Addiction & Health

https://ahj.kmu.ac.ir
10.34172/ahj.2023.1307
Vol. 15, No. 4, 2023, 289-297

Review Article

A Review on the Disruption of Novel Object Recognition Induced by Methamphetamine

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Abstract

Background: Methamphetamine (MA), is a widely abused synthetic psychostimulant that leads to irreversible brain damage manifested as cognitive impairments in humans and animals. The novel object recognition (NOR) task is a commonly used behavioral assay for the investigation of non-spatial memory in rodents. This test is based on the natural tendency of rodents to spend more time exploring a novel object than a familiar one. NOR test has been used in many studies investigating cognitive deficits caused by MA in rodents. The objective of the present study was to review neurobiological mechanisms that might be responsible for MA-induced NOR alterations.

Methods: A PubMed search showed 83 publications using novel object recognition and methamphetamine as keywords in the past 10 years.

Findings: The present study revealed different MA regimens cause recognition memory impairment in rodents. In addition, it was found that the main neurobiological mechanism involved in MA-induced recognition deficits is the dysfunction of monoaminergic systems.

Conclusion: NOR is a useful test to assess the cognitive functions following MA administration and evaluate the efficacy of new therapeutic agents in MA-addicted individuals.

Keywords: Methamphetamine, Novel object recognition test, Monoaminergic systems, Cognitive impairment, Rodents

Citation: Seyedhosseini Tamijani SM, Beirami E, Ghazvini H, Rafaiee R, Nazeri M, Razavinasab M. A review on the disruption of novel object recognition induced by methamphetamine. *Addict Health*. 2023;15(4):289–297. doi:10.34172/ahj.2023.1307

Received: September 21, 2021, **Accepted:** November 7, 2021, **ePublished:** October 29, 2023

Introduction

Methamphetamine (MA), an illicit psychostimulant, is the second most highly abused drug worldwide after cannabis. It has been reported that MA abusers show structural brain abnormalities in the prefrontal cortex (PFC) and hippocampus[1] and exhibit impairments in cognitive functions such as episodic memory as well as executive functions[2] that can be partially recovered following MA abstinence.[3] The mechanisms underlying cognitive impairments are not fully understood currently; nevertheless, a considerable number of studies have indicated that oxidative stress, neuroinflammation, excitotoxicity, reactive oxygen and nitrogen species microglial activation, as well as various apoptotic pathways play an essential role in the MA-induced neurotoxic effects leading to cognitive impairments.[4-6] Meta-analysis studies have also demonstrated that impairments in episodic memory are one of the most common cognitive impairments in relapsing and abstinent long-term MA users.[2] Episodic memory is a form of declarative memory that refers to the use of a previously experienced autobiographical event for conscious recall in humans.[7] The visual paired comparison task is used to test declarative memory in human subjects[8] while a modified version of the task is recruited for rodents.[9] One such task is the novel object recognition (NOR) task that reflects components of episodic memory and assesses non-spatial object memory in rodents based on their natural tendency toward the exploration of novel objects and environments.[10] Several original studies have evaluated molecular mechanisms underlying recognition memory impairments induced by MA and reported different neurobiological mechanisms that are involved in NOR deficit in rodents. The present study aims to review these mechanisms as well as the effect of different regimens of MA administration on the NOR memory.

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Methods

Search strategy and selection criteria

A literature search was conducted in the PubMed electronic database from January 2000 to December 2020 for relevant studies using the following search strategy: (object recognition OR novel object recognition OR object memory) AND (mice OR rat OR mouse) AND (methamphetamine).

Inclusion and exclusion criteria

The search was limited to articles in the English language. To determine the inclusion of the articles, the search was performed independently by two researchers and then, all peer-reviewed relevant articles were identified. A flowchart of the process for selecting studies is depicted in Figure 1.

Results

The NOR task

Ennaceur and Delacour developed the NOR task based on the innate tendency of animals to explore novel objects over familiar ones.[9,11] This test is widely used for the investigation of genetic, pharmacological, and neurological changes related to cognition disorders. Besides, it can be used to measure working and episodic memory, attention, anxiety, and preference for novelty in rodents.[10] NOR test has several advantages compared to other rodent memory tests, which have made it attractive to researchers studying cognitive disturbances. Basically, in the NOR test, there are no positive or negative reinforcers, hence it does not create stressful conditions. Moreover, this test can be performed in shorter time frames compared to other memory tests such as the Morris water maze. It is also cost-effective as it does not require expensive tools.[12] This test assesses the preference for the exploration of a novel object that is presented to the animal measuring time spent exploring the novel object in the apparatus and recognizing previously encountered objects.

NOR test can be modified to evaluate different phases of learning and memory (e.g., acquisition, consolidation, or recall), different types of memory (e.g., non-spatial memory), or different retention intervals (e.g., short-term or long-term memory).[13] Despite the numerous advantages of the NOR test, it has some limitations. Sometimes, animals spend less time on novelty exploration which makes it difficult to analyze the results. Therefore, to obtain significant differences, group sizes must be increased. Moreover, potential differences in the rate of learning cannot be measured in this test as there is only one training session. In addition, the search activity can increase in a large open field and animals might also show anxiety-like behavior in the form of increased movement and exploration of different parts of the testing apparatus, making the analysis more difficult.[10] Hence, it is necessary to accommodate the animals to the testing chamber prior to the implementation of the test and also consider the confounding effects of the anxiety caused by the exposure to a novel object.

The NOR task procedures

There is considerable variation among the studies in terms of NOR procedure. However, the most commonly used procedure consists of three sessions: habituation, familiarization or training, and test (Figure 2). In the habituation session, each animal is allowed to freely explore an open field without objects. Then, the animal is taken from the arena and put in its cage. During the familiarization session, animals are placed in the arena containing two similar objects (A + A), which is considered the acquisition trial. After a retention interval, in the test session, animals are exposed to two objects in the open-field arena; one is a familiar object from the familiarization session and the other is novel (A + B).[14] The recognition index is measured as a ratio of the time spent exploring the novel object over the total time spent exploring both objects in the test session.[15] The time that animals spend during each session as well as the interval between them are not constant and variations in the timing of the procedure are a norm. In our animal laboratory, normal rats could discriminate between the familiar and novel objects when the retention interval was at least 90 minutes and also 24 hours after the familiarization session

