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The effects of amphetamine on the neurobiology of memory consolidation from a pharmacodynamic and toxicological perspective

Executive Summary

The psychostimulant drug amphetamine improves animal and human short-term and long-term memory via its direct and indirect impact on several neurotransmitters. One possible account suggests that amphetamine aids the process of memory formation, referred to as consolidation. This idea is supported by independent findings on the drug-induced neurobiological and –chemical effects, and memory consolidation. Despite a substantial overlap, the link between these findings has not yet been extensively

investigated. Additionally, both acute and chronic amphetamine use can cause neurotoxicity, which affects consolidation. Therefore, the aim of this executive summary was to examine the effects of amphetamine on the neurobiology of consolidation taking the drug's pharmacodynamic and toxic properties into account. The presented evidence shows that amphetamine facilitates consolidation, since it engages receptors, neurotransmitters and neuromodulators that are essential for memory formation. One example is dopamine, which is the main mediator of the amphetamine-induced memory effect. However, chronic amphetamine treatment has to be regarded with caution due to receptor down-regulation and toxicity.

Keywords: amphetamine, consolidation, memory, toxicity, neuroplasticity

INTRODUCTION

The psychostimulant drug amphetamine (AMPH) has recently gained increased interest in research, since it was found to aid memory via its impact on neurotransmission and neuroplasticity (Giorgetti, Hotsenpiller, Ward, Teppen, & Wolf, 2001; Myhrer, 2003). For instance, AMPH improved short-term and long-term memory (STM and LTM) of multiple sclerosis (MS) patients with baseline memory deficits as measured by an auditory/verbal-learning task (Sumowski et al., 2011). Moreover, 0.25 mg/kg acutely administered AMPH improved working memory of patients with schizophrenia (Barch & Carter, 2005). The STM drug effects can be explained by AMPH's capacity to improve attention as evidenced in both rat (Meneses et al., 2011; Turner & Burne, 2016) and human studies (Servan-Schreiber, Carter, Bruno, & Cohen, 1998; Silber, Croft, Papafotiou, & Stough, 2006). Thus, AMPH via its direct enhancing effect on attention may contribute to better STM, and thus, may facilitate encoding (i.e., maintaining information in memory for short term).

However, the above mechanism might not fully account for improved LTM. The reason is that creation of new LTM traces is known to involve a process by which a particular memory is transformed from an unstable short-term state into a stable long-term state. This is referred to as consolidation (Debiec, LeDoux, & Nader, 2002). Thus, one possibility is that AMPH affects consolidation (Leri et al., 2013). This process is rather complicated and fragile involving several neurotransmitters and cascades of molecular processes (Cooke, 2006; Debiec et al., 2002; Nicoll & Malenka, 1995) which can be influenced by AMPH (Carvalho et al., 2012; Nicoll & Malenka, 1995; Stahl, 2013). Despite this link between AMPH and consolidation the drug's neurochemical and neurobiological effects on memory formation specifically have not yet been investigated extensively. There are only a few studies exploring this connection. Therefore, the aim of this executive summary was to examine how AMPH might influence the neurobiology of consolidation. Several animal and human studies investigating the process of consolidation and AMPH either in connection or independently are reviewed in this paper. Furthermore, links

and overlaps between the drug-induced CNS effects and the process of memory consolidation are established. In addition, this drug is known to cause oxidative stress, toxicity and inflammation in the central nervous system (CNS) (Carvalho et al., 2012; Patrick & Markowitz, 1997). For this reason the drug's pharmacodynamic and toxic properties were taken into account, as well in order to able to weigh the evidence for AMPH to be used as a memory enhancing drug.

Memory consolidation

Formation of memory relies on synaptic changes and modified gene expression initiated by several neurotransmitter systems in the brain involving brain structures such as the cortex, the hippocampus and the striatum (Squire, 2004; Porras & Mora, 1992). Long-term potentiation (LTP) has been suggested as a likely candidate for the neurophysiological substrate of memory formation (Cooke, 2006). LTP implies a long-term change in post-synaptic potentials upon brief stimulation triggered and

maintained by robust calcium (Ca2+) influx. This on the one hand leads to functional changes; that is strengthening of existing synapses. On the other hand it results in structural changes whereby new neuronal connections are established (Cooke & Bliss, 2006). Finally, as a result of persistent modifications of the synaptic architecture new ribonucleinic acid (RNA) is produced, and new proteins are synthesized with temporary alterations in synaptic transmission (Debiec et al., 2002).

