Impulsive Behavior and Nicotinic Acetylcholine Receptors

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Received October 19, 2011; Accepted January 11, 2012

Abstract. Higher impulsivity is thought to be a risk factor for drug addiction, criminal involvement, and suicide. Excessive levels of impulsivity are often observed in several psychiatric disorders including attention-deficit/hyperactivity disorder and schizophrenia. Previous studies have demonstrated that nicotinic acetylcholine receptors (nAChRs) are involved in impulsive behavior. Here, we introduce recent advances in this field and describe the role of the following nAChR-related brain mechanisms in modulating impulsive behavior: dopamine release in the ventral striatum; α4β2 nAChRs in the infralimbic cortex, which is a ventral part of the medial prefrontal cortex (mPFC); and dopamine release in the mPFC. We also suggest several potential therapeutic drugs to address these mechanisms in impulsivity-related disorders and explore future directions to further elucidate the roles of central nAChRs in impulsive behavior.

Keywords: nicotine, inhibitory control, impulsive action, attention-deficit/hyperactivity disorder (ADHD), nucleus accumbens

1. Introduction

Impulsive behavior is broadly defined as “actions that are poorly conceived, prematurely expressed, unduly risky, or inappropriate to the situation and that often result in undesirable outcomes” (1). We have previously shown that the degree of impulsivity in each person is relatively stable over time (2), and it has the potential to predict future behavior.

A higher degree of impulsivity is not always maladaptive and largely depends on one’s situation (3, 4). To survive in a highly uncertain situation, an individual has to make quick decisions; therefore, impulsivity is required for survival.

In most modern human societies, however, impulsive behavior is maladaptive. For example, higher impulsivity may be a risk factor for drug addiction, criminal involvement, and suicide (5 – 8). Moreover, higher impulsivity is observed in several psychiatric disorders such as attention-deficit/hyperactivity disorder (ADHD) (9), schizophrenia (10), substance abuse (11), bipolar disorder (12), and borderline personality disorder (13). Thus, elucidating the neural mechanism that underlies impulsive behavior is necessary to develop treatments for impulsivity-related disorders.

Our aims in this review are two-fold: to review the involvement of nicotinic acetylcholine receptors (nAChRs) and related mechanisms in “a deficit in waiting”, a subordinate concept of impulsive behavior, and to incorporate previous findings into a suggestion of several potential therapeutic drugs for impulsivity-related disorders.

Subordinate concepts of impulsive behavior

First, we will describe the four subordinate concepts of impulsive behavior. As stated earlier, impulsive behavior is defined as poorly conceived, prematurely expressed, and unduly risky. As easily inferred from the definition, impulsive behavior includes different aspects that might not be closely correlated with each other (14). Impulsive behavior can be divided into four subordinate concepts: “reflection impulsivity”, “impulsive action”, “impulsive choice”, and “risky behavior” (15), although these definitions are not always exclusive. Impulsive action is further divided into “a deficit in waiting” and “a deficit in stopping”. Impulsive choice is also further divided into “delay

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Published online in J-STAGE on March 22, 2012 (in advance) doi: 10.1254/jphs.11R06CR
Invited article
Impulsive behavior

“actions that are poorly conceived, prematurely expressed, unduly risky, or inappropriate to the situation and that often result in undesirable outcomes” (Reference 1)

Reflection impulsivity
the tendency to make a decision without gathering available/enough information
- IST

Impulsive action
a failure of motor inhibition

Impulsive choice
the tendency to choose small immediate or likely rewards versus large delayed or unlikely ones

Risky behavior
to place oneself in an unsafe manner that can lead to dangerous consequences
- Gambling task