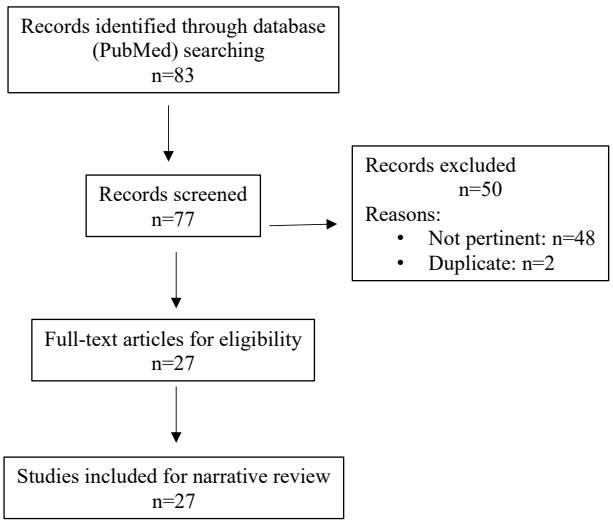

Figure 1. Flow chart of the study selection process

Figure 2. Schematic representation of the novel object recognition task

for the evaluation of short- and long-term memory in the test session, respectively.[16,17] In the NOR paradigm, exploratory behavior is considered as touching or sniffing the objects with the nose but not standing or sitting on the objects. Objects can be made of plastic, metal, or glass (similar in height and volume but different in shape and color) and chosen after determining in preliminary experiments with other animals that they were equally preferred by the test subjects.

Brain regions involved in NOR task

It has been reported that the hippocampus and perirhinal (PRh) cortex are the main brain regions involved in NOR memory. PRh cortex has a critical role in the object recognition memory and is essential for presenting basic information about the familiarity or novelty of an object and also coding information about the objects in a short retention interval. Nonetheless, it is not responsible for maintaining information about the object during longer retention intervals.[18] On the other hand, the hippocampus, by coding object memory, maintains strong novel object preference after long but not short durations.[19] Other studies have also reported the role of PFC in the object recognition memory.[20,21] Moreover, there is evidence suggesting that the nucleus accumbens (NAc) is involved in the behavioral response to novelty and other tasks that rely on object familiarity discrimination.[22]

Discussion

Molecular mechanisms underlying MA-induced NOR memory deficit

In this study, the articles that investigated the effect of different MA regimens on the recognition memory in the NOR test were reviewed. Earlier research has demonstrated that the binge-exposure paradigm is a common model to study MA neurotoxicity in rodents and also escalating dose paradigm appears to mimic the human pattern of escalating drug intake.[23,24] As illustrated in Table 1, most of the studies using single-day high-dose as well as repeated or chronic exposure models reported novel object memory deficits following MA administration. These patterns have also been observed in MA self-administration paradigms. Self-administration paradigms are valid and reliable animal models for rodents that mimic drug abuse conditions in humans.[25] In this way, the administration starts with a low dose of the drug and gradually increases over time.[26]

In most of these drug administration models, object recognition memory impairments persist for a long time after MA discontinuation. This suggests that cognitive impairments are the result of MA-induced molecular disruptions involved in cognitive functions beyond the effects of early drug withdrawal[48] or MA-deprivation-induced neural changes. MA-induced behavioral consequences depend vastly on the pattern of MA administration. However, in the case of recognition memory, the consequences appear to be sensitive to MA intake, regardless of the types of MA dosing regimen and administration routes. This can be related to brain structures involved in recognition memory that are affected by this psychostimulant drug.

In association with the molecular mechanisms involved in MA-induced NOR memory deficits, several studies have shown that MA-induced biochemical and structural changes occur in the monoaminergic systems such as dopaminergic terminals.[54,55] In these cases, MA enters dopaminergic terminals via the dopamine transporter (DAT) and passive diffusion, causing dopamine (DA) efflux from the storage vesicles into the cytoplasm. DA then intracellularly autoxidizes and produces several reactive oxygen and nitrogen species as well as DA quinones. These lead to oxidative stress followed by mitochondrial dysfunction and dopaminergic terminal damage[56] (Figure 3). It has been reported that MA damages the dopaminergic system primarily in the striatum; however, this system is less affected in the hippocampus and PRh.[34,36] Moreover, a recent study has demonstrated that MA exposure through the excessive release of DA in the PFC leads to the activation of the neuronal apoptosis pathway and finally induces damage to recognition memory function, including NOR memory.[51] Other studies have also indicated that MA disrupts the serotonergic system in the hippocampus, PFC, and PRh which are important regions for object recognition memory.[34,36] Reichel et al have shown that MA impairs recognition memory by reducing serotonin and norepinephrine transporters (SERT and NET, respectively) in the hippocampus and PRh cortex.[57] Therefore, impairments in the monoaminergic systems can be considered one of the main molecular mechanisms of MA-induced recognition memory deficits in most cases (Table 1). Nevertheless, a few studies have demonstrated no change in the NOR test after MA administration, although dopaminergic markers were affected. According to these studies, this non-alteration could be attributed to various mechanisms including neuroadaptation after the administration of escalating MA regimen,[58] use of C57BL/6 mice for modeling cognitive deficits,[35] compensatory mechanisms, tolerance to the neurotoxic effect of MA, and finally a non-critical injury to monoamine terminals.[37]

Dysfunction of the extracellular signal-regulated kinase 1/2 (ERK1/2) pathway in the PFC is another molecular mechanism involved in MA-induced NOR memory deficits.[45] ERK1/2, a member of the mitogen-activated protein kinase (MAPK) family, is necessary for the consolidation of different forms of long-term memory.[59] Furthermore, it has been reported that the ERK1/2 signaling pathway linked to dopamine D1 receptors is involved in protein synthesis-dependent long-term retention of recognition memory in the PFC.[60] Tran et al

Table 1. NOR performance in MA-treated animals and involvement of molecular mechanisms underlying MA neurotoxic effects

