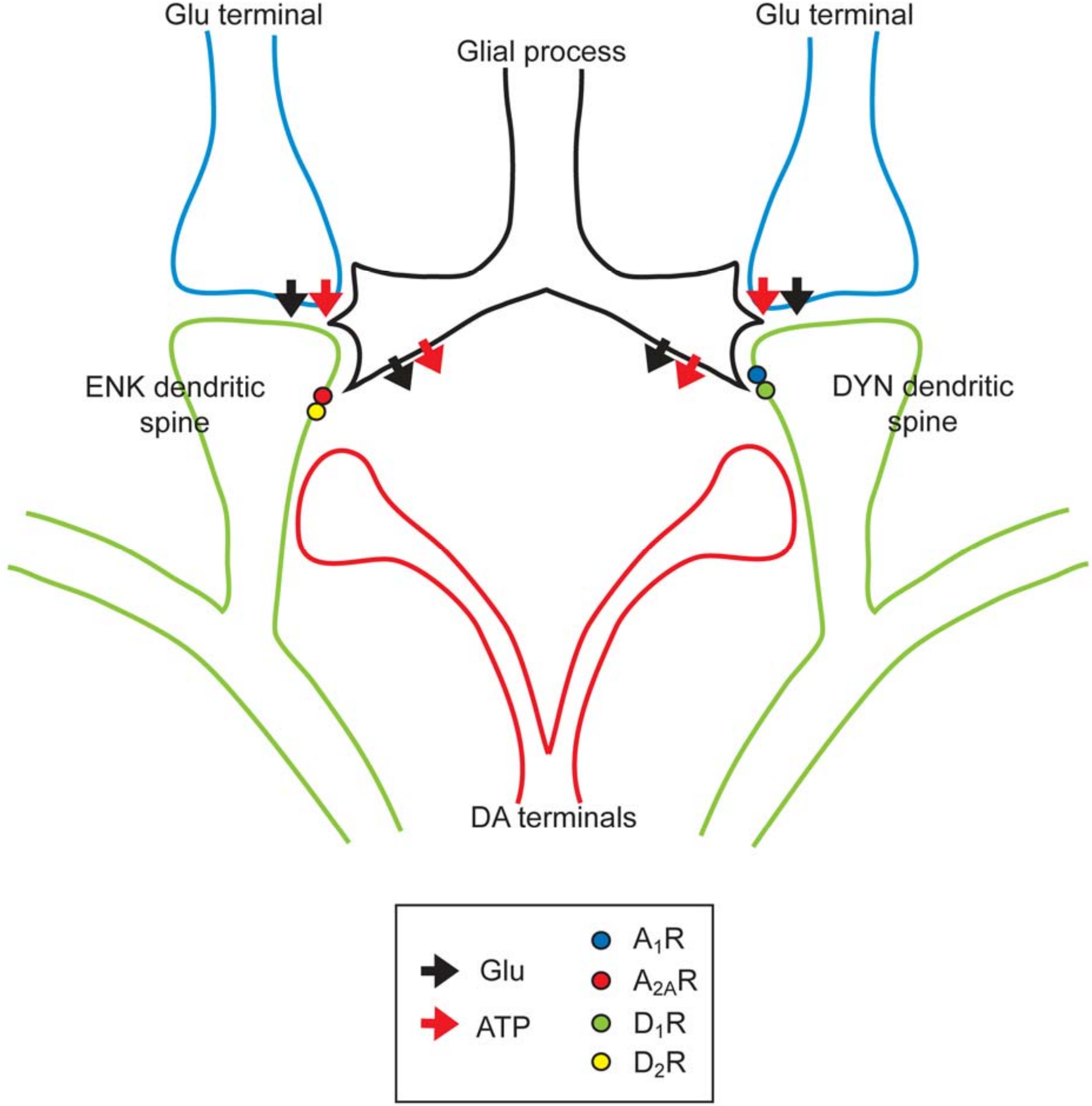
Cerebral Cortex
GLU
GLU
Caudate Putamen
A_{2A}
D_2
A_1
D1
GABA
GABA
Enkephalin
Dynorphin
GP
GABA
THAL
GLU
STN
GLU
SNc
DA
GABA
EPN/SNr

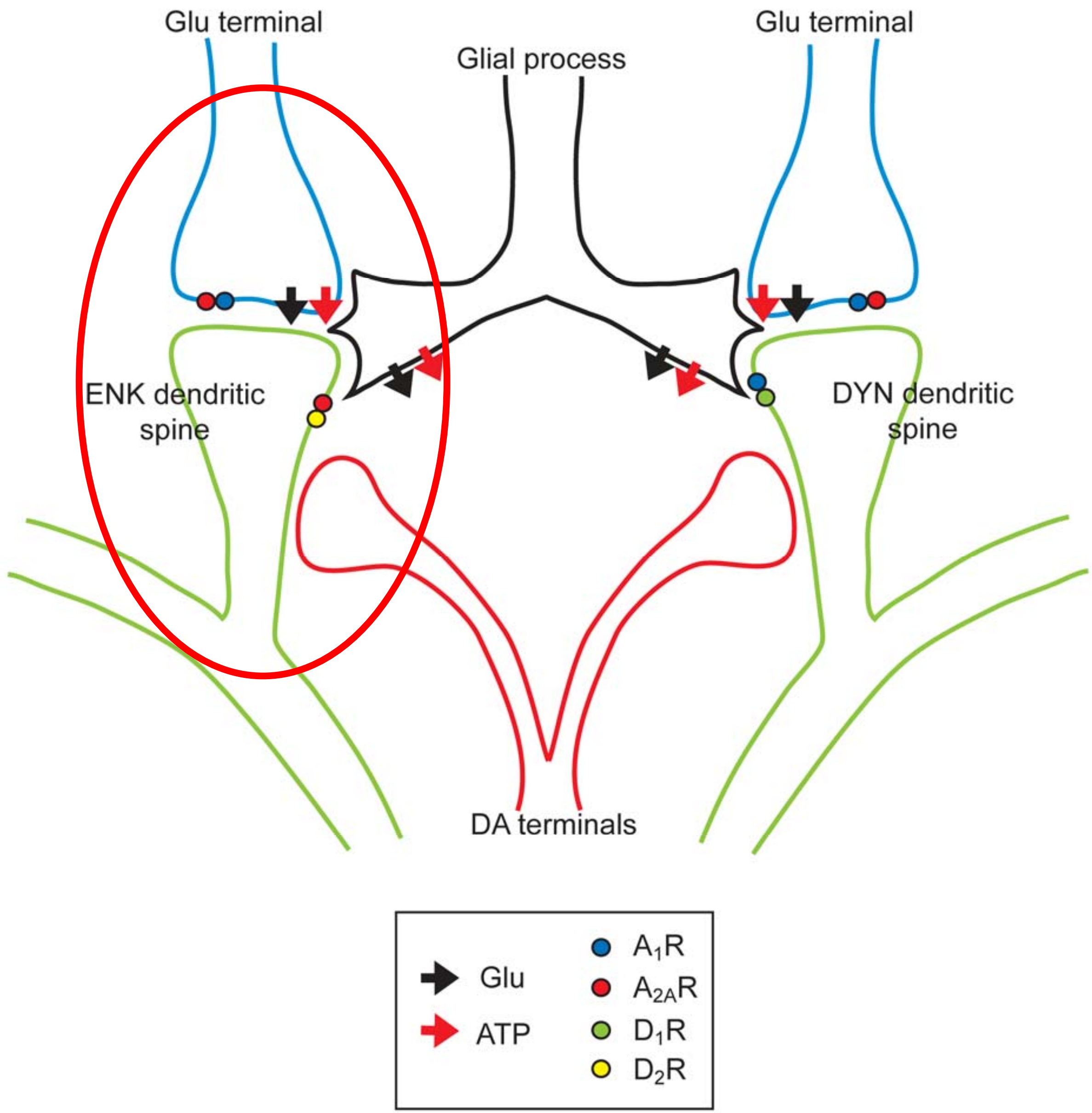


Watanabe et al.
in preparation

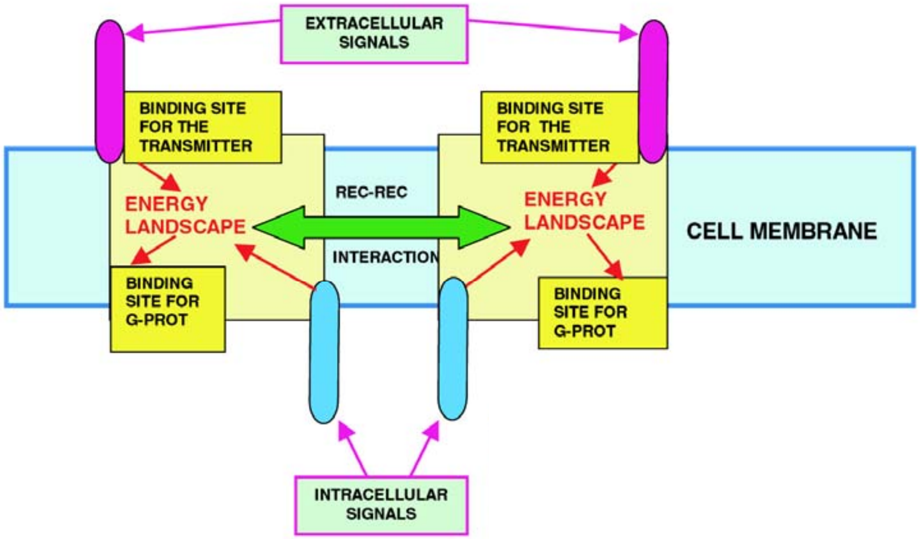


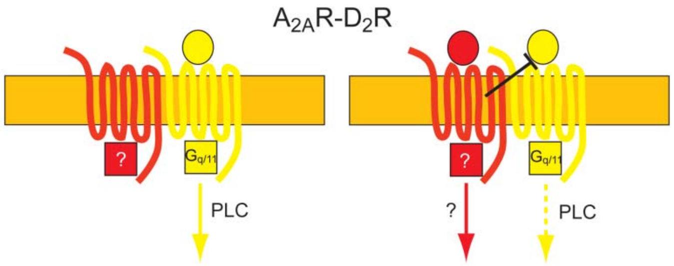
Cerebral Cortex
GLU
GLU
Caudate Putamen
A2A
D2
A1
D1
GABA
GABA
Enkephalin
Dynorphin
GP
GABA
STN
GLU
SNc
DA
GABA
EPN/SNr
THAL
GLU
A2AR-D2R
PLC
?
PLC
A1R-D1R
AC V
AC V

