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N-ACETYLCYSTEINE: POTENTIAL PHARMACOTHERAPY FOR WITHDRAWAL SYMPTOMS IN METHAMPHETAMINE USERS

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Abstract

Substance use disorders (SUDs) represent a dramatic public health concern synergistically related to escalation of crime rate, burden of healthcare, and productivity loss. Despite advancements in treatment of substance use disorders, most people fail to obtain adequate treatment resources resulted in long term abstinence. Methamphetamine abuse has recently increased up to total of 33 million people worldwide, scattered widely in various nations for last few decades. Mechanism of methamphetamine addiction has been related closely with neurotoxicity, involving damage to dopaminergic or serotonergic terminals via dysregulation of dopamine transporter (DAT) and vesicular monoamine transporter-2 (VMAT2).

Methamphetamine increases the release of dopamine in the brain subdivision of striatum, like putamen, caudate, and ventral striatum. Nevertheless, low level of neuronal striatal dopamine produces unpleasant feeling during withdrawal and aspects of cognitive impairments. Constant research on developing agonist replacement therapy on methamphetamine has come to the usage of N-acetylcysteine. Its anti-inflammatory properties through reduction in cytokines production provided by N-acetylcysteine treatment could be a potential mechanism by which it modulates the overlying symptoms. Inhibition of IL-1, IL-6, and TNF-alpha at proteomic level exerts direct effect on GSH production, antioxidant properties, and regulation of glutamatergic excitatory neuronal activity in the central nervous system.

There are still no approved pharmacotherapies for managing methamphetamine dependence with clear clinically related endpoints even though N-acetylcysteine has been found to reduce the craving for methamphetamine despite two published trials in human conducting preliminary researches to observe the efficacy of N-acetylcysteine.

As a result, deeper understanding in the mechanism of N-acetylcysteine in curing the adverse effects of methamphetamine might give better insights for future research.

Keywords: *methamphetamine, drug abuse, N-acetylcysteine, craving*

Introduction

Substance use disorders (SUDs) represent a dramatic public health concern synergistically related to escalation of crime rate, burden of healthcare, and productivity loss. Its estimated costs for those factors have totaled up to approximately 621 billion dollars annually when considering both illicit and licit substances globally. In 2011, around 20.6 billion American aged 12 years or older has been reported to abuse drugs. Despite advancements in treatment of substance use disorders, most people fail to obtain adequate treatment resources resulted in long term abstinence. Its effort requires significant refinement in order to achieve optimal recovery from this relapsing disorder. As this disorder seems to be complex to be closely aligned with current medical model of disease pathogenesis, first-line pharmacotherapy interventions have been explored in research to search for the most effective ones. Promising agents have been identified well throughout the years representing pivotal situations regarding therapy for substance use disorder. Replacement therapy is one of the key strategies implemented into guidelines for drug dependence, such as utilization of agonist replacement methadone for opioid addiction. A major weakness of this strategy is its low potential application for multiple substance of abuse despite its substance-specificity.[1]

One of the substances widely abused is methamphetamine. Methamphetamine abuse has recently increased up to total of 33 million people worldwide, scattered widely in various nations for last few decades.[2] It is the second most common abused illicit drug in the world outnumbering heroin and cocaine users combined. About two-thirds of the world's methamphetamine users are found in East and Southeast Asia, followed by Americas in which the estimation suggests over 12 million users aged over 12 years old and older (4.7% of total responders) have used methamphetamine in their lifetimes.[3] Confiscation of methamphetamine distribution in Southeast Asia and East Asia grew 1.5 folds from 34 tons in 2009 to 88 tons in 2013. More than 800 thousand US people were diagnosed as methamphetamine addicts in 2015 which outnumber the WHO current target.[2,4] Importantly, these estimates seems to be growing as expansion of methamphetamine abuse happens in terms of locations of the manufacture and trafficking routes, as well as in terms of demands.[5] Due to the number of meth addicts, there would be an increased burden of treatment, including medical expenses for withdrawal therapy. In 2009, the RAND corporation approximates the entire economic burden of methamphetamine use to be around 23.4 billion dollars, which include cost associated with rehabilitation, intangible burden of morbidity and mortality, productivity loss, and crime acts.

Neuronal message travelling between brain and body increases during methamphetamine abuse, thus potentially creating 'high' phenomenon. Dopamine is involved in the process that serves as primary neurotransmitter related to reward system of brain. Its slower metabolism causes its existence to persist much longer in the neuronal system, and further blocks dopamine uptake. Chronic use of methamphetamine has shown deteriorating effects in brain ability to independently regulate dopamine levels. Craving can be the ultimate consequence of abnormal behavior in order to fulfill the necessity of reward system through methamphetamine consumption. Nevertheless, there is no current medications approved for treating withdrawal except psychotherapy or agonist replacement therapy.[6] Constant research on developing agonist replacement therapy on methamphetamine has come to the usage of N-acetylcysteine. N-acetylcysteine has been used widely to treat productive cough, or acetaminophen overdose; however, it also works by protecting tissues from oxidative damage in the central nervous system. Previous randomized controlled trials have been done to test the effectivity of N-acetylcysteine on alleviating methamphetamine dependence. Difficulty in generalizing the potential efficacy of N-acetylcysteine due to limitation in research, trials, and psychiatric treatment encourages author to do preliminary review onto studies of N-acetylcysteine towards methamphetamine withdrawal treatment.

As a result, profound comprehension towards methamphetamine's clinical and biochemical characteristics, as well as N-acetylcysteine's anti-neurotoxic capability, in human hope to provide insights for the alternative withdrawal therapy of using N-acetylcysteine.[7]

Methods

Materials for the review are obtained from several databases, such as Science Direct and PubMed, which are accessed via Universitas Indonesia's remote library. There are several literatures found closely related to N-acetylcysteine and methamphetamine addict, comprising of textbooks, research papers, and journal reviews. Selection steps consist of matching key words, skimming abstract, summarizing main information, and connecting facts into finely organized review for which search terms are key words stated in the abstract. Inclusion criteria for the available sources are N-acetylcysteine medication towards methamphetamine addiction as the subject discussion and clinical or pre-clinical practices. On the other hand, the exclusion criteria are unauthentic, inaccessible, and non-English or non-Indonesian journals. Search terms include N-acetylcysteine, methamphetamine addiction, withdrawal symptoms, and clinical psycho pharmacotherapy.

Results and Discussion

Methamphetamine

Methamphetamine have a long history of use in the United States which soldiers used it to reduce fatigue and suppress appetite. It is widely prescribed in 1950s as primary medication for depression or weight problem, reaching its top 31 million intakes in 1967 with roughly estimated 9.7 million people was identified as past-year users. The increasing demand of methamphetamine escalates its popularity in early 2000s until U.S. National Survey on Drug Use and Health (NSDUH) suggest over 210,000 individuals aged older than 12 years old tried methamphetamine for the first time. As the passage of the combat methamphetamine epidemic art in 2005 start to restrict over-the-counter prescription of products containing methamphetamine, the rates of usage eventually decrease by a drop to 192,000 users in 2005. That estimates by Treatment Episode Data Set (TEDS) provides information on admissions to methamphetamine usage that are licensed by agencies suggest that treatment admissions for primary methamphetamine increased from 78,000 individuals aged 12 years old and older in 2001, then decreased to 102,384 individuals in 2011.

Furthermore, the rates of methamphetamine dependence are seen to be similar between male and female with 53% of the total admissions being male.[5] Dependence of methamphetamine occurs via several neurochemical processes, consisting of vesicular dysfunction through inhibition of monoamine oxidase and facilitation of tyrosine hydroxylase. Its sustainable effect for hours makes this drug available in the blood stream for long time, potentiating its psychopathological results of hallucination, delusions, suicidality, or aggression. Long-term health effects are considerable for associative cognitive impairment, sexual transmitted disease due to its high comorbidities, and cardio cerebrovascular damage. Noted for its addictiveness, evidence shows that methamphetamine-seeking behavior may persist even when tolerance is reached compared with cocaine or heroin. Its trajectory usage of 10-year period has been found exceeding that of other drugs.[8]

Chemical and biological characteristics

Methamphetamine ($C_5H_{10}N_1$), or N-methylamphetamine, is one of the drugs developed in the 20th century for nasal decongestion and bronchial reliever (**figure 1**). Its ability to easily cross blood brain barrier poses potent addictive-stimulatory effect in the central nervous system, resulting longer lasting and harmful effect on chronic usage.[9,10] Its enantiomer, D-methamphetamine, possesses stronger therapeutic effect in the central nervous system for its higher potency to release neural dopamine, as well as TAAR1 receptor modulator in pre-synaptic dopaminergic neurons.

Its medical usage restricted as an off-label prescription indicating for narcolepsy or hypersomnia pharmacotherapy, further classified as schedule-type II controlled-drug in the United States.[9,11] High dosage of meth consumed by drug addicts could result in excessive mood swings, psychosis, or violent behavior.[10] Physiologically, it triggers substantial sympathetic activities causing tachycardia, systemic vasoconstriction, raised body temperature, and mucosal decongestion, for it has similar structure with monoamine.[4] Acute effects of

the drug closely resemble the physiological effects of epinephrine-provoked fight or flight response, consisting of vasoconstriction, gluconeogenesis, and bronchodilation. The methyl group of methamphetamines is responsible for its higher potential effects compared to amphetamine. Methylation of amphetamine into methamphetamine rendering its substance on the one hand more hydrophobic and easily crosses the blood-brain barrier, stabilizing its against the enzymatic degradation of MAO. Methamphetamine causes the norepinephrine, dopamine, and serotonin transporters to reverse their direction of flow. Inverted release of these transmitters from the vesicles to the cytoplasm cause increased stimulation of post-synaptic receptors, thereby resulting them to retain in the synaptic cleft for a prolonged period. Its potent neurotoxicity has been shown to prove dopaminergic degeneration. Dopamine and serotonin concentrations, dopamine and 5HT uptake sites, and tyrosine-tryptophan hydroxylase activities are reduced following administration of methamphetamine.

Moreover, dopamine plays main role in methamphetamine induced neurotoxicity because the experiments which reduce dopamine production or inhibit the release of dopamine diminish its toxic effects of methamphetamine administration. Excessive breakdown of dopamine into high radical species of peroxide would trigger cellular oxidative stress. Recent studies suggest methamphetamine group binds to specific receptor of TAAR that is primarily affected by amphetamine-like substance called trace amines.[12]

Mechanism of addiction

Mechanism of methamphetamine addiction has been related closely with neurotoxicity. Neurotoxicity is defined as reversible or irreversible adverse effect of a substance, in this case methamphetamine, on neuronal tissues which cause histologic signs of damage, behavior abnormalities, or disruption of neuronal components.[2] Methamphetamine-induced neurotoxicity involves damage to dopaminergic or serotonergic terminals via dysregulation of dopamine transporter (DAT) and vesicular monoamine transporter-2 (VMAT2).[2,13] Not only inhibit VMAT2 activity, methamphetamine also reduces VMAT2 expression in neuronal cells (**figure 2**). Normally, dopamine transporter DAT functions to export intracellular dopamine towards synaptic cleft, while vesicular transporter VMAT2 enable produced dopamine to be concentrated in the neural vesicles. Both of the transporters ultimately distribute dopamine out of the cells, preventing subsequent neurotransmitter intoxication. Thus, dopamine intoxication, as results of this pathogenesis, would impair normal cognition, episodic memory, language skills, visual-constructional abilities, or psychomotor drive.[4]