A deficit in waiting
- 5-CSRTT/3-CSRTT
- CPT
- Go/NoGo task *
- Stroop task *

A deficit in stopping
- SST
- Go/NoGo task *
- Stroop task *

Delay discounting
- DDT
- DGT

Probability discounting
- PDT

Fig. 1. Main and subordinate concepts of impulsive behavior. The representative tasks that have been used to assess each subordinate concept are shown in italics. These subordinate concepts are not always exclusive of each other. For example, subordinate concepts connected by dotted lines are thought to be correlated to some extent. The tasks with an asterisk assess two concepts. IST: information sampling task, 5-CSRTT: 5-choice serial reaction time task, 3-CSRTT: 3-choice serial reaction time task, CPT: continuous performance task, SST: stop-signal task, DDT: delay discounting task, DGT: delay gratification task, PDT: probability discounting task.
nAChR is a pentameric combination of the subunits \( \alpha_4 \) and \( \beta_2 \) (25 – 28). The intraperitoneal injection of nicotine provokes a deficit in waiting or systemic nicotine administration by subcutaneous or intravenous routes (14, 22, 23). Several studies have demonstrated that nicotine decreases the number of cigarettes smoked per day (14, 22, 23), and some researchers including us have shown that the number of cigarettes smoked per day is positively correlated with the number of cigarettes smoked per day (14, 22, 23). Moreover, smokers (40) have shown that tobacco smoking stimulates dopamine release in the ventral striatum of smokers (38, 39). However, another study using the same radiolabeled ligand failed to show an effect of intranasal nicotine administration on dopamine release in the striatum of smokers (40). Although further human studies are needed, systemic nicotine administration likely stimulates dopamine release in the ventral striatum and the mPFC (Fig. 2).

Increased dopamine release in the nucleus accumbens is required to stimulate impulsive behavior (41, 42). Thus, it is thought that nicotine injection/smoking stimulates dopamine release in the ventral striatum and thereby evokes impulsive behavior (Fig. 2). Dopaminergic activation affects the subjective speed of an internal clock (43) and enhances incentive salience to rewards (44). These effects of dopaminergic activation might be involved in nicotine-evoked impulsive behavior.

In contrast, normal dopamine release in the mPFC plays a role in suppressing impulsive behavior in rats (45, 46). Indeed, most drugs that suppress impulsive behavior (e.g., noradrenalin reuptake inhibitors and atypical antipsychotic drugs; see section 5. Clinical Implications) stimulate dopamine release in the mPFC in rats (27, 47 – 56). Moreover, we recently found that the suppressive effects of milnacipran on impulsive behavior were reversed by the intra-mPFC injection of a D1 dopamine–receptor antagonist (I. Tsutsui-Kimura et al., unpublished results). However, too much dopamine release in the prefrontal cortex might stimulate impulsive behavior because the intra-mPFC injection of higher doses of D1 dopamine–receptor agonist provokes impulsive behavior (46). Given that milnacipran increases extracellular dopamine release in the mPFC approximately to 300% of baseline levels (47) and suppresses impulsive behavior (27), further increase of dopamine release (> 300%) might disrupt the functions of the mPFC. It should be noted that nicotine increases extracellular dopamine release in the mPFC to 150% – 160% of baseline levels (35). Thus, in contrast with the ventral striatum, it is thought that nicotine injection/smoking stimulates dopamine release in the mPFC and thereby suppresses impulsive behavior.

2. The involvement of nAChRs in impulsive behavior in normal subjects

Nicotine, a major addictive component of tobacco, stimulates nAChRs in the central nervous system. Smoking cessation is difficult because of nicotine withdrawal symptoms (20, 21). Several studies have demonstrated that tobacco smokers show a higher degree of impulsivity in the DDT than nonsmokers (14, 22, 23), and some researchers including us have shown that the number of cigarettes smoked per day is positively correlated with impulsive decision making in the DDT (19, 24). Many animal studies have indicated that both acute and repeated systemic nicotine administration by subcutaneous or intraperitoneal injection provoke a deficit in waiting or impulsive choice (i.e., delay discounting) (25 – 28). The nAChR is a pentameric combination of \( \alpha \) and \( \beta \) subunits. Six \( \alpha \) subunits (\( \alpha_2 – \alpha_7 \)) and three \( \beta \) subunits (\( \beta_2 – \beta_4 \)) have been described in the mammal nervous system. Several combinations of these subunits have been detected, of which the \( \alpha_4\beta_2 \) and \( \alpha_7 \) subtypes are the most widely distributed (29).

A nicotine-induced deficit in waiting is mediated by the \( \alpha_4\beta_2 \) subtype of nAChRs, but not by the \( \alpha_7 \) subtypes (25, 30). Although \( \alpha_7 \) nAChR–deficient mice displayed a deficit in waiting under one experimental condition, this result was not replicated under another experimental condition that required more inhibitory control (31). Our previous study also demonstrated that the intracerebroventricular injection of an \( \alpha_4\beta_2 \) nAChR antagonist in the absence of nicotine suppressed impulsive behavior in the 3-CSRTT, while an \( \alpha_7 \) nAChR antagonist did not (32). Thus, stimulating nAChRs (most likely the \( \alpha_4\beta_2 \) subtype) has been relatively well established in provoking impulsive behavior (a deficit in waiting) in normal animals and in people without psychiatric disorders.

Mechanisms of nicotine-induced impulsive behavior in normal subjects

The putative mechanisms of nicotine-induced impulsive behavior (a deficit in waiting) are complicated; therefore, we have summarized them schematically in Fig. 2.

Several studies using microdialysis have demonstrated that the subcutaneous administration of nicotine stimulates dopamine release in the rat nucleus accumbens (33 – 35) and medial prefrontal cortex (mPFC) (35) via the activation of nAChRs in the ventral tegmental area (33). Previous studies using knockout mice have suggested that these effects of nicotine are largely due to the activation of \( \alpha_4\beta_2 \) nAChRs (36, 37). Human studies using positron emission tomography (PET) with \([11C]raclopride have shown that tobacco smoking stimulates dopamine release in the ventral striatum of smokers (38, 39). However, another study using the same radiolabeled ligand failed to show an effect of intranasal nicotine administration on dopamine release in the striatum of smokers (40). Although further human studies are needed, systemic nicotine administration likely stimulates dopamine release in the ventral striatum and the mPFC (Fig. 2).

In contrast, normal dopamine release in the mPFC is required to stimulate impulsive behavior (41, 42). Thus, it is thought that nicotine injection/smoking stimulates dopamine release in the ventral striatum and thereby evokes impulsive behavior (Fig. 2). Dopaminergic activation affects the subjective speed of an internal clock (43) and enhances incentive salience to rewards (44). These effects of dopaminergic activation might be involved in nicotine-evoked impulsive behavior.
impulsive behavior (Fig. 2).

Our recent study using rats demonstrated that systemic nicotine administration provoked impulsive behavior via the activation of $\alpha_4\beta_2$ nAChRs in the ventromedial prefrontal cortex (28). In the mPFC, $\alpha_4\beta_2$ nAChRs are expressed on interneurons, which extend inhibitory signals to layer 5 pyramidal neurons (57). These recent findings are consistent with previous studies showing that quinolinic acid–induced lesions of the mPFC evoke impulsive behavior in rats (58, 59) and with our recent finding that the neural activity in a ventral part of the mPFC is linked to impulsive behavior (I. Tsutsui-Kimura et al., unpublished results). Thus, it is likely that nicotine injection/smoking stimulates nAChRs in the mPFC and thereby evokes impulsive behavior (Fig. 2).

Taken together, the effects of systemic nicotine administration on impulsive behavior depend on the neural location that is affected by the nicotine. Nicotine evokes impulsive behavior by promoting dopamine release in the ventral striatum and by stimulating $\alpha_4\beta_2$ nAChRs in the mPFC; in contrast, it suppresses impulsive behavior by facilitating dopamine release in the mPFC. As a result of these complicated effects, systemic nicotine administration stimulates impulsive behavior in normal subjects (Fig. 2). Recent studies have shown that dopamine release in the nucleus accumbens is involved in desire but not reward itself, even though dopamine release had been regarded as a reward transmitter (44). Additionally, the frontal cortex is thought to be involved in inhibitory control (60). Thus, it is plausible that nicotine stimulates impulsive behavior both by enhancing the desire for rewards and by disrupting inhibitory control.