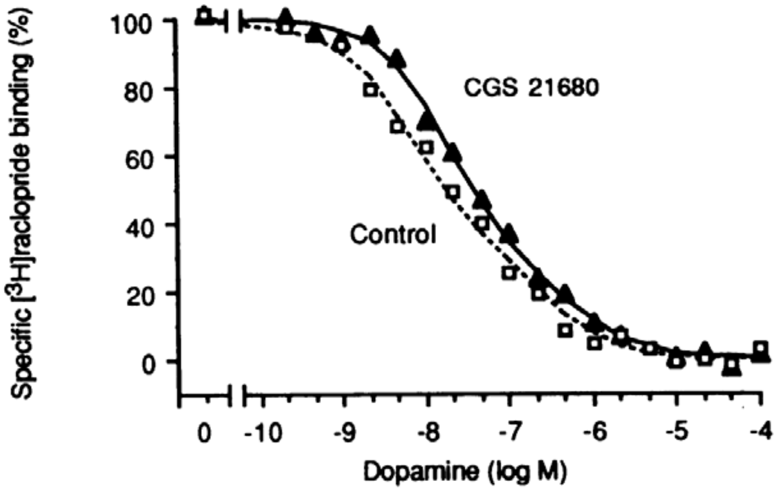

Glu terminal
Glial process
Glu terminal
ENK dendritic spine
DYN dendritic spine
DA terminals
Glu
ATP
A_1R
$A_{2A}R$
D_1R
D_2R


Glu terminal
Glial process
Glu terminal
ENK dendritic spine
DYN dendritic spine
DA terminals
Glu
ATP
A_1R
$A_{2A}R$
D_1R
D_2R

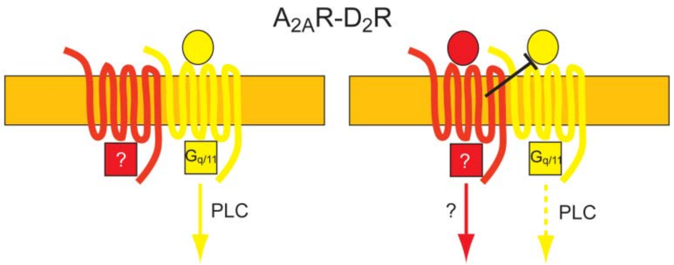
Intramembrane Receptor-Receptor Interactions

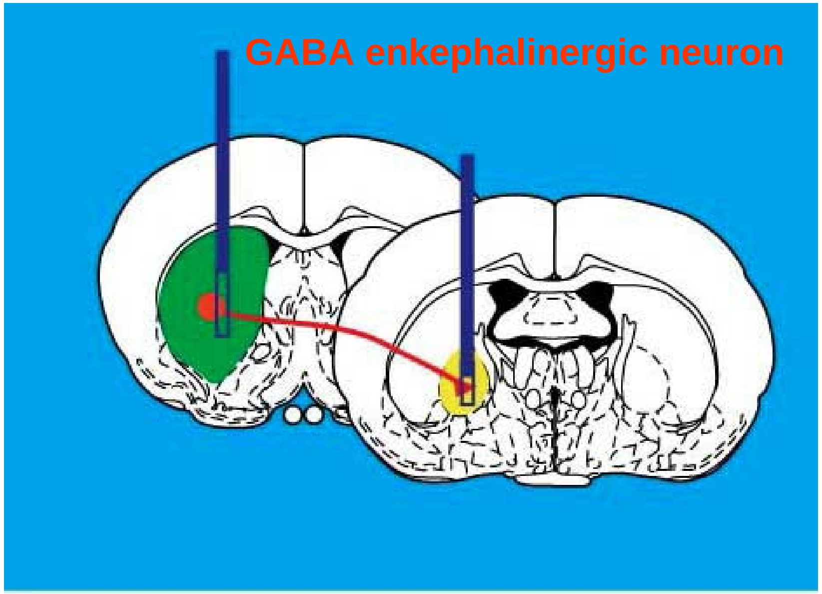


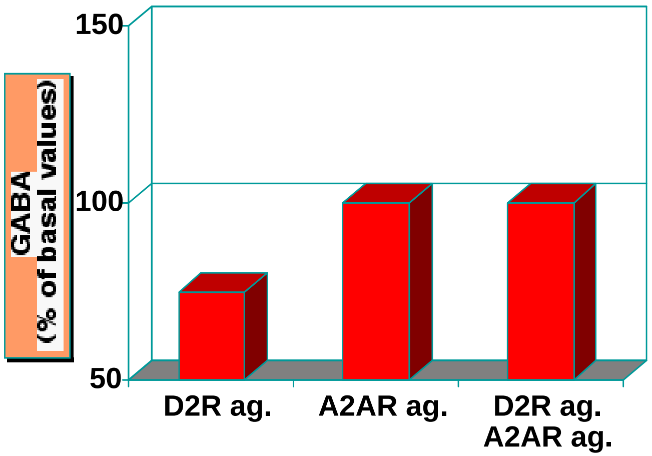




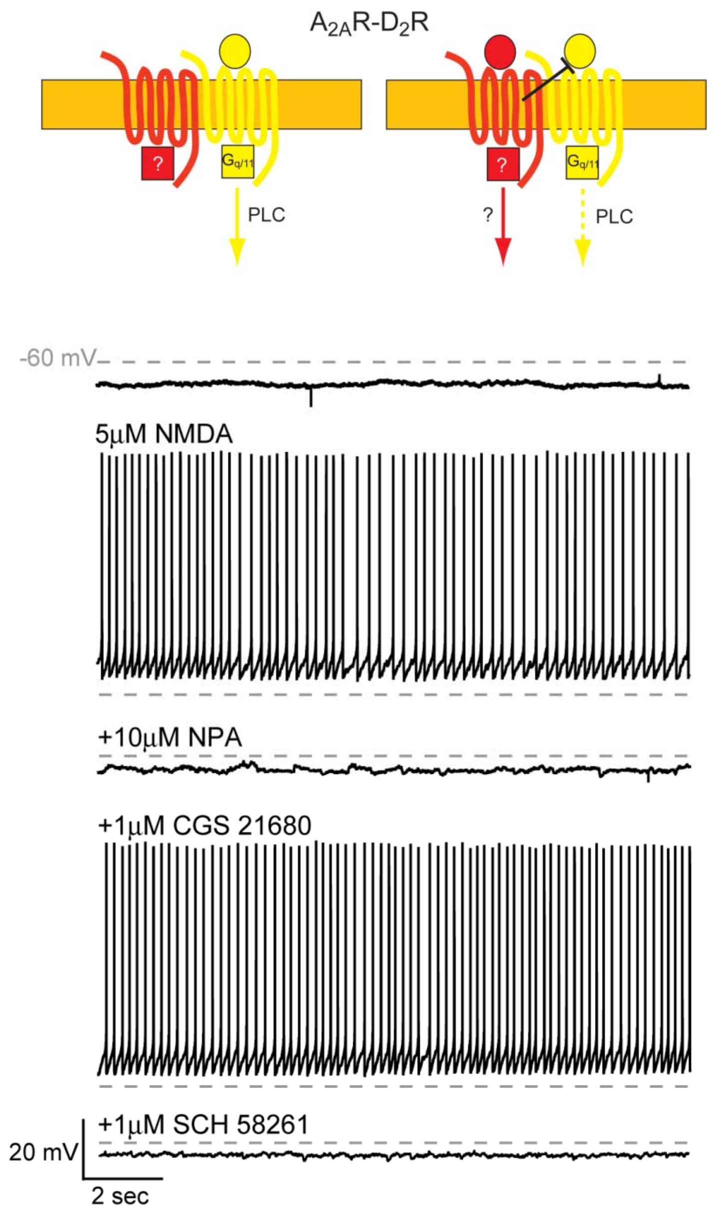
Rat striatal tissue: Ferré et al (1991) Proc Natl Acad Sci USA 88:7238-7241; Dixon et al (1997) J Neurochem 69:315-321
Human striatal tissue: Diaz-Cabiale et al (2001) Neuroreport 12:1831-1834
Ltk^- fibroblast cells: Dasgupta et al (1996) Eur J Pharmacol 316:325-331
CHO cells: Kull et al (1999) Biochem Pharmacol 58:1035-1045
SH-SY5Y neuroblastoma cells: Salim et al (2000) J Neurochem 74:432-439
HEK cells: Kuldacek et al (2003) Neuropsychopharmacology 29:1317-1327





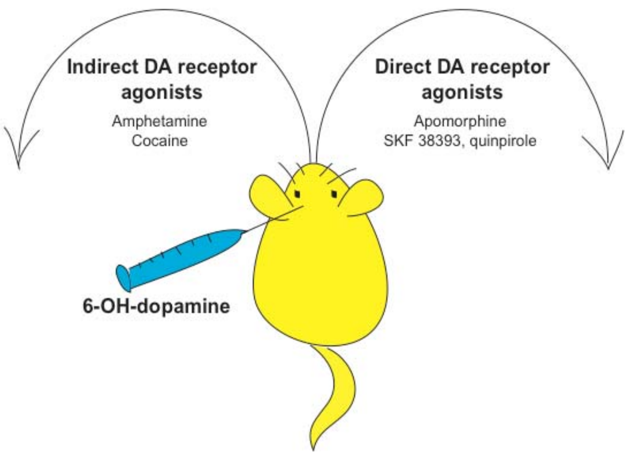


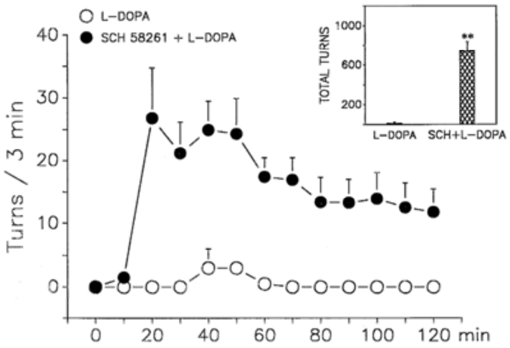
Ferré et al (1993)
Eur J Neurosci 13:5402-5406



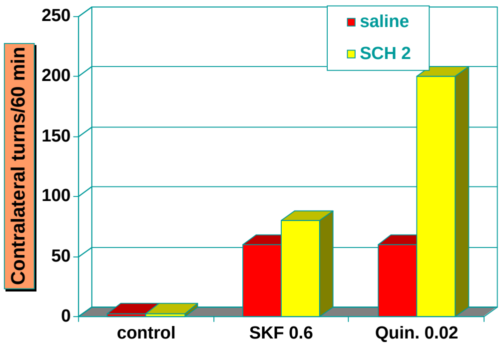
Azdad et al (submitted)