Pathophysiology associated with dopamine intoxication results in cellular oxidative stress. Excessive amount of dopamine in the presynaptic cytosol promote auto-oxidation into quinone to generate large amounts of free radical species. Abundant reactive oxygen species generate series of oxidative chain reactions, such as lipid peroxidation, protease activation, and ultimately apoptotic cascades. Peroxynitrite produced by the reaction between reactive oxygen species with nitric oxide further disrupts nucleic acid stability, tertiary protein conformation, and membrane integrity. This would eventually cause neural degeneration in the dopaminergic system of the brain.[2,13]

Furthermore, excitotoxicity is related to glutamate accumulation in the synaptic cleft, which is triggered by cross-feedback mechanism between glutamatergic and dopaminergic system in the striatal area. Glutamate excess in the cleft over-activates calcium influx, thereby initiating cascade of intracellular signaling associated with kinase-phospatase reaction and nitric oxide synthase, leading to endoplasmic reticulum stress. Endoplasmic stress activates transmembrane protein translocator, transcription factor ATF-6, inositol-requiring protein-1 (IRE-1), and RNA-like kinase (PERK), causing reduction in protein synthesis, coping with proteotoxic stress, and altering expression level of NMDA ionotropic receptors and mGluR metabotropic receptors. Besides, neurogliocytes disorder shows sensitive markers of neuroinflammation.

Results in methamphetamine exposure following microglial activation could result in neuronal release of damage-associated molecular patterns (DAMPs). Excessive dopamine release, production of dopamine-quinone, and sequential reactive oxygen

species into the cleft stimulate regional glial cells triggering signal cascade, such as NF-kB, TNF-α, and IL-6. Consequently, long-term neurotoxicity impairs expression of tyrosin, tyrosin hydroxylase (TH), dopamine transporter (DAT), serotonin transporter, and dopamine depletion (**figure 3**).

In studies, methamphetamine abusers have lower expression of dopamine, tyrosin hydroxylase, and dopamine transporter in prefrontal cortex, striatal region, and nucleus accumbens through positron-emission tomography scan. It also shows structural and metabolic dysfunction in brain regions that correlate with several behavior abnormalities induced by methamphetamine.[2,14]

Abstinence from methamphetamine resulted in less excess microglial activation over time. Similar study found that while biochemical markers for nerve damage and viability persist in the brain for half a year of methamphetamine abstinence, those markers return to normal level similar to normal person. A neuroimaging study showed neuronal recovery in some brain regions following methamphetamine abstinence of 14 months associated with improved motor and verbal performance. Functions in other area of the brain did not fully recover indicating that some methamphetamine-induced changes are long-lasting. It increases one's risk of stroke exacerbating irreversible damage to brain and higher incidence of Parkinsonism.[15,16]

Identification of the psychoactive substance used may be made on basis of self-report data, questionnaire, or laboratory analysis of patient's bodily fluid. Diagnostic guidelines for patients to be suspected with dependence syndrome could be defined as "a cluster of physiological, behavioural, and cognitive phenomena in which the use of a substance or a class of substances takes on a much higher priority for a given individual than other behaviors that once had a greater value. A central descriptive characteristics of dependence syndrome of methamphetamine is the desire to take the psychoactive drugs, difficulties in controlling substance-taking behavior, physiological withdrawal stage, evidence of methamphetamine tachyphylaxis, as well as progressive neglect of alternative pleasures.

This psychopathological diagnosis could be classified as axis F1x.2, that might overlap with the diagnosis axis F1x.3 withdrawal state. It is an essential characteristic of patient to serve as basis for psychology-related clinical diagnosis. Moreover, this diagnostic requirement would exclude, for example, surgical patients given analgesic drugs for relief of pain who may show signs of withdrawal but who have no desire to continue taking the drugs. Further specification of dependence syndrome diagnosis is written in five-character axis codes such as F1x.20 to F1x.25.[17]

Methamphetamine withdrawal treatment

Drug withdrawal is a group of symptoms that happen following drug discontinuation or decrease in dosage intake of certain medications. Withdrawal symptoms only occur when one has developed drug dependence, in this case methamphetamine addicts. Drug dependence arises in a dose-dependent manner, producing various effect according to the types of drug that is consumed. Stages of methamphetamine withdrawal starts in the form of bad intrapersonal feeling, progression towards depression, hitting a plateau, and finally symptoms dissipation.[18] Methamphetamine increases the release of dopamine in the brain subdivision of striatum, like putamen, caudate, and ventral striatum.

Nevertheless, low level of neuronal striatal dopamine produces unpleasant feeling during withdrawal and aspects of cognitive impairments. It also exerts multiple effects in the central nervous system closely associated with its ability to release monoamines by increasing the cytoplasmic concentration of neurotransmitter, such as dopamine or serotonin, through VMAT2 blockage and suppression of surface DAT expression. Brain imaging studies did show changes in brain anatomical structures in which the methamphetamine users demonstrated severe grey-matter deficits in the cingulate and limbic cortices, dramatic white-matter hypertrophy, diminished hippocampal volumes, medial temporal lobe damage, and striatal enlargement.[19] This is closely related to acute cease of methamphetamine usage, apart from the habit of drug addicts in consuming methamphetamine chronically.