MA regimen	Molecular mechanisms involved in recognition memory dysfunction	NOR test after the last inj. of MA	Retention interval	NOR performance	References
3 × 10 mg/kg; i.p., at 2 h intervals	Depletion of DA and 5-HT (striatum), ↔DA and 5-HT (PFC, hippocampus, VTA, and substantia nigra)	4 days	1, 2, and 4 h after the training session	↓NOR performance in the MA-treated rats	27
4 × 4 mg/kg; s.c., at 2 h intervals	↓DAT (striatum), ↓SERT (hippocampus)	1 week and 3 weeks	90 min and 24 h after the training session	↓NOR performance in the MA-treated rats	28
4 × 4 mg/kg; s.c., at 2 h intervals	↓DAT (ventral caudate putamen), ↓SERT (hippocampus, PRh cortex, and neocortex), cell degeneration in the primary somatosensory cortex	1 week	90 min after the training session	↓NOR performance in the MA-treated rats	29
3 mg/kg; i.p., once every other day for 20 days	↔DAT (striatum), ↔SERT (hippocampus and PRh cortex)	1 week	90 min after the training session	↓NOR performance in the MA-treated rats	30
4 × 5 mg/kg; s.c., at 2 h intervals	↓TH (caudate putamen of striatum), dopaminergic terminal deficit, ↑hyperthermia	27 days	1 and 24 h after the training session	↓NOR performance in the MA-treated rats	31
4 × 4 mg/kg; s.c., at 2 h intervals	↓DAT (striatum), ↓SERT (hippocampus and PRh cortex), ↑neuronal degeneration (primary somatosensory cortex), ↓Fos expression (ventrolateral striatum, NAc, cingulate cortex, and the deeper layers of motor cortex)	1 week and 3 weeks	90 min and 24 h after the training session	↓NOR performance in the MA-treated rats	32
4 × 10 mg/kg; s.c., every 2 h or 24 × 1.67 mg/kg; s.c., once every 15 min	↓DA and DOPAC, (striatum), ↓5-HT and 5-HIAA (hippocampus), ↑GFAP (striatum and hippocampus), ↑plasma corticosterone level	1 week	24 h after the training session	↓NOR performance in the MA-treated rats, regardless of dosing regimen	33
1 mg/kg; s.c., once a day for 7 days	↓DA content (PFC), ↓5-HT content (hippocampus), ↑HVA/DA ratio and ↑DOPAC + HVA/DA ratio (PFC), ↑5-HIAA/5-HT ratio (hippocampus), ↔DOPAC/DA or 5-HIAA/5-HT ratio (PFC), ↔ DOPAC/DA, HVA/DA or DOPAC + HVA/DA ratio (hippocampus)	1 week	24 h after the training session	↓NOR performance in the MA-treated mice	34
4 × 10 mg/kg; s.c., at 2 h intervals	↓DA and DOPAC (striatum), ↑GFAP (striatum), ↑basal plasma corticosterone, hyperthermia	1 week	1 h after the training session	↔NOR performance in the MA-treated mice	35
4 × 5 mg/kg; i.p., every 2 h from postnatal day 91 to 100	↓DA (striatum and hippocampus), ↓DOPAC (striatum and PFC), ↓HVA (striatum), ↓5-HT and 5-HIAA (hippocampus)	24 h	15 min and 24 h after the training session	↔ NOR after 15 min, ↓NOR performance after 24 h in the MA-treated rats	36
24 mg/kg; i.p., once a day for 14 consecutive days	↔Synaptic plasticity (hippocampus), ↓TH (cortex, hippocampus, and striatum), ↓low MW of DAT and ↑high MW of DAT (striatum), ↔low MW of DAT and ↑high MW of DAT (cortex), ↓low MW of DAT ↔ High MW of DAT, (hippocampus)	Day 0 (no drug treatment) and 7 and 14 days	1 h after the training session	↔NOR performance in the MA-treated mice	37
Low dose of MA (4 mg/kg) or high dose of MA (8 mg/kg); i.p., once a day for 16 weeks	↓DAT, dopamine D1 and D2 receptor levels and distribution (striatum, NAc, and OT) in low and high doses of MA	24 h	1 h after the training session	↓NOR performance in the high dose of MA-treated rats	38
1 mg/kg; s.c., once a day for 7 consecutive days	↓Total level of H3ac and H4ac, ↑5-mC, ↓H3ac enrichment at promoters of dopamine D2 receptor, Hcrtr1/2, Hrh1, and Grin1, ↑H4ac enrichment at promoters of dopamine D1 receptor, Hrh1 and Grin1, (mPFC)	24 h	24 h after the training session	↓NOR performance in the MA-treated mice	39
10 mg/kg; i.p., once a day for 7 consecutive days	↑Protein expression of dopaminergic D2 receptors, ↓protein expression of DAT, ↑protein expression of p-PKA, ↑protein expression of HCN1 channel (hippocampus)	24 h	4 h after the training session	↓NOR performance in the MA-treated mice	40
1mg/kg; s.c., once a day for 7 days	↓p-ERK1/2 and dysfunction of dopamine D1 receptor-ERK1/2 pathway (PFC)	1, 7, 14, or 28 days	1 h or 24 h after the training session	↔ NOR after 1 h, ↓NOR performance after 1, 7, 14, or 28 days in the MA-treated mice	41
1 mg/kg; s.c., once a day for 7 days	↓p-ERK(PFC)	1 day and 3 weeks	24 h after the training session	↓NOR performance in the MA-treated mice	42
1 mg/kg; s.c., once a day for 7 days	disruption of ERK1/2 signaling (PFC)	1 week	24 h after the training session	↓NOR performance in the MA-treated mice	43
1 mg/kg; s.c., once a day for 7 days	↓p-ERK (mPFC)	24 h	24 h after the training session	↓NOR performance in the MA-treated mice	44
1 mg/kg; s.c., once a day for 7 consecutive days	↔Extracellular ACh levels, ↔extracellular DA levels, ↓p-ERK1/2, ↓nAChRs (PFC)	1 day and 3 days	24 h after the training session	↓NOR performance in the MA-treated mice	45
4 × 7.5 mg/kg; s.c., at 2 h intervals	↓SERT density (hippocampal CA1 and CA3 regions and PRh), ↓α4β2 nAChR density (hippocampal CA1 region)	4 days	90 min after the training session	↓NOR performance in the MA-treated rats	46

Table 1. Continued.

