AI-00386 Summary: Psychostimulant Effects of Caffeine

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An update on the mechanisms of the psychostimulant effects of caffeine by Sergi Ferre, Journal of Neurochemistry 2008

The part 1 of this page talks about:

- **Psychostimulant effects of caffeine**: Caffeine is the most consumed psychoactive drug in the world, with similar behavioral effects as cocaine and amphetamine1. Caffeine can produce dependence, reinforcement, and withdrawal symptoms in humans and animals2.
- **Caffeine and the central dopaminergic system**: Caffeine interacts with the dopaminergic system by blocking adenosine receptors, which modulate dopamine release and receptor function34. Caffeine mimics and potentiates the effects of dopamine receptor agonists.
- **Adenosine A1 or A2A receptor antagonism?**:5 Both A1 and A2A receptors are involved in the motor-activating and arousal-enhancing effects of caffeine, but A1 receptors play a more important role in its discriminative-stimulus effects. Chronic exposure to caffeine induces tolerance to A1 receptor blockade, but not to A2A receptor blockade.
- **Adenosine in the striatal spine module**: Adenosine modulates dopaminergic and glutamatergic neurotransmission in the striatum by acting on different adenosine receptor heteromers localized in the dendritic spines of medium spiny neurons.

Caffeine can release the pre- and post-synaptic brakes that adenosine imposes on dopaminergic neurotransmission6.

The part 2 of this page talks about:

- **Adenosine and dopamine release**: Caffeine or an A1 receptor antagonist increases dopamine and glutamate release in the dorsal striatum and the shell of the nucleus accumbens2. A2A receptor antagonists do not affect dopamine release, but potentiate glutamate release. The effects of caffeine depend on the subregional distribution of adenosine receptors.
- **A1 and A2A receptors in striatal terminals**: A1 receptors are present in dopaminergic and glutamatergic terminals, where they inhibit dopamine and glutamate release, respectively2. A2A receptors are also present in glutamatergic terminals, where they stimulate glutamate release3. A1 and A2A receptors form heteromers that modulate each other's function1.
- **Mechanisms of adenosine receptor modulation**: A1 receptors inhibit calcium channels and neurotransmitter release through Gi proteins. A2A receptors activate cAMP–PKA signaling and neurotransmitter release through Gs proteins. A2A receptors also inhibit A1 receptor binding and signaling through intramembrane interactions.
- **Tolerance to caffeine effects**: Chronic caffeine exposure induces tolerance to the effects of A1 receptor blockade, but not to A2A receptor blockade. This may involve changes in the function of A1–A2A receptor heteromers, as well as increased adenosine levels.

The part 3 of this page talks about:

- **Dopamine receptors in the mammal brain**: There are five subtypes of dopamine receptors (D1-D5) that belong to two families: D1-like (D1 and D5) and D2-like (D2, D3 and D4)12. They have different effects on intracellular cAMP levels and modulate various neuronal functions.
- **The substantia nigra dopamine system and motor control**: Dopamine neurons in the substantia nigra project to the striatum and other parts of the basal ganglia, which are involved in response selection and motor learning. Dopamine sets the effort threshold for initiating behaviors and acts as a teaching signal for reward prediction error3.

- **The ventral tegmental area, reward, and cognition**: Dopamine neurons in the VTA project to the nucleus accumbens, prefrontal cortex, and other areas, forming the mesolimbic and mesocortical pathways. They play a role in reward, motivation, salience, cognition, and addiction4. Dopamine encodes not only reward itself, but also reward prediction error and incentive salience5.
- **Diseases and disorders**: Dopamine is implicated in several neurological and psychiatric conditions, such as Parkinson's disease, ADHD, drug addiction, pain, nausea, and psychosis6. These disorders involve alterations in dopamine levels, receptors, or functions in different brain regions. Various drugs can modulate dopamine activity to treat these conditions.

The part 4 of this page talks about:

- **Psychostimulant effects of dopamine**: Dopamine is a neurotransmitter that enhances attention, motivation, and reward-seeking behavior12. Psychostimulants such as cocaine and amphetamine increase dopamine activity in the brain, producing euphoria and addiction.
- **Dopamine receptors in the brain**: There are five subtypes of dopamine receptors (D1-D5) that belong to two families: D1-like and D2-like. They have different effects on intracellular signaling and neuronal functions, such as motor control, reward, cognition, and psychosis.
- **Diseases and disorders related to dopamine**: Dopamine is involved in several neurological and psychiatric conditions, such as Parkinson's disease, ADHD, drug addiction, pain, nausea, and schizophrenia. These disorders involve alterations in dopamine levels, receptors, or functions in different brain regions. Various drugs can modulate dopamine activity to treat these conditions.
- **Dopamine in other organisms**: Dopamine is found in many types of organisms, including bacteria, plants, and animals. It has diverse functions, such as modulating stress response, growth, metabolism, pigmentation, and anti-herbivore defense. Dopamine consumed in food cannot cross the blood-brain barrier and affect the brain34.