Evidences suggest for disturbances of mood and anxiety in recently abstinent methamphetamine dependent patients. Withdrawal symptoms

mediating drug seeking behavior involves structure and neurotransmitter system that interacts complexly with dopamine-rich neuronal subdivision.

To counter the effect of the behavior, most common therapeutic approach would utilize partial agonist drug. Partial agonist substitutes methamphetamine in generating similar response, but with lower potency. Therefore, tapering off the partial agonist drug would help compensate the side effect of withdrawal symptoms during rehabilitation. Furthermore, drug-substitution therapy with cognitive-enhancing agents or deep brain stimulation aim at reversible inactivation of brain areas suspected of being involved in drug addiction.[20]

Several researches on drug replacement therapy to treat methamphetamine addict were conducted to see for agents with any potent response towards behavioral therapy. For instance, a single-blind trial of 16-week usage of modafinil combined with cognitive behavioral therapy (CBT) for treatment of methamphetamine dependence results in 50% reduction of methamphetamine usage in 60% of the participants. It may therefore have some beneficial effects in regulating craving behavior of methamphetamine-dependent subjects, although no clear evidence of its efficacy in fully recovering the withdrawal symptoms is reported.[21]

Another phase I clinical trial evaluating interactions between intravenous methamphetamine and sustained release of 300 mg/day bupropion showed significant control of behavioral response including euphoria and substance craving.[22] In the other randomized trials, bupropion was no more effective than placebo in reducing methamphetamine craving. This shows that bupropion could manage to reduce the methamphetamine withdrawal response among baseline light, but not heavy, users in a *posthoc* analysis.[23]

Reports suggest that immediate release of oral methylphenidate has more potential for abuse in a 20-week randomized study treatment of methamphetamine addicts. Interim analysis showed that methylphenidate was an effective treatment in reducing stimulant use with severe dependence based on its lower proportion of amphetamine-positive urine samples.[24] Besides dopaminergic agent, GABAergic agent also exerts modulatory role in controlling the discriminative stimulus effects of methamphetamine. Clinical trials in a double-blind study of topiramate compared to placebo appear to enhance the positive effects of methamphetamine and could act as an anti-craving agent but worsening psychomotor retardation. One possible explanation may be that this agent increases plasma methamphetamine concentration.[25]

N-Acetylcysteine

Chemical and biological characteristics

N-acetylcysteine ($C_5H_9NO_3S$) is a synthetic N-acetyl derivative of amino acid L-cysteine, which is a precursor for glutathione enzyme regeneration in the liver. It is written as (2R)-2-acetamido-3-sulfanylpropanoic acid in IUPAC consensus of chemical nomenclature (**figure 6**).[26] Additionally, N-acetylcysteine is a prodrug that would be converted into L-cysteine in the central nervous system. Increased level of cysteine would enhance activity of glutamate-cysteine antiporter, that turns out to release more glutamate in the synaptic cleft. Glutamate would further promote activation of mGlu2/3 (lower dosage) or mGlu5 (higher dosage) metabotropic receptor or NMDAR modulation.[27]

Furthermore, N-acetylcysteine has recently been used as main therapy of acetaminophen overdose, nitrate tolerance, and mucus breakdown through support of antioxidative activities glutathione system and nitric oxide during stress. As *de novo* synthesis of glutathione is limited by availability of cysteine intracellularly, supplementation of cysteine would significantly elevate the production of glutathione in the liver.[28] Reduced glutathione would function as antioxidant defense system counteracting against significant production of free radicals during respirations or inflammations.

Moreover, it detoxifies electrophilic xenobiotics, modulates reduction-oxidation process, regulates immune response and cell proliferation.[29] Its potent antiinflammation would also inhibit sustain activation of NF-kB through redox reaction with Kappa kinases, in order to control cytokine synthesis.[27]

Its anti-inflammatory properties through several cellular processes are also linked to oxidative pathways, which may provide another potential mechanism of action in psychiatry. This includes

alteration of cytokines regulatory release in psychiatric disorder, such as depression. Reduction in cytokines production provided by N-acetylcysteine treatment could be a potential mechanism by which it modulates the overlying symptoms. Inhibition of IL-1, IL-6, and TNF-alpha at proteomic level exerts direct effect on GSH production, antioxidant properties, and regulation of glutamatergic excitatory neuronal activity in the central nervous system.[30]

Clinical Indication

N-acetylcysteine is indicated as mucolytics as it has role in breaking down mucopolysaccharides complex to reduce mucus adhesion. N-acetylcysteine also prevents hepatotoxicity by replenishing amount of glutathione, potentially conjugating toxic sulphate side chain following acetaminophen overdosage.[31]

Randomized controlled trials and a meta-analysis suggested evaluation of N-acetylcysteine efficacy in non-acetaminophen induced liver failure. It is associated with improved free-transplant survival, not overall survival, in adults due to non-acetaminophen induced liver injury.[32]

Several diseases, such as polycystic ovary syndrome, idiopathic pulmonary fibrosis, influenza, COPD, and contrast-induced nephropathy, use N-acetylcysteine as symptomatic treatment. However, clinical usage of N-acetylcysteine should be cautiously determined to reduce risk of drug-related injury.