MA regimen	Molecular mechanisms involved in recognition memory dysfunction	NOR test after the last inj. of MA	Retention interval	NOR performance	References
1 mg/kg; i.p., once a day for 7 consecutive days	↑PKCδ and p- PKCδ expression, ↓GPx1 expression, ↓M1, M3 and M4 mAChRs and β2 nAChR expression, ↓p-ERK1/2, ↑Nrf2 (PFC)	1 week	24 h after the training session	↓NOR performance in the MA-treated mice	47
1 mg/kg; s.c., once a day for 7 days	↑p-PKCδ expression, ↓p-ERK1/2, ↓GPx-1 (PFC)	1, 7, 14, or 28 days	24 h after the training session	↓NOR performance in the MA-treated mice	48
30 mg/kg, ip., single dose	↑NPY, Y2, and Y5 receptor mRNA levels, changes in NPY receptor binding, disruption of the AKT/mTOR signaling pathway (hippocampus)	5 min after or before MA inj.	24 h after the training session	↓NOR performance in the MA-treated mice	49
0.02 mg/infusion; i.v., 7 daily 1 h sessions followed by 6 h daily sessions for 14 days	↓mGluR5 (PRh cortex)	1 week	90 min and 24 h after the training session	↓NOR performance in the MA-treated rats	50
4 × 5 mg/kg; i.p., every 2 h	↓Expression level of Bcl-2 and ↑expression level of cleaved caspase-3 (PFC)	2 days	24 h after the training session	↓NOR performance in the MA-treated mice	51
Four injections of 6 mg/kg, s.c, at 2 h intervals	Cannabinoid type 1 receptor antagonist	1 week	24 h after the training session	↓NOR performance in the MA-treated rats	52
Daily injection of 5 mg/kg METH for 5 consecutive days	↑Histamine H3 receptor protein expression, ↑hippocampal apoptosis	1 week	24 h after the training session	↓NOR performance in the MA-treated mice	53

Abbreviations: MA: methamphetamine, NOR: novel object recognition, inj.: injection, i.p.: intraperitoneal, DA: dopamine, 5-HT: 5-hydroxytryptamine (serotonin), PFC: prefrontal cortex, VTA: ventral tegmental area, s.c.: subcutaneous, DAT: dopamine transporter, SERT: serotonin transporter, PRh: perirhinal, TH: tyrosine hydroxylase, NAc: nucleus accumbens, DOPAC: 3,4-dihydroxyphenylacetic acid, 5-HIAA: 5-hydroxyindoleacetic acid, GFAP: glial fibrillary acidic protein, HVA: homovanillic acid, MW: molecular weight, OT: olfactory tubercle, H3ac and H4ac: histone 3 and 4 acetylation, 5-mC: 5-methylcytocine, Hcrtr1/2: orexin receptor 1 and 2, Hrh1: histamine receptor1, Grin1: glutamate ionotropic receptor NMDA type subunit1, mPFC: medial prefrontal cortex, p-PKA: phospho-protein kinase A, HCN1: hyperpolarization-activated cyclic-nucleotide-gated non-selective cation 1, p-ERK1/2:phospho-extracellular signal-regulated protein kinases 1 and 2, ACh: acetylcholine, nAChRs: nicotinic acetylcholine receptors, CA1: cornu ammonis1, PKCδ: protein kinase C delta, GPx1: glutathione peroxidase1, mAChRs: muscarinic acetylcholine receptors, Nrf2: nuclear factor erythroid-2-related factor 2, NPY: neuropeptide Y, AKT/mTOR: protein kinase B/mammalian target of rapamycin, i.v.: intravenous, mGluR5: metabotropic glutamate receptor5, Bcl-2: B-cell lymphoma-2, ↔: without change, ↑: increase, ↓: decrease

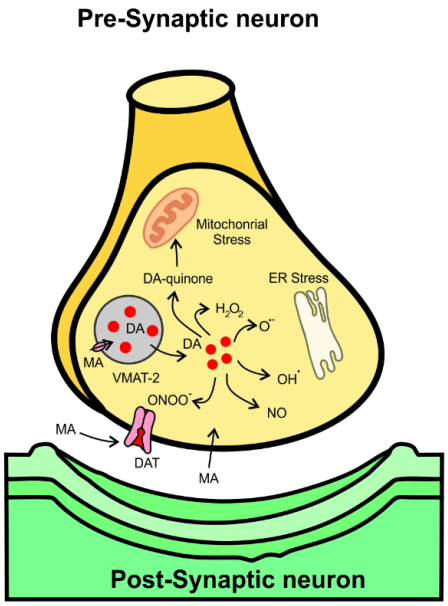

Figure 3. Schematic drawing of cellular and molecular events involved in MA-induced DA terminal damage. This figure summarizes the findings of many studies that have addressed the role of DA, oxidative stress, and other mechanisms in MA neurotoxicity. MA enters dopaminergic terminals via DAT and passive diffusion, causing the efflux of DA from intraneuronal vesicles into the cytoplasm. Then, DA auto-oxidizes to produce toxic DA quinones and several reactive oxygen and nitrogen species. These events lead to oxidative stress, mitochondrial dysfunctions, and dopaminergic terminal damage

demonstrated that pharmacological inhibition of ERK1/2 using a selective antagonist impairs long-term memory in rodents.[48] There is also accumulating evidence implicating the role of the ERK pathway in behavioral responses to addictive drugs such as MA.[61] Kamei et al indicated that repeated MA exposure impairs NOR memory through the impairment of the ERK1/2 pathway in the PFC brain region in mice.[41] Thus, PFC activation of ERK1/2 immediately after exposure to novel objects appears to be necessary for the long-term retention of NOR memory.[60]

Other studies have revealed that muscarinic and nicotinic acetylcholine receptors (mAChR and nAChR, respectively) are also affected by MA.[46,62] It is known that the Ach system is involved in the cognitive functions, and Ach receptors are expressed at high levels in the hippocampus and PFC.[63] It has been revealed that MA exposure during the brain development induces mAChR alterations and causes long-term cognitive impairments in rodents.[62] Furthermore, nicotine administration in MA-treated rats attenuates NOR memory deficit by increasing α4β2 nAChRs in the PRh cortex and hippocampus.[46] Berkeley et al reported that M1 mAChR significantly activates ERK1/2 in the CA1 pyramidal neurons of the hippocampus.[64] As previously mentioned, ERK1/2 is involved in the cognitive functions and is

affected by MA toxicity. Therefore, MA administration might hypothetically impair NOR memory through the malfunction of Ach receptor-ERK1/2 signaling.

Some studies have also observed that exposure to psychostimulants, including MA, causes neuroinflammatory responses which may produce memory impairments.[65,66] Protein kinase Cδ (PKCδ), a member of the novel PKC isoform family, is a major proinflammatory kinase that is involved in a variety of biological events such as DA regulation, neuroinflammation, oxidative stress, and apoptosis[67] and also is associated with memory dysfunction.[68] Shin et al also demonstrated that MA exposure significantly increases PKCδ expression in mice striatum and causes NOR memory deficits.[69] Accordingly, MA can induce recognition memory impairment via the activation of the PKCδ pathway in rodents.