3. Clinical implications

Based on the model shown in Fig. 2, drugs that are developed to treat excessive impulsivity should meet the following requirements: 1) induce a targeted release of dopamine in the mPFC, 2) not stimulate dopamine release in the ventral striatum, 3) not stimulate $\alpha_4\beta_2$ nAChRs in the mPFC.

If a drug meets these criteria, the drug does not need to be a cholinergic drug. To achieve requirement 3, non-cholinergic drugs are preferable. For example, noradrenaline reuptake inhibitors could be candidate therapeutic drugs for excessive impulsivity because they meet these criteria. Noradrenaline transporters in some brain regions including the prefrontal cortex take up dopamine (61). That is, noradrenaline transporter inhibitors would increase the extracellular levels of dopamine in the mPFC.
indicating that such drugs meet above requirement 1. Atomoxetine, a selective noradrenalin reuptake inhibitor, has recently been used as a pharmacotherapy to treat ADHD. Atomoxetine meets requirement 2 in addition to requirement 1. Atomoxetine has been shown to induce a mild/prolonged increase in dopamine release in the rat prefrontal cortex without affecting dopamine release in the nucleus accumbens (48); consequently, it suppresses impulsive behavior in rats (27, 49). Because there is so far no study proving the affinity of atomoxetine for α4β2 nAChRs, atomoxetine will meet requirement 3. Thus, atomoxetine meets all of the above three requirements.

Like atomoxetine, milnacipran, which is a serotonin/noradrenalin reuptake inhibitor, can also induce a mild/prolonged increase in dopamine release in the mPFC (47). We have previously demonstrated that milnacipran suppresses impulsive behavior in rats (27). Thus, the use of a noradrenalin reuptake inhibitor should be considered in the future as a therapy for excessive impulsivity. Because milnacipran is an antidepressant, it might be useful for depressive patients showing excessive impulsivity.

The following drugs also meet most or all of above three requirements. Many animal studies using microdialysis have demonstrated that several atypical antipsychotic drugs increase dopamine release in the mPFC (50, 62), whereas some only mildly or slightly increase dopamine release in the nucleus accumbens (63). A previous study demonstrated that clozapine can mitigate repeated phencyclidine-induced impulsive behavior in rats (51). Thus, atypical antipsychotic drugs should also be considered as candidate therapeutic drugs for impulsivity-related disorders even though their side effects are relatively severe. A recent study showed that clozapine-induced dopamine release in the rat mPFC was blocked by the local perfusion of a muscarinic acetylcholine receptor M1 antagonist into the mPFC, which suggests that the stimulation of the M1 receptor would evoke dopamine release. Thus, M1 agonists might also be therapeutic candidates to suppress impulsive behavior (50).

A previous animal study showed that lithium administration can significantly decrease dopamine release in the nucleus accumbens while mildly increasing dopamine release in the mPFC, although this effect was not statistically significant (64). We have also recently shown that lithium administration can suppress impulsive behavior in rats (65). Because lithium is a mood stabilizer, it might be useful for patients with bipolar disorder showing excessive impulsivity.

Some animal studies have demonstrated that LY379268, a group II metabotropic glutamate receptor (mGluR2/3) agonist, stimulates dopamine release in the mPFC but not in the nucleus accumbens. This agonist also decreases dopamine release in the nucleus accumbens shell (52, 66). Moreover, LY379268 has been found to suppress phencyclidine-induced impulsive behavior in rats (53).

In another animal study, SR141716A (rimonabant), a type 1 cannabinoid receptor antagonist, stimulated dopamine release in the mPFC but did not increase dopamine release in the nucleus accumbens (54). Moreover, SR141716A could prevent nicotine-induced dopamine release in the rat nucleus accumbens (67). Moreover, SR141716A has been shown to suppress impulsive behavior in rats (68).