LTP mechanisms are primarily dependent on glutamatergic receptors, such as the N-methyl-D-aspartate (NMDA) and the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subtypes. The crucial role of NMDA receptors in the cascade of chemical events related to memory consolidation has been demonstrated in several animal (Rodrigues, Schafe, & LeDoux, 2001; Rubin, 2004) and human studies of fear conditioning (Kalisch et al., 2009; Parwani et al., 2005). In particular, Kalisch et al. (2009) showed using a fear conditioning and extinction paradigm that the NMDA partial agonist D-cycloserine (500mg) improved fear

memory consolidation relative to placebo in healthy human subjects.

Induction of LTP relies on large synaptic depolarisation caused by increased glutamate (Glu) influx via the NMDA receptors. Moreover, the coagonist glycine (Gly) is essential for the removal of the magnesium block in the NMDA receptors, since it enables Ca2+ influx (Stahl, 2013). This is vital as LTP strongly depends on Ca2+ availability (Nicoll & Malenka, 1995; Stahl, 2013). Ca2+ does not only trigger, but also maintains LTP for both short-term (< 1hour) and long-term (1hour < LTP > 3hours). Additionally, it activates an enzyme called calcium-calmodulin-dependent kinase II (CaMKII). This enzyme on the one hand makes AMPA receptors more permeable to sodium ions, which increases the sensitivity of the cell to incoming information. On the other hand, it promotes the synthesis of new AMPA receptors (Cooke & Bliss, 2006).

Furthermore, several second messengers such as nitric oxide (NO), cyclic guanosine monophosphate (cGMP) and cAMP response element-binding protein (CREB) are required for LTP (Cooke, 2006). Interestingly, Ca2+ has been suggested to

stimulate the diffusion of NO from the post-synaptic membrane into the pre-synaptic terminal (Cooke, 2006) where NO can encourage Glu production (Raju et al., 2015). Additionally, CREB is known to be involved in synthesis of brain-derived neurotropic factor (BDNF), which is necessary for successful memory consolidation (Cooke, 2006). For instance, Lee & colleagues (2004) found that when the BNDF synthesis inhibitor oligodeoxynucleotides was infused into the dorsal hippocampus of the rat 90 min prior to contextual fear conditioning LTM was impaired. In contrast, the protein synthesis independent STM was intact. Thus, encoding was successful, but the protein dependent memory consolidation and subsequent retrieval was dysfunctional without BDNF.

BDNF was reported to rapidly and reversibly potentiate postsynaptic gamma-amino butyric acid (GABA) subtype a (GABAa) receptors in the rat hippocampus leading to increased intracellular Ca2+ influx, which promotes LTP (Mizoguchi, Ishibashi, & Nabekura, 2003). In addition, activation of the inhibitory presynaptic GABAa receptors was found to enhance LTP in the rat hippocampus (Ruiz, Campanac, Scott, Rusakov, &

Kullmann, 2010). In particular, Ruiz et al. (2010) presented evidence that muscimol, a selective endogenous neurosteroid with high-affinity for GABAa receptors led to increased depolarization in the rat hippocampus while it enhanced action potential dependent Ca2+ transients and facilitated glutamatergic transmission. In contrast, the GABAa antagonist gabazine led to hyperpolarization and attenuation of action potential dependent Ca2+ transients. Proper functioning of these receptors requires the neurotransmitter GABA (Stahl, 2013). Thus, both pre- and postsynaptic GABAa receptors are necessary for successful LTP. The presented evidence collectively suggests that successful consolidation relies on cascades molecular processes that necessitate the availability of Ca2+, Glu, GABA, NO, CREB and BDNF.

