

PHARMACOLOGY OF AMPHETAMINE

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SUMMARY

Amphetamine is the most highly addictive drug in Japan, but apart from that, the dependence, addiction, and sensitization it causes are intriguing phenomena in the neurosciences. Amphetamine-induced psychiatric disorders are classified into “substance-related and addictive disorders” in DSM-5. They are divided into “substance use disorders” and “substance-induced disorders.” “Substance use disorders” involve craving for substances. “Substance-induced disorders” are divided into “substance intoxication” and “substance withdrawal.” In Japan, amphetamine is recognized to cause psychiatric disorders that cannot be distinguished from schizophrenia, though DSM-5 concludes that, in that case, amphetamine per se does not induce schizophrenia. I believe amphetamine causes schizophrenia because schizophrenia induced by amphetamine is different in symptoms and age of onset from idiopathic schizophrenia. In DSM-5, the term “dependency” is not adopted and included in the term “addiction.” I believe, however, that substance dependence is a condition in which the organism’s homeostasis cannot be maintained without substances, and substance addiction is an uncontrollable craving for substances, both of which are different in meaning. There are two types of cravings, one is “liking,” which involves enjoying the uplifting sensation obtained from substances, and the other is “wanting,” which is a need for substances to escape withdrawal symptoms.

Amphetamine has a stimulant effect and decreases the sense of fatigue. The mechanism of action is an increase in dopamine in the synaptic cleft due to suppression of dopamine uptake and induction of reverse transport through dopamine transporters (DATs). Since DATs are absent at the dopaminergic terminals in the prefrontal cortex, and noradrenaline transporters take up dopamine instead, the mechanism of amphetamine in the prefrontal cortex (PFC) is not similar to that at other sites.

Repeated administration of amphetamine causes addiction. The addiction cycle consists of a binge period, a withdrawal period, and a preoccupation period. The nucleus accumbens (NAc), which forms the reward system, plays an important role during the binge period. Repeated administration of amphetamine also causes abnormalities in the reward system. Physiologically “pleasant” stimuli easily cause the reward system to stop responding. In addition, conditioning is established, and it becomes responsive to cues related to amphetamine, such as syringes. During the withdrawal period, dopamine release in the mesolimbic dopaminergic system decreases, leading to anhedonia, which is involved in the amygdala. Stress releases glucocorticoids from adrenal glands, and glucocorticoids excite dopamine neurons through their glucocorticoid receptors. This is the mechanism by which stressed humans are more likely to become amphetamine-dependent, and stress causes release of dopamine. During the preoccupation period, the function of the PFC, which inhibits instinctive behaviors, deteriorates, and delay discounting is impaired. Therefore, reuse of amphetamine cannot be avoided. Repeated administration of amphetamine overactivates incentive salience, and then it causes cue-induced craving. The decrease in the function of the inhibitory system induces craving and excess excitement of the reward system. When individuals get what they want, the reward system is activated, and associative learning mobilizes incentive salience to form a “pleasant” state. Amphetamine overstimulates the

reward system, and then the reward system becomes uncontrollable, resulting in addiction. In addition, homeostasis cannot be maintained without “liking” stimulation by amphetamine, and “liking” transforms into “wanting”, so that people want amphetamine regardless of their likes and dislikes. It is the mechanism of addiction that the “wanting” becomes craving. Furthermore, although different from the above theory, there is also a theory that substance addiction occurs in order to self-treat agony that cannot be dealt with by oneself.

The mechanism of dependence, addiction, and sensitization is induced by plastic changes in the brain. The molecular mechanism is assumed to involve the phosphorylation triggered by Ca^{2+} and cAMP. Amphetamine is taken up in dopaminergic terminals via DATs or by simple diffusion. When DATs are used, extracellular Na^{+} is also taken up with amphetamine through DATs, and then increased intracellular Na^{+} depolarizes the presynaptic membrane. The depolarization induces the L-type voltage-gated Ca^{2+} channel that coexists with DATs open. The increased Ca^{2+} activates protein kinase C (PKC) and Ca^{2+} /calmodulin-dependent kinase II (CaMKII), then PKC phosphorylates DATs, and phosphorylated DATs are internalized. Alternately, amphetamine that enters dopaminergic terminals activates TAAR1, which increases intracellular cAMP. Protein kinase A activated by cAMP phosphorylates DATs and enhances the reverse transport of DATs. The action of amphetamine is due to an increase in dopamine in the synaptic cleft, but plastic changes in the brain are caused by changes in the glutamatergic nervous system, acting on the dopamine nervous system. This is the mechanism of addiction and sensitization. In addition, individuals with amphetamine addiction have decreased PFC function, which is considered the cause of impaired self-control function and executive dysfunction. The precise mechanisms of addiction of amphetamine are an open question, because the effects of amphetamine vary from person to person, are psychologically context-dependent, and the intracellular signal transduction systems elicited by amphetamine are complex. However, clinical trials obtained from human functional imaging studies are being accumulated, and abnormalities in the PFC, the insular cortex have been reported. The relationship with human-specific functions that have been black boxes until now is being clarified.

Keywords : addiction, amphetamine, dependence, methamphetamine, sensitization

Abbreviations: ACC, anterior cingulate cortex; AMPA, alpha-amino-3-hydroxy-5-methyl-isoxazole propionic acid; Arc, activity-regulated cytoskeleton-associated protein; CaMKII, Ca^{2+} /calmodulin-dependent kinase II; CNS, central nervous system; CREB, cAMP response element-binding protein; DARPP-32, dopamine- and cAMP-regulated neuronal phosphoprotein-32; DSM, Diagnostic & Statistical Manual of Mental Disorders; DAT, dopamine transporter; EGR1, early growth response protein 1; EPSP, excitatory postsynaptic potential; ERK, extracellular signal-regulated kinase; FDG, 2-deoxy-2 [18F] fluoro-deoxy glucose; IAAs, individuals with amphetamine or methamphetamine addiction; LTD, long-term depression; LTP, long-term potentiation; MAPK, mitogen-activated protein kinase; mGluR, metabolic glutamate receptor; MSN, medium spiny neuron; NAc, nucleus accumbens; NMDA, N-methyl-D-aspartate; PET, positron emission tomography; PFC, prefrontal cortex; PKA, protein kinase A; PKC, protein kinase C; SN, substantia nigra; TAAR1, trace amine-associated receptor 1; TH, tyrosine hydroxylase; VMAT2, vesicle monoamine transporter 2; VTA, ventral tegmental area; WCST, Wisconsin card sorting test.

1. Introduction

I have studied a mechanism of amphetamine sensitization using experimental animals and found that the mechanism of enhanced dopamine release is recruitment of Ca^{2+} -dependent dopamine release, which is a regular mechanism of neurotransmitter release, in addition to Ca^{2+} -independent dopamine release, which is called reverse transport through dopamine transporters (DATs) (Iwata et al. 1996, 1997a, 1997b). Amphetamine is not only a central nervous system (CNS)-acting drug, but it also induces neural plasticity. Neural plasticity is a molecular mechanism of addiction and sensitization.

Amphetamine is more prevalent than methamphetamine in the USA. Therefore, the amount of research on amphetamine is greater than on methamphetamine. However, the relationship between amphetamine and methamphetamine is the reverse in Japan. The pharmacological features of both amphetamine and methamphetamine are similar, though other amphetamine derivatives e.g., 3,4-methylenedioxymethamphetamine and p-chloroamphetamine, are different from amphetamine and methamphetamine. Therefore, the term “amphetamine” used in this review means both or either of amphetamine or methamphetamine. Many reviews mix the results for amphetamine and cocaine, because both drugs are classified as psychostimulants. However, in this review, I only deal with amphetamine, not cocaine, because cocaine is an uptake inhibitor, whereas amphetamine is a releaser (Heikkilä et al. 1975, Raiteri et al. 1975). Furthermore,

amphetamine, but not cocaine, phosphorylates DATs (Cervinski et al. 2005). There has been more research on cocaine than on amphetamine; therefore, I sometimes refer to the results of cocaine experiments to understand the action of amphetamine.

Chronic means both repeated or continuous. Repeated intermittent administration induces sensitization, though continuous administration induces tolerance to amphetamine. I convert the term “chronic” in the cited references to repeated or continuous as much as possible.

2. Amphetamine-induced psychiatric disorders

Psychiatric disorders elicited by amphetamine are classified into “substance-related and addictive disorders” in DSM-5. An important point is that they are defined as intractable diseases, not as merely an acute reaction to amphetamine. They are divided into two groups, “substance use disorders” and “substance-induced disorders.” Individuals are diagnosed with “substance use disorders” when they keep using amphetamine despite significant amphetamine-related problems. Symptoms of “substance use disorders” are a cluster of cognitive, behavioral, and physiological aspects. Severity is verified on the basis of the number of symptom criteria present. These criteria of diagnosis are (1) craving for amphetamine, which is manifested by an intense desire for amphetamine that occurs at any time, but is more likely when or where amphetamine was previously used, (2) social impairment, (3) risky use, or (4) pharmacological features, i.e., tolerance and withdrawal, which are not always necessary

for the diagnosis, because tolerance is a simple physiological reaction to the continuous use of a drug, and because withdrawal symptoms are a simple reaction when individuals stop taking a drug. Severe tolerance and withdrawal, however, suggest excess intake of a drug.

“Substance-induced disorders” are further classified into “substance intoxication,” “substance withdrawal,” and “substance-induced mental disorders.” “Amphetamine intoxication” is a syndrome in which impairment is derived from recent intake of amphetamine, and there are reversible problematic behaviors or psychological changes in the acute phase. “Amphetamine withdrawal” is caused by the cessation of heavy and prolonged amphetamine use, whose symptoms are opposite to the effects of amphetamine, e.g., crash, anxiety, shivering, anhedonia, somnolence, fatigue, hyperhidrosis, cramps, gastrospasm, and morbid hunger. These symptoms last for approximately one week and are maximal on the third day. The most problematic symptom is depression, which can lead to suicide. “Amphetamine-induced mental disorders” are psychotic disorders, depressive disorders, neurocognitive disorders, all of which satisfy the criteria of each disorder. Characteristic symptoms of “amphetamine-induced psychotic disorders” are hallucinations, formication, and delusions. The definition of “amphetamine-induced mental disorders” in DSM-5 is controversial. The diagnostic criteria for “substance-induced mental disorders” in DSM-5 say “substance-induced mental disorders are temporary, but persisting.” However, the section on neurocognitive disorders

in DSM-5 explains that “amphetamine-induced major or mild neurocognitive impairments are not persisting beyond the usual duration of intoxication and acute withdrawal.” This implies that, when individuals persist in psychotic symptoms, they are diagnosed with neurocognitive disorders in DSM-5. This diagnosis reflects a concept of the American Psychiatric Association that amphetamine does not induce irreversible mental disorders, which is contrary to the common understanding of Japanese psychiatrists, who believe that high-dose or long-term administration of amphetamine causes irreversible impairment of the brain (Wakuda 2014).

Repeated or high-dose use of amphetamine induces psychosis resembling schizophrenia (Sato 1992, Yui et al. 2000). Positive symptoms of amphetamine psychosis are delusions, grandiosity, paranoia, and hallucinations. The contents of hallucinations and delusions are related to the life histories of IAAs and the circumstances of amphetamine abuse. The contents are easily understandable to others, although those in patients with schizophrenia are incomprehensible. Personality is not severely damaged in patients with amphetamine psychosis. Negative symptoms are blunted affect, disorganization, and social withdrawal. Hallucinations and delusions reappear when patients with amphetamine psychosis suffer from stress or drink alcohol, even though they are free from amphetamine for a long time.

The terms “addiction” and “dependence” have been confused; therefore, “dependence” is eliminated in DSM-5. “Addiction” has merged the abuse and dependence construct into one

continuum defined as “substance use disorders” in DSM-5. O’Brien (2011) explains the reason in his paper. I notice that there is a significant difference in the meaning of “addiction” and “siheki”, as well as “dependence” and “izon.” DSM-5 is the first edition that uses “addiction”. Addiction is used not only for substances, but also for behavior, e.g., gambling addiction, in DSM-5. Individuals cannot stop doing problematic behaviors (= addiction) knowing that such behaviors will result in a serious outcome. Koob and Le Moal (1997) defined addiction as a chronically relapsing disorder that is characterized by (1) compulsion to seek and take a drug, (2) loss of self-control in limiting the intake of a drug, and (3) the emergence of a negative emotional state when access to a drug is prevented. Hamada (2009) defines dependence on psychostimulants as chronic intoxication by repeated intake of a drug, characterized by tolerance and craving for psychostimulants because of the interaction between the drugs and the brain. He defines addiction as craving induced by dependence. I define “dependence” as a state or condition of organisms in which substances are necessary to maintain their homeostasis, and “addiction” as a behavioral abnormality induced by dependence, which is characterized by craving.

In DSM-5, problematic symptoms in amphetamine intoxication listed in the diagnostic criteria are: euphoria or affective blunting; changes in sociability; hypervigilance; interpersonal sensitivity; anxiety, tension, or anger; stereotyped behavior; and impaired judgment. These symptoms become obvious during or shortly after the use of amphetamine.

Repetitive acts, e.g., cleaning an item continuously, endless dismantling, and putting things back together, such as a clock, are considered a complex expression of stereotyped behavior, which is termed *punding* by Rylander (1971). *Punding* is defined as an organized, goal-directed, but meaningless activity. Stereotyped behavior is defined as integrated behavior sequences that acquire a stereotyped character, being performed at an increasing rate repetitively (Randrup and Munkvad 1970).

3. Acute effects of amphetamine

Amphetamine is classified into miscellaneous sympathomimetic agonists in a popular textbook on pharmacology (Westfall et al. 2018). It has α and β agonist activities. It raises blood pressure, contracts smooth muscle, stimulates the respiratory center in the brain stem, and inactivates the appetite center. It induces wakefulness, decreases the sense of fatigue, and causes elation. The stimulant effect of amphetamine is more prominent in individuals who are exhausted, but it fails to improve performance in well-functioning individuals (Kornetsky 1958, Balloch et al. 1952, Hauty and Payne 1957). In other words, no augmentation in complex tasks or tests of intelligence is observed, though amphetamine enhances performance in simple motor and cognitive tasks. There is no dose-effect relationship in the enhancement of performance, probably because different brain regions that hamper the enhancement would be stimulated, e.g., a small dose of amphetamine increases locomotion, but it inhibits it and

stereotyped behaviors such as head swing start as the dose of amphetamine increases in experimental animals. The other reason is that appropriate dopamine levels in synapses are required to achieve the best performance, and small concentrations of dopamine cannot facilitate performance. In contrast, excess dopamine causes the neural system to become out of control, as in patients with schizophrenia.

The pharmacological mechanism of amphetamine in the CNS is an increase in the concentration of dopamine in the synaptic cleft by reverse transport and inhibition of dopamine uptake. The first mechanism is also called exchange diffusion (Fischer and Cho 1979, Raiteri et al. 1979). Presynaptic dopamine receptors do not control dopamine release by reverse transport (Shenoy and Ziance 1979, Kamal et al. 1981). Amphetamine also inhibits the function of VMAT2. Amphetamine is taken up into nerve terminals through simple diffusion because of its lipophilicity or through DATs (Lentzen and Philippu 1981). Amphetamine enters synaptic vesicles via VMAT2 and collapses the vesicular pH gradient, because amphetamine is a base. Synaptic vesicles are kept in a weakly acidic condition that keeps dopamine inside the vesicles. An increase in pH inside the vesicles results in a leak of dopamine into the cytosol. The increased concentration of dopamine in the cytosol increases the amount of dopamine available for the reverse transport of dopamine. The uptake inhibitory mechanism of dopamine by amphetamine through DATs is different from the reverse transport of dopamine through DATs (Reith and Gnegy 2020).

Amphetamine also enhances noradrenaline and serotonin release through noradrenaline and serotonin uptake sites, respectively (Kuczenski and Segal 1989, 1992). Although amphetamine has a rank order of potency in monoamine uptake of noradrenaline \geq dopamine $>$ serotonin (Rothman et al. 2001), the primary actions responsible for the psychostimulant and reinforcing effects are on the dopaminergic system in the CNS.

The half-lives of amphetamine are approximately 7 h and 2 h for the (+) and (-) enantiomers, respectively (Vree 1973). Therefore, the effect of a single administration of amphetamine persists for most of a whole day. The distribution of amphetamine in different areas of the brain (cortex, striatum, cerebellum) is the same (Jori and Caccia 1974, Melega et al. 1992), though amphetamine acts on catecholamine terminals.

4. Effect of amphetamine on DAT phosphorylation

DAT is a 12 transmembrane protein that is in the cell body and dendrites of dopaminergic neurons in the substantia nigra (SN) and the VTA. Although DAT is also localized in nerve terminals in the striatum and the NAc, it is not found in the PFC, where noradrenaline transporters take up dopamine instead of DAT (Carboni et al. 1990, Sulzer et al. 2016). Dopamine is taken up with two Na⁺ and one Cl⁻ through DATs. Therefore, the dopamine uptake is electrogenic. Na⁺ binds to the extracellular domain of DATs, and the transport rate and direction of dopamine depend on the Na⁺ gradient (Wheeler et al. 1993). DATs have high-affinity zinc-binding sites, and zinc inhibits

dopamine uptake and amplifies amphetamine-induced reverse transport of dopamine (Scholze et al. 2002). Phosphorylation of the N-terminus of DATs facilitates DAT-mediated dopamine reverse transport without impacting other aspects of DAT physiology (Karam and Javitch 2018).

Amphetamine causes rapid up-regulation and slower down-regulation of DATs (Zahniser and Sorkin 2009). TAAR1 controls slower regulation. TAAR1 is a G protein-coupled receptor that produces cAMP (Borowsky et al. 2001) and regulates DATs (Miller 2011). In the CNS, TAAR1 is present in nerve terminals of monoaminergic neurons and can bind tyramine, β -phenethylamine, dopamine, and amphetamine. Amphetamine must enter the cytosol to interact with TAAR1, because TAAR1 is in the cytosol. Amphetamine activates TAAR1 and then activates PKA. Although PKA increases DA uptake in rat striatal synaptosomes (Batchelor and Schenk 1998, Page et al. 2004), neither the PKA activator forskolin nor 8-bromo-cAMP increases the metabolic incorporation of [32 P] orthophosphate in DATs, indicating an indirect effect of PKA on DATs (Vaughan et al. 1997). TAAR1 decreases the firing rate of dopaminergic neurons in the VTA (Lindemann et al. 2008) because TAAR1 and dopamine D2 receptors form a heterodimer (Lam et al. 2015) that negatively regulates D2 autoreceptors (Leo et al. 2014) in the dopaminergic cell body.

DAT is coupled to L-type voltage-gated Ca^{2+} channels, which are expressed in all dopaminergic neurons (Cameron et al. 2015). Amphetamine depolarizes the cell membrane through DATs,

opens L-type voltage-gated Ca^{2+} channels, and then activates CaMKII. CaMKII binds with the C-terminus of DATs and enhances amphetamine-induced reverse transport of DA via N-terminal phosphorylation (Fog et al. 2006, Steinkellner et al. 2012, Underhill et al. 2014).

DAT is phosphorylated by PKC, which facilitates DAT internalization (Kokoshka et al. 1998, Saunders et al. 2000, Gulley et al. 2002, Chi and Reith 2003, Sorkina et al. 2003, Zahniser and Sorkin 2009, Schmitt and Reith 2010, Ramamoorthy et al. 2011) through clathrin-dependent processes (Daniels and Amara 1999, Sorkina et al. 2005, 2013). The internalization is induced by N-terminal ubiquitylation of the DAT (Vina-Vilaseca and Sorkin 2010) and by Rin 1 binding to the C-terminal endocytosis motif (Boudanova et al. 2008). Flotillin-1 is essential for PKC-triggered endocytosis and membrane microdomain localization of DAT, but involvement of PKC is controversial (Cremona et al. 2011, Sorkina et al. 2013). PKC phosphorylates residues in the N-terminal of the DAT to regulate amphetamine-induced reverse transport of dopamine (Wang et al. 2016). PKC stimulates phosphorylation of the distal N-terminus of the DAT, which includes a cluster of serines at positions 2, 4, 7, 12, and 13, but the deletion of this region does not eliminate PKC-mediated internalization (Granás et al. 2003). PKC δ phosphorylates the DAT, which facilitates reverse transport of dopamine through the DAT, but it has no effect on the uptake function of the DAT (Johnson et al. 2005, Zestos et al. 2016).

ERK phosphorylates the N-terminus of

the DAT and tonically maintains DAT surface levels and uptake activity (Ramamoorthy et al. 2011). Stimulation of D2 receptors activates ERK and then promotes the surface expression of the DAT (Bolan et al. 2007, Lee et al. 2007). The palmitoylation of the DAT functions to promote reverse transport capacity (Foster and Vaughan 2011). Syntaxin 1A binds to the distal N-terminus of the DAT, which suppresses the uptake of dopamine and induces the reverse transport of dopamine (Carvelli et al. 2008, Cervinski et al. 2010). Amphetamine potentiates this interaction between syntaxin 1 and the DAT in a manner dependent on CaMKII α activity. In addition, dephosphorylation of T48 in the DAT by phosphatase PP1/2A up-regulates reverse transport velocity (Yang et al. 2019).

Karan and Javitch (2018) propose an intriguing hypothesis as to how amphetamine induces reverse transport of dopamine. Amphetamine drives dopamine out from synaptic vesicles, which increase the concentration of dopamine in the cytosol of nerve terminals. In order that synaptic terminals are not injured by excess dopamine, because dopamine is toxic (Kita et al. 2009, Segura-Aguilar et al. 2014), the excess cytosolic dopamine effluxes through the DAT.

5. Repeated administration of amphetamine

Besides its stimulating action after acute administration, amphetamine has a specific function after repeated administration, e.g., addiction and sensitization. Both phenomena are based on the plasticity of the brain, which is called drug-evoked synaptic plasticity (Lüscher

and Malenka 2011).

5.1. Neural plasticity caused by amphetamine

Neural plasticity is the mechanism of addiction and sensitization (Gnegy 2000, Kauer and Malenka 2007). LTP, LTD, kindling, central sensitization of nociceptive stimuli, and synaptic scaling are the physiological expressions of neural plasticity. Amphetamine induces LTP in the hippocampus (Delanoy et al. 1983), which is induced in glutamatergic inputs on dopaminergic neurons in the VTA by a Ca²⁺ mediating mechanism through D2 receptors (Jones et al. 2000). LTD is also involved in amphetamine-induced sensitization (Choi et al. 2014).

Van Huijstee and Mansvelder (2014) showed time-dependent alteration of glutamate transmission in the VTA, the NAc, and the PFC in drug (mainly cocaine) addiction. The enhancement of glutamate transmission is caused by an increase in the AMPA receptor/NMDA receptor ratio in these dopaminergic neurons. The activation of AMPA receptors is induced by exchange to GluA2-lacking AMPA receptors, which are permeable for Ca²⁺, from GluA2-containing AMPA receptors, which are not permeable for Ca²⁺. This AMPA receptor activation is induced by recruitment of NMDA receptors. In the early withdrawal period after repeated administration of the stimulants, the AMPA receptor/NMDA receptor ratio decreases in the NAc. Prolonged withdrawal induces an increased AMPA receptor/NMDA receptor ratio. This alteration of glutamate receptors is a mechanism of sensitization. Another projection area of the VTA dopaminergic neurons

is the medial PFC, where pyramidal neurons receive glutamatergic inputs from many different brain areas, including the basolateral nucleus of the amygdala, and send glutamatergic outputs to the VTA and the NAc (Gabbott et al. 2005, Hoover and Vertes 2007). The medial PFC is divided into the dorsal part and the ventral part; the former innervates the NAc core, and the latter innervates the NAc shell. Functionally, the dorsal part of the medial PFC is related to drug-seeking and cue-induced relapse to drug-seeking (Gipson et al. 2013).

Glutamate is the most abundant excitatory neurotransmitter, which has different features from other neurotransmitters, such as monoamine neurotransmitters. Glutamate not only functions as a neurotransmitter, but is involved in neural plasticity. The glutamatergic system plays an important role in addiction and sensitization, though amphetamine does not act on the glutamatergic system directly. Excess activation of the dopaminergic system by amphetamine induces molecular alterations in the glutamatergic system. Different from this idea that the dopaminergic and glutamatergic systems are mutually exclusive, it has been reported that glutamate is released together with dopamine in a certain population of dopaminergic neurons in the VTA, and disruption of this co-release is the cause of amphetamine use disorders (Bimpisidis and Wallén-Mackenzie 2019). Symptoms of sensitization and addiction are explainable by impairment of the dopaminergic system, but the mechanism of this plasticity is caused by the alteration in the glutamatergic system.

Two studies showed that amphetamine enhances motor and verbal recovery in patients with cerebrovascular disease (Crisostomo et al. 1988, Walker-Batson et al. 2001), which is consistent with animal studies. Whether this effect is derived from neuronal plasticity or merely from an increase in desire for rehabilitation is uncertain, and the effect itself is controversial (Gladstone et al. 2006, Sonde and Lökk 2007).

5.2. Amphetamine addiction

Drug addiction (dependence) is defined as a particular physical or psychiatric condition in which organisms cannot maintain homeostasis without a drug after the repeated use of the drug. Addiction was initially defined as intense physical disturbances when the administration of a drug is suspended (Eddy et al. 1965). However, it was soon recognized that the psychiatric aspect is more important than the physical one. It is characterized by a morbid craving for a drug to experience pleasure or to avoid withdrawal symptoms. Not all individuals experience such symptoms. Those who have a positive feeling with amphetamine are prone to become addicted. This positive feeling is examined using questionnaires in humans. A representative questionnaire is the Addiction Research Center Inventory (Haertzen et al. 1963).

The self-administration paradigm is used as the most reliable experimental method for clarifying addiction in experimental animals, especially in rhesus monkeys, rats, and mice (Funada and Aowo 2007). Self-administration of a drug is achieved as a result of positive reinforcement of the drug. The animal is prepared

for intravenous infusion of the drug, then trained to infuse the drug by depressing a lever. When the drug has features of addiction, the animal infuses the drug by depressing the lever. The stronger the power of reinforcement the drug has, the more the animal depresses the lever. This response ceases at some point in the session, when the response effort exceeds the reinforcing value of the drug. The number of depressions of the lever is correlated with the addictive strength of the drug.

IAs take amphetamine intensively and successively for several hours or days, which is called a binge, followed by severe discomfort. They crave amphetamine driven by obtaining positive feelings from amphetamine or escaping from the severe discomfort. They notice their strong desire to take amphetamine when they perceive something related to amphetamine use. This phenomenon is called the associated cue effect.

5.2.1. Stage cycle of amphetamine addiction

Amphetamine addiction is classified heuristically in three-stage cycles, (1) binge/intoxication, (2) withdrawal/negative affect, and (3) preoccupation/anticipation. These three stages are each formed by a different neural system (Koob and Le Moal 1997, Kwako et al. 2019).

Alteration in the mesolimbic dopaminergic system plays a main role in forming the binge/intoxication stage. In addition to the genuine neuronal system changes, glial cells influence the psychostimulant reward by stimulating the release of proinflammatory cytokines (Loftis and Janowsky 2014, Kohno et al. 2019, Papageorgiou et

al. 2019). Amphetamine enhances dopamine release excessively in the NAc. This dopaminergic pathway is a constituent of the reward system and the reward prediction error system. Furthermore, repeated amphetamine administrations form conditioned stimulation to something-related amphetamine use. Once conditioned stimulation is formed, the release of dopamine in the NAc is enhanced. Furthermore, this conditioning persists for a long time even if amphetamine is not abused anymore.

In the withdrawal/negative affect stage, the extended amygdala is involved. The extended amygdala is a conceptualized structure in the medial part of the ventral forebrain that is implicated in reward cognition. It consists of the bed nucleus of the stria terminals, the central nucleus of the amygdala, the medial part of the NAc (= the shell), and the subnucleus of the substantia innominata. Anhedonia induced by withdrawal is caused by decreased dopaminergic function in the extended amygdala. Stimulation of AMPA receptors occurs in the MSNs of the NAc shell, where most MSNs are GABAergic, send their axons to the VTA, and release GABA. GABA inhibits the activity of dopaminergic neurons in the VTA, and then symptoms of withdrawal, such as anhedonia and depression, are induced. Therefore, IAs continue using amphetamine to avoid anhedonia, and they want to take amphetamine to re-activate the reward system, which is the mechanism of craving (Koob and Bloom 1988, Miyata et al. 2011). In the NAc, the spine density of MSNs increases because of compensation for the reduced release of dopamine. The reward system does not respond to physiological rewards once the system is adapted to

amphetamine addiction. The physiological stimuli enhance dopamine release in the NAc little, and basal dopamine release becomes less in this stage. Further, the hypothalamic-pituitary-adrenal axis, which has important functions to adapt to stressors, overreacts after repeated amphetamine stress that induces glucocorticoid release from adrenal glands. Dopaminergic neurons expressing corticosteroid receptors enhance the release of dopamine by the glucocorticoids. The glucocorticoid administration causes experimental animals that would not be trained to self-administer amphetamine at low doses of amphetamine to actually self-administer amphetamine (Piazza et al. 1991). This implies that stress intensifies amphetamine addiction. Clinical imaging data also show that glucocorticoids enhance dopamine release in humans (Wand et al. 2007). Depression of the activity of the dopaminergic system induces anhedonia. Therefore, IAAs have a strong desire to take amphetamine during the withdrawal period. Re-administration of amphetamine temporarily eases the anhedonia, but this re-administration will make uncomfortable withdrawal symptoms worse.

In the preoccupation/anticipation stage, dysfunction of the PFC plays a role. This stage is a key element of relapse and craving. The impairment of the PFC in this stage consists of two factors, cognitive impairment and associated cue-induced craving. The cognitive impairment of this stage implies impatient delay discounting (Volkow et al. 2011, Jentsch and Taylor 1999). The capability of delay discounting is endurance for reward-delay impulsivity. Delay discounting is the tendency of individuals to discount rewards

as they approach a temporal horizon in the future (https://en.wikipedia.org/wiki/Time_preference). Reward-delay impulsivity is one aspect of impulsivity, i.e., a tendency that individuals prefer a reward that can be expeditiously obtained but not valuable, to a reward that is more valuable but requires a longer time to obtain. Addiction is the product of an imbalance between two separate but interacting neural systems that control decision-making. One is an impulsive system, in which the amygdala system is involved, such as the pleasure of immediate prospects. The other is a reflective system, in which the prefrontal cortex system is involved, such as the pleasure of future prospects (Bechara 2005). Cue-induced craving is brought by the activation of the reward salience system, which involves the dorsolateral PFC, the ACC, and the medial orbital cortex (Jasinska et al. 2014, Niendam et al. 2012). At the same time, cue-induced craving is facilitated by the impairment of the behavioral inhibitory system, i.e., the PFC. In this stage, IAAs are in the condition of allostatic load. This means wear-and-tear on the brain and body (McEwen and Stellar 1993), because of functions of the PFC whereby allostasis functions are reduced (Koob and Schulkin 2019). Allostasis is the process of achieving stability or homeostasis through physiological or behavioral change (McEwen and Stellar 1993). The function of the PFC that suppresses compulsive behavior by logical thinking is impaired by excessive activation of the dopaminergic reward system. Hypofunction of the PFC induces craving for amphetamine that cannot be self-regulated in IAAs (Sora 2019).

Kalivas and Volkow (2005) have proposed

another stage cycle of addiction. It consists of (1) an acute drug effects stage, (2) the transition to the addiction stage, and (3) end-stage addiction. In the first stage, amphetamine enhances dopamine transmission in the VTA-NAc pathway. D1 receptor stimulation by enhanced dopamine release activates the PKA. In the second stage, the VTA-PFC and the VTA-amygdala dopaminergic system form exploratory behavior. Craving, which drives the exploratory behavior, is involved in the glutamatergic system in the amygdala to the PFC and the NAc. In the end-stage, morphological changes occur in the brain (Nestler and Aghajanian 1997).

5.2.2. Mechanism of amphetamine addiction

Not all individuals are prone to become addicted to amphetamine. In most diseases, genetic and environmental factors play roles. Genetic factors prevail for the formation of addiction for one person, whereas environmental factors are the main background for amphetamine use disorders for another person. O'Brien (2018) organized the factors inducing addiction into three categories: drug, user, and environment. A drug that has strong reinforcing properties induces addiction. Reinforcing properties of the drug are associated with its capacity to increase neuronal activity in brain reward areas. Although the mesolimbic dopaminergic system, especially the NAc, has an intense relationship with the induction of addiction, 5-HT, glutamate, noradrenaline, endogenous opioids, and GABA mediate the reinforcing effects. Liability to addiction is enhanced by the

rapid onset of drug concentration in the brain. As for the user, individuals with lower levels of self-control, which reflect the impairment of brain inhibitory mechanisms, are predisposed to amphetamine use disorders (Pokhrel et al. 2007), which suggests that the roots of amphetamine use disorders for individuals can be seen in behaviors long before the onset of actual amphetamine use itself (DSM-5). Approximately half of individuals with amphetamine addiction have developed personality disorders (Eslami-Shahrbabaki et al. 2015). Individuals with a high risk of substance use disorders exhibit a lower dopamine response to amphetamine challenge that predates addiction (Casey et al. 2014). Estrogen α receptor gene (Kishi et al. 2009), 5-HT_{1A} receptor gene (Kishi et al. 2010), AKT1 gene (Ikeda et al. 2006, Nohesara et al. 2016), β -arrestin gene (Ikeda et al. 2007), and γ subunit gene of GABAA receptors (Nishiyama et al. 2005) are involved in the risk of amphetamine addiction. Genetic deletion of arrestin3 in mice results in disinhibition of AKT, phosphorylation-induced inactivation of GSK-3 β , and consequently an attenuated response to amphetamine-induced locomotor activity (Beaulieu et al. 2005). As for the environment, several factors have been proposed, including: social setting; community attitudes (peer influence, role models); availability of other reinforcers (sources of pleasure or recreation); employment or educational opportunities; and conditioned stimuli (environmental cues become associated with a drug after repeated use in the same environment) (O'Brien 2018). In an animal study, one group of rats was housed in small cages, and another group of rats was placed in

a large cage wide enough to run around and communicate with each other. Both groups could drink both water and water with morphine. The first group of rats became addicted to morphine, though the latter did not. This result means that environmental factors play an important role in amphetamine addiction (McMillen 2019).

From the theory of the self-medication hypothesis (Khantzian 1997, Khantzian and Albanese 2013), one reason why individuals are involved in drug addiction is that a drug can ease or remove their agony. People with anxiety, depression, insomnia, or even shyness find that a certain drug can give them relief. However, the obvious beneficial effects are transient, and repeated use of a drug leads to tolerance and eventually compulsive, uncontrolled drug use.

Addiction to amphetamine can be induced by impairment of the reward system. Amphetamine addiction, whose essential feature is craving, is formed by repetitive intake of amphetamine. The craving is derived from the intense activation of the reward system. Amphetamine induces a decreased sense of fatigue and elation. This pleasant feeling acts as a positive reinforcement in operant conditioning. Some individuals use amphetamine to escape negative feelings, i.e., depression, fatigue, and anhedonia during the withdrawal of amphetamine (negative reinforcement, May et al. 2020). Both types of reinforcement induce individuals to take amphetamine repeatedly. This repeated intake enhances the reward system too strongly to be controlled by oneself. Physiological non-drug stimuli, e.g., get a good mark on an examination

or eat delicious food, indirectly activate the reward system, and the release of dopamine by the non-drug stimuli undergoes habituation (tolerance) following repeated exposure (Di Chiara 2002). Amphetamine, however, stimulates the reward system directly and shows no tolerance, but sensitization, after repeated administration of the drug. Its function is, therefore, far stronger than the physiological reward (Wise 2002), and then the individual cannot stop taking amphetamine, even knowing that there is no beneficial outcome for the individual's life.

Reward prediction errors, which indicate a discrepancy between the obtained reward value and the expected value, are proposed as a mechanism of addiction. The phasic activity in dopaminergic neurons encodes reward prediction errors. Dopaminergic neurons react positively when an expected reward is obtained and react negatively when an expected reward is not obtained (Schultz et al. 1997, Glimcher 2011). Dopaminergic neurons in the ventromedial SN and the VTA whose axons terminate in the NAc (especially in the core, Saddoris et al. 2015), the ventromedial PFC, and the amygdala respond to reward prediction errors. This result is transduced to downstream brain regions that are involved in reward learning and habit formation (Keiflin and Janak 2015). The reward learning is as follows. Individuals decide how and what to do next expecting the outcome of behaviors done right now (goal-directed behavior). When anything unexpected happens in the present, they will correct the next planned behaviors. Habituation occurs in reward prediction error,

i.e., dopaminergic neurons react to acquisition of reward at the beginning of learning, but this reaction becomes gradually extinct. However, addictive substances do not show habituation because of excess increases in dopamine. Therefore, the intake of the addictive substance provides undiminished signals related to positive reward prediction errors (Lee 2013). Therefore, IAAs over-react positively to reward prediction errors (Schultz 2016a, b). The reward system is then highly activated. In the same mechanism, dopaminergic neurons react to an associated reward cue, e.g., IAAs feel elation when they see syringes. Dopaminergic neurons in the dorsolateral SN, whose axons terminate in the dorsal striatum and the dorsolateral PFC, do not respond to reward prediction errors, but respond to salience (Matsumoto 2016) and habituation. “Salience” is a psychological term used to describes a stimulus that elicits attention and thus orients responses, i.e., behavioral preference. Dopaminergic neurons in the dorsolateral SN are continuously activated during reward tasks to activate the mental state to take a better reward. The NAc plays an important role to form goal-directed behavior. IAAs activate not only the dorsolateral striatum, which is required to form the goal-directed behavior, but also the medial striatum, where addiction (autonomic output of stereotypic reaction) is formed (Shitara 2018). Amphetamine generates and amplifies the dopamine reward signal and induces exaggerated, uncontrolled dopamine effects on neurons. Abnormal reward prediction errors are the mechanism of amphetamine addiction. However,

this hypothesis is more acceptable for gambling addiction, because individuals with gambling addiction are excited by risky, unexpected bets.

The incentive-sensitization theory posits the essence of drug addiction to be excessive amplification of “wanting” without amplification of “liking” (Berridge and Robinson 2016). The reward mechanism allots “wanting” and “liking” to a certain stimulation. “Wanting” does not mean “liking” because individuals want an addictive drug to avoid unpleasant withdrawal symptoms. Therefore, “wanting” is an essential symptom of addiction. “Wanting” processes are controlled by dopamine, and the “liking” process is affected by opiate-dopamine interaction in the NAc and the ventral globus pallidus (Smith and Berridge, 2007).

Paulus and Stewart (2014) proposed a mechanism to explain why IAAs are compelled to commit risky behaviors as impairment of interoception, i.e., a reduced sensitivity to internal states or to afferent signals from the body, which serve as an embodied warning signal, due to damage of the insular area in the brain by the drug. Volume reductions in the insular areas are common findings across different studies (Mackey and Paulus 2012), and the insular area is the CNS hub to process and integrate body-relevant signals with external stimuli to affect ongoing motivated behavior. The insular cortex is activated when individuals with cocaine addiction are exposed to environmental cues that trigger a craving (Wang et al. 1999). A functional MRI study in IAAs showed that the insular cortex is hypo-active during cognitive control processes, but hyperactive

during cue reactivity and drug-specific, reward-related processes (Paulus and Stewart 2014).

Δ FosB is the most significant gene transcription factor related to drug addiction (Nestler 2008, Robinson and Nestler 2011, Ruffle 2014), which persists for weeks in neurons even after cessation of drug administration (Ulery et al. 2006). Δ FosB is a splice variant of FosB, which is a protein encoded by the FBJ murine osteosarcoma viral oncogene homolog B (FOSB) gene. FosB works as a transcription factor (AP-1) dimerized with JunD. Δ FosB forms homodimers, which specifically bind cyclin-dependent kinase 5 (cdk5) and GluA2 AP-1 consensus sequences (Jorissen et al. 2007). Δ FosB is implicated in cell proliferation, differentiation, and transformation. Δ FosB is activated by amphetamine in the NAc shell and the basolateral amygdala (Murphy et al. 2003). Repeated methamphetamine administration with a sensitized regime increases the level of Δ FosB in the NAc and pallidum (McDaid et al. 2006). Besides the transcriptional effect, Δ FosB also mediates epigenetic desensitization of the c-fos gene after repeated amphetamine exposure (Renthal et al. 2008). Repeated administration with amphetamine decreases histone methylation at the c-fos promoter, which is involved in the induction of addiction and craving for cocaine addiction (Grueter et al. 2013). Δ FosB is a responsible transcription factor for neuronal plasticity by amphetamine because it regulates synapse-forming molecules e.g., actin-related protein-4 (ARP4) and Arc (Russo et al. 2010). A single administration of amphetamine induces

activation of the c-fos gene in striosome-matrix compartments and limbic subdivisions of the striatum (Graybiel et al. 1990).

Blockade of the ERK1/2 pathway with MAPK and ERK kinase (MEK) inhibitors attenuates the rewarding properties of amphetamine, e.g., place preference induced by nucleus accumbens injection with amphetamine is impaired by antagonists of ERK or p38 MAP kinases in rats (Gerdjikov et al. 2004).

Not all compounds with DAT-binding properties are addictive, because atypical benztrapine-like DAT inhibitors lack a cocaine-like rewarding effect (Schmitt et al. 2013).

5.3. Amphetamine sensitization (reverse tolerance)

When experimental animals are administered amphetamine repeatedly, the intensity of locomotion increases progressively (Segal and Kuczenski 1994). In humans, subjective ratings of vigor and euphoria show high marks after repeated administration of amphetamine (Strakowski et al. 2001). Amphetamine-induced symptoms, i.e., activity/energy level, mood, rate and amount of speech, and eye-blink rates have been reported to be enhanced after repeated amphetamine administration in a double-blind study in volunteers (Strakowski et al. 1996, Strakowski and Sax 1998). Sato et al. (1983) showed that a small dose of methamphetamine, which does not induce hallucinations, brings hallucinations in patients with methamphetamine psychosis. This phenomenon is called behavioral sensitization, reverse tolerance, or super-sensitivity, which

was first reported in cocaine administration by Seevers' group (Tatum and Seevers 1929).

Amphetamine-sensitized organisms become sensitized to other stimulants related to the dopaminergic system, e.g., cocaine, ephedrine, apomorphine, and mazindol (Tadokoro and Kurihara 1990), which is called cross-sensitization. Not only drugs, but stress is also cross-sensitized to amphetamine (Booij et al. 2016).

Expression of sensitization is state-dependent, i.e., experimental animals need enough space for locomotion to express their sensitization, that is, when animals are housed in a small box that is too small to move around, no locomotive sensitization is expressed (Hirabayashi and Alam 1981). Furthermore, sensitization is conditioned to place, e.g., mice trained in locomotion on wheel rolling do not show enhanced locomotion on a flat floor. These phenomena indicate that sensitization has features of learning.

Responsible brain regions for amphetamine sensitization are the NAc, the frontal cortex, the amygdala, and the hippocampus (Heysieattalab et al. 2016). The frontal cortex, the amygdala, and the hippocampus are constituents of the reward system and associative memories between amphetamine intake and circumstances, e.g., a place where individuals take amphetamine, or friends with whom individuals take amphetamine. The NAc has two types of projecting neurons, both of which are GABAergic and receive glutamatergic inputs from the cerebral cortex, the amygdala, and the hippocampus. The first type of neurons has D1 receptors in the cell body, and dopamine facilitates glutamatergic inputs. In contrast, the

second type has D2 receptors in the cell body. Therefore, dopamine depresses the glutamatergic inputs. D1 receptors are related to the induction of amphetamine sensitization. Stimulation of D1 receptors activates many intracellular molecules associated with neural plasticity.

The withdrawal period is critical to develop sensitization (Pierce and Kalivas 1997, White and Kalivas 1998, Wolf 1998, Vanderschuren and Kalivas 2000, Magendzo and Bustos 2003). Just after amphetamine administration, no behavioral sensitization is expressed; however, after a certain period, it becomes obvious (Robinson and Camp 1987). The time course of forming sensitization is classified into initiation and expression. Initiation depends on dopaminergic regulation in the mesolimbic pathway, specifically within the VTA (Kalivas and Weber 1988). Expression is involved in the NAc (Paulson et al. 1991). Behavioral expression of sensitization is due to increased activity of the mesolimbic dopaminergic system.

Phosphorylation is involved in the formation of amphetamine sensitization. An intra-NAc injection of the PKC inhibitor chelerythrine blocks the development of sensitization to dopamine release (Narita et al. 2004). More enhanced phosphorylated PKC substrate, GAP-43, is detected in amphetamine-sensitized rats than in the single administered rats, even though a single administration with amphetamine also increases phosphorylated GAP-43 (Iwata et al. 1996, 1997a, 1997b). Enhanced phosphorylation of the CaMKII substrate synapsin I is detected after sensitization, though there was no effect on a single administration with amphetamine

on the phosphorylation of synapsin I in vivo and in vitro (Iwata et al. 1996, 1997a, 1997b). Although amphetamine increases dopamine in the synaptic cleft through a Ca^{2+} non-dependent manner, Ca^{2+} -dependent dopamine release is recruited after sensitization (Iwata et al. 1996). This recruitment is CaMKII-dependent (Kantor et al. 1999). PKA knock-out mice display no changes in locomotor behavior after acute administration of amphetamine, but they exhibit a heightened sensitization to repeated administration of amphetamine (Brandon et al. 1998). D1 receptor knock-out mice show no sensitization in locomotion (Crawford et al. 1997), which means that the D1 receptor is crucial for induction of amphetamine sensitization, though PKA is activated via D1 receptors. Amphetamine through D1 receptor stimulation induces the phosphorylation of CREB in the striatum (Konradi et al. 1994). Phosphorylated CREB increases in amphetamine-sensitized animals (Turgeon et al. 1997). CREB regulates c-fos, TH, BDNF, neuropeptides and has a role in neural plasticity (Silva et al. 1998).

Although enhanced activity of the dopaminergic system is due to an increase in dopamine release, a post synaptic mechanism is also proposed. Amphetamine-sensitized animals show a marked increase in dopamine D2 high receptors occupied by endogenous dopamine, though the total number of D2 receptors is unchanged (Seeman et al. 2002). D4 receptor knock-out mice show an enhanced dose-dependent sensitized response to repeated amphetamine administration (Kruzich et al. 2004). Wang et al.

(2017) showed increased levels in the postsynaptic density (PSD) of PKA and CaMKII, as well as phosphorylation by these kinases of the GluA1 S845 and S831 residues of AMPA receptors in amphetamine-sensitized rat's NAc with no increase in cell surface levels of GluA1 or GluA2 AMPA receptor subunits, which is induced in cocaine-sensitized animals. T34-phosphorylated DARPP-32, which inhibits phosphatase 1, inhibits dephosphorylation of phosphorylated GluA2, which facilitates internalization of GluA2. Alteration of AMPA receptors' composition enhances Ca^{2+} -required kinase activation. AMPA receptors phosphorylated in the S831 slow miniature excitatory postsynaptic current (mEPSC) decay times, as the effects are regulated by channel open probability and duration, as well as conductance. Repeated administration with amphetamine that induces behavioral sensitization produced a long-lasting increase in the length of dendrites, in the density of dendritic spines, and in the number of branched spines on the MSNs in the NAc. The treatment produces similar effects on the apical dendrites of layer III pyramidal neurons in the PFC (Robinson and Kolb 1997, 2004), which is the first report to show morphological change in amphetamine sensitization.

A role of the GABAergic system in amphetamine-induced sensitization has been reported. Pretreatment with clonazepam (GABAA receptor agonist) prevents the acquisition of behavioral sensitization of methamphetamine in rats (Ito et al. 2000). The GABAB receptor agonist baclofen blocks the development of amphetamine-induced behavior sensitization (Bartoletti et al. 2005).

5.4. Amphetamine tolerance

In DSM-5, tolerance is defined as either markedly increased amounts of amphetamine to achieve the desired effect or a markedly diminished effect with continued use of the same amount.

The development of tolerance depends on organs, e.g., a weak tolerance grows in peripheral organs such as the autonomic nervous system, in contrast to severe tolerance in psychoactive actions. In humans, rapid tolerance develops to the anorexic and lethal effects of amphetamine (Angrist and Sudilovsky 1978). The development of tolerance also depends on the route and manner of intake. No tolerance of sensitivity of behavioral responses is observed after repeated daily oral doses of 10 mg amphetamine (Johanson et al. 1983), but the response decreases after sequential oral doses of amphetamine, despite high plasma levels of amphetamine (Angrist et al. 1987). The degree of tolerance is different in each individual. Tolerance is distinguished from individual variability in the initial sensitivity to the effect of amphetamine, i.e., individuals who need much amphetamine to obtain some effects do not always develop tolerance quickly. Tolerance develops when amphetamine is administered continuously (Kokkinidis 1984, Gately et al. 1987, Hollingsworth and Mueller 1988), repeatedly for a short period (Götestam 1976) such as in a “binge,” or when the increase in the concentration of the blood level of amphetamine is slow. Oral administration of amphetamine results in locomotor tolerance in experimental animals (Turner et al. 2018), though intermittent administration induces locomotor sensitization.

Three mechanisms of tolerance are proposed (O’Brien 2018), pharmacokinetic, pharmacodynamic, and learned. Pharmacokinetic tolerance is induced by an increase in the rate of metabolism of a drug. Pharmacodynamic tolerance involves adaptive changes that take place within the system affected by a drug, so that the response to a given concentration of a drug is reduced, e.g., a decrease in the number of receptors available to bind a drug. Learned tolerance is a reduction in the effects of a drug due to compensation that has been learned from past experience, e.g., an individual with alcohol intoxication can walk a straight line despite motor impairment by alcohol.

5.5. Amphetamine withdrawal

Withdrawal is a syndrome that occurs when the tissue concentration of amphetamine decreases in individuals who have maintained prolonged use of amphetamine. Withdrawal symptoms vary across the classes of substances. Marked physiological signs of withdrawal are common with alcohol, opioids, sedatives, and hypnotics. Withdrawal symptoms with amphetamine are present, but less obvious (DSM-5). Acute withdrawal symptoms, which is referred to as “crash,” are unpleasant feelings of lassitude, depression, and increased appetite. Psychosis can also develop during withdrawal (Askevold 1959). The pharmacological state in individuals with amphetamine withdrawal is hypofunction of the dopaminergic system; therefore, they want to take amphetamine to maintain the dopaminergic system stable, which is the mechanism of craving (Koob and Bloom 1988, Miyata et al.

2011). Antidepressants reverse or shorten psychostimulant withdrawal, e.g., paroxetine reverses reward deficits during amphetamine withdrawal in rats (Markou et al. 2005).

6. Amphetamine-induced phosphorylation and gene expression

Phosphorylation is involved in the effect of amphetamine and amphetamine-induced plasticity. Phosphorylation of proteins is an important mechanism to activate or inactivate reactions in organisms.

Amphetamine increases intracellular Ca^{2+} in bovine chromaffin cells (Mundorf et al. 1999) and PC12 cells (Kantor et al. 2001). The Ca^{2+} is derived from synaptic vesicles, because blockage of Ca^{2+} pumps in endoplasmic reticulum and mitochondria does not affect the calcium spike, or is derived from extracellular interstitium through voltage-gated L-type Ca^{2+} channels that are activated by DAT-dependent depolarization by amphetamine (Cameron et al. 2015). Increased intracellular Ca^{2+} activates Ca^{2+} -dependent kinases, e.g., PKC and CaMKII. PKC has long-term activation even after Ca^{2+} -induced activation has gone, because it is also activated by diacylglycerol. Similarly, CaMKII is also activated for a long period because CaMKII makes a homo- or hetero-oligomer, which then activate each other. Therefore, they play an important role in learning and memory, especially CaMKII, because it occupies 1%-2% of whole-brain proteins (Bennett et al. 1983, Erondur and Kennedy 1985). Amphetamine dose-dependently increased the phosphorylation of GAP-43 by PKC and the

CaMKII substrate synapsin I (Iwata et al. 1996). Increased phosphorylated GAP-43 in the striatum from rats that received a sensitizing regimen of amphetamine compared to drug-naïve controls has been reported (Iwata et al. 1997a, 1997b).

Acute treatment of mice with amphetamine increases the phosphorylation of T34-DARPP-32 and S130-DARPP-32, but decreases the phosphorylation at T75 (Svenningsson et al. 2003). Acute methamphetamine administration also increases DARPP-32 phosphorylation at T34 in the nucleus accumbens, but repetitive administration of methamphetamine decreases the T34 phosphorylation (Chen and Chen 2005). DARPP-32 is now known as protein phosphatase 1 regulatory subunit 1B (PPP1R1B), which inhibits phosphatase 1. DARPP-32 is expressed in the MSNs expressing D1 and NMDA receptors in the striatum (Ouimet and Greengard 1990, Walaas and Greengard 1984). Stimulation of D1 induces cAMP formation, resulting in the phosphorylation of DARPP-32 (Walaas and Greengard 1984). The phosphorylated DARPP-32 is a potent protein phosphatase 1 inhibitor (Hemmings et al. 1984). On the other hand, activation of NMDA receptors increases Ca^{2+} , which activates calcineurin. Calcineurin dephosphorylates phospho-DARPP-32. Therefore, dopamine and glutamate function in opposite directions (Halpain et al. 1990). DARPP-32 is involved in dopamine-dependent striatal synaptic plasticity (Yagishita et al. 2014).

Single administration of amphetamine decreases the level of phosphorylated AKT (Zheng et al. 2013). Repeated methamphetamine displays an initial increase and subsequent

decrease in AKT phosphorylation (Shi et al. 2007). AKT is a serine/threonine-specific protein kinase that is involved in nerve growth factor-related signal transduction. The effect of AKT on dopaminergic neurons is doubtful, because AKT mRNA levels are low in dopaminergic neurons (Iwata et al. 2004). Amphetamine activates Fyn, which is a tyrosine kinase related to neuronal cell development, in striatal neurons via a D1 receptor-dependent mechanism (Jin et al. 2019). Amphetamine elevates the phosphorylation of eukaryotic initiation factor 2 α , which is a transcription factor activated by several serine kinases and related to neuronal plasticity in the rat forebrain by activating dopamine D1 and D2 receptors (Xue et al. 2016). Amphetamine phosphorylates many molecules, but the significance of these phosphorylated molecules is still an open question.

7. Toxicity of amphetamine

Postmortem studies show that levels of dopamine, TH, and DAT are reduced in the striatum of IAAs (Wilson et al. 1996, Moszczynska et al. 2004). In addition, another postmortem study showed reduced levels of dopamine, TH, and DAT in the striatum and the NAc of IAAs, though levels of DOPA decarboxylase and VMAT2 were normal (Wilson et al. 1996). Dopamine content is reduced more in the caudate than in the putamen, and this pattern of reduction is reverse to that seen in patients with Parkinson's disease (Moszczynska et al. 2004, Kish et al. 2017).

Structural MRI studies show that the volume of the temporal lobe decreases in IAAs (Bartzikis

et al. 2000). Lower cortical gray matter volume and higher striatal volume are consistently reported in IAAs (Berman et al. 2008). Smaller volumes of the medial PFC (Daumann et al. 2011), the basolateral amygdala, the dorsal striatum, and the left basolateral amygdala are observed in IAAs (Becker et al. 2015). Surface-based computational image analyses show severe gray matter deficits in the cingulate, limbic, and paralimbic cortices, small hippocampal volume, and significant white matter hypertrophy in IAAs (Thompson et al. 2004). Severe gray matter atrophy in the cingulate, limbic, and paralimbic cortices and smaller hippocampal volume are correlated with memory impairment on a word recall test in IAAs (Thompson et al. 2004). A diffusion tensor imaging study showed low fractional anisotropy values in the bilateral frontal white matter of IAAs who showed impairment of the Wisconsin Card Sorting Test (WCST) (Chung et al. 2007). Progenitor cells in the hippocampus decrease four weeks after repeated amphetamine intake (Barr et al. 2010). Several mechanisms of amphetamine-induced neurodegeneration are proposed (Shin et al. 2017), e.g., the excite-toxic effect of dopamine through D1 receptors and glutamate through NMDA receptors. Amphetamine induces apoptosis of MSNs in the striatum via the mitochondria-dependent pathway (Krasnova et al. 2005). Methamphetamine-induced mitochondrial impairment enhances susceptibility to oxidative stress, pro-apoptosis, and neuroinflammation (Shin et al. 2018).

As to brain metabolism, blood oxygen level-dependent functional MRI shows dysfunction of the orbitofrontal cortex and the dorsolateral

PFC in IAAs who exhibit fundamental cognitive deficits during decision-making (Paulus et al. 2002). In individuals with relapse and those with non-relapse of methamphetamine addiction, several brain areas, e.g., the right insular area and the caudate, have different values on functional MRI (Paulus et al. 2005). A perfusion MRI study showed a decrease in relative regional cerebral blood flow in the striatum, the insular area, and parietal, occipital, and temporal cortices in abstinent IAAs (Chang et al. 2002). The results of functional MRI show hypoactivity in the PFC during executive examination tests, which means poor self-control, and hypofunction of the reward system (Goldstein and Volkow 2011). FDG-PET studies show lower activity in the thalamus and the striatum, and higher functional activity in the parietal cortex (Volkow et al. 2001d). IAAs who feel depression and anxiety have been found to have lower glucose metabolic rates in the anterior cingulate and insular cortices and higher rates in the lateral orbitofrontal areas, the middle and posterior cingulate, the amygdala, the ventral striatum, and the cerebellum (London et al. 2004). Hypometabolism in the left inferior frontal white matter in IAAs is related to impairment on the WCST (Kim et al. 2009).

As to functional studies specific to the dopaminergic system, dopamine release, DAT densities, and D2 receptors decrease. Dopamine release is consistently reported to be decreased in IAAs (Ashock et al. 2017). IAAs display significantly blunted dopamine release to an acute amphetamine challenge and a blunted subjective response (Schrantee et al. 2015).

IAAs who showed relapse have lower dopamine, but those who are completely detoxified did not differ from controls (Wang et al. 2012). D2 receptors in the striatum are consistently reported to be reduced in IAAs (Ashock et al. 2017). Oral administration with amphetamine causes prolonged displacement of [11C] raclopride as measured by PET (Cárdenas et al. 2004). A decrease in D2 receptors in the orbitofrontal cortex is correlated with hypofunction of the brain area (Volkow et al. 2001c). IAAs display lower striatal D2 receptor binding in the basal condition (Schrantee et al. 2015), even after nine months of abstinence (Volkow et al. 2015). Individuals who previously experienced methamphetamine psychosis show no difference in D2 receptors in the striatum and 5-HT₂ receptors in the frontal cortex assessed by [11C] N-methylspiperone binding compared with controls (Iyo et al. 1993). D2 receptor availability measured with PET and [11C] raclopride decreases in IAAs (Wang et al. 2012). Low D2 receptor availability measured by PET scanning with [18F] fallypride is reported, and it is associated with steep discounting of delayed rewards in IAAs (Ballard et al. 2015). PET with [18F] fallypride to assay D2 receptor availability showed a significant decrease in IAAs in the striatum, and no significant alteration in the amygdala, the hippocampus, the thalamus, the globus pallidus, the ACC, the insula, and the orbitofrontal cortex (Okita et al. 2016). DAT density is consistently reported to be lower in IAAs (Ashock et al. 2017). DAT loss in the orbitofrontal cortex and the dorsolateral PFC is associated with methamphetamine-related psychiatric symptoms

(Sekine et al. 2003). DAT reduction is correlated with motor slowing and memory impairment (Volkow et al. 2001a). Recovery of DAT binding was asymmetric and possibly parallel with the improvement of cognitive function (Chou et al. 2007). Imaging studies in IAAs show reductions of DAT in the striatum (McCann et al. 1998, 2008, Sekine et al. 2001, Volkow et al. 2001a, b). PET showed a 15% reduction in [11C] methylphenidate binding in abstinent IAAs (Johanson et al. 2006). Striatal DAT binding ratios measured by single photon emission computed tomography (SPECT) scanning with [123I] FP-CIT (ioflupane) are low in IAAs (Schouw et al. 2013). DAT binding in IAAs is also low, as detected by [99mTc] TRODAT-1 (Yuan et al. 2014). [11C] cocaine PET shows decreased DAT binding in the striatum of IAAs (Volkow et al. 2014). As to VMAT2 binding, in early abstinence from methamphetamine, it increased, and it then gradually decreased below the control level in a PET study (Boileau et al. 2008). Collectively, reductions of DAT and VMAT2 are compensatory changes rather than degeneration of neurons.

NF κ B, which is a transcriptional factor and expressