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Methamphetamine use causes cognitive impairment and altered decision-making

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ABSTRACT

Methamphetamine is a widely abused psychostimulant. It reverses transport through the dopamine transporter, thereby increasing the extracellular level of dopamine in the brain, which is associated with the rewarding effect. Repeated intake of methamphetamine leads to drug addiction, a chronically relapsing disorder characterized by compulsive drug taking, inability to limit intake, and intense drug cravings. The molecular and cellular mechanisms of drug addiction are not well understood, but have been proposed to involve neural plasticity and the remodeling of specific brain circuits. Accumulating evidence also indicates that patients addicted to methamphetamine exhibit impaired cognitive functions such as executive function, attention, social cognition, flexibility, and working memory. Furthermore, decision-making is altered in patients with drug addiction, including methamphetamine abusers. Cognitive impairment as well as altered decision-making in methamphetamine abusers may contribute to the high rate of relapse even after long-term withdrawal with psychosocial support.

In this article, we review the effect of methamphetamine on cognition and decision-making in rodents. We also discuss possible mechanisms underlying cognition and decision-making impairments, including neuronal circuits, molecular and cellular events, and action control, as well as potential therapeutic targets.

1. Introduction

Methamphetamine is a widely abused drug, with over 17.2 million users worldwide (Degenhardt and Hall, 2012; Degenhardt et al., 2010). A previous meta-analysis quantified the magnitude of cognitive deficits associated with methamphetamine use, and found that methamphetamine users have deficits relative to healthy control subjects in multiple cognitive functions, including executive function, impulsivity, attention, social cognition, and working memory, among others (Potvin et al., 2018). The largest cognitive deficits are observed in the case of reward- or impulse-related functions and social cognition; the smallest effects are observed in speed of processing and visual-spatial abilities (Potvin et al., 2018).

The childhood grade point average of methamphetamine users was found to be significantly lower than that of the control group, which is consistent with evidence that addicts have premorbid cognitive limitations that predispose them to drug use (Dean et al., 2018). Methamphetamine users' overall cognitive function is lower, and memory deficits are associated with whole brain cortical thickness, suggesting that methamphetamine use causes a decline in cognition and/or a failure to develop typical cognitive abilities (Dean et al., 2018). Methamphetamine exposure during development also affects brain function (Buck and Siegel, 2015; Jablonski et al., 2016). Children exposed to intrauterine methamphetamine show altered levels of white matter metabolites, changes in myelination, axonal density disturbances, and changes in cellular metabolism in the striatum and frontal lobe (Smith et al., 2001). Significant volume reductions in the putamen, caudate nucleus, globus pallidus, and hippocampus correlate with abnormal attention, verbal memory, and reaction time in exposed children (Jablonski et al., 2016).

Recently, it has been shown that sleep is disrupted during active use of methamphetamine, during withdrawal, and during abstinence from

Abbreviations: CNO, clozapine-N-oxide; DREADD, designer receptor exclusively activated by designer drug; hM3Dq, human M3 muscarinic receptor Dq-DREADD; GAD, glutamic acid decarboxylase; GAT, GABA transporter; GWAS, Genome Wide Association Studies; hM4Di, human M4 muscarinic receptor Di-DREADD; MeCP2, CpG-binding protein 2; nAChRs, nicotinic acetylcholine receptors; PPI, prepulse inhibition; RPE, reward prediction error; SNP, single-nucleotide polymorphism; VTA, ventral tegmental area

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its use (Lipinska et al., 2015). Sleep is important for emotion and memory, and there are predictable relationships between methamphetamine abuse, sleep disruption, and memory deficits (Lipinska et al., 2015). Melatonin attenuates methamphetamine-induced inhibition of neurogenesis in the adult mouse hippocampus (Singhakumar et al., 2015).

Executive function includes the domains of decision-making, attentional control, and working memory; these cognitive functions all require intact corticostriatal function. Methamphetamine users exhibit deficits in working memory, memory recall, response inhibition and set-shifting performance, and psychomotor function (Bernheim et al., 2016). These impairments likely relate, at least in part, to continued drug taking, drug seeking, and the impaired decision-making secondary to addiction. In rodents, greater risk-taking in a reward-based decision process predicted larger intake of self-administered cocaine, and cocaine intake in turn caused increased risk-taking behavior (Mitchell et al., 2014).

In this article, we review the effect of methamphetamine on cognition and decision-making in rodents, and discuss possible mechanisms underlying cognition and decision-making impairments as well as potential therapeutic targets.