It has been reported that disruption in the neuropeptide Y (NPY) system is another mechanism involved in NOR memory impairment induced by MA.[49] NPY, one of the most abundant peptides in the central nervous system, is involved in several important functions such as learning and memory. Gonçalves et al. showed MA-induced recognition memory impairment in the NOR test is accompanied by significant alterations in the striatal and hippocampus NPY and NPY receptors (especially Y2 receptor) mRNA levels in rodents.[49] Indeed, these findings confirm that NPY system alterations are involved in memory deficits induced by MA administration in the NOR test.

It has been shown that MA induces recognition memory impairment by the dysfunction of the AKT/mTOR pathway in the hippocampus of rodents.[49] The AKT/mTOR pathway is an important signaling cascade involved in protein synthesis-dependent synaptic plasticity required for hippocampus-dependent learning and memory processes.[70] A few studies have also indicated that MA administration induces NOR memory deficit via the damage of somatosensory cortical neurons that could linger for a long time after MA.[29,32] Furthermore, other studies have reported that MA administration reduces the expression of several ionotropic and metabotropic glutamate receptor subunits in the hippocampus, PRh, and PFC of rodents which seems to be correlated with the recognition memory impairments.[50,71] Besides, several lines of evidence have shown the interaction between NMDA (N-methyl-D-aspartate) and dopamine D1 receptors required for the consolidation of recognition memory in the PFC.[72,73] Ishikawa et al. revealed that repeated MA administration impairs recognition memory through the modulating NMDA receptors in the hippocampus and PFC of rodents.[74] Decreased Bcl-2 expression level and increased cleaved caspase-3 expression level in PFC as well as increased hyperpolarization-activated cyclic-nucleotide-gated non-selective cation 1 (HCN1) channel, as the key regulators of memory function in the hippocampus are other mechanisms involved in NOR impairment induced by MA.[40]

As reported in Table 1, it seems that NOR memory is affected by MA administration through diverse pathophysiological mechanisms,[28,52,53] and looking at the mechanisms of this alteration needs consideration of different molecular pathways, though the use of the NOR paradigm is extremely helpful in elucidating the neurobiological consequences of MA administration and also the cognitive dysfunctions associated with long term use of psychostimulants including MA. It consider that the main mechanism of recognition memory deficit is the alternation in the monoaminergic system.[28,30]

The limitation of this study was that exclusively the PubMed database was employed to scrutinize related articles. It is evident that the inclusion of other databases such as Scopus, Web of Science (ISI), and EMBASE would have yielded more extensive data.

Conclusion

This review indicated that several mechanisms are involved in NOR memory impairment after MA administration, and monoaminergic system disruption in the hippocampus, striatum, PRh, and PFC could be the pivotal mechanisms impairing NOR memory following MA exposure. Thus, targeting these specific pathways can provide promising therapeutic approaches against MA-induced recognition memory deficits. Moreover, the NOR test is a simple method to assess cognitive functions such as learning and memory and also novelty exploration in psychostimulant dependence animal models as well as other cognitive deficit models in rodents.

Acknowledgments

The authors are grateful to Prof. Mohammad Shabani for providing practical comments on the manuscript.

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Competing Interests

The authors declare no competing interests.

Funding

This research did not receive any specific grant from funding

agencies in the public, commercial, or not-for-profit sectors.