Administration of N-acetylcysteine more than 1.2 g/day might induce headache, tinnitus, urticaria, and skin rash. Additionally, this drug is prohibited for pregnant women and history of drug allergenicity.[29] Furthermore, ototoxicity as main side effect of aminoglycosides antibiotics has been reported to be reduced by 33% following administration N-acetylcysteine in 146 patients in three studies with end-stage renal failure. It appears to protect against drug-induced hearing loss by exerting its antioxidative capacity against aminoglycosides.[33] Its thiol compound contained in the molecular structure acting as electron donor of cysteine is capable of inhibiting further proliferation of fibroblasts and keratinocytes, causing vasodilatation and serving as adjuvant for any dermatology problems, such as toxic epidermal necrolysis, contact dermatitis, melasma, photocarcinogenesis, or pseudoporphyria.

Reviews and studies have been being done to explore various uses in the field of dermatology, the evidence supporting the same, the possible mechanisms of action and the adverse effects of N-acetylcysteine.[34] In human study, the intravenous perfusion of N-acetylcysteine during hyperglycemic clamp improves insulin sensitivity and increases peripheral glucose uptake via protection on pancreatic beta cells in diabetic mice.

Moreover, N-acetylcysteine supplementation prevents oxidative stress, decrease plasma insulin concentrations and improves peripheral insulin sensitivity in rat fed a high sucrose diet. This shows significant clinical indication of using N-acetylcysteine to treat several kinds of disorders out of psychomotor context.[35]

Pharmacology of N-acetylcysteine

Uptake of N-acetylcysteine is mainly facilitated by the ubiquitous sodium-dependent amino acids transporter on the membrane. Secondary active transport of N-acetylcysteine would maximize its efficacy in certain cells, such as neurons or hepatocytes. Its ability to cross the blood-brain barrier enables to exert its pharmacotherapeutic effect towards central nervous system. After its uptake, hydrolysis of N-acetylcysteine produces cysteine as the main amino acid that would be synthesized into reduced glutathione by c-glutamyl cysteine synthetase and GSH synthetase.

Besides, this transformation would neutralize free radical species formation during respiration or drug therapy, preventing neurotoxicity and inflammation.[29] Alteration of cysteine levels have also been shown to modulate neuro-transmitter pathways glutamate and dopamine in particular. Assistance of cysteine in regulating the exchange of glutamate through cysteine-glutamate transporter concurrently occurs with the release of non-vesicular glutamate following stimulation of presynaptic metabotropic glutamate receptor mGluR2/3, which functions to negatively auto-regulate feedback towards release of presynaptic glutamate.

Studies showed that protracted treatment of N-acetylcysteine in restoring the expression level of GLT-1 (high affinity astroglial glutamate transporter)

could significantly bring back the normal synaptic potentiation and plasticity, that are hypothesized to be involved in the development of various psychiatric disorder including substance craving or drug abuse.[30]

N-acetylcysteine, taken orally up to 400 mg dose, would be distributed in the plasma with peak concentration of 0.35-0.4 mg/L within 1-2 hours ingestion. Its volume distribution differs from ages ranging from 0.33 – 0.47 L/kg, yet it has significant binding towards 50% of plasma protein at 4 hour following dose administration. N-acetylcysteine forms disulphides in plasma which prolongs the distribution of the drug in plasma up to more than 6 hours, even though its renal clearance rate eliminates 70% of the drug or approximately 0.19 – 0.21 L/kg/hour. N-acetylcysteine has half-life of 6.25 hours after oral administration, so it needs regular intake to exert its optimal efficacy.[29]

Good safety profile of N-acetylcysteine has brought to its popularity as over-the-counter drug prescription in many countries in the world. Frequent reports of its side effects consist of nausea, vomiting, and diarrhea with its significant interaction observed with paracetamol, GSH, and anticancer agents.[30]

Pharmacotherapy modality of N-acetylcysteine against methamphetamine withdrawal treatment

Discovery of cysteine-glutamate exchanger provides important role in understanding the drug seeking behavior, leading to research in addiction pharmacotherapies. N-acetylcysteine is a promising candidate because of its capacity to restore glutamate homeostasis in nucleus accumbens. Besides, pre-treatment with N-acetylcysteine could attenuate the reduction of dopamine transporter density on synaptic terminals that is seen subsequent to high-dose methamphetamine intake. This evidence suggests that N-acetylcysteine might alleviate neurotoxic damages associated with cognitive impairments or neuropsychiatric symptoms.[36,37]

Until now, there have been two published trials in human conducting preliminary researches to observe the efficacy for N-acetylcysteine as a potential pharmacotherapy in methamphetamine addiction. A randomized controlled trial done by Grant et al. (2010) involving 31 methamphetamine-dependent seekers treated with 600-2400 mg N-acetylcysteine incremental dosing over 6 weeks shows no significant effect on craving of methamphetamine. However, the trial's results appear to have been affected by treatment combination of N-acetylcysteine with opioid antagonist naltrexone, making it hard to infer any effects of N-acetylcysteine *per se*.[37,38]

A most recent randomized placebo-controlled cross-over study conducted in Iran by Mousavi et al. (2015) found that N-acetylcysteine significantly reduce seeking behavior. This study used 4 weeks of daily N-acetylcysteine dosing, starting from 600 mg/day for the first week, then increasing the dose to 1200 mg/day for the next 3 weeks with its largest effect at 4 weeks compared to placebo. None of these trials reported any serious adverse events related to N-acetylcysteine pharmacotherapy usage.[37,39]