Ungerstedt's model



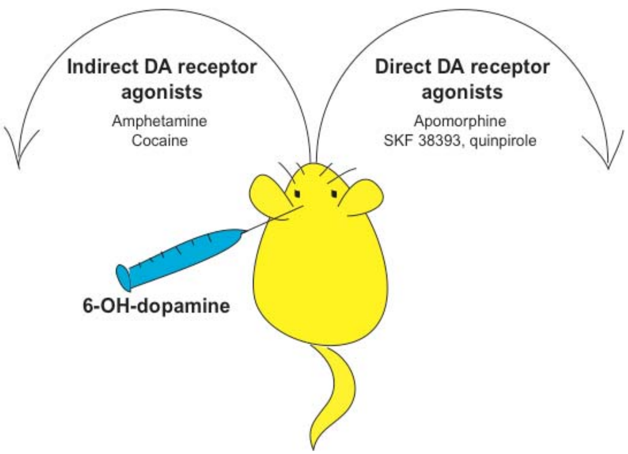


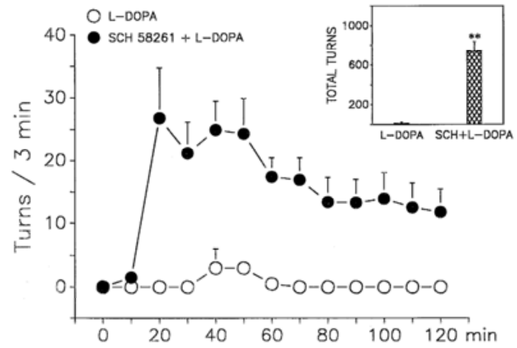
Fenu et al (2001)
Eur J Pharmacol 321:143-147



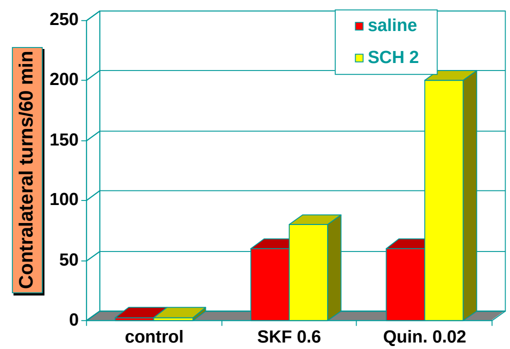
Ferré et al (2001)
Parkinsonism Relat Disord 7:235-241

Ungerstedt's model





Fenu et al (2001)
Eur J Pharmacol 321:143-147



Ferré et al (2001)
Parkinsonism Relat Disord 7:235-241

Adenosine A_{2A} receptor antagonist treatment of Parkinson's disease

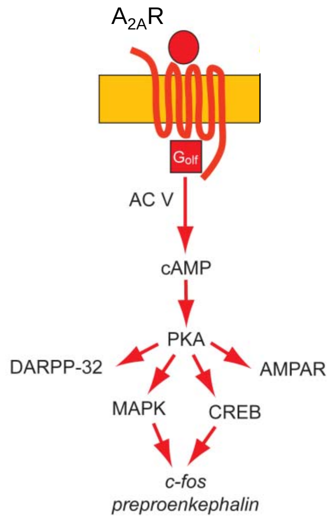
W. Bara-Jimenez, MD; A. Sherzai, MD; T. Dimitrova, MD; A. Favit, MD; F. Bibbiani, MD; M. Gillespie, NP; M.J. Morris, MRCPsych; M.M. Mouradian, MD; and T.N. Chase, MD

NEUROLOGY 2003;61:293–296

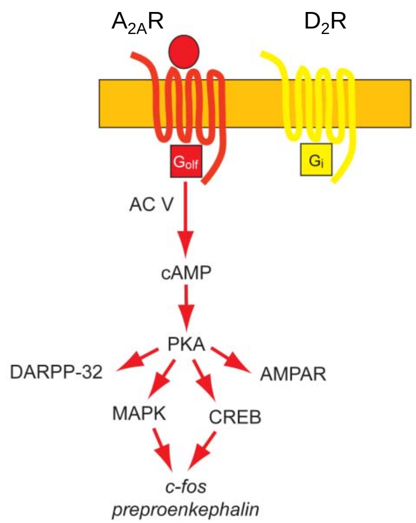
Randomized trial of the adenosine A_{2A} receptor antagonist istradefylline in advanced PD

Robert A. Hauser, MD; Jean P. Hubble, MD; Daniel D. Truong, MD; and the Istradefylline US-001 Study Group*

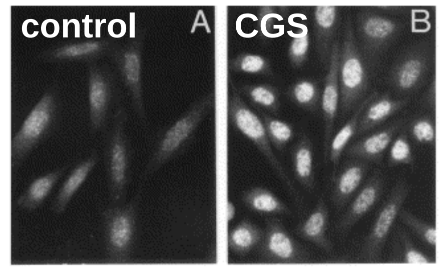
NEUROLOGY 2003;61:297–303



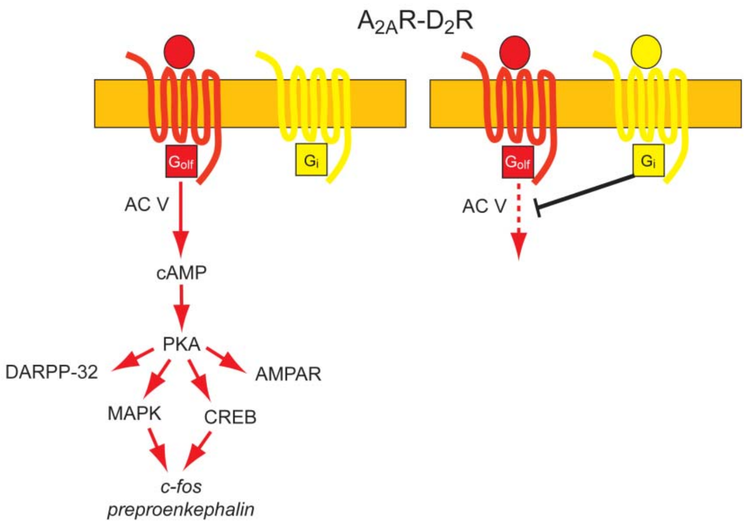
$A_{2A}R$
G_{olf}
AC V
cAMP
PKA
DARPP-32
AMPAR
MAPK
CREB
c-fos
preproenkephalin



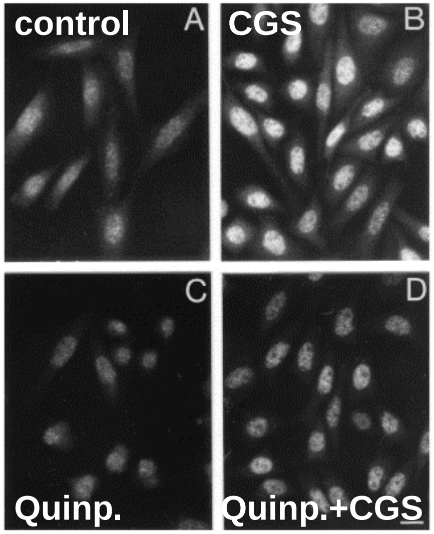
Immunofluoresce with phospho-CREB antibody In A2A/D2 cotransfected CHO cells



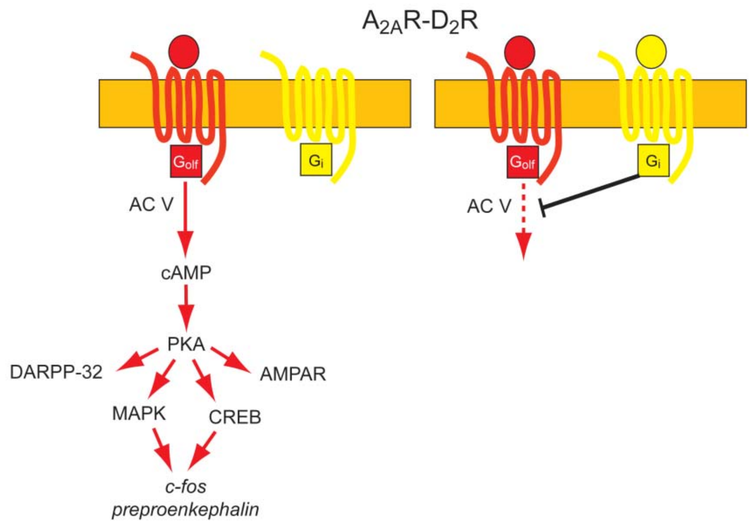
Kull et al (1999)
Biochem Pharmacol 96:482-488