AMPHETAMINE

Pharmacodynamics

This section presents evidence how AMPH can affect processes underlying consolidation based on the drug's pharmacodynamic properties, whereby it is ultimately suggested to affect consolidation.

The core structure of AMPH is made up of β-phenylethylamine and a α- methylgroup. The latter prevents the oxidation of the amine group by monoamine oxidase enzymes (MAO) and potentiates the ability of AMPH to easily cross membranes (Carvalho et. al, 2012), including the blood-brain barrier (BBB) (Kousik, Napier, & Carvey, 2012). In the brain AMPH interacts with monoamine transporters of dopamine (DA), norepinephrine (NE) and serotonin (5-HT). As such, it blocks the reuptake of these monoamines (Carvalho et al., 2012; Stahl, 2013). Additionally, AMPH promotes DA, NE, 5-HT, acetylcholine (ACh), Glu, Gly and GABA release from nerve

terminals (Carvalho et al., 2012; Porras & Mora, 1993). Most of these neurotransmitters are also involved in consolidation. For this reason, AMPH's impact on Glu, GABA, Gly and their neuromodulator DA will be further investigated.

Dopamine

AMPH most prominently affects brain DA levels via interactions with several subtypes of DA (1-5) receptors, which are found in brain structures crucial for memory such as the hippocampus, striatum and the prefrontal cortex (Stahl, 2013). Acutely, AMPH enhances extracellular DA levels via the above outlined mechanisms and inhibition of MAO, the enzyme that normally breaks down monoamines (Hutson, Tarazi, Madhoo, Slawecki, & Patkar, 2014). According to evidence AMPH-induced DA discharge enhanced the level of occupancy of the inhibitory DA2 receptors. This was confirmed by decreased binding of the specific DA2 receptor radio tracer IBZM [(I)(S)-(-)-3-iodo-2-hydroxy-6-methoxy-N-(1-ethyl-2-pyrrolidinyl)methyl benzamide] in human subjects (Laruelle et al., 1996).

Furthermore, it was found using immunochemistry of hippocampal slices of DA1 knock-out mice that DA1 receptors are critical for LTP induction (Granado et al., 2007). In sum, as AMPH increases DA levels and the engagement of several subtypes of DA receptors in the hippocampus it is reasonable to assume that it affects LTP, and thus, memory consolidation.

Furthermore, AMPH is postulated to a mediate interactions between 5-HT and DA (Pehek & Bi, 1997; Porras & Mora, 1993). For instance, Pehek and Bi (1997) examined the effects of pre-treatment of rats with the DA2 antagonist haloperidol (1.0 mg/kg/ml, ip), the 5-HT type 2 antagonist ritasterin (1.0 mg/kg/ml, ip and 5.0 mg/kg/ml, ip), and vehicle on AMPH-stimulated (5.0 mg/kg/ml, ip) cortical DA-efflux using *in vivo* microdialysis. According to the findings ritaserin on the one hand reduced the AMPH induced DA increase in the nucleus accumbens (NAc) and the striatum. On the other hand it enhanced the AMPH-induced DA release in the cortex. These findings show dependency of AMPH induced DA release on 5-HT and DA receptors.

Glutamate

AMPH has been found to induce excessive Glu efflux and availability, and increased expression of AMPA and NMDA receptors in the NAc and striatum (Hutson et al., 2014; Stahl, 2013). For example, it was found that AMPH-induced (0.5 or 2.0 mg/kg, sc) Glu efflux in the NAc of the rat was hindered by the NMDA receptor antagonist MK-801 (0.25 mg/kg, ip) (Rahman & Bardo, 2008). Moreover, in the same experiment reduced surface expression of AMPA receptors was reported. Taken together this evidence suggests that AMPH acts on Glu receptors via downstream mechanisms by changing their expression. Another study found similar results concerning AMPA expression in the NAc of rat upon chronic AMPH treatment (Nelson, Milovanovic, Wetter, Ford, & Wolf, 2009). Thus, it seems that these effects on the glutamatergic receptors can contribute to elevated excitatory transmission and improved consolidation. Additionally, a recent study presented evidence that AMPH influx into the ventraltegmental brain neurons *in vitro* caused endocytosis of

the excitatory amino acid transporter type 3, which is known to be a Glu transporter subtype in DA neurons. Therefore, the authors suggested that AMPH modulates Glu transmission via its impact on the DA transporter (DAT) system (Underhill et al., 2014). Taken together, these findings further support AMPH's ability to enhance LTP, and as such, consolidation due to direct and indirect effects on Glu transmission via DA.

