Mechanisms of the Central Effects of Caffeine

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Caffeine is a psychostimulant, with the same central effects as cocaine and amphetamine.

- Increase in Motor Activity
- Arousal
- Reinforcing Effects
<table>
<thead>
<tr>
<th>Compound</th>
<th>A₁ (rat brain cortical membranes)</th>
<th>A₂ₐ (rat brain striatal membranes)</th>
<th>A₂₈ (human recombinant receptors)</th>
<th>A₃ (rat recombinant receptors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine</td>
<td>26,900</td>
<td>32,500</td>
<td>10,400</td>
<td>&gt;100,000</td>
</tr>
<tr>
<td>CPT</td>
<td>24</td>
<td>3,17</td>
<td>902</td>
<td>&gt;10,000</td>
</tr>
<tr>
<td>MSX-2</td>
<td>900</td>
<td>9.1</td>
<td>2,900</td>
<td>&gt;10,000</td>
</tr>
</tbody>
</table>
Adenosine → Dopamine

Frontal lobe → Striatum → Nucleus Accumbens → Amygdala → VTA → BNST → Substantia Nigra
Postsynaptic Adenosine A$_{2A}$-Dopamine D$_2$ receptor interactions in the reserpinized mouse model

![Graph showing locomotion comparison between saline and bromocriptine treatment]

Bromocriptine: D$_2$ agonist

Ferré et al (1991)
E J Pharmacol192:25-30
Postsynaptic Adenosine $A_{2A}$-Dopamine $D_2$ receptor interactions in the reserpinized mouse model

Bromocriptine: $D_2$ agonist  
NECA: $A_1/A_{2A}$ agonist  
L-PIA: $A_1$ agonist

Ferré et al (1991)  
E J Pharmacol192:25-30
Postsynaptic Adenosine $A_{2A}$-Dopamine $D_2$ receptor interactions in the reserpinized mouse model

Bromocriptine: $D_2$ agonist
Caffeine: $A_1/A_{2A}$ antagonist
Theophylline: $A_1/A_{2A}$ antagonist

Ferré et al (1991)
E J Pharmacol192:31-37
Adenosine $A_{2A}$-receptor Agonists Produce Catalepsy

Ferré et al (1991)
Neurosci Lett 130:162-164
Adenosine A$_{2A}$-receptor Antagonists Produce Locomotor Activation

Orru et al (2011)
PLoS ONE 6:e16088
Adenosine $A_{2A}$-Dopamine $D_2$ Receptor Interactions in Striatal Membrane Preparations

Ferré et al (1991)
Proc Natl Acad Sci USA 88:7238-7241
Adenosine A$_{2A}$-Dopamine D$_2$ Receptor Interactions in Striatal Membrane Preparations

Ferré et al (1991)
Proc Natl Acad Sci USA 88:7238-7241

CGS 21680: A$_{2A}$ agonist
Efferent Striatal GABAergic Medium Spiny Neuron (MSN)

Modified from Gerfen (2008)
The Rat Nervous System
Efferent Striatal GABAergic Medium Spiny Neuron (MSN)
Striatal Adenosine $A_{2A}$ Receptors

Schiffmann et al (2007)
Prog Neurobiol 83:277-292
Efferent Striatal GABAergic Medium Spiny Neuron (MSN)

Indirect MSN

Pergolide: D₂ agonist
CGS 21680: A₂A agonist
Theophylline: A₁/A₂A antagonist

GABA (% of basal values)

control  pergolide  perg. + CGS  perg. + theoph.

Ferré, O’Connor, Fuxe, Ungerstedt (1993)
J Neurosci 13:5402-5406
The Receptor Concept
(1878)

John Newport Langley

Paul Ehrlich
The Receptor Heteromer Concept

Macromolecular complex composed of at least two (functional) receptor units (protomers) with biochemical properties that are demonstrably different from those of its individual components
Efferent Striatal GABAergic Medium Spiny Neuron (MSN)
**Local Module:** The minimal portion of one or more neurons and/or one or more glial cells that operates as an independent integrative unit.

Ferré et al (2007)
Brain Res Rev 55:55-67
Local Module: The minimal portion of one or more neurons and/or one or more glial cells that operates as an independent integrative unit.

Ferré et al (2007)
Brain Res Rev 55:55-67
A$_{2A}$-D$_2$ Receptor Heteromer

**A₂A-D₂ Receptor Heteromer**

NPA: D₂ agonist
CGS 21680: A₂A agonist

Neuropsychopharmacology 34:972-986
A2A-D2 Receptor Heteromer

SAQEpSQGNT peptide

NPA: D2 receptor agonist
CGS 21680: A2A receptor agonist

Neuropsychopharmacology 34:972-986
A$_{2A}$-D$_2$ Receptor Heteromer

Orru et al (2011)
PLoS ONE 6:e16088
A$_{2A}$-D$_2$ Receptor Heteromer

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

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
A₁ Receptor-mediated Mechanisms of Caffeine

MSX: A₂A antagonist
CPT: A₁ antagonist

Neuropsychopharmacology 28:1281-1291
A₁ Receptor-mediated Mechanisms of Caffeine
(A₁-D₁ Receptor heteromers)

SKF 38393: D₁ agonist
L-PIA: A₂A agonist

GABA (% of basal values)

Ferré et al (1996)
Eur J Neurosci 8:1545-1553
A₁ Receptor-mediated Mechanisms of Caffeine (Dopamine and Glutamate Release)

Solinas et al (2002)
J Neurosci 22:6321-6324
Psychostimulant Pharmacological Profile of Paraxanthine, the Main Metabolite of Caffeine in Humans
Paraxanthine: Connecting Caffeine to Nitric Oxide Neurotransmission

Orru et al (2013)
Neuropharmacol 67:476-484
Ferré et al (2013)
J Caff Res 3:72-78
Role of the Multiple Interconnected Ascending Arousal Systems in the Psychostimulant Effects of Caffeine

Ferré (2010)
J Alzheimer’s Dis
Suppl 1:S35-S49
Conclusions

1. Two new concepts, “receptor heteromer” and “local module” facilitate the understanding of the functional role of interactions between neurotransmitters in the central nervous system, as well as the mechanisms of central acting drugs, such as caffeine.
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2. The motor and rewarding effects of caffeine depend on its ability to release the pre- and postsynaptic brakes that adenosine imposes on dopaminergic neurotransmission by acting on different adenosine $A_{2A}$ and $A_{1}$ receptor heteromers localized in different elements of the striatal spine module.
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3. The arousal effects of caffeine depend on its ability to release the A$_{1}$ receptor-mediated inhibitory modulation of the highly interconnected multiple ascending arousal systems.

4. Paraxanthine, the main metabolite of caffeine in humans displays a strong psychostimulant profile which depends on its selective ability to potentiate NO neurotransmission.