2. Methamphetamine addiction impairs cognitive function

2.1. Recognition memory and attention

Episodic memory is a form of declarative memory that implies the use of previously acquired autobiographic information for conscious recall (Bernheim et al., 2016; Tulving, 2002). Methamphetamine impacts this particular type of memory, and this impairment has been proposed to contribute to relapse in methamphetamine addicts (Bernheim et al., 2016; Simon et al., 2004). Because the mechanisms underlying the relationship between impaired episodic memory and relapse are still unknown, rodent models would be useful to examine the roles of different cognitive functions in features of addiction. Mice chronically treated with methamphetamine exhibit impaired long-term recognition memory after withdrawal, which is associated with a dysfunctional dopamine D1 receptor-extracellular signal-regulated kinase (ERK) 1/2 pathway in the prefrontal cortex (Ito et al., 2007; Kamei et al., 2006) and that methamphetamine-induced cognitive impairment is reversed by the atypical antipsychotic clozapine, but not haloperidol (Kamei et al., 2006). In general, the hippocampus, perirhinal cortex, and entorhinal cortex are related to recognition memory (Daselaar et al., 2006). Our results show that methamphetamine treatment leads to dysregulation in the prefrontal cortex, including the cingulate cortex, and the parietal cortex, resulting in impairments in recognition memory. Thus, the prefrontal cortex may be a key region in the development of methamphetamine-related psychosis. Recently, it was reported that memantine ameliorates impairment of recognition memory induced by methamphetamine, and its effectiveness may be due to its anti-apoptotic activity (Long et al., 2017).

2.2. Sensorimotor gating

Prepulse inhibition (PPI) of the startle reflex is considered a good measure of sensorimotor gating. Patients suffering from neuropsychiatric disorders often exhibit PPI disruption (Castellanos et al., 1996; Swerdlow et al., 1994). Many studies have shown that there are two distinct but interacting neuronal circuits in PPI of the startle reflex, PPI-mediating and regulating circuits (Fendt et al., 2001; Swerdlow et al., 2001). We have found that neural circuits containing pallidotegmental GABAergic neurons from the lateral globus pallidus to pedunculopontine tegmental neurons play a crucial role in PPI of the acoustic startle reflex in mice (Takahashi et al., 2007). Furthermore, treatment with methamphetamine or MK-801 impairs PPI of the startle reflex in a dose-dependent fashion (Arai et al., 2008). These results suggest that impaired functioning of the pallidotegmental neurons is involved in the disruption of PPI caused by methamphetamine and MK-801 in mice (Arai et al., 2008). Consistent with our findings, ketamine and phencyclidine treatment also disrupt PPI (Chiou et al., 2018). Some α6-$GABA_A$ receptors positive allosteric modulators attenuate disruption of PPI induced by ketamine and phencyclidine, indicating GABAergic dysfunction in the disruption of PPI induced by ketamine and phencyclidine (Chiou et al., 2018).

2.3. Spatial memory and flexibility

Repeated methamphetamine treatment also impairs working memory in a delayed spatial win-shift task using a radial arm maze. This impairment persisted at least 14 days after the withdrawal of methamphetamine in rats, and is associated with a malfunction of the ERK 1/2 pathway in the hippocampus (Nagai et al., 2006). Clozapine, but not haloperidol, is effective in improving the methamphetamine-induced working memory deficit (Nagai et al., 2007).

Other reports demonstrate that methamphetamine use induces deficits in working memory and cognitive flexibility, and identify malfunctions of dopamine receptors, glutamate receptors, serotonin receptor, and protein kinase in cognitive deficits (Ballard et al., 2015; Braren et al., 2014; Hankosky et al., 2018; Izquierdo et al., 2016). Chronic methamphetamine self-administration alters cognitive flexibility in mice (Cox et al., 2016). There is a positive correlation between methamphetamine-seeking behavior and perseverative errors during reversal learning, whereas no significant correlations are seen between cue-induced seeking behavior and error. These results indicate that two domains, relapse and cognitive flexibility, may constitute independent pathologies of methamphetamine addiction (Cox et al., 2016). Thus, methamphetamine-induced cognitive impairment in rodents may be a useful animal model for cognitive deficits in methamphetamine abusers as well as schizophrenic patients (Table 1).