GABA and Glycine

GABA has an important inhibitory role in the CNS (Stahl, 2013) that can be attenuated by AMPH (Jiao, Liu, Li, Liu, & Zhao, 2015). A recent review suggested a possible account according to which the activation of GABAa receptors by AMPH decreases DA transmission (Jiao et al., 2015). This is plausible as neuronal excitability is assumed to be a result of a synergy between excitatory and inhibitory activities. Since, GABAergic neurons often have Glu receptors and GABA is known to modulate Glu release compensatory changes in any or both of these systems may reflect an interaction between them (Stahl, 2013). In other

words, if AMPH increases Glu excitation directly and indirectly via DA, a compensatory inhibitory mechanism is required to increase the inhibition in order to produce homeostasis. Indeed, systematic injections of 5 mg/kg AMPH into the neostriatum of living rats resulted in increase in Gly and GABA levels (Porras & Mora, 1993). This effect could be blocked by intraperitoneally injected DA2 antagonist haloperidol (3mg/kg) suggesting indirect mediating effects of DA via a possible interplay between excitatory (i.e., Glu, Gly) and inhibitory (i.e., Gly, GABA) pathways. In explanation, Gly is known to sub-serve both inhibitory and excitatory functions within the CNS. Furthermore, it promotes the action of Glu via its role as a coagonist at NMDA receptors (Stahl, 2013). Thus, neuroplasticity can be affected by AMPH-induced changes directly and indirectly with DA being the crucial mediator of the excitatory and inhibitory actions.

Neurotoxicity

Psychostimulant drugs are assumed to alter the function of the BBB, which likely contributes to their neurotoxicity (Kousik et al., 2012). AMPH produces excessive monoamine levels, since it is a weak MAO inhibitor, and as a potent releaser and regulator of monoamine transporter function (Patrick & Markowitz, 1997). Surplus availability of these monoamines and the Glu-induced intracellular Ca2+ influx leads to severe oxidative stress and production of reactive oxygen species (ROS) via two mechanisms: auto-oxidation and monoamine metabolism via MAO (Carvalho et al., 2012).

Furthermore, excitotoxic consequences of extensive Glu discharge caused by AMPH have been linked to neuronal cell death and NO-mediated nitration of proteins in DA terminals resulting in reactive nitrogen species (RNS) and apoptosis (Carvalho et al., 2012). Hence, AMPH-induced ROS and RNS may activate apoptotic pathways. Indeed, in support of this toxic route it has been proposed that chronic administration of 4mg/day AMPH into the rat brain via an implanted osmotic

pump led to significant striatal DA depletion, nerve terminal swelling and fiber degeneration (Ricaurte, Bryan, Strauss, Seiden, & Schuster, 1985). Additionally, hyperthermia is another mechanism whereby AMPH causes severe oxidative stress. Since, AMPH is a stimulant it can cause dysfunctional thermoregulation in the CNS via monoamine modulation, and changes in blood flow and tissue thermoregulation (Carvalho et al., 2012).

CONCLUSION

Based on the presented evidence AMPH influences the cellular and nuclear events required for synaptic plasticity and consolidation via its direct and indirect neurochemical impact on neurotransmission and gene expression. It has indirect effects on the glutamatergic system mostly mediated via DA, triggered by increased intracellular Ca2+ and co-agonized by elevated extracellular Gly availability (Cooke & Bliss, 2006; Porras & Mora, 1992). The elevated availability of Ca2+ further induces

and maintains plasticity (Cooke & Bliss, 2006); hence, improves consolidation. Indeed, it has been shown that AMPH-induced plasticity is dependent on DA receptor activity with DA1 increasing and DA2 decreasing AMPA expression in the rat prefrontal cortex (Hutson et al., 2014).