The drugs discussed above all have the potential to suppress impulsive behavior in several psychiatric disorders such as ADHD, schizophrenia, substance abuse, bipolar disorder, and borderline personality disorder. These and/or other drugs that meet the three requirements suggested above should be considered as potential therapeutic drugs to suppress impulsive behavior in these patients.

4. Limitations

Although promising, there are at least two limitations on the logic presented here. First, although we have focused primarily on nAChRs and the dopaminergic system here, other systems may also have non-negligible impacts on impulsive behavior. In addition to dopamine, nicotine administration stimulates the release of several other neurotransmitters that are involved in impulsive behavior. For example, systemic nicotine administration has been shown to stimulate serotonin release in the prefrontal cortex (69), and central serotonin depletion has been found to enhance impulsive responses in rats (70). Previous studies have shown that noradrenalin release in the amygdala, hippocampus, and mPFC is stimulated by systemic nicotine administration (35, 71) and that α1 and α2 adrenoceptors are involved in impulsive behavior (72, 73).

Second, our model is based mainly on previous studies that involve normal rats. Because the neural mechanisms that underlie impulsive behavior have become clear, future studies should attempt to construct animal models of impulsivity-related disorders and to examine the effects of drugs on impulsive behavior in these animal models. This is necessary because drugs can have extremely different effects on normal, healthy people and patients with psychiatric disorders. Indeed, Potter and Newhouse have demonstrated that the acute administration of nicotine using a nicotine patch can improve behavioral disinhibition in adolescent and young adult ADHD patients who are non-smokers (74, 75). The same group recently reported that a partial agonist of the α4β2 nAChR (AZD3480), which is currently undergoing phase II
demonstrated that the patterns of neural activity in the volumetric reductions in their frontal lobes (80 – 84). It has shown that patients with ADHD and schizophrenia have important in controlling impulsivity. Several studies have investigated the effects of a nicotine patch on impulsive behavior in bipolar disorder or borderline personality disorder.

Taken together, these results suggest that further studies are necessary to resolve the still controversial idea that stimulating nAChRs attenuates impulsive behavior in people with psychiatric disorders. At least, it is likely that the application of a nicotine patch does not stimulate impulsive behavior in patients with some types of psychiatric disorders. Furthermore, it is also worth noting that the route of administration in the aforementioned studies (i.e., a nicotine patch) is different from the route used in studies that were discussed in previous sections (i.e., tobacco smoking in humans or an intraperitoneal, subcutaneous, or intravenous injection in animals).

5. Future directions

Considering the above limitations, we suggest the following two future directions: 1) construct animal models of impulsivity-related disorders and test the previously suggested potential therapeutic drugs on these animals and 2) examine whether differences in the route of administration change the effects of nicotine on impulsive behavior, and if so, elucidate the reasons.

Animal models of impulsivity-related disorders

Constructing animal models of impulsivity-related disorders based on the neural mechanisms described in Fig. 2 might help to clarify why the effects of nicotine on impulsive behavior in psychiatric patients are different from those in normal subjects (see section 4. Limitations). One potential animal model is the mPFC-lesioned rodent model. As discussed in a previous section (2. The involvement of nAChRs in impulsive behavior in normal subjects), lesions in the mPFC evoke impulsive behavior in rats (58, 59, 79).

Human studies also support the idea that the mPFC is important in controlling impulsivity. Several studies have shown that patients with ADHD and schizophrenia have volumetric reductions in their frontal lobes (80 – 84). Moreover, some studies that involve meta-analysis have demonstrated that the patterns of neural activity in the prefrontal cortex during cognitive tasks that assess executive function are different in ADHD patients and schizophrenic patients compared with healthy subjects (60, 85).

Thus, it is likely that the higher degree of impulsivity that is seen in psychiatric patients is due to the dysfunction of the prefrontal cortex. However, one caveat is that these human studies mainly used the Go/NoGo task and the Stroop task that can reflect both “a deficit in waiting” and “a deficit in stopping”. Although somewhat simplified, animals with a lesion in the mPFC would be a partially valid model of impulsivity-related disorders.