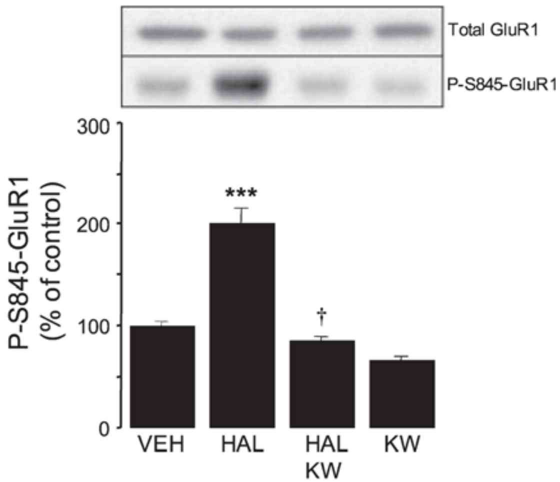


Immunofluoresce with phospho-CREB antibody In A2A/D2 cotransfected CHO cells

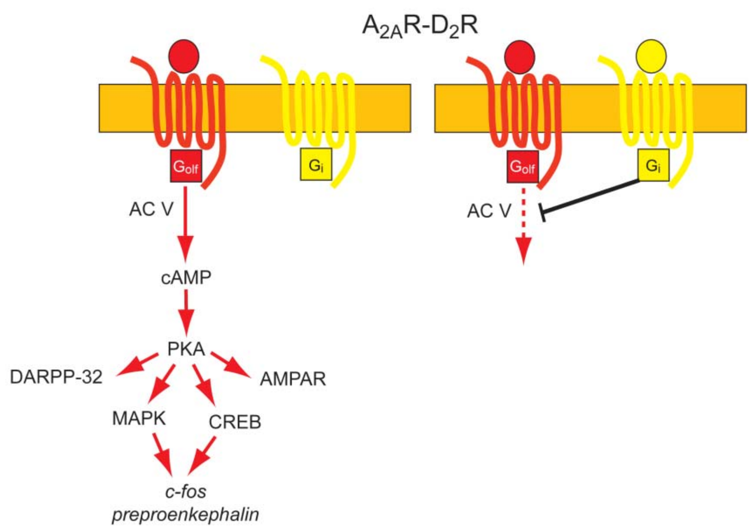


Kull et al (1999)
Biochem Pharmacol 96:482-488

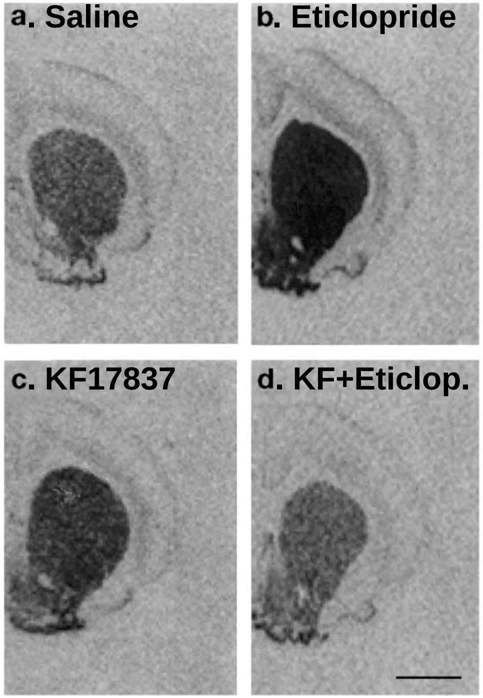




Hakansson et al (2006)
J Neurochem 96:482-488

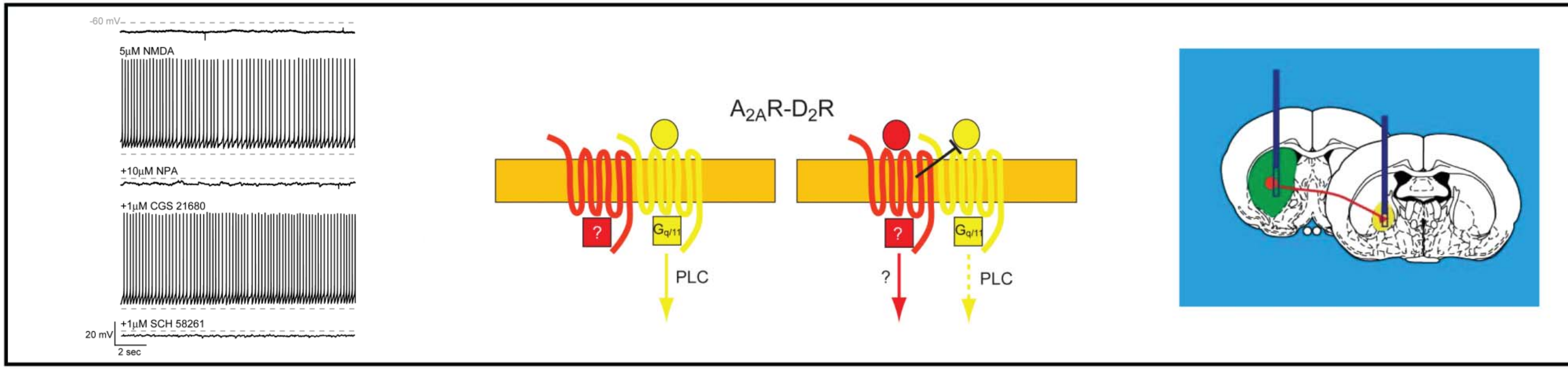


Preproenkephalin mRNA

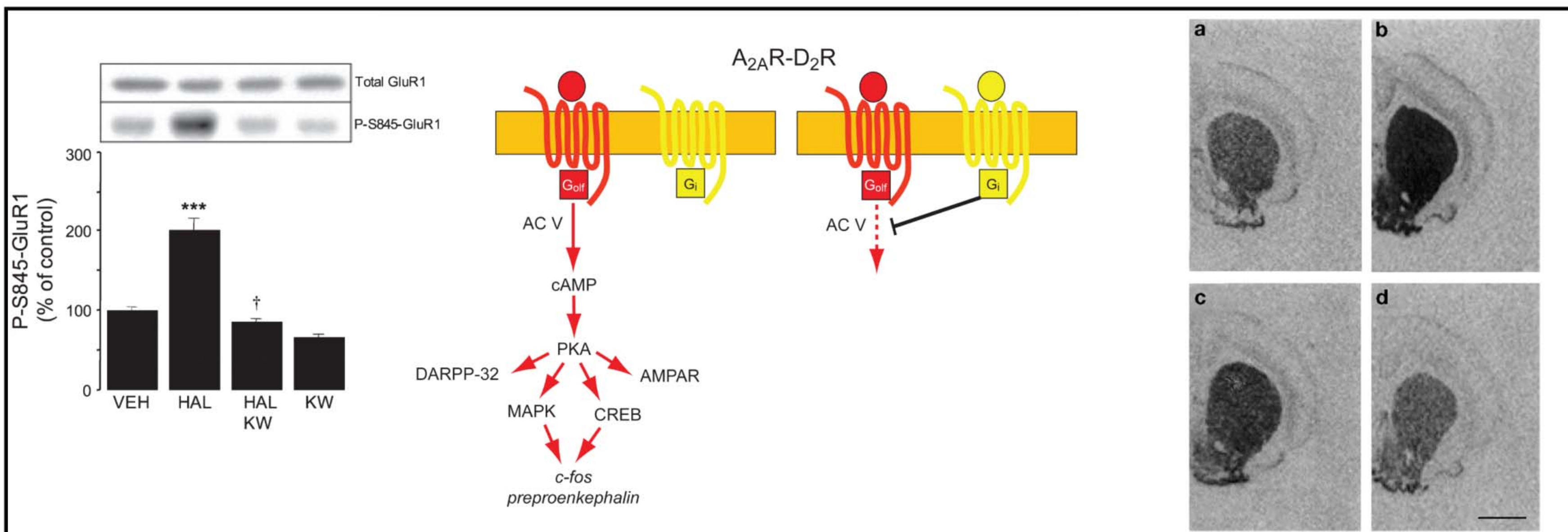


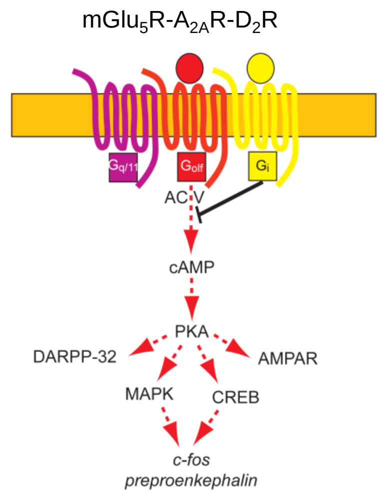
Richardson et al (1997)
Trends Pharmacol Sci 18:338-344

Neuronal Excitability and Neurotransmitter Release

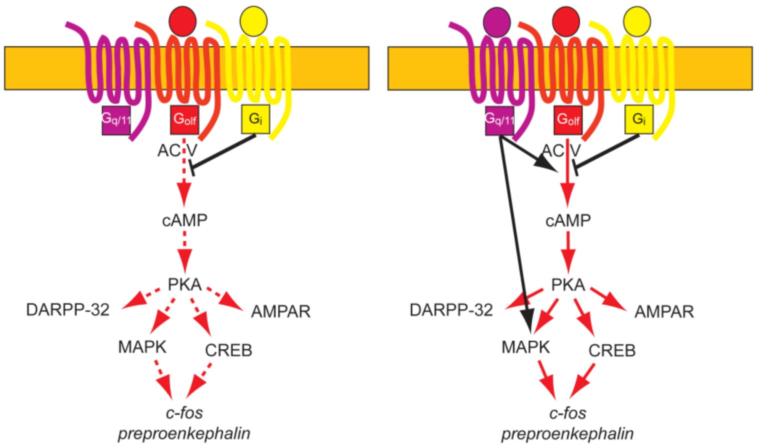


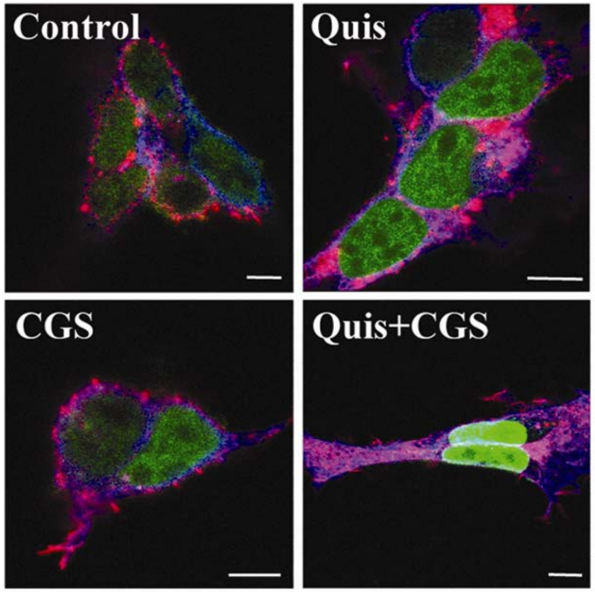
Protein Phosphorylation and Gene Expression



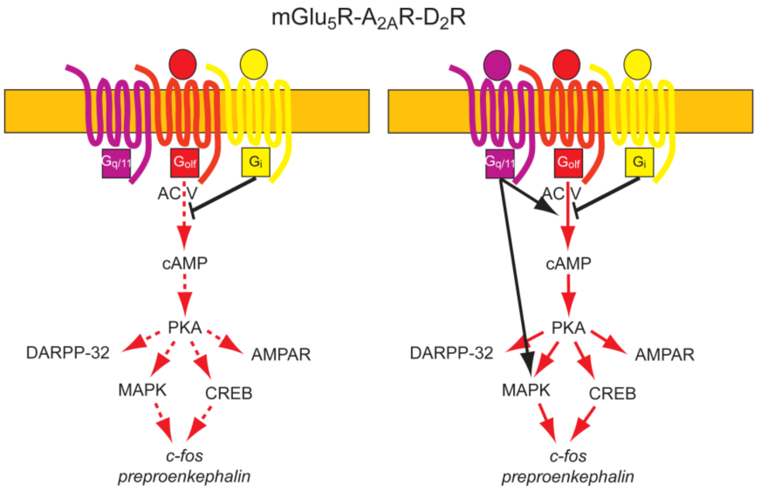

mGlu$_5$R-A$_{2A}$R-D$_2$R
$G_{q/11}$
G_{olf}
G_i
AC V
cAMP
PKA
DARPP-32
AMPAR
MAPK
CREB
c-fos
preproenkephalin

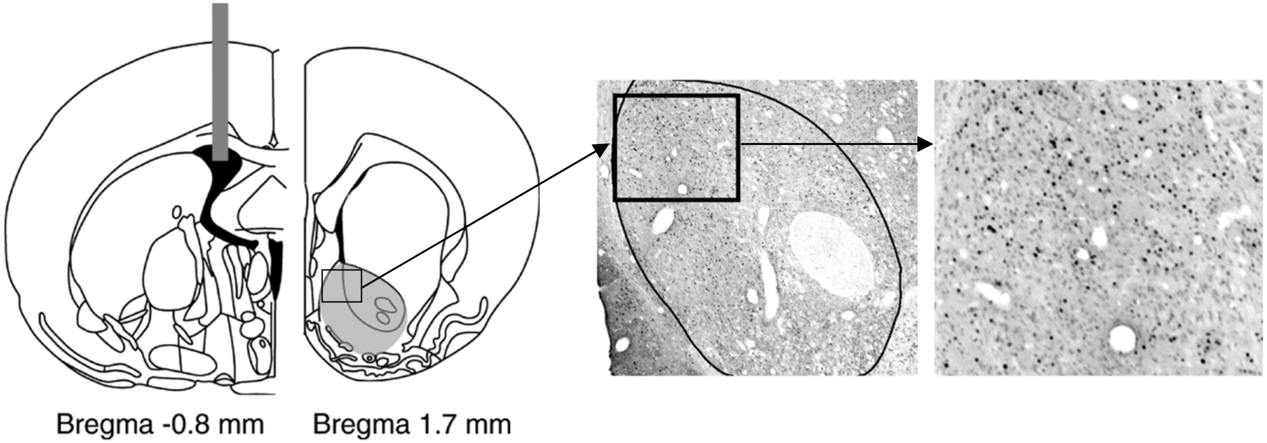
mGlu5R-A2AR-D2R

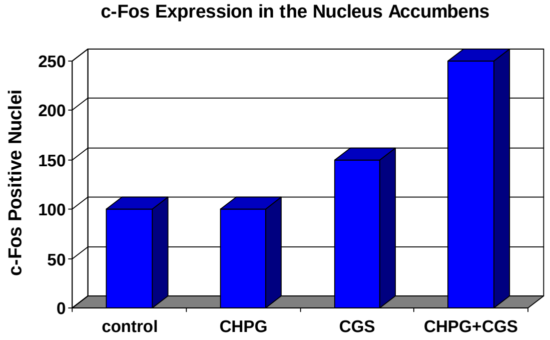




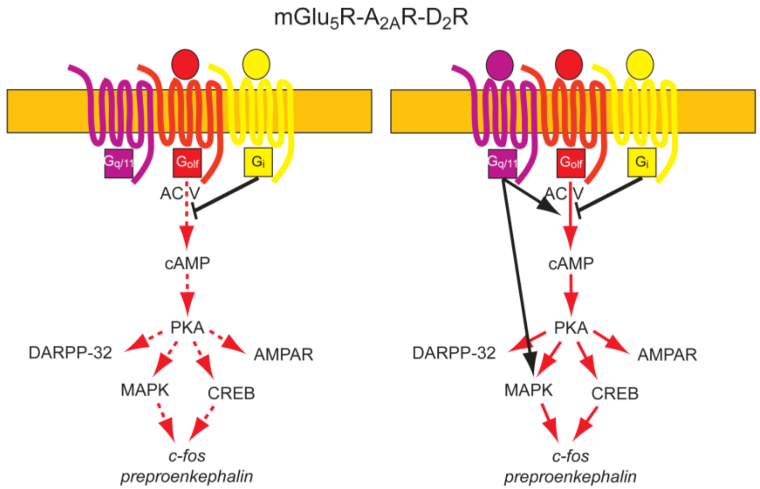
Ferré et al (2002)
Proc Natl Acad Sci USA 99:11940-11945

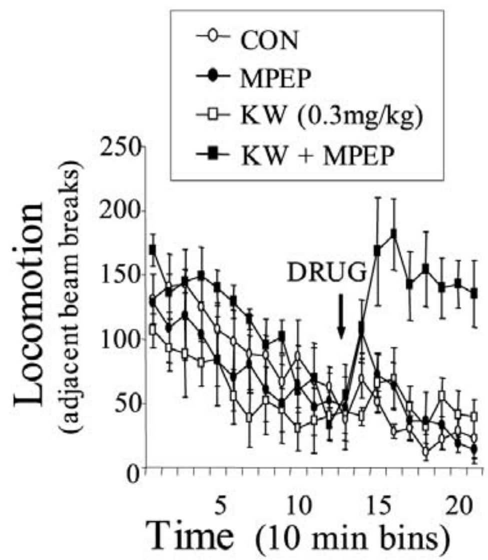




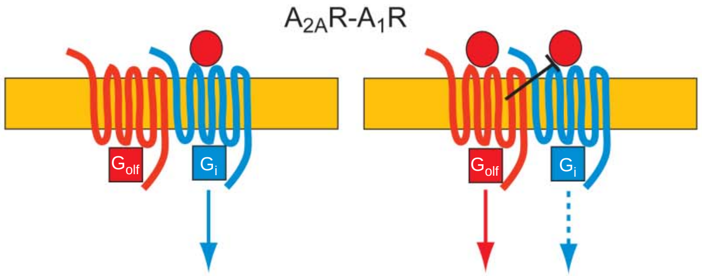


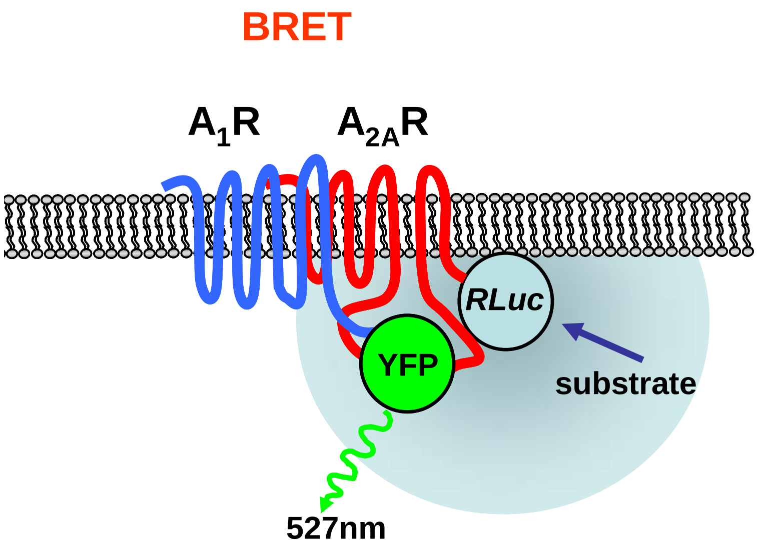
Ferré et al (2002)
Proc Natl Acad Sci USA 99:11940-11945



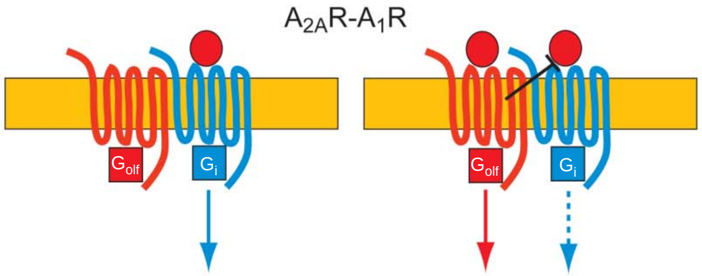


Kachroo et al (2005)
J Neurosci 25:10414-10419

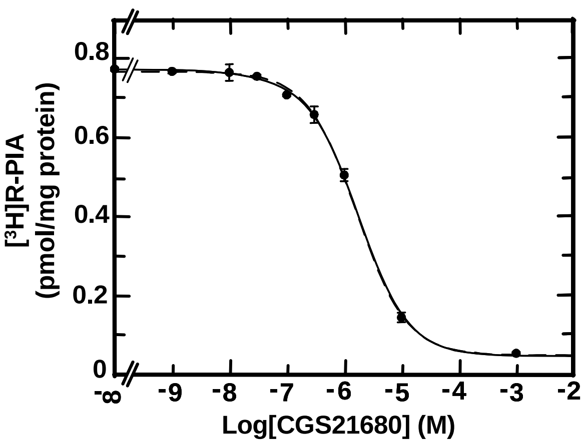




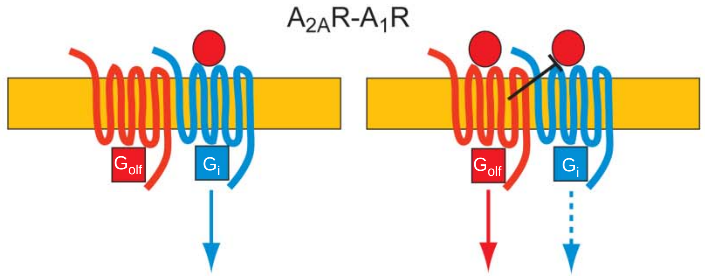
Ciruela et al (2006)
J Neurosci 26:2080-2087