3. Methamphetamine addiction impairs decision-making

Decision-making is a key function in everyday life. Decision-making is included in executive function. Decision-making process is divided into three stages: 1) the assessment and formation of preferences among possible options, 2) the selection and execution of an action, and 3) the experience or evaluation of an outcome (Ernst and Paulus, 2005). After these stages, modification of option values is occurred when the action-outcome sequence is completed. Empirical learning modifies the each option values for the next assessment. Brain functions such as attention, working memory, and recognition memory, are certainly involved in final decision in choice behavior. Consequently, disturbances in the ability to make appropriate decisions or anticipate their possible consequences can result in massive social, medical, and financial problems. Impaired decision-making are associated with many neuropsychiatric diseases and addictive disorders, and patients with these conditions have a greater tendency to engage in risk-taking behaviors and to choose actions that confer short-term rewards at the cost of long-term disadvantages. However, the neural substrates underlying these deficits are not yet determined. Animal models have been a useful tool in investigating decision-making and its neural basis.

Recently, the two-step task was developed to investigate the learning of strategies for choosing actions that lead to positive outcomes (Daw et al., 2011; Voon et al., 2015). In this task, the subject either follows an action by using information given in the two-step process of choices (model-based learning) or performs an action based on the value of the outcome but without taking into account the information provided (model-free learning) (Daw et al., 2011; Duka, 2017). Clinical studies show a bias towards model-free (habit) acquisition in disorders involving both natural (binge eating) and artificial (methamphetamine) rewards, and obsessive-compulsive disorder (Voon et al., 2015). This habit formation bias is associated with lower gray

Table 1
Performance of methamphetamine-treated animals.

Behavioral experiments and performance	Performances		Key regions	References
Sensitization, hyperlocomotion	Locomotion	⬆	NAc, Striatum	Mizoguchi et al., 2007
Startle response test	Pre-pulse inhibition	⬇	PnC, PPTg	Arai et al. (2008) Mizoguchi et al. (2009)
Startle response test	Pre-pulse inhibition	⬇	Cerebellum	Chiou et al. (2018)
Sucrose preference test	Preference	⬇	NAc	Ren et al., 2015
Forced swim test	Immobility time	⬆	NAc	Ren et al., 2015
Novel object recognition test	Exploratory time	⬇	PFc	Kamei et al. (2006) Long et al. (2017)
Novel object recognition test	Exploratory time	⬇	Hip, PRh	Vieira-Brock et al. (2015b)
Working memory in radial maze test	Error	⬆	Hip	Nagai et al. (2007) Mizoguchi et al. (2011)
Reversal learning test (Operant box, radial maze)	Error	⬆	Hip, Striatum, OFC	Braren et al. (2014) Cox et al. (2016) Izquierdo et al. (2016) Hankosky et al. (2018)
Rat gambling task	Risk choice	⬆	INS, NAc, Striatum	Mizoguchi et al. (2015) Mizoguchi et al. (2019)

Hip, hippocampus; INS, insular cortex; NAc, nucleus accumbens; OFC, orbitofrontal cortex; PFc, prefrontal cortex; PnC, caudal pontine reticular nucleus; PPtg, pedunculopontine tegmental neurons; PRh, perirhinal cortex.

matter volumes in the caudate and medial orbitofrontal cortex. In basic studies using rats, the two-step task may be useful for investigating neural mechanisms of model-based learning (Miller et al., 2017). This method may lead to new findings about neural mechanisms of planning in the hippocampus as well as throughout the brain.

Methyl CpG-binding protein 2 (MeCP2) is an epigenetic factor that regulates transcription by directly binding to methylated DNA. Methamphetamine treatment increases MeCP2 expression, and MeCP2 knockdown in the core of the nucleus accumbens reduces methamphetamine self-administration (Lewis et al., 2016). MeCP2 expression is also altered in the medial prefrontal cortex and nucleus accumbens, and correlates with risky decision-making (Deng et al., 2018). Thus, epigenetic factors may be an important component of the molecular mechanisms underlying risky decision-making processes.

3.1. Physiological centers of decision-making: the insular cortex and orbitofrontal cortex

Preclinical and clinical research has sought to model and evaluate decision-making processes in order to better understand mechanisms underlying addiction and to develop more effective interventions (Stoops and Kearns, 2018). The striatum, insular cortex, anterior cingulate cortex, and ventromedial prefrontal cortex are essential brain regions, and each is implicated in different aspects of decision-making (Stoops and Kearns, 2018).