Another possible animal model would involve transgenic mice that lack or have reduced expression of dopamine transporter (DAT) in the ventral striatum or dopamine D2/3 receptors in the ventral striatum and/or ventral tegmental area. The involvement of the DAT in impulsivity in psychiatric patients is controversial because several studies using PET have indicated that DAT availability is higher in the striatum of ADHD patients than in healthy subjects (86 – 88), whereas other studies have suggested that the opposite is true (89 – 91). The basal binding potential of [11C]raclopride in the striatum of adult ADHD patients was shown to be lower than that of control subjects (89, 90), which indicates that there is a higher basal dopamine release or a lower number of D2/3 receptors in ADHD patients. Interestingly, a lower availability of D2/3 receptors in the striatum or the ventral tegmental area has been associated with higher impulsivity (92, 93).

Theoretically, the recent development of transgenic technologies such as conditional knock out/down has rendered it possible to make these types of mice. However, the previously mentioned dysfunctions have so far only been found in ADHD patients; therefore, these transgenic mice might be regarded as animal models of ADHD rather than animal models of impulsivity-related disorders.

The route of nicotine administration

To address the importance of the route of nicotine administration, it is important to examine whether the slow infusion of nicotine (i.e., the nicotine patch) induces impulsive behavior. Previous studies suggesting that nicotine can suppress impulsive behavior in ADHD and schizophrenic patients have used the transdermal nicotine patch (10, 74, 75), while most studies suggesting that nicotine can provoke impulsive behavior in normal animals have used a subcutaneous or intraperitoneal injection of nicotine (25 – 27, 94). Additionally, most human studies that involve healthy people have focused on tobacco smokers who inhale nicotine (14, 19, 22 – 24). The application of a nicotine patch gradually increases the
blood levels of nicotine (95), while cigarette smoking results in a rapid increase and subsequent rapid decrease in blood nicotine levels (96). The subcutaneous injection of nicotine rapidly increases nicotine levels in the brain with a rapid decrease after the peak (97). Thus, the effects of a gradual increase in blood nicotine levels on the dopaminergic/cholinergic systems that are described in Fig. 2 might be different from the effects of a rapid increase in blood nicotine levels.

Although applying a transdermal nicotine patch might be difficult in animal studies, osmotic minipumps (e.g., ALZET pumps) would be useful as an alternate method to accomplish a slow infusion (20, 98, 99). The patch or an osmotic minipump implant might implement a more effective drug administration. However, one group has already demonstrated that the continuous infusion of a high dose of nicotine using an osmotic minipump evoked impulsive behavior in rats, although the effects gradually disappeared over a period of days (51, 100). Further studies using osmotic minipumps with smaller doses of nicotine are necessary to confirm this result.

6. Concluding remarks

In this article, we reviewed the involvement of nAChRs and related mechanisms in “a deficit in waiting”, a subordinate concept of impulsive behavior, and summarized them in Fig. 2.

Considering the current understanding of these mechanisms underlying impulsive behavior, we suggested three requirements for therapeutic drugs: 1) induction of a targeted release of dopamine in the mPFC, 2) no stimulation of dopamine release in the ventral striatum, and 3) no stimulation of α4/2 nAChRs in the mPFC. To explore/develop drugs meeting these requirements would be a promising strategy to develop therapeutic drugs for impulsivity-related disorders.

Furthermore we proposed future directions for further advancement in this field: 1) construction of animal models of impulsivity-related disorders and test the previously suggested potential therapeutic drugs on these animals, and 2) examination of the differences in the route of administration on the effects of nicotine on impulsive behavior, and elucidation of associated reasons.

Clarifying these issues would provide a clear explanation for the differences between the effects of nAChR agonists on impulsive behavior in healthy subjects and psychiatric patients. Moreover, screening the drugs discussed above while taking into consideration the route of administration and presence of brain dysfunction in psychiatric patients would accelerate the development of therapeutic drugs for these psychiatric patients.

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