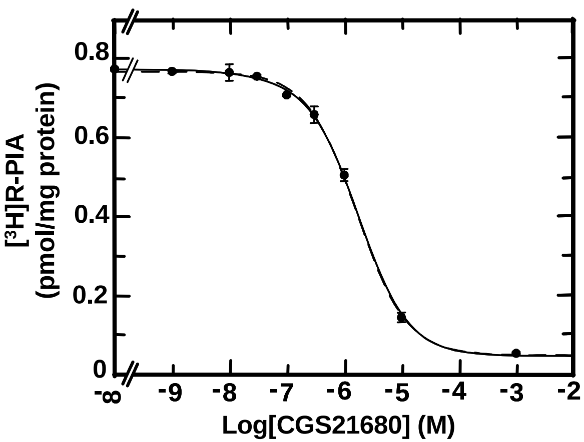
A1 cells



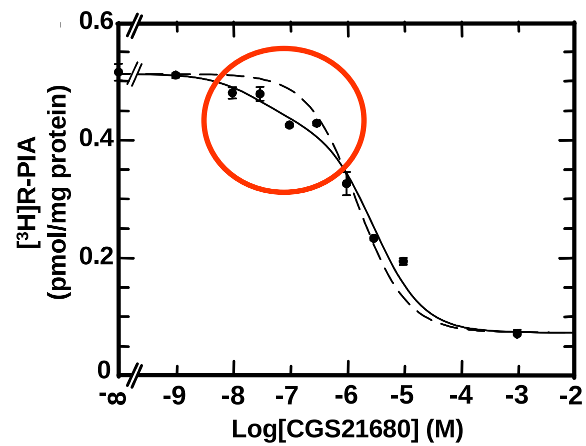
Ciruela et al (2006)
J Neurosci 26:2080-2087



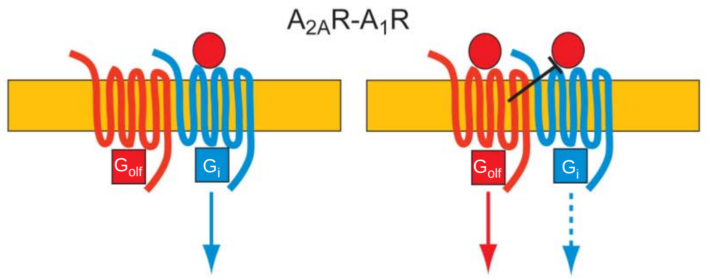
A_1 cells



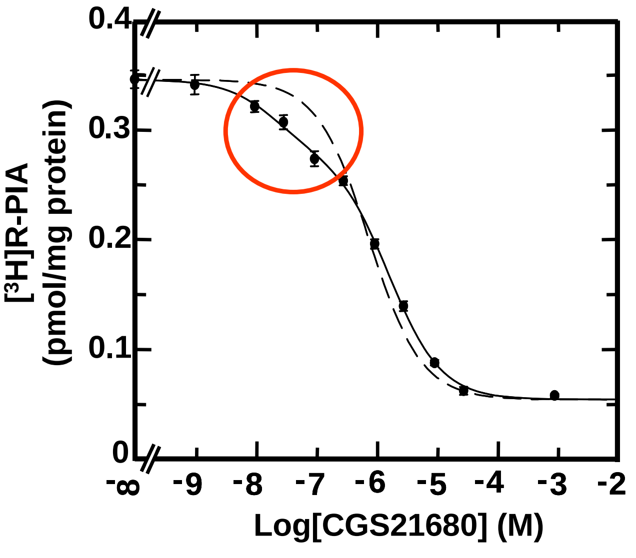
A_1-A_{2A} cells



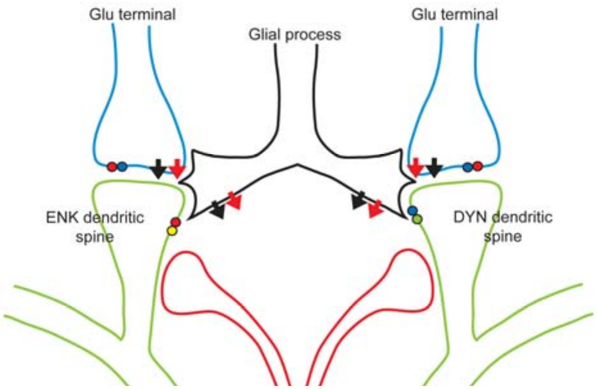
Ciruela et al (2006)
J Neurosci 26:2080-2087

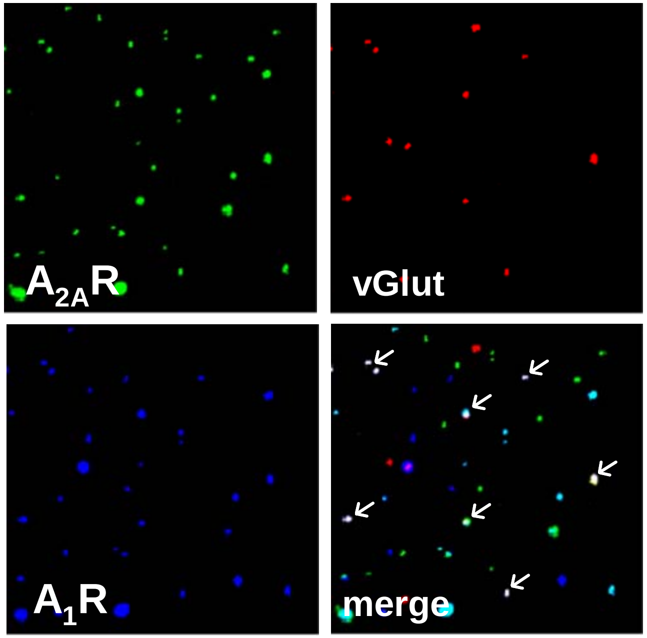


Striatum

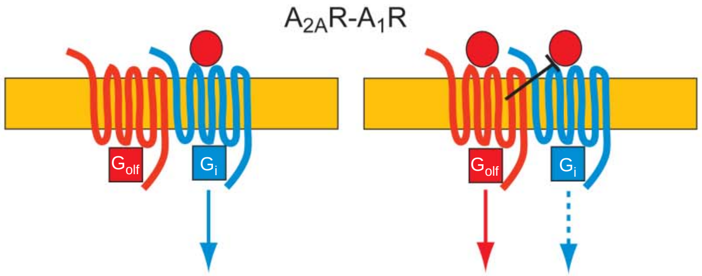


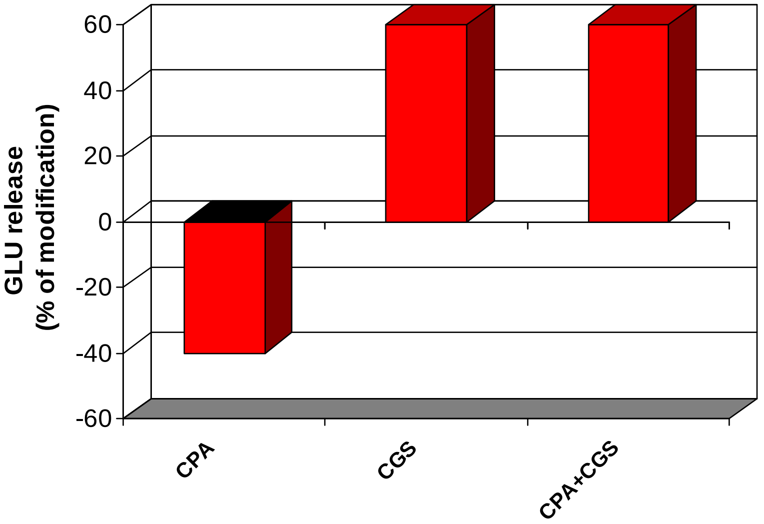
Ciruela et al (2006)
J Neurosci 26:2080-2087



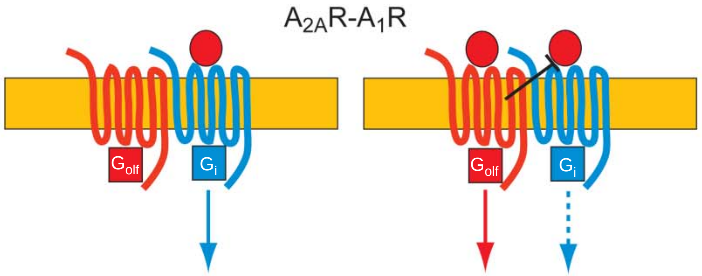


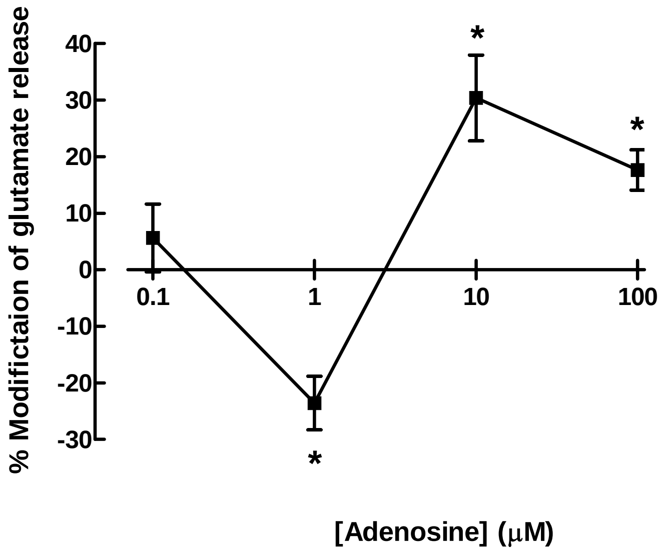
Ciruela et al (2006)
J Neurosci 26:2080-2087