References

1. Kutlu MG, Gould TJ. Effects of drugs of abuse on hippocampal plasticity and hippocampus-dependent learning and memory: contributions to development and maintenance of addiction. Learn Mem. 2016;23(10):515-33. doi: 10.1101/lm.042192.116.
2. Scott JC, Woods SP, Matt GE, Meyer RA, Heaton RK, Atkinson JH, et al. Neurocognitive effects of methamphetamine: a critical review and meta-analysis. Neuropsychol Rev. 2007;17(3):275-97. doi: 10.1007/s11065-007-9031-0.
3. Baicy K, London ED. Corticolimbic dysregulation and chronic methamphetamine abuse. Addiction. 2007;102 Suppl 1:5-15. doi: 10.1111/j.1360-0443.2006.01777.x.
4. Shin EJ, Shin SW, Nguyen TT, Park DH, Wie MB, Jang CG, et al. Ginsenoside Re rescues methamphetamine-induced oxidative damage, mitochondrial dysfunction, microglial activation, and dopaminergic degeneration by inhibiting the protein kinase Cδ gene. Mol Neurobiol. 2014;49(3):1400-21. doi: 10.1007/s12035-013-8617-1.
5. Moratalla R, Khairnar A, Simola N, Granado N, García-Montes JR, Porceddu PF, et al. Amphetamine-related drugs neurotoxicity in humans and in experimental animals: main mechanisms. Prog Neurobiol. 2017;155:149-70. doi: 10.1016/j.pneurobio.2015.09.011.
6. Beirami E, Oryan S, Seyedhosseini Tamijani SM, Ahmadiani A, Dargahi L. Intranasal insulin treatment alleviates methamphetamine induced anxiety-like behavior and neuroinflammation. Neurosci Lett. 2017;660:122-9. doi: 10.1016/j.neulet.2017.09.026.
7. Davis KE, Easton A, Eacott MJ, Gigg J. Episodic-like memory for what-where-which occasion is selectively impaired in the 3xTgAD mouse model of Alzheimer's disease. J Alzheimers Dis. 2013;33(3):681-98. doi: 10.3233/jad-2012-121543.
8. Burbacher TM, Grant KS. Measuring infant memory: Utility of the visual paired-comparison test paradigm for studies in developmental neurotoxicology. Neurotoxicol Teratol. 2012;34(5):473-80. doi: 10.1016/j.ntt.2012.06.003.
9. Ennaceur A. One-trial object recognition in rats and mice: methodological and theoretical issues. Behav Brain Res. 2010;215(2):244-54. doi: 10.1016/j.bbr.2009.12.036.
10. Antunes M, Biala G. The novel object recognition memory: neurobiology, test procedure, and its modifications. Cogn Process. 2012;13(2):93-110. doi: 10.1007/s10339-011-0430-z.
11. Ennaceur A, Delacour J. A new one-trial test for neurobiological studies of memory in rats. 1: behavioral data. Behav Brain Res. 1988;31(1):47-59. doi: 10.1016/0166-4328(88)90157-x.
12. Grayson B, Leger M, Piercy C, Adamson L, Harte M, Neill JC. Assessment of disease-related cognitive impairments using the novel object recognition (NOR) task in rodents. Behav Brain Res. 2015;285:176-93. doi: 10.1016/j.bbr.2014.10.025.
13. Lueptow LM. Novel object recognition test for the investigation of learning and memory in mice. J Vis Exp. 2017(126):55718. doi: 10.3791/55718.
14. Gaskin S, Tardif M, Cole E, Piterkin P, Kayello L, Mumby DG. Object familiarization and novel-object preference in rats. Behav Processes. 2010;83(1):61-71. doi: 10.1016/j.beproc.2009.10.003.
15. Cohen SJ, Stackman RW Jr. Assessing rodent hippocampal involvement in the novel object recognition task. A review. Behav Brain Res. 2015;285:105-17. doi: 10.1016/j.bbr.2014.08.002.
16. Seyedhosseini Tamijani SM, Beirami E, Ahmadiani A, Dargahi L. Effect of three different regimens of repeated methamphetamine on rats' cognitive performance. Cogn Process. 2018;19(1):107-15. doi: 10.1007/s10339-017-0839-0.
17. Beirami E, Oryan S, Seyedhosseini Tamijani SM, Ahmadiani A, Dargahi L. Intranasal insulin treatment restores cognitive deficits and insulin signaling impairment induced by repeated methamphetamine exposure. J Cell Biochem. 2018;119(2):2345-55. doi: 10.1002/jcb.26398.
18. Aggleton JP, Albasser MM, Aggleton DJ, Poirier GL, Pearce JM. Lesions of the rat perirhinal cortex spare the acquisition of a complex configural visual discrimination yet impair object recognition. Behav Neurosci. 2010;124(1):55-68. doi: 10.1037/a0018320.
19. Hammond RS, Tull LE, Stackman RW. On the delay-dependent involvement of the hippocampus in object recognition memory. Neurobiol Learn Mem. 2004;82(1):26-34. doi: 10.1016/j.nlm.2004.03.005.
20. Christoffersen GR, Simonyi A, Schachtman TR, Clausen B, Clement D, Bjerre VK, et al. MGlu5 antagonism impairs exploration and memory of spatial and non-spatial stimuli in rats. Behav Brain Res. 2008;191(2):235-45. doi: 10.1016/j.bbr.2008.03.032.
21. Uslaner JM, Parmentier-Batteur S, Flick RB, Surles NO, Lam JS, McNaughton CH, et al. Dose-dependent effect of CDPPB, the mGluR5 positive allosteric modulator, on recognition memory is associated with GluR1 and CREB phosphorylation in the prefrontal cortex and hippocampus. Neuropharmacology. 2009;57(5-6):531-8. doi: 10.1016/j.neuropharm.2009.07.022.
22. Nelson AJ, Thur KE, Marsden CA, Cassaday HJ. Dissociable roles of dopamine within the core and medial shell of the nucleus accumbens in memory for objects and place. Behav Neurosci. 2010;124(6):789-99. doi: 10.1037/a0021114.
23. Ghazvini H, Shabani M, Asadi-Shekaari M, Khalifeh S, Esmaeilpour K, Khodamoradi M, et al. Estrogen and progesterone replacement therapy prevent methamphetamine-induced synaptic plasticity impairment in ovariectomized rats. Addict Health. 2016;8(3):145-56.
24. Khalifeh S, Khodamoradi M, Hajali V, Ghazvini H, Eliasy L, Kheradmand A, et al. Naloxone ameliorates spatial memory deficits and hyperthermia induced by a neurotoxic methamphetamine regimen in male rats. Galen Med J. 2019;8:e1182. doi: 10.31661/gmj.v0i0.1182.
25. Rafaiee R, Ahmadiankia N, Mousavi SA, Rezaeian L, Niroumand Sarvandani M, Shekari A, et al. Inhalant self-administration of methamphetamine: the most similar model to human methamphetamine addiction. Iran J Psychiatry Behav Sci. 2019;13(3):e90561. doi: 10.5812/ijpbs.90561.
26. Madden LJ, Flynn CT, Zandonatti MA, May M, Parsons LH, Katner SN, et al. Modeling human methamphetamine exposure in nonhuman primates: chronic dosing in the rhesus macaque leads to behavioral and physiological abnormalities. Neuropsychopharmacology. 2005;30(2):350-9. doi: 10.1038/sj.npp.1300575.
27. Bisagno V, Ferguson D, Luine VN. Short toxic methamphetamine schedule impairs object recognition task in male rats. Brain Res. 2002;940(1-2):95-101. doi: 10.1016/s0006-8993(02)02599-4.
28. Schröder N, O'Dell SJ, Marshall JF. Neurotoxic methamphetamine regimen severely impairs recognition memory in rats. Synapse. 2003;49(2):89-96. doi: 10.1002/syn.10210.
29. Belcher AM, O'Dell SJ, Marshall JF. Impaired object recognition memory following methamphetamine, but not p-chloroamphetamine- or d-amphetamine-induced neurotoxicity. Neuropsychopharmacology.