Many reports have shown that the insular cortex is critically involved in decision-making (Clark et al., 2008; Ishii et al., 2012; Sanfey et al., 2003a, 2003b). The insular cortex integrates interoceptive signals from throughout the body with taste information and influences action selection by weighing predicted interoceptive consequences associated with responding to learned cues in the context of current physiological needs (Livneh et al., 2017). The insular cortex is associated with motivation-related subcortical circuits. Insular cortex activation is related to reward expectation in decision-making, along with activation of the amygdala, basal ganglia, and orbitofrontal cortex (Gleichgerrcht et al., 2010). Because the insular cortex is connected to the amygdala (Ernst and Paulus, 2005) and striatum (Schilman et al., 2008), it constructs the frontostriatal and limbic loops related to decision-making. In the Cambridge gambling task, ventromedial prefrontal cortex damage is associated with increased betting regardless of the odds of winning, consistent with a role of the ventromedial prefrontal cortex in biasing healthy individuals towards conservative options under risk (Clark et al., 2008). Notably, patients with insular cortex lesions fail to adjust their bets according to the odds of winning, consistent with a role for the insular cortex in signaling the probability of aversive outcomes (Clark et al., 2008). The insular lesion group attained a lower point score on the task and experienced more "bankruptcies." Several neuroimaging studies have revealed dysfunctions of the prefrontal cortex in stimulant-dependent subjects (Chiu et al., 2008; Critchley et al., 2001; London et al., 2000; O'Doherty et al., 2003; Paulus et al., 2002; Paulus et al., 2005; Tanabe et al., 2013); a close correlation between risky responses, harm avoidance, and insular cortex activation suggests a role for the insular cortex in punishment (Critchley et al., 2001; O'Doherty et al., 2003). Insular cortex inactivation would be consistent with a diminished ability to differentiate between choices that lead to good vs. poor outcomes, which may be a key factor in methamphetamine relapse (Paulus et al., 2005). Thus, addicts may have dysfunction in the insular cortex, which is associated with increased risk-taking.

The orbitofrontal cortex is thought to encode value, as well as mediate response inhibition and choice (Jean-Richard-Dit-Bressel et al., 2018). Patients with methamphetamine addiction show dysfunction in the orbitofrontal cortex (Dom et al., 2005; Ernst and Paulus, 2005). Insular cortex inactivation decreases risk preference, whereas orbitofrontal cortex inactivation increases risk preference in the risky gambling task for rats (Ishii et al., 2012). In the insular cortex, dopamine D2 and serotonin 1A receptors are involved in risky decision-making, whereas in the orbitofrontal cortex, serotonin 1A receptors are involved (Ishii et al., 2015). Inactivation of the lateral orbitofrontal cortex increases drinking behavior in ethanol-treated mice (den Hartog et al., 2016). Thus, imbalance in the function or output of the prefrontal cortex may be a critical factor underlying the gradual loss of control over drinking in people with alcoholism.

3.2. The insular GABAergic system in altered decision-making secondary to addiction

A hallmark of addiction is continued use of substances despite negative consequences or the absence of positive consequences (Kalivas and Volkow, 2005). Addicts are less able to flexibly adapt their behavior to changes in reward contingencies, and they have difficulty integrating reinforcements to guide future behavior (Park et al., 2010). Several altered decision-making patterns have been observed in patients with addiction; in particular, they tend to preferentially select actions associated with larger short-term gains but long-term losses over actions associated with smaller short-term gains and overall long-term gains (Dom et al., 2005; Ernst and Paulus, 2005). Moreover, patients with cocaine addiction show decreased cortical thickness in the insular cortex and dorsolateral prefrontal cortex in association with poor judgment and decision-making (Makris et al., 2008), and patients with methamphetamine addiction show dysfunction in the orbitofrontal cortex (Dom et al., 2005; Ernst and Paulus, 2005) and activation in the insular cortex (Ernst and Paulus, 2005; Paulus, 2007; Paulus et al., 2008). Conversely, methamphetamine users are reported to have lower relative regional cerebral blood flow bilaterally in the insular cortex (Chang et al., 2002; Hart et al., 2012). Smoking cravings were less frequent in study participants with insular lesions compared with control groups (Naqvi et al., 2007). The insular cortex is a part of the reflective system within this framework as an important component in decision-making processes that control drug use; the insular cortex may be involved because functional engagement in response to drug-related signals exacerbates the imbalance between the impulsive and reflective systems, intensifying activity of the impulsive system and further disabling its regulatory function (Naqvi and Bechara, 2010).

The specific contributions of these regions to altered decision-making remain unclear, and it is not known whether the dysfunctions in decision-making and its underlying neural substrates are preexisting conditions that contribute to the initiation of drug use, or are instead a consequence of repeated use. To address this issue, we discuss our data showing the effect of chronic methamphetamine treatment on decision-making in rats, obtained using a previously developed gambling test for rodents (Mizoguchi et al., 2015).

3.3. Chronically methamphetamine-treated rats choose the high-risk/high-reward option more frequently than control animals

We developed a gambling test for rodents that follows rules similar to those of the Iowa gambling test for humans (Mizoguchi et al., 2015). Using this test, naive rats gradually prefer the low-risk/low-reward option (avoidance of risky choice), as do participants in the Iowa gambling test, but chronically methamphetamine-treated rats with prior chronic methamphetamine treatment prefer the high-risk/high-reward option (increase in risky choice) (Mizoguchi et al., 2015). We found that this abnormal choice behavior depends on assigning higher motivational value to high returns, and results from impairments in the neural systems that control responses evoked by both large positive and negative reward prediction errors, leading to impulsive choice behaviors. Immunohistochemical analysis following the gambling test revealed aberrant activation of the insular cortex, nucleus accumbens, and striatum in methamphetamine-treated animals, suggesting that dysfunction in the frontostriatal network may contribute to the observed change in choice strategy in methamphetamine-treated rats, and that the outcome of processing and modification of option values in the decision-making process may be altered by chronic methamphetamine treatment.

3.4. Manipulation of insular GABAergic activity modifies choice behavior in the gambling test

When GABA receptor agonists was injected into the insular cortex of methamphetamine-treated rats, their elevated risky choice ratio gradually decreased. Conversely, when GABA receptor antagonists was injected into the insular cortex of naive rats that showed avoidance of risky choice, they began to make risky choices more frequently than vehicle-treated control rats. Moreover, in the insular cortex of methamphetamine-treated rats, depolarization-evoked GABA release was reduced compared to that in the insular cortex of control rats, suggesting that methamphetamine-treated rats have impairments in activity-dependent GABA release in the insular cortex. These findings lead us to believe that the inhibitory GABA system in the insular cortex plays a crucial role in choice behavior in the gambling test, and that dysfunction in GABA neurotransmission in the insular cortex may be associated with the altered decision-making of methamphetamine-treated rats (Mizoguchi et al., 2015).

To determine whether aberrant activation of the insular cortex was necessary and sufficient to alter the choice strategy of methamphetamine-treated rats, we utilized a mutant human M4 muscarinic receptor (hM4Di) transgene to suppress the aberrant neural activity in the insular cortex of methamphetamine-treated rats, and we injected mutant human M3 muscarinic receptor (hM3Dq) to activate insular cortex neurons in naive rats. When hM3Dq was overexpressed in the insular cortex of naïve rats, clozapine-N-oxide (CNO) treatment resulted in an increase of risky choice compared to vehicle treatment. When hM4Di was overexpressed in the insular cortex of rats of methamphetamine-treated rats, CNO treatment resulted in a decrease of risky choice compared to vehicle treatment, indicating that inactivation of the insular cortex can improve altered decision-making in methamphetamine-treated rats (Mizoguchi et al., 2015).

Taken together, these results indicate that disinhibition of glutamatergic neurons and dysfunction of GABAergic interneurons in the insular cortex both contribute to risky decision-making and drug-taking behavior (Fig. 1).

3.5. Cell-specific manipulation in decision-making

The green fluorescent protein (GFP)-dependent Cre recombinase system uses a fusion protein of split Cre-GFP binding protein (GBP) such that GFP controls the activity of Cre recombinase; GBP-Split Cre fusion proteins assemble as a complex on the GFP scaffold, initiating Cre recombination (Tang et al., 2015). The system requires two components, N-CreintG and C-CreintG, for direct activation of Cre recombination. This system is powerful tool for cell-specific manipulation of GFP-positive cells if it is applied to behavioral experiments.

Recent reports introduced a possible role for a cell-specific neuronal pathway from the insular cortex in reward-based, goal-directed actions. The insular cortex to amygdala pathway is involved in relapse as an addiction- and motivation-related projection (Venniro et al., 2017), and optogenetic manipulation of the basolateral amygdala can either inhibit or promote risky choice, depending on the phase of the decision-making process (Orsini et al., 2017). A specific pathway from hypothalamic agouti-related peptide neurons to the insular cortex is important for food cue responses (Livneh et al., 2017). Silencing the insular cortex to nucleus accumbens core pathway decreases alcohol self-administration, but does not affect sucrose self-administration (Jaramillo et al., 2018a, 2018b). These findings suggest a critical role for the insular cortex and its projections to the nucleus accumbens core in modulating ongoing alcohol self-administration, and emphasize circuit-specificity in this process (Jaramillo et al., 2018a, 2018b). Moreover, many researchers use a designer virus that permits efficient retrograde access to projection neurons in anatomical and behavioral experiments (Tervo et al., 2016). Further research on the insular-striatal pathway and possible GABAergic deficits is necessary to understand the mechanisms underlying cognitive deficit and impaired decision-making, and to provide insights into better treatment for addiction.

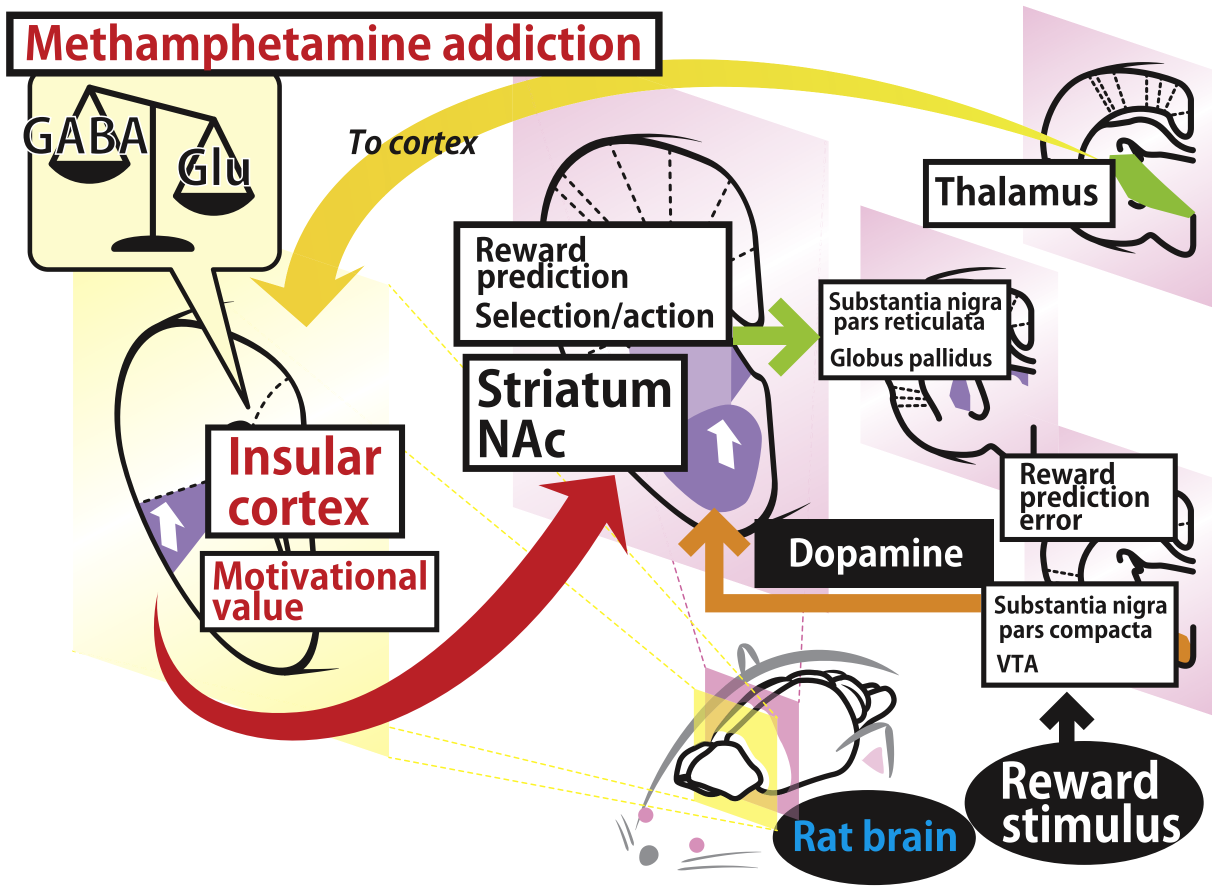

Fig. 1. Neural circuits underlying impaired decision-making in methamphetamine addiction. Methamphetamine influences the function of dopaminergic neurons that code reward prediction errors and also affects basal ganglion neurons for selection and action. We found that the insular cortex is a critical region involved in altered decision-making in methamphetamine-treated rats. In the context of drug dependence, the insular GABA system is dysfunctional, leading to disinhibition of glutamatergic neurons from the insular cortex to the striatum and nucleus accumbens. Moreover, our computational approach found that methamphetamine-treated rats assigned higher value to high returns than control rats. We believe that the insular cortex may be related to motivational value. NAc, nucleus accumbens; VTA, ventral tegmental area.