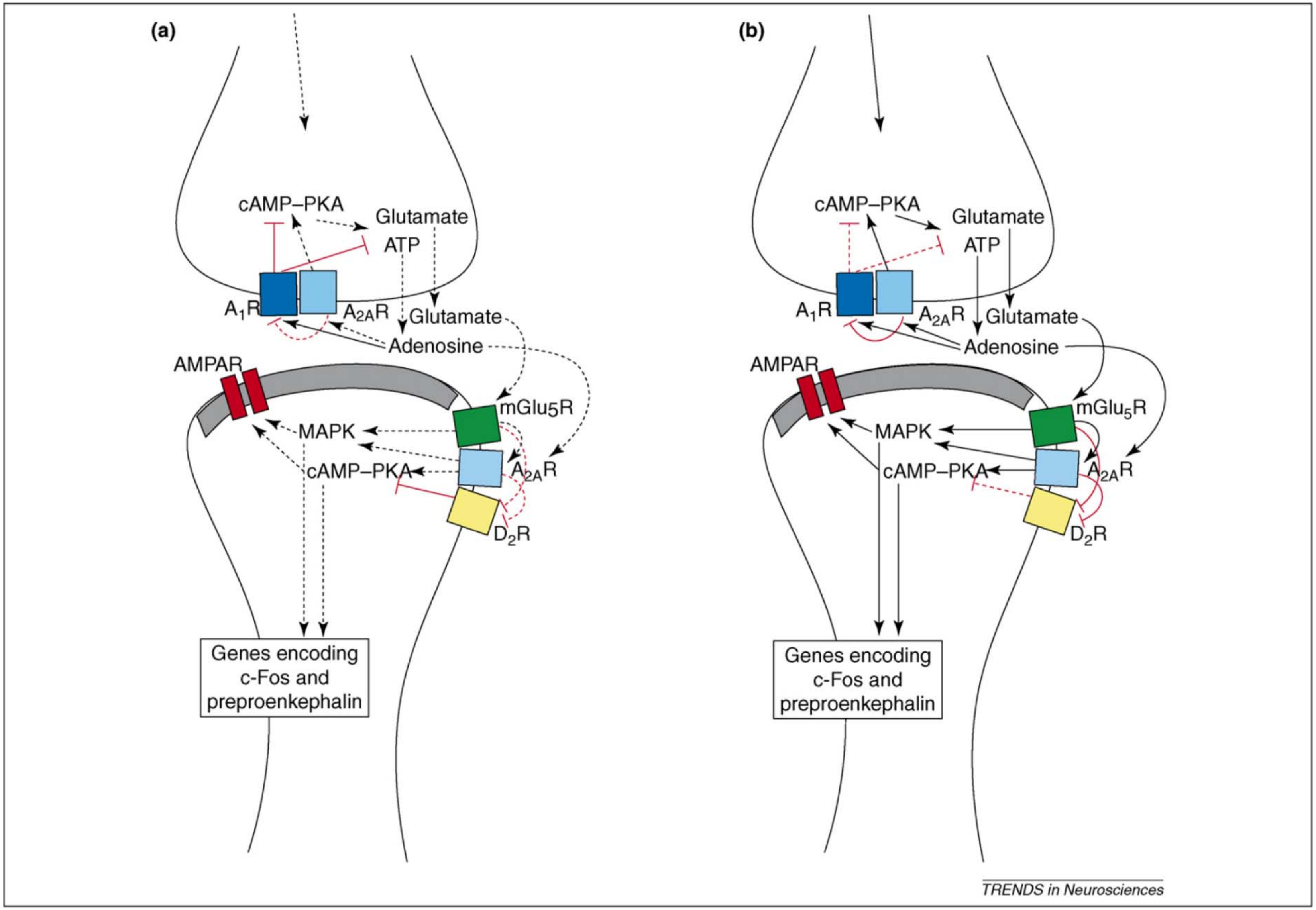


Ciruela et al (2006)
J Neurosci 26:2080-2087

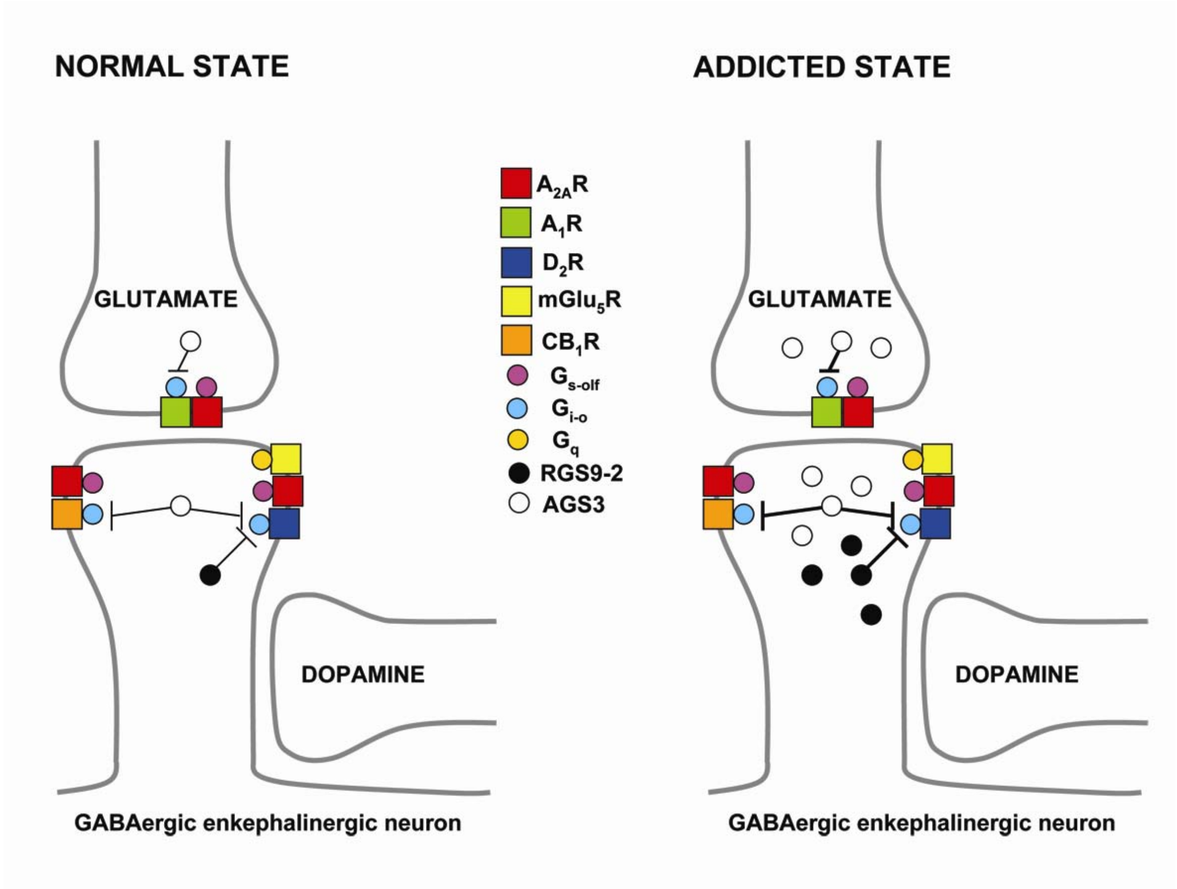




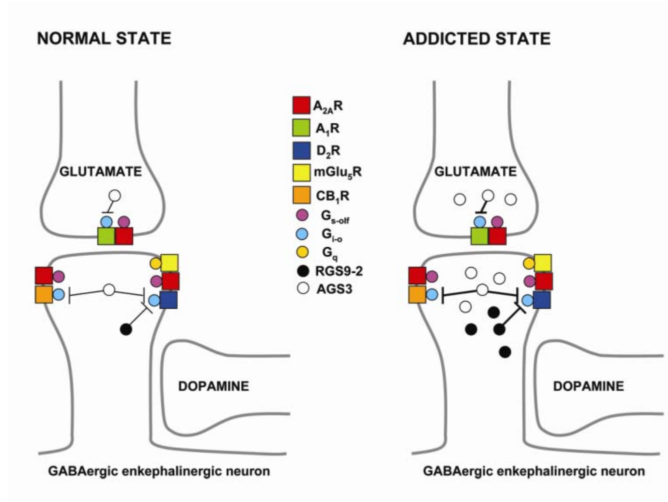
Ciruela et al (2006)
J Neurosci 26:2080-2087

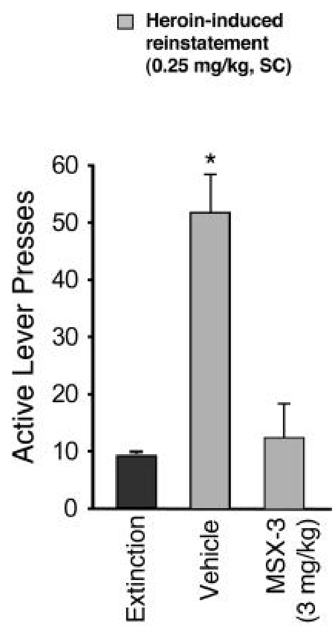


Ferré et al (2007)
Trends Neurosci 30:440-446



Ferré et al (2007)
Prog Neurobiol (in press)





Yao et al. (2006)
Proc Natl Acad Sci USA 103:7877-7882

Conclusions

•Adenosine plays a key integrative role in the computation of information at the level of the striatal spine module (SSM)

•In the SSM, adenosine acts pre- and postsynaptically through multiple mechanisms, which depend on heteromerization of A_1 and A_{2A} receptors among themselves and with different dopamine and glutamate receptors.

•Adenosine receptor heteromers localized in the SSM should be considered as new targets for the treatment of basal ganglia disorders and drug addiction .

Acknowledgements

NIDA IRP

Steven R. Goldberg
Janusz Borycz
César Quiroz-Molina
Marzena Karcz-Kubicha
Davide Quarta
Bruce T. Hope
Marisela Morales
Amina S. Woods