Furthermore, AMPH can facilitate BDNF production as evidenced by rat studies in which both acute and chronic AMPH administration increased BDNF micro RNA expression in the cortex and amygdala respectively (Hutson et al., 2014). Moreover, co-transmitter Gly is needed for removing the magnesium block of the NMDA receptors during LTP induction (Stahl, 2013). Hence, as AMPH increases Gly levels it can foster LTP induction.

In support of the idea that AMPH aids memory as a result of enhanced consolidation Leri et al. (2013) conducted an experiment in which rats were infused subcutaneously with AMPH (0.03, 0.5, 1 or 2 mg/kg) or vehicle immediately or 4h post-training for 13 consecutive days. According to their findings based on the win-stay and fear conditioning tasks only lower

AMPH doses (0.03 and 0.05) improved performance significantly. Moreover, this was only apparent when AMPH was injected immediately after training, but not later. This led the authors to conclude that lower AMPH doses increase memory consolidation.

Despite the outlined enhancing effects on consolidation chronic AMPH use may deplete endogenous antioxidants leading to down-regulation of the enzyme tyrosine hydroxylase, which is involved in the endogenous biosynthesis of DA from tyrosine. Moreover, it can lead to down-regulation of these receptors (Angelucci, Gruber, El Khoury, Tonali, & Mathe, 2007). This could negatively affect consolidation in the long-term. Nevertheless, current investigations suggest that mixed AMPH salts at therapeutic doses are unlikely to directly kill DA neurons (Angelucci et al., 2007).

Furthermore, NO acts as a second messenger during LTP and is involved in RNS caused by AMPH (Cooke, 2006). In addition, AMPH induced Glu influx has severe excitotoxic properties resulting in apoptosis (Carvalho et al., 2012). These

toxic effects indicate caution in regards to therapeutic application. However, for the time being there is no evidence specifically investigating AMPH's neurotoxic effects on memory formation. Therefore, further research is needed in order to explore this field.

In conclusion, AMPH has a facilitating impact on consolidation both acutely and chronically. However, more animal and human studies are needed to define appropriate dosing required for improving memory consolidation. Additionally, AMPH both directly and indirectly influences neuroplasticity in a positive manner. In this process DA is the critical mediator of the excitatory and inhibitory actions that promote memory formation. However, due to the drug's neuro- and excitotoxic properties caution is required when it comes to chronic treatment, as long-term application can result in down-regulation of receptors involved in consolidation. This can lead to memory depletion rather than improvement. Future research should investigate the specific impact of both acute and chronic AMPH treatment on memory consolidation especially in humans.

REFERENCES

Angelucci, F., Gruber, S. H., El Khoury, A., Tonali, P. A., & Mathe, A. A. (2007). Chronic amphetamine treatment reduces NGF and BDNF in the rat brain. *Eur Neuropsychopharmacol, 17*(12), 756-762. doi: 10.1016/j.euroneuro.2007.03.002

Barch, D. M., & Carter, C. S. (2005). Amphetamine improves cognitive function in medicated individuals with schizophrenia and in healthy volunteers. *Schizophrenia Research, 77*(1), 43-58. doi: 10.1016/j.schres.2004.12.019

Carvalho, M., Carmo, H., Costa, V. M., Capela, J. P., Pontes, H., Remião, F., . . . Bastos, M. d. L. (2012). Toxicity of amphetamines: an update. *Archives of Toxicology, 86*(8), 1167-1231. doi: 10.1007/s00204-012-0815-5

Cooke, S. F. (2006). Plasticity in the human central nervous system. *Brain, 129*(7), 1659-1673. doi: 10.1093/brain/awl082

Debiec, J., LeDoux, J. E., & Nader, K. (2002). Cellular and Systems Reconsolidation in the Hippocampus *Neuron, 36*, 527-538.