There are still no approved pharmacotherapies for managing methamphetamine dependence with clear clinically related endpoints even though N-acetylcysteine has been found to reduce the craving for methamphetamine. The N-ICE trial was conducted to evaluate the safety and efficacy of N-acetylcysteine as take-home therapy for methamphetamine dependence. This two-arm parallel double-blind placebo-controlled three-site randomized trial with ratio of 1:1 using permuted block randomization stratifies participants by site, gender, and methamphetamine injection availability. Subjects would receive either 2400 mg of oral N-acetylcysteine or a matched placebo for straight 12 weeks. Its primary outcome is the methamphetamine use during 12-week trial assessed via timeline follow-back and saliva test. Moreover, secondary outcome measures weekly assessment of methamphetamine craving and dependency through Treatment Satisfaction Questionnaire for Medication. The novel aspects of trial procedure are the direct community engagement strategy to recruit participants and the outreach methods for follow-up assessments within the community, given the challenge of standardization inadequacy for evidence-based treatment options for methamphetamine dependence.[40]

Conclusion

Extensive research has been conducted to develop rehabilitative treatment towards withdrawal symptoms of methamphetamine users. However, this therapy development poses a challenge as it is associated with psychiatric management in the methamphetamine addicts. Using medication that reverses the side effects of methamphetamine towards central nervous system is the major key target in providing optimal pharmacotherapy. Thus, N-acetylcysteine could prevent subsequent neurotoxicity, neuroinflammation, or oxidative stress due to methamphetamine activity in the synaptic terminals of neurons. Numbers of trials have been conducted to observe whether N-acetylcysteine could function as withdrawal symptoms therapy of methamphetamine. As a result, deeper understanding in the mechanism of N-acetylcysteine in curing the adverse effects of methamphetamine might give better insights for future research.

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Figure 1. Molecular structures of methamphetamine.[9]

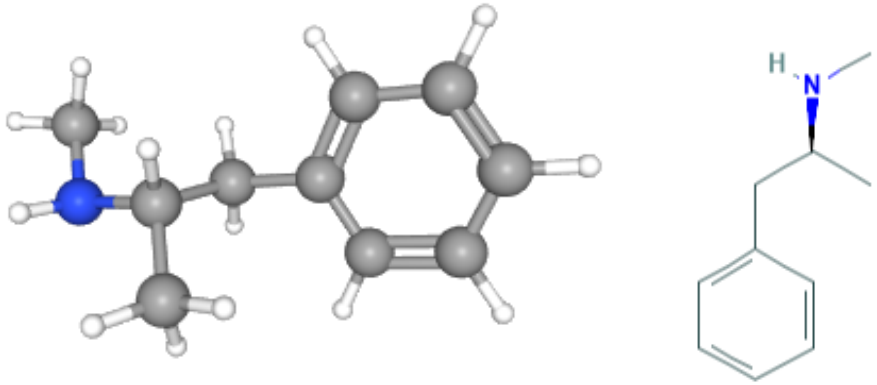

Figure 2. VMAT2: [3H]DA uptake in subcellular fractions. TAAR1 Wild-Type WT and knocked out KO mice received intraperitoneal injections of saline or MA (5 mg/kg), 2 hours apart. Striatal tissue from 4-5 mice per genotype per treatment group was pooled and values normalized to the amount of protein in each sample. Mean ± SEM of TAAR1 WT control group: synaptosomal, 13.4 ± 3.1 pmol/mg protein; membrane-associated, 13.9 ± 3.5 pmol/mg protein; vesicular, 72.9 ± 21.6 pmol/mg. *: p < 0.0001 compared to salinetreated controls +: p < 0.05 between genotypes; #: p < 0.0001 for the main effect of treatment; †: p < 0.01 for the main effect of genotype.[13]

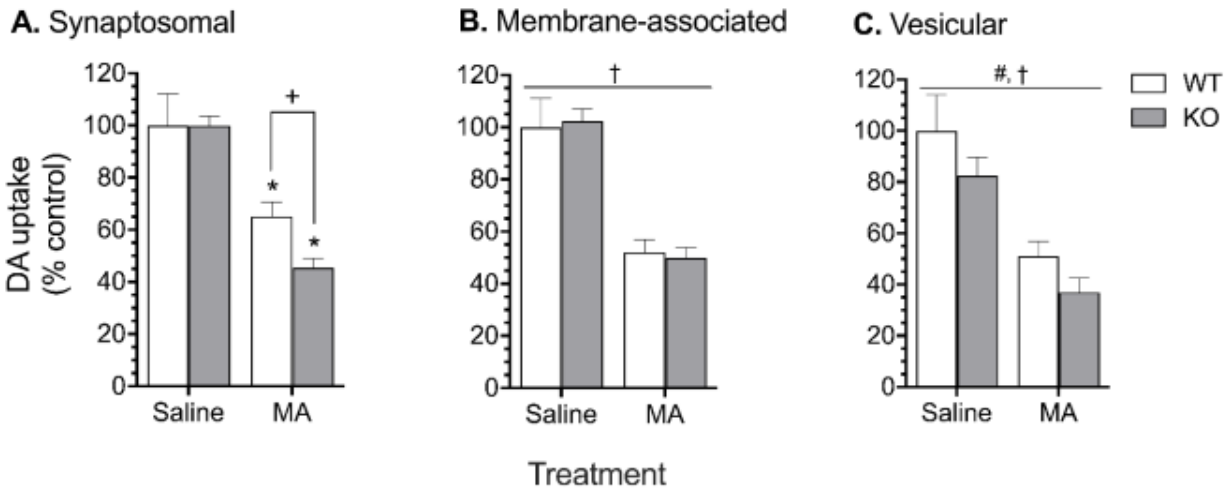

Figure 3. The illustration summarizes the main mechanisms of Methamphetamine-elicited neurotoxic effects, which involve excessive glutamate production, generation of ROS, DA oxidation, and subsequently leading to endoplasmic reticulum stress and mitochondrial dysfunction. Thus, neuronal cells may undergo terminal degeneration or apoptosis due to triggered neuroinflammaton.[2]