The part 5 of this page talks about:

- **Dopamine and norepinephrine**: These are catecholamines that act as hormones and neurotransmitters in the brain and body. They have multiple roles in attention,

arousal, reward, and stress response.

- **Medical uses of norepinephrine**: Norepinephrine is used as a vasopressor medication to treat patients with critical hypotension1. It increases blood pressure by stimulating α1 and α2 adrenergic receptors and causing vasoconstriction2.
- **Norepinephrine system in the brain**: Norepinephrine is released from the locus coeruleus and the lateral tegmental field, which project to many brain regions. Norepinephrine modulates cortical activity, sensory processing, learning, memory, and emotion.
- **Role of norepinephrine in cognition**: Norepinephrine is involved in attention, decision making, and probabilistic learning. It enhances signal detection, outcome evaluation, and behavioral responses to relevant stimuli. It also mediates the P300 potential, which reflects attentional allocation and updating of prior knowledge.
- **Diseases and disorders related to norepinephrine**: Norepinephrine is implicated in several neurological and psychiatric conditions, such as hypotension, shock, ADHD, depression, anxiety, and PTSD. These disorders involve alterations in norepinephrine levels, receptors, or functions in different brain regions. Various drugs can modulate norepinephrine activity to treat these conditions.
- **Norepinephrine in other organisms**: Norepinephrine is found in many types of organisms, including bacteria, plants, and animals. It has diverse functions, such as modulating stress response, growth, metabolism, pigmentation, and anti-herbivore defense. Norepinephrine consumed in food cannot cross the blood-brain barrier and affect the brain.

The part 6 of this page talks about:

- **Dopamine and norepinephrine**: These are **catecholamines** that act as **hormones** and **neurotransmitters** in the brain and body. They have multiple roles in **attention**, **arousal**, **reward**, and **stress response**.
- **Medical uses of norepinephrine**: Norepinephrine is used as a **vasopressor** medication to treat patients with **critical hypotension**. It increases blood pressure by stimulating **α1 and α2 adrenergic receptors** and causing **vasoconstriction**.
- **Norepinephrine system in the brain**: Norepinephrine is released from the **locus coeruleus** and the **lateral tegmental field**, which project to many brain regions.

Norepinephrine modulates **cortical activity**, **sensory processing**, **learning**, **memory**, and **emotion**.

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- **Diseases and disorders related to norepinephrine**: Norepinephrine is implicated in several neurological and psychiatric conditions, such as **hypotension**, **shock**, **ADHD**, **depression**, **anxiety**, and **PTSD**. These disorders involve alterations in norepinephrine levels, receptors, or functions in different brain regions. Various drugs can modulate norepinephrine activity to treat these conditions.
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The part 7 of this page talks about:

- **Methylphenidate overdose**: The symptoms of methylphenidate overdose are usually mild and include tachycardia, agitation, lethargy, vomiting, dizziness, mydriasis, and tremor. Severe cases may cause chest pain, fever, insomnia, dystonia, or necrosis.
- **Methylphenidate abuse**: Methylphenidate has a low potential for abuse compared to other stimulants, but it can still be misused for recreational or cognitive enhancement purposes. The most common sources of abuse are diversion from legitimate prescriptions or injection of crushed tablets1.
- **Methylphenidate pharmacology**: Methylphenidate acts as a dopamine-norepinephrine reuptake inhibitor (DNRI), increasing the levels of these neurotransmitters in the brain2. It also binds to sigma-1 receptors and adenosine receptors, modulating their function. It has four isomers, of which only d-threo-methylphenidate is active3.

- **Methylphenidate legal status**: Methylphenidate is a controlled substance in many countries, with varying schedules and penalties for possession and distribution. It is usually classified as a stimulant or a psychotropic drug, and requires a prescription for medical use.
- **Methylphenidate controversy**: Methylphenidate has been the subject of debate regarding its use in the treatment of ADHD, especially in children and adolescents[4][5]. Some of the issues include the diagnosis and prevalence of ADHD, the efficacy and safety of methylphenidate, the ethical and social implications of stimulant therapy, and the risk of addiction and diversion.