Giorgetti, M., Hotsenpiller, G., Ward, P., Teppen, T., & Wolf, M. E. (2001). Amphetamine-Induced Plasticity of AMPA Receptors in the Ventral Tegmental Area: Effects on Extracellular Levels of Dopamine and Glutamate in Freely Moving Rats. *The journal of Neuroscience, 21*(16), 6362-6369.

Granado, N., Ortiz, O., Suarez, L. M., Martin, E. D., Cena, V., Solis, J. M., & Moratalla, R. (2007). D1 but not D5 Dopamine Receptors Are Critical for LTP, Spatial Learning, and LTP-Induced arc and zif268 Expression in the Hippocampus. *Cerebral Cortex, 18*(1), 1-12. doi: 10.1093/cercor/bhm026

Hutson, P. H., Tarazi, F. I., Madhoo, M., Slawecki, C., & Patkar, A. A. (2014). Preclinical pharmacology of amphetamine: Implications for the treatment of neuropsychiatric disorders. *Pharmacology & Therapeutics, 143*(3), 253-264. doi: 10.1016/j.pharmthera.2014.03.005

Jiao, D., Liu, Y., Li, X., Liu, J., & Zhao, M. (2015). The role of the GABA system in amphetamine-type stimulant use disorders. *Front Cell Neurosci, 9*, 162. doi: 10.3389/fncel.2015.00162

Kalisch, R., Holt, B., Petrovic, P., De Martino, B., Kloppel, S., Buchel, C., & Dolan, R. J. (2009). The NMDA agonist D-cycloserine facilitates fear memory consolidation in humans. *Cereb Cortex, 19*(1), 187-196. doi: 10.1093/cercor/bhn076

Kousik, S. M., Napier, T. C., & Carvey, P. M. (2012). The Effects of Psychostimulant Drugs on Blood Brain Barrier Function and Neuroinflammation. *Frontiers in Pharmacology, 3*. doi: 10.3389/fphar.2012.00121

Laruelle, M., Abi-Dargham, A., van Dyck, C. H., Gil, R., D'Souza, C. D., & Erdos, J. (1996). Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects
Proc Natl Acad Sci, 93, 9235–9240.

Leri, F., Nahas, E., Henderson, K., Limebeer, C. L., Parker, L. A., & White, N. M. (2013). Effects of post-training heroin and d-amphetamine on consolidation of win-stay learning and fear conditioning. *J Psychopharmacol, 27*(3), 292-301. doi: 10.1177/0269881112472566

Meneses, A., Ponce-Lopez, T., Tellez, R., Gonzalez, R., Castillo, C., & Gasbarri, A. (2011). Effects of d-amphetamine on short- and long-term memory in spontaneously hypertensive, Wistar–Kyoto and Sprague–Dawley rats. *Behavioural Brain Research, 216*(1), 472-476. doi: 10.1016/j.bbr.2010.08.035

Mizoguchi, Y., Ishibashi, H., & Nabekura, J. (2003). The action of BDNF on GABAA currents changes from potentiating to suppressing during maturation of rat hippocampal CA1 pyramidal neurons. *The Journal of Physiology, 548*(3), 703-709. doi: 10.1113/jphysiol.2003.038935

Myhrer, T. (2003). Neurotransmitter systems involved in learning and memory in the rat: a meta-analysis based on studies of four behavioral tasks. *Brain Research Reviews, 41*(2-3), 268-287. doi: 10.1016/s0165-0173(02)00268-0

Nelson, C. L., Milovanovic, M., Wetter, J. B., Ford, K. A., & Wolf, M. E. (2009). Behavioral sensitization to amphetamine is not accompanied by changes in glutamate receptor surface expression in the rat nucleus accumbens. *J Neurochem, 109*(1), 35-51. doi: 10.1111/j.1471-4159.2009.05911.x

Nicoll, R. A., & Malenka, R. C. (1995). Contrasting properties of two forms of long-term potentiation in the hippocampus. *Nature, 377*, 115-118.