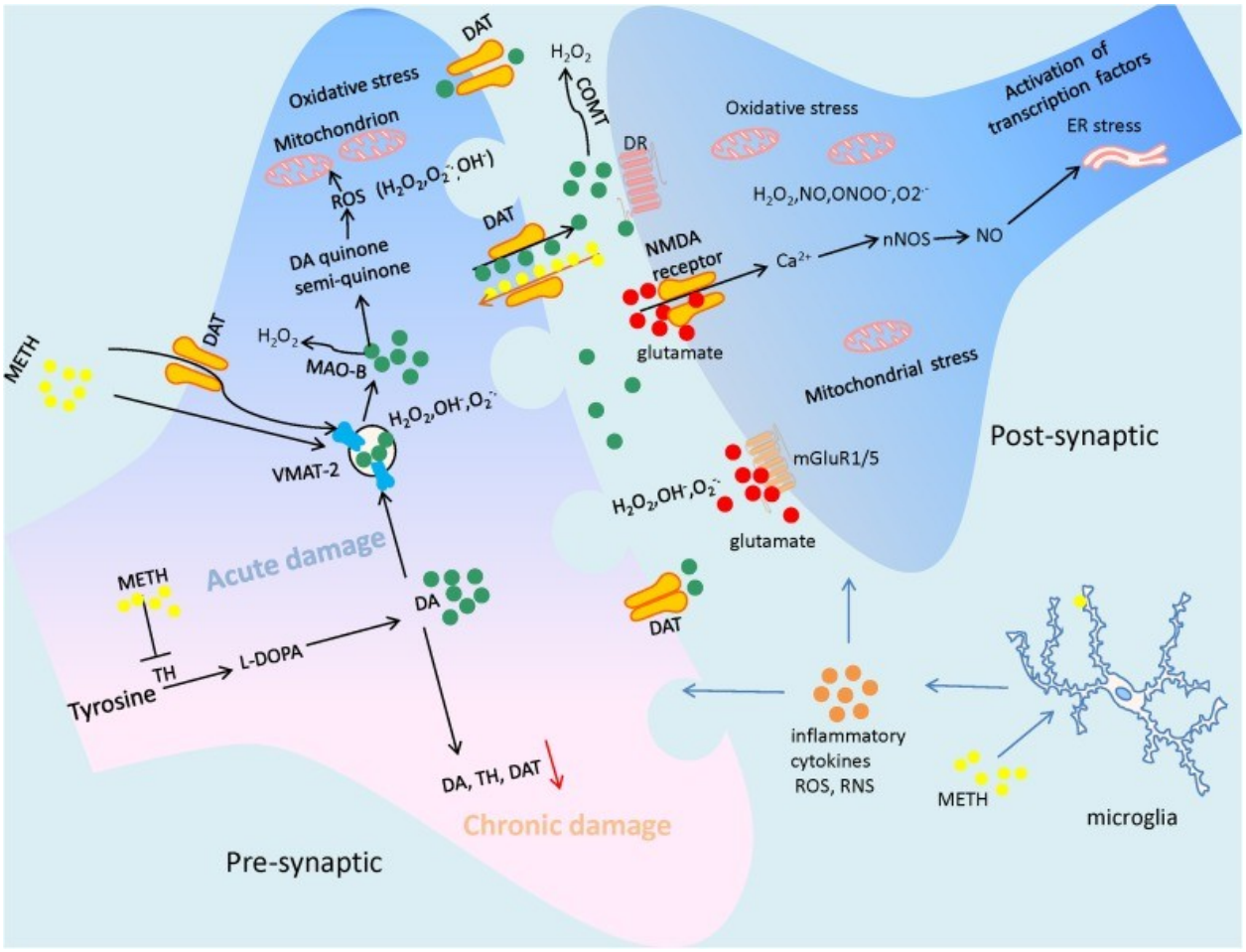

Figure 4. *Methamphetamine misuse reduces binding of dopamine to its respective transporters in the striatum (highlighted in red and green). Prolonged methamphetamine abstinence, dopamine transporters in this area could be restored.*[15]