4. Therapeutic targets for impaired cognition and decision-making

4.1. GABA and NMDA receptors

Candidate gene association studies for addiction suggest the involvement of the dopamine system, opiate system, GABAergic system, and nicotinic cholinergic system. Genome-wide association studies (GWAS) of addiction have identified the same genes or gene loci associated with addiction. In particular, several case-control association studies suggest that the human $GABA_A$ receptor γ2 subunit gene is marginally associated with methamphetamine use disorder, and may be a susceptibility gene for this disorder (Lin et al., 2003; Nishiyama et al., 2005). Serum levels of $GABA_A$ receptor α1 subunit protein are reduced in methamphetamine users compared to a healthy control group (Zhang et al., 2016). GABA agonists including topiramate, baclofen, and GABA transaminase inhibitor show promise in reducing methamphetamine use and cravings (Rose and Grant, 2008).

In a rat sensitized to methamphetamine treatments, glutamic acid decarboxylase (GAD) 67, GAD65, GABA transporter (GAT) 1, GAT3, vesicular GABA transporter, and GABA mRNA expression are upregulated in the prelimbic cortex, and $GABA_A$ receptor subunits α1, α3, α5, and β2 are upregulated in the orbitofrontal cortex (Wearne et al., 2016b). $GABA_B$ receptors are also upregulated in the prefrontal cortex of sensitized rats compared with controls (Wearne et al., 2016a). These results suggest that alterations of GABAergic gene expression are biologically dissociated between these brain regions. At a minimum, GABAergic gene expression appears to be altered following chronic methamphetamine exposure. Expression of the $GABA_A$ receptor α1 subunit protein is decreased in the dorsal striatum, which plays a role in methamphetamine-associated reward memory (Jiao et al., 2016).

These changes may lead to profound consequences on central inhibitory mechanisms in localized regions of the corticostriatum and may underpin common behavioral phenotypes seen across psychotic disorders. Recently, it was reported that cerebellar α6 subunit-containing $GABA_A$ receptors are related to PPI disruption by methamphetamine, so these receptors may be a good candidate for a novel targeted therapy for neuropsychiatric disorders (Chiou et al., 2018). Further studies are necessary to clarify the role of α6 subunit-containing $GABA_A$ receptors because thus far it has only been demonstrated by pharmacological behavioral assays.

We have found that acute treatment with baclofen (1–2 mg/kg), a $GABA_B$ receptor agonist, improves methamphetamine-induced impairment in recognition memory without affecting motor function (Arai et al., 2009). Although further studies are necessary to clarify the molecular mechanisms of baclofen, its ameliorating effect on methamphetamine-induced cognitive deficits may be, at least in part, due to its inhibitory effect in the prefrontal cortex.

Memantine, a low-affinity, voltage-dependent uncompetitive antagonist of NMDA receptors, has a neuroprotective effect against methamphetamine-induced cognitive deficits. Pretreatment with memantine prevents methamphetamine-induced changes in protein levels of apoptosis-related genes (Bcl-2 and caspase-3) in the prefrontal cortex (Long et al., 2017). Thus, glutamatergic transmission plays a crucial role in the development of methamphetamine psychosis and dependence (Miyazaki et al., 2013). Methamphetamine over-activates NMDA receptors and induces an imbalance in excitation and inhibition as well as tonic excitement. The neuroprotective effect of memantine is due to its inhibitory effect achieved by normalizing methamphetamine-induced NMDA receptor activation.