Parwani, A., Weiler, M. A., Blaxton, T. A., Warfel, D., Hardin, M., Frey, K., & Lahti, A. C. (2005). The effects of a subanesthetic dose of ketamine on verbal memory in normal volunteers. *Psychopharmacology, 183*(3), 265-274. doi: 10.1007/s00213-005-0177-2

Patrick, K. S., & Markowitz, J. S. (1997). Pharmacology of Methylphenidate, Amphetamine Enantiomers and Pemoline in Attention-De®cit Hyperactivity Disorder. *Human Psychopharmacology, 12*, 527-546.

Pehek, E. A., & Bi, Y. (1997). Ritanserin administration potentiates amphetamine-stimulated dopamine release in the rat prefrontal cortex. *Prog. Neuro-Psychopharmacol. & Biol. Psychiat., 21*, 671-682.

Porras, A., & Mora, F. (1993). Dopamine receptor antagonist blocks the release of glycine, GABA, and taurine produced by amphetamine. *Brain Research Bulletin, 31*, 305-310.

Rahman, S., & Bardo, M. T. (2008). Environmental enrichment increases amphetamine-induced glutamate neurotransmission in the nucleus accumbens: a neurochemical study. *Brain Res, 1197*, 40-46. doi: 10.1016/j.brainres.2007.12.052

Raju, K., Doulias, P.-T., Evans, P., Krizman, E. N., Jackson, J. G., Horyn, O., . . . Ischiropoulos, H. (2015). Regulation of brain glutamate metabolism by nitric oxide and S-nitrosylation. *Science Signaling, 8*(384), ra68-ra68. doi: 10.1126/scisignal.aaa4312

Ricaurte, G. A., Bryan, G., Strauss, L., Seiden, L. S., & Schuster, C. R. (1985). Hallucinogenic amphetamine selectively destroys brain serotonin nerve terminals. . *Science, 229*, 986-988.

Rodrigues, S. M., Schafe, G. E., & LeDoux, J. E. (2001). Intra-amygdala blockade of the NR2B subunit of the NMDA receptor disrupts the acquisition but not the expression of fear conditioning..pdf>. *Journal of Neuroscience, 21*(17), 6889-6896.

Rubin, M. A. (2004). Intra-Amygdala Administration of Polyamines Modulates Fear Conditioning in Rats. *Journal of Neuroscience, 24*(9), 2328-2334. doi: 10.1523/jneurosci.1622-03.2004

Ruiz, A., Campanac, E., Scott, R. S., Rusakov, D. A., & Kullmann, D. M. (2010). Presynaptic GABAA receptors enhance transmission and LTP induction at hippocampal mossy fiber synapses. *Nat Neurosci, 13*(4), 431-438. doi: 10.1038/nn.2512

Servan-Schreiber, D., Carter, C. S., Bruno, R. M., & Cohen, J. D. (1998). Dopamine and the Mechanisms of Cognition: Part II. D-Amphetamine Effects in Human Subjects Performing a Selective Attention Task. *Biological Psychiatry*, 723-729.

Silber, B. Y., Croft, R. J., Papafotiou, K., & Stough, C. (2006). The acute effects of d-amphetamine and methamphetamine on attention and psychomotor

performance. *Psychopharmacology (Berl), 187*(2), 154-169.

Stahl, S. M. (2013). *Stahl's essential psychopharmacology: neuroscientific basis and practical applications* (4 ed.): Cambridge University Press. .

Sumowski, J. F., Chiaravalloti, N., Erlanger, D., Kaushik, T., Benedict, R. H., & DeLuca, J. (2011). L-amphetamine improves memory in MS patients with objective memory impairment. *Mult Scler, 17*(9), 1141-1145. doi: 10.1177/1352458511404585

Turner, K. M., & Burne, T. H. J. (2016). Improvement of attention with amphetamine in low- and high-performing rats. *Psychopharmacology, 233*(18), 3383-3394. doi: 10.1007/s00213-016-4376-9

Underhill, S. M., Wheeler, D. S., Li, M., Watts, S. D., Ingram, S. L., & Amara, S. G. (2014). Amphetamine modulates excitatory neurotransmission through endocytosis of the glutamate transporter EAAT3 in dopamine neurons. *Neuron, 83*(2), 404-416. doi: 10.1016/j.neuron.2014.05.043