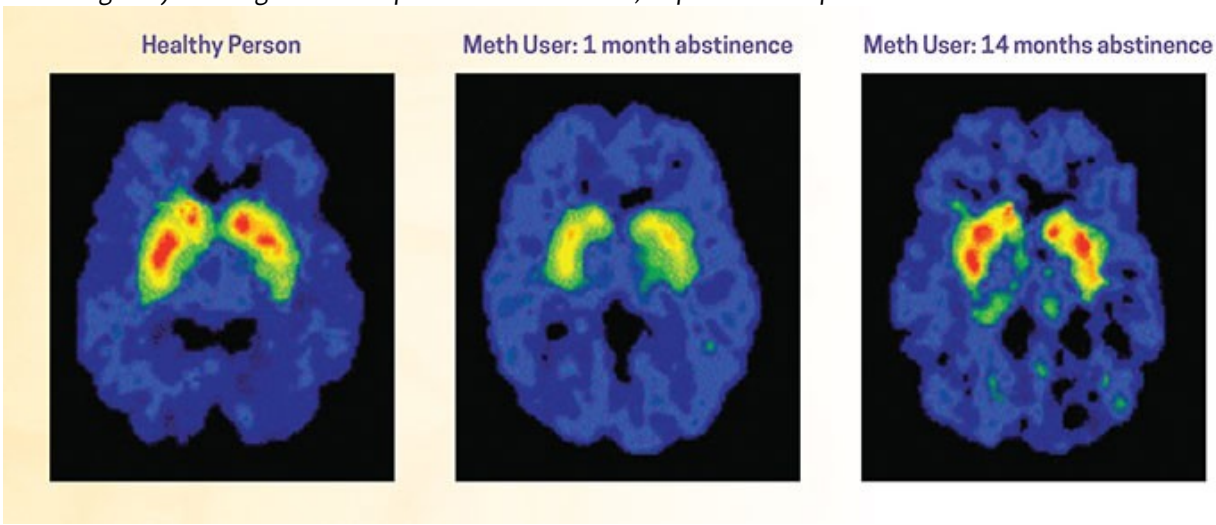

Figure 5. Schematic diagram of the human dopamine-rich striatum, which is made up of the caudate nucleus, putamen and ventral striatum (left), and a striatal dopamine nerve ending (right). Methamphetamine causes dopamine release from the nerve endings towards striatal areas of the brain which responsible for methamphetamine-liking and craving. This likely involves the translocation of dopamine from the synaptic vesicle to the neuronal cytoplasm via the vesicular monoamine transporter 2 and the reverse transport of dopamine from the cytoplasm into the synapse via the dopamine transporter.[18]

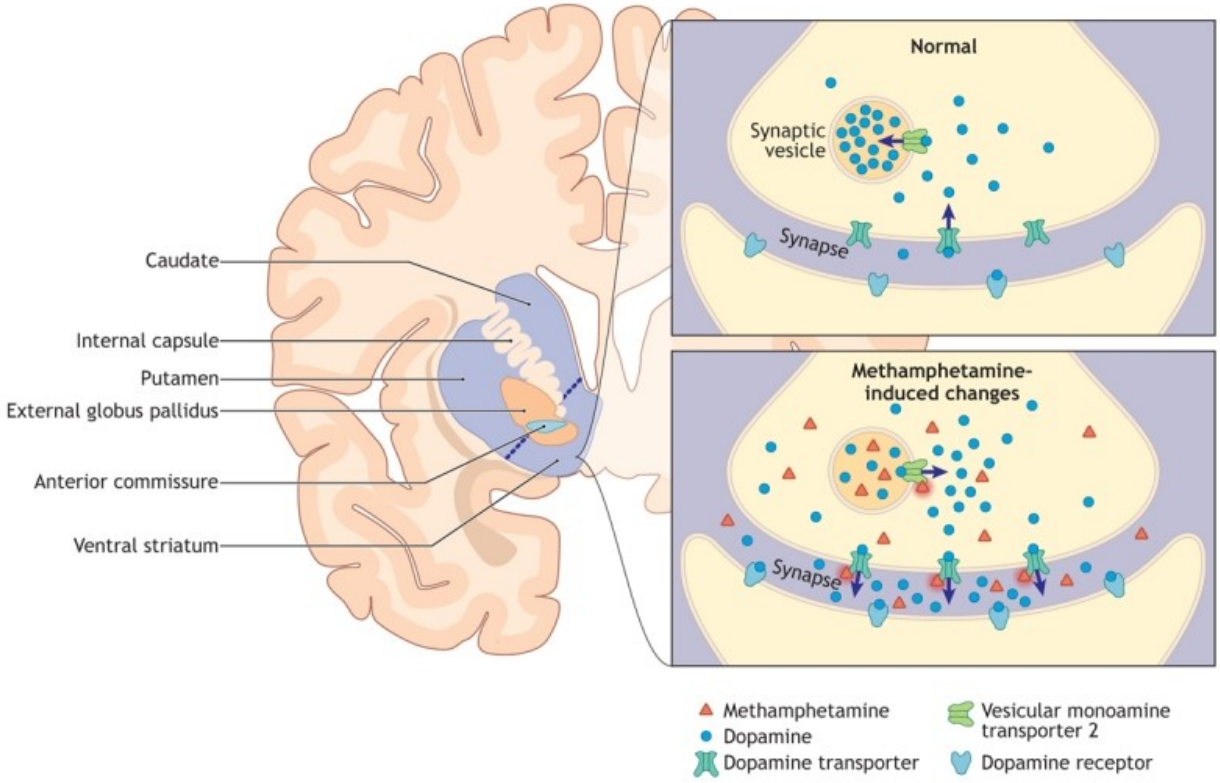

Figure 6. Molecular structures of N-acetylcysteine.[26]

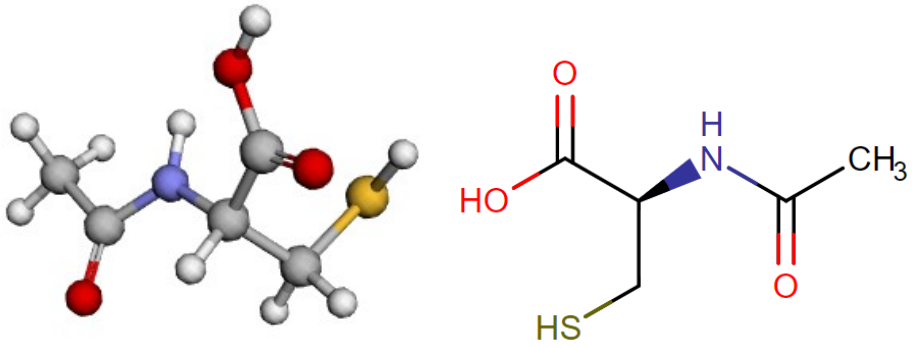

Figure 7. Mechanism of action of *N*-acetylcysteine (NAC). ASC, alanine-serine-cysteine (ASC) transport system; c-GCS, c-glutamylcysteine synthetase; cys, cysteine; glu, glutamine; gly, glycine; GSH, glutathione.[29]