University of Barcelona

Rafael Franco
Carme Lluis
Francisco Ciruela

University of Coimbra

Rodrigo A. Cunha
Ricardo Rodrigues
Nelson Rebola

University of Castilla-La Mancha

Rafael Luján

Hokkaido University

Masahiko Watanabe

Université Libre de Bruxelles

Serge N. Schiffmann

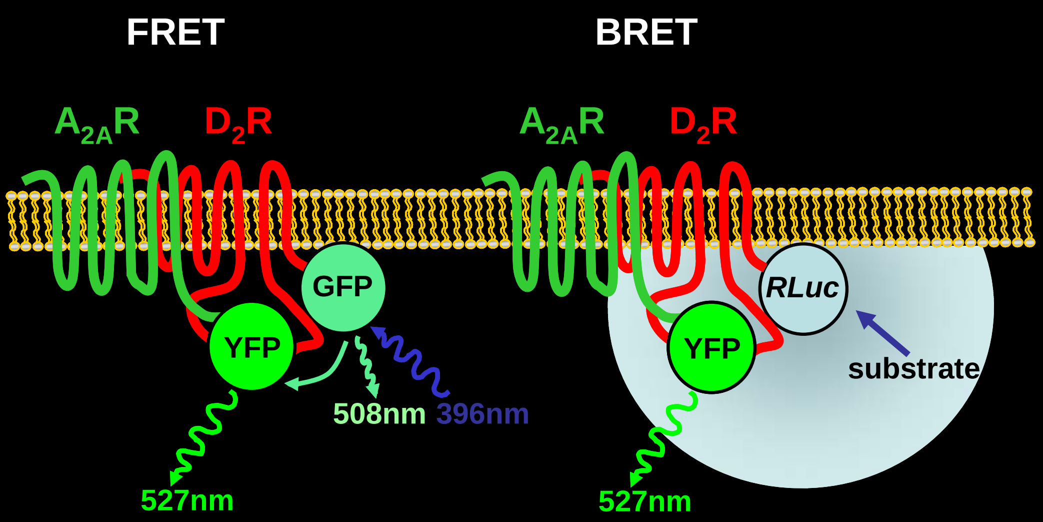
Karolinska Institute

Kjell Fuxe

University of Modena

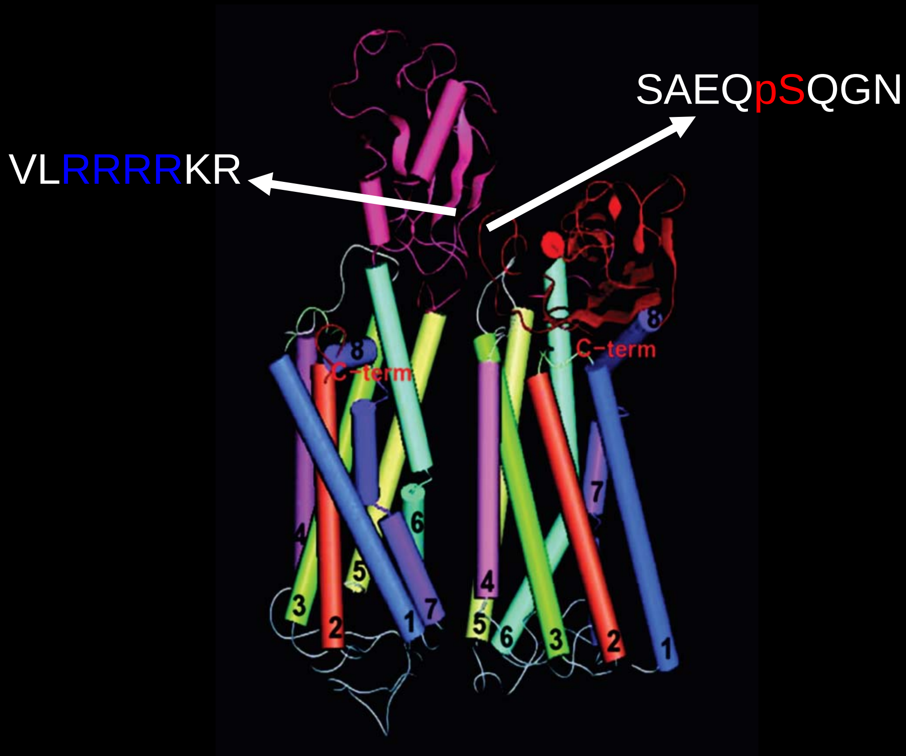
Luigi F. Agnati

Hillion et al (2002)
J Biol Chem 277:18091-18097

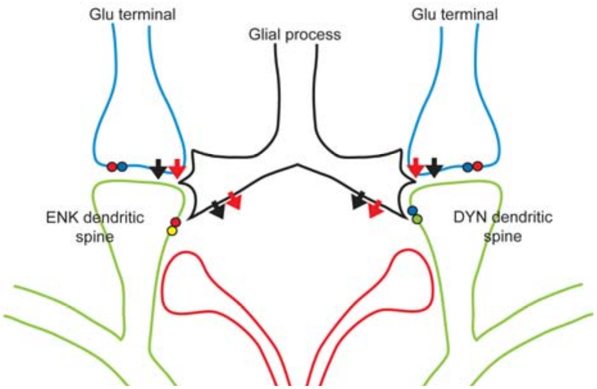


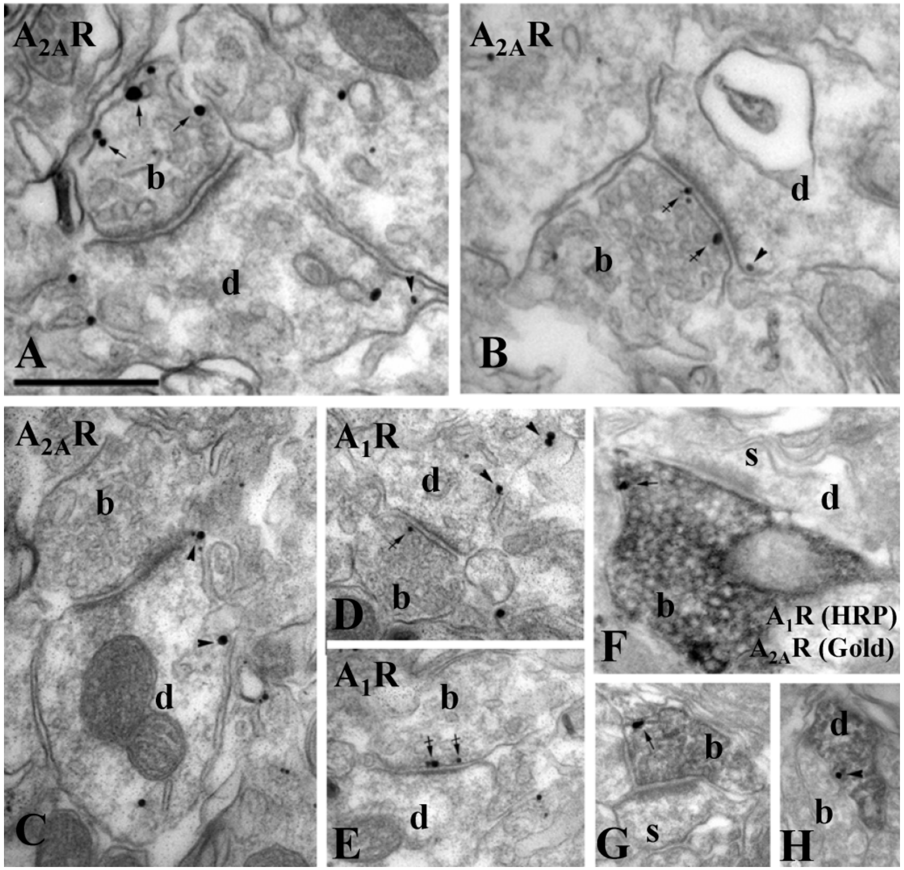
Canals et al (2003)
J Biol Chem 46741-46749

Hillion et al (2002)
J Biol Chem 277:18091-18097

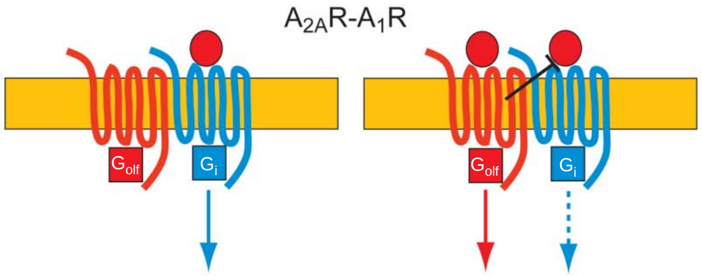


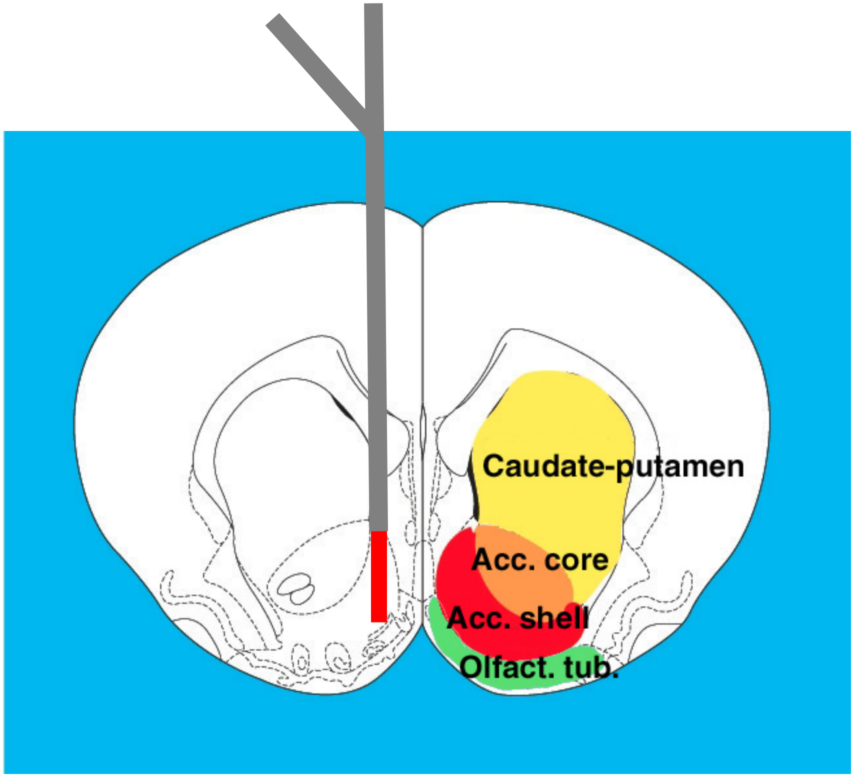
Canals et al (2003)
J Biol Chem 278:46741-46749
Woods and Ferré (2005)
J Proteome Res 4:1397-1402

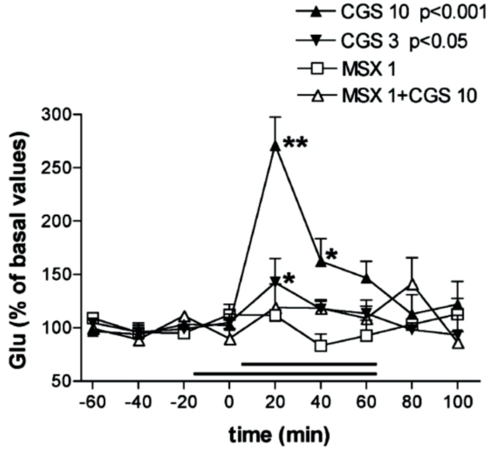


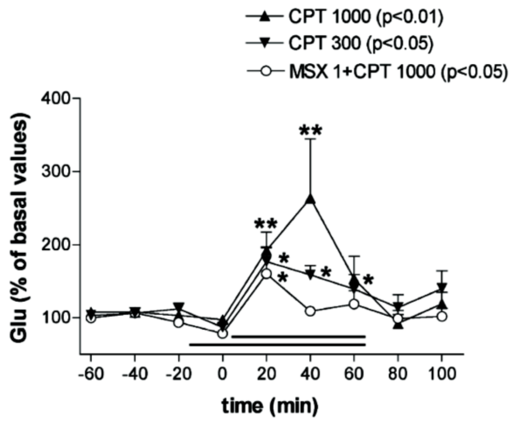


Ciruela et al (2006)
J Neurosci 26:2080-2087









Quarta et al (2004)
J Neurochem 91:873-880