4.2. Nicotinic acetylcholine receptor (nAChR)

Nicotine has a therapeutic effect on attentional abnormalities associated with schizophrenia (Adler et al., 1992). Clinical studies have demonstrated that nicotine treatment improves cognition in patients with schizophrenia and neurocognitive disorders. Galantamine, a cholinesterase inhibitor, ameliorates the impairment of recognition memory in methamphetamine treated mice repeatedly (Noda et al., 2010). Nicotine treatment improves impaired PPI and working memory in methamphetamine-treated animals, indicating that nicotine receptors are a therapeutic target for treating cognitive deficits in methamphetamine-treated animals. (Mizoguchi et al., 2009, 2011). In the rodent gambling test, we observed that nicotine treatment in methamphetamine-treated rats significantly reduces risky choice behavior, and reduces lose-shift behavior, but has little effect on win-stay behavior (Mizoguchi et al., 2019). Varenicline, an α4β2-nAChR partial agonist, also inhibits risky choice behavior in methamphetamine-treated rats. These results suggest that nicotine and varenicline ameliorate changes in the reward-based choice strategy in methamphetamine-treated rats.

Chronic nicotine exposure increases striatal α4β2 nAChR density *in vitro* and recovers deficits in dopamine transporter activity in methamphetamine-treated rats (Vieira-Brock et al., 2015a). Methamphetamine treatment reduces α4β2-nAChR density in the hippocampus, and nicotine treatment attenuates the deficit. These effects may be associated with impairment of recognition memory in methamphetamine-treated rats (Vieira-Brock et al., 2015b). Despite changes in the expression level or function of some nAChR subunits in methamphetamine-treated rats, nAChRs, especially α4β2-nAChR, may represent a potential target for curing patients with neuropsychiatric disorders and addiction of perturbed decision-making (Mizoguchi et al., 2011, 2019).

Notably, there is a close relationship between nAChR localization and GABAergic function in the frontal cortex. Recent studies demonstrated that single-nucleotide polymorphisms (SNPs) in the human *CHRNA5* gene, which encodes the α5 nAChR subunit, increase the risk of both smoking and schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics, 2014; Tobacco and Genetics, 2010). The brains of mice expressing the α5-SNP exhibit hypofrontality, which is also observed in patients with addiction and some neuropsychiatric disorders including schizophrenia, and chronic treatment with nicotine reverses this hypofrontality (Koukouli et al., 2017). The α5-subunit is localized on vasoactive intestinal peptide-positive neurons, the α7 subunit is expressed on somatostatin- and parvalbumin-positive neurons, and the β2 subunit is expressed on somatostatin-positive neurons. The β2-containing nAChRs on somatostatin interneurons are involved in the normalization effect of nicotine on hypofrontality. Thus, the use of nAChR agonists affecting the frontal cortex may represent a therapeutic approach for patients with neuropsychiatric disorders.

In a probabilistic reversal learning task, abstinent smokers are more likely to shift responses following a loss (lose-shift choice) compared with smokers who receive nicotine or varenicline, whereas neither drug affects lose-shift behavior in nonsmokers, indicating that acute nicotine and varenicline treatment reduces lose-shift behavior (Lesage et al., 2017). Thus, nicotine and varenicline may exert some preventive effects on compulsive behaviors following negative reward prediction error via nAChRs, including the α4β2-nAChR. Cognitive or pharmacological strategies to shift the bias away from habit formation towards forward planning and goal-directed approaches may be therapeutically useful (Voon et al., 2015). However, impairments in uncertainty modulation in the anterior cingulate cortex disrupt reinforcement learning processes in chronic nicotine users; nicotine treatment leads to lower learning rates of reward prediction errors in rats, and serotonin receptor gene expression decreases in nicotine-treated rats (Wei et al., 2018). Thus, chronic nicotine exposure would impair uncertainty modulation on reinforcement learning in the anterior cingulate cortex and serotonin system. Further studies are necessary to clarify the pharmacological role of nAChR in decision-making by healthy participants and addicts.

5. Summary

We hypothesize that activation of glutamatergic neurons, associated with dysfunction of GABAergic neurons in the frontal cortex, contributes to cognitive deficits and altered decision-making in methamphetamine-treated rats. The balance of excitation and inhibition in the frontal cortex may play an important role in cognition and decision-making. Furthermore, nAChR agonists may have beneficial effects on methamphetamine-induced abnormalities. Varenicline has already been used clinically for smoking addiction. According to our findings, varenicline may also be useful for treatment for altered decision-making and cognitive impairment in methamphetamine addiction. α5-containing nAChR and α4β2-nAChR could be candidate molecular targets to prevent their phenomenon. Accordingly, we propose the development of specific agonists for these receptors, and to clarify the molecular mechanisms underlying their ameliorating effects.

Conflicts of interest

There are no conflicts of interest in this study.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.neuint.2018.12.019.

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