The part 8 of this page talks about:

- **Methylphenidate overdose and abuse**: The symptoms of methylphenidate overdose are usually mild and include tachycardia, agitation, lethargy, vomiting, dizziness, mydriasis, and tremor. Severe cases may cause chest pain, fever, insomnia, dystonia, or necrosis. Methylphenidate has a low potential for abuse compared to other stimulants, but it can still be misused for recreational or cognitive enhancement purposes. The most common sources of abuse are diversion from legitimate prescriptions or injection of crushed tablets.
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The part 9 of this page talks about:

- **Low arousal theory**: A psychological theory that explains why people with ADHD and antisocial personality disorder seek self-stimulation by excessive activity to overcome their low arousal state1.
- **Noise and performance**: ADHD is related to a dysfunction of the dopamine system2. Noise can help brain function by increasing arousal, but people with ADHD need more noise than normal to improve their performance3. This is called stochastic resonance.
- **See also**: A list of related concepts, such as Yerkes–Dodson law, neophile, novelty seeking, and sensation seeking.
- **References**: A list of sources that support the information in the page.

The part 10 of this page talks about:

- **Catecholamines and brain function**: Caffeine, dopamine, and norepinephrine are catecholamines that act as hormones and neurotransmitters in the brain and body. They have multiple roles in attention, arousal, reward, and stress response.
- **Norepinephrine as a vasopressor**: Norepinephrine is used as a medication to treat patients with critical hypotension. It increases blood pressure by stimulating adrenergic receptors and causing vasoconstriction.
- **Norepinephrine system in the brain**: Norepinephrine is released from the locus coeruleus and the lateral tegmental field, which project to many brain regions. Norepinephrine modulates cortical activity, sensory processing, learning, memory, and emotion.
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- **Diseases and disorders related to norepinephrine**: Norepinephrine is implicated in several neurological and psychiatric conditions, such as hypotension, shock, ADHD, depression, anxiety, and PTSD. These disorders involve alterations in norepinephrine levels, receptors, or functions in different brain regions. Various drugs can modulate norepinephrine activity to treat these conditions.
- **Norepinephrine in other organisms**: Norepinephrine is found in many types of organisms, including bacteria, plants, and animals. It has diverse functions, such as

modulating stress response, growth, metabolism, pigmentation, and anti-herbivore defense. Norepinephrine consumed in food cannot cross the blood-brain barrier and affect the brain.

The part 11 of this page talks about:

- **Prefrontal cortex and brain images**: A link to the BrainMaps project, which provides stained brain slice images of the prefrontal cortex and other brain regions.
- **Childhood lead exposure and brain volume**: A study that found a negative correlation between lead exposure in childhood and brain volume in adulthood, especially in the prefrontal cortex.
- **Early damage to prefrontal cortex and social behavior**: A study that showed that patients with early damage to the prefrontal cortex had impaired social and moral behavior, such as lack of empathy, guilt, and remorse1.
- **Brain size and cognitive ability**: A study that found no correlation between brain size and general cognitive ability within families, suggesting that other factors, such as brain structure and function, are more important.
- **House & Psychology**: A book that analyzes the psychology of the TV show House, which features a brilliant but antisocial doctor who suffers from chronic pain and addiction. The book explores how House's prefrontal cortex is affected by his condition and personality.
- **Descartes' Error**: A book that argues that reason and emotion are not separate, but rather depend on the integration of the prefrontal cortex and other brain regions. The book presents cases of patients with prefrontal cortex damage who have impaired decision making and emotional regulation.
- **Phineas Gage**: A famous case of a railroad worker who survived an accident that damaged his prefrontal cortex. His personality changed from being calm and responsible to being irritable and reckless, demonstrating the role of the prefrontal cortex in executive functions and social behavior.
- **Adenosine receptors and dopamine release**: A study that investigated how caffeine and adenosine receptor antagonists affect dopamine and glutamate release in different parts of the striatum. The study found that caffeine increased dopamine release in the dorsal striatum and the nucleus accumbens shell, but not in the core. The study also found that adenosine receptor antagonists had different

effects on glutamate release depending on the receptor subtype (A1 or A2A) and the location (dorsal or ventral striatum).

- **Adenosine receptors in striatal terminals**: A review that described how adenosine receptors are located in dopaminergic and glutamatergic terminals in the striatum, where they modulate neurotransmitter release. The review also explained how adenosine receptors form heteromers that interact with each other and influence their function.
- **Tolerance to caffeine effects**: A review that discussed how chronic caffeine exposure induces tolerance to some of its effects, such as blocking adenosine A1 receptors, but not to others, such as blocking adenosine A2A receptors. The review also suggested possible mechanisms for this phenomenon, such as changes in adenosine receptor heteromer function and increased adenosine levels.