2005;30(11):2026-34. doi: 10.1038/sj.npp.1300771.
30. Belcher AM, O'Dell SJ, Marshall JF. A sensitizing regimen of methamphetamine causes impairments in a novelty preference task of object recognition. Behav Brain Res. 2006;170(1):167-72. doi: 10.1016/j.bbr.2006.02.025.
31. He J, Yang Y, Yu Y, Li X, Li XM. The effects of chronic administration of quetiapine on the methamphetamine-induced recognition memory impairment and dopaminergic terminal deficit in rats. Behav Brain Res. 2006;172(1):39-45. doi: 10.1016/j.bbr.2006.04.009.
32. Marshall JF, Belcher AM, Feinstein EM, O'Dell SJ. Methamphetamine-induced neural and cognitive changes in rodents. Addiction. 2007;102 Suppl 1:61-9. doi: 10.1111/j.1360-0443.2006.01780.x.
33. Herring NR, Schaefer TL, Gudelsky GA, Vorhees CV, Williams MT. Effect of + -methamphetamine on path integration learning, novel object recognition, and neurotoxicity in rats. Psychopharmacology (Berl). 2008;199(4):637-50. doi: 10.1007/s00213-008-1183-y.
34. Lu P, Mamiya T, Lu L, Mouri A, Niwa M, Kim HC, et al. Silibinin attenuates cognitive deficits and decreases of dopamine and serotonin induced by repeated methamphetamine treatment. Behav Brain Res. 2010;207(2):387-93. doi: 10.1016/j.bbr.2009.10.024.
35. Grace CE, Schaefer TL, Herring NR, Graham DL, Skelton MR, Gudelsky GA, et al. Effect of a neurotoxic dose regimen of (+)-methamphetamine on behavior, plasma corticosterone, and brain monoamines in adult C57BL/6 mice. Neurotoxicol Teratol. 2010;32(3):346-55. doi: 10.1016/j.ntt.2010.01.006.
36. Melo P, Magalhães A, Alves CJ, Tavares MA, de Sousa L, Summavielle T, et al. Methamphetamine mimics the neurochemical profile of aging in rats and impairs recognition memory. Neurotoxicology. 2012;33(3):491-9. doi: 10.1016/j.neuro.2012.03.002.
37. North A, Swant J, Salvatore MF, Gamble-George J, Prins P, Butler B, et al. Chronic methamphetamine exposure produces a delayed, long-lasting memory deficit. Synapse. 2013;67(5):245-57. doi: 10.1002/syn.21635.
38. Thanos PK, Kim R, Delis F, Rocco MJ, Cho J, Volkow ND. Effects of chronic methamphetamine on psychomotor and cognitive functions and dopamine signaling in the brain. Behav Brain Res. 2017;320:282-90. doi: 10.1016/j.bbr.2016.12.010.
39. González B, Jayanthi S, Gomez N, Torres OV, Sosa MH, Bernardi A, et al. Repeated methamphetamine and modafinil induce differential cognitive effects and specific histone acetylation and DNA methylation profiles in the mouse medial prefrontal cortex. Prog Neuropsychopharmacol Biol Psychiatry. 2018;82:1-11. doi: 10.1016/j.pnpbp.2017.12.009.
40. Zhou M, Gong X, Ru Q, Xiong Q, Chen L, Si Y, et al. The neuroprotective effect of L-stepholidine on methamphetamine-induced memory deficits in mice. Neurotox Res. 2019;36(2):376-86. doi: 10.1007/s12640-019-00069-z.
41. Kamei H, Nagai T, Nakano H, Togan Y, Takayanagi M, Takahashi K, et al. Repeated methamphetamine treatment impairs recognition memory through a failure of novelty-induced ERK1/2 activation in the prefrontal cortex of mice. Biol Psychiatry. 2006;59(1):75-84. doi: 10.1016/j.biopsych.2005.06.006.
42. Ito Y, Takuma K, Mizoguchi H, Nagai T, Yamada K. A novel azaindolizinone derivative ZSET1446 (spiro[imidazo[1,2-a]pyridine-3,2-indan]-2(3H)-one) improves methamphetamine-induced impairment of recognition memory in mice by activating extracellular signal-regulated kinase 1/2. J Pharmacol Exp Ther. 2007;320(2):819-27. doi: 10.1124/jpet.106.114108.
43. Mizoguchi H, Takuma K, Fukakusa A, Ito Y, Nakatani A, Ibi D, et al. Improvement by minocycline of methamphetamine-induced impairment of recognition memory in mice. Psychopharmacology (Berl). 2008;196(2):233-41. doi: 10.1007/s00213-007-0955-0.
44. González B, Raineri M, Cadet JL, García-Rill E, Urbano FJ, Bisagno V. Modafinil improves methamphetamine-induced object recognition deficits and restores prefrontal cortex ERK signaling in mice. Neuropharmacology. 2014;87:188-97. doi: 10.1016/j.neuropharm.2014.02.002.
45. Noda Y, Mouri A, Ando Y, Waki Y, Yamada SN, Yoshimi A, et al. Galantamine ameliorates the impairment of recognition memory in mice repeatedly treated with methamphetamine: involvement of allosteric potentiation of nicotinic acetylcholine receptors and dopaminergic-ERK1/2 systems. Int J Neuropsychopharmacol. 2010;13(10):1343-54. doi: 10.1017/s1461145710000222.
46. Vieira-Brock PL, McFadden LM, Nielsen SM, Smith MD, Hanson GR, Fleckenstein AE. Nicotine administration attenuates methamphetamine-induced novel object recognition deficits. Int J Neuropsychopharmacol. 2015;18(12):pyv073. doi: 10.1093/ijnp/pyv073.
47. Mai HN, Sharma N, Shin EJ, Nguyen BT, Nguyen PT, Jeong JH, et al. Exposure to far-infrared rays attenuates methamphetamine-induced recognition memory impairment via modulation of the muscarinic M1 receptor, Nrf2, and PKC. Neurochem Int. 2018;116:63-76. doi: 10.1016/j.neuint.2018.03.009.
48. Tran TV, Shin EJ, Nguyen LTT, Lee Y, Kim DJ, Jeong JH, et al. Protein kinase Cδ gene depletion protects against methamphetamine-induced impairments in recognition memory and ERK1/2 signaling via upregulation of glutathione peroxidase-1 gene. Mol Neurobiol. 2018;55(5):4136-59. doi: 10.1007/s12035-017-0638-8.
49. Gonçalves J, Baptista S, Olesen MV, Fontes-Ribeiro C, Malva JO, Woldbye DP, et al. Methamphetamine-induced changes in the mice hippocampal neuropeptide Y system: implications for memory impairment. J Neurochem. 2012;123(6):1041-53. doi: 10.1111/jnc.12052.
50. Reichel CM, Schwendt M, McGinty JF, Olive MF, See RE. Loss of object recognition memory produced by extended access to methamphetamine self-administration is reversed by positive allosteric modulation of metabotropic glutamate receptor 5. Neuropsychopharmacology. 2011;36(4):782-92. doi: 10.1038/npp.2010.212.
51. Long JD, Liu Y, Jiao DL, Wang YJ, Zan GY, Ju YY, et al. The neuroprotective effect of memantine on methamphetamine-induced cognitive deficits. Behav Brain Res. 2017;323:133-40. doi: 10.1016/j.bbr.2017.01.042.
52. Khodamoradi M, Tirgar F, Ghazvini H, Rafaiee R, Seyedhosseini Tamijani SM, Karimi N, et al. Role of the cannabinoid CB1 receptor in methamphetamine-induced social and recognition memory impairment. Neurosci Lett. 2022;779:136634. doi: 10.1016/j.neulet.2022.136634.
53. Luo H, Li X, Fan R, Ruan Y, Qian L, Shen Y, et al. Neuroprotective effect of histamine H3 receptor blockade on methamphetamine-induced cognitive impairment in mice. Pharmacol Biochem Behav. 2023;222:173512. doi: 10.1016/j.pbb.2022.173512.
54. Thanos PK, Kim R, Delis F, Ananth M, Chachati G, Rocco MJ, et al. Chronic methamphetamine effects on brain structure and function in rats. PLoS One. 2016;11(6):e0155457. doi: 10.1371/journal.pone.0155457.
55. Westbrook SR, Dwyer MR, Cortes LR, Gulley JM. Extended access self-administration of methamphetamine is associated with age- and sex-dependent differences in drug taking behavior and recognition memory in rats. Behav Brain Res. 2020;390:112659. doi: 10.1016/j.bbr.2020.112659.

56. Yang X, Wang Y, Li Q, Zhong Y, Chen L, Du Y, et al. The main molecular mechanisms underlying methamphetamine-induced neurotoxicity and implications for pharmacological treatment. Front Mol Neurosci. 2018;11:186. doi: 10.3389/fnmol.2018.00186.
57. Reichel CM, Ramsey LA, Schwendt M, McGinty JF, See RE. Methamphetamine-induced changes in the object recognition memory circuit. Neuropharmacology. 2012;62(2):1119-26. doi: 10.1016/j.neuropharm.2011.11.003.
58. Clark RE, Kuczenski R, Segal DS. Escalating dose, multiple binge methamphetamine regimen does not impair recognition memory in rats. Synapse. 2007;61(7):515-22. doi: 10.1002/syn.20397.
59. Kelleher RJ 3rd, Govindarajan A, Jung HY, Kang H, Tonegawa S. Translational control by MAPK signaling in long-term synaptic plasticity and memory. Cell. 2004;116(3):467-79. doi: 10.1016/s0092-8674(04)00115-1.
60. Nagai T, Takuma K, Kamei H, Ito Y, Nakamichi N, Ibi D, et al. Dopamine D1 receptors regulate protein synthesis-dependent long-term recognition memory via extracellular signal-regulated kinase 1/2 in the prefrontal cortex. Learn Mem. 2007;14(3):117-25. doi: 10.1101/lm.461407.
61. Mizoguchi H, Yamada K, Mizuno M, Mizuno T, Nitta A, Noda Y, et al. Regulations of methamphetamine reward by extracellular signal-regulated kinase 1/2/ets-like gene-1 signaling pathway via the activation of dopamine receptors. Mol Pharmacol. 2004;65(5):1293-301. doi: 10.1124/mol.65.5.1293.
62. Siegel JA, Craytor MJ, Raber J. Long-term effects of methamphetamine exposure on cognitive function and muscarinic acetylcholine receptor levels in mice. Behav Pharmacol. 2010;21(7):602-14. doi: 10.1097/FBP.0b013e32833e7e44.
63. Alexander MP, Stuss DT, Picton T, Shallice T, Gillingham S. Regional frontal injuries cause distinct impairments in cognitive control. Neurology. 2007;68(18):1515-23. doi: 10.1212/01.wnl.0000261482.99569.fb.
64. Berkeley JL, Gomeza J, Wess J, Hamilton SE, Nathanson NM, Levey AI. M1 muscarinic acetylcholine receptors activate extracellular signal-regulated kinase in CA1 pyramidal neurons in mouse hippocampal slices. Mol Cell Neurosci. 2001;18(5):512-24. doi: 10.1006/mcne.2001.1042.
65. Beardsley PM, Hauser KF. Glial modulators as potential treatments of psychostimulant abuse. Adv Pharmacol. 2014;69:1-69. doi: 10.1016/b978-0-12-420118-7.00001-9.
66. Borgmann K, Ghorpade A. HIV-1, methamphetamine and astrocytes at neuroinflammatory crossroads. Front Microbiol. 2015;6:1143. doi: 10.3389/fmicb.2015.01143.
67. Gordon R, Singh N, Lawana V, Ghosh A, Harischandra DS, Jin H, et al. Protein kinase Cδ upregulation in microglia drives neuroinflammatory responses and dopaminergic neurodegeneration in experimental models of Parkinson's disease. Neurobiol Dis. 2016;93:96-114. doi: 10.1016/j.nbd.2016.04.008.
68. Talman V, Pascale A, Jäntti M, Amadio M, Tuominen RK. Protein kinase C activation as a potential therapeutic strategy in Alzheimer's disease: is there a role for embryonic lethal abnormal vision-like proteins? Basic Clin Pharmacol Toxicol. 2016;119(2):149-60. doi: 10.1111/bcpt.12581.
69. Shin EJ, Duong CX, Nguyen XT, Bing G, Bach JH, Park DH, et al. PKCδ inhibition enhances tyrosine hydroxylase phosphorylation in mice after methamphetamine treatment. Neurochem Int. 2011;59(1):39-50. doi: 10.1016/j.neuint.2011.03.022.
70. Cammalleri M, Lütjens R, Berton F, King AR, Simpson C, Francesconi W, et al. Time-restricted role for dendritic activation of the mTOR-p70S6K pathway in the induction of late-phase long-term potentiation in the CA1. Proc Natl Acad Sci U S A. 2003;100(24):14368-73. doi: 10.1073/pnas.2336098100.
71. Lee KW, Kim HC, Lee SY, Jang CG. Methamphetamine-sensitized mice are accompanied by memory impairment and reduction of N-methyl-d-aspartate receptor ligand binding in the prefrontal cortex and hippocampus. Neuroscience. 2011;178:101-7. doi: 10.1016/j.neuroscience.2011.01.025.
72. Wang J, O'Donnell P. D1 dopamine receptors potentiate NMDA-mediated excitability increase in layer V prefrontal cortical pyramidal neurons. Cereb Cortex. 2001;11(5):452-62. doi: 10.1093/cercor/11.5.452.
73. Akirav I, Maroun M. Ventromedial prefrontal cortex is obligatory for consolidation and reconsolidation of object recognition memory. Cereb Cortex. 2006;16(12):1759-65. doi: 10.1093/cercor/bhj114.
74. Ishikawa A, Kadota T, Kadota K, Matsumura H, Nakamura S. Essential role of D1 but not D2 receptors in methamphetamine-induced impairment of long-term potentiation in hippocampal-prefrontal cortex pathway. Eur J Neurosci. 2005;22(7):1713-9. doi: 10.1111/j.1460-9568.2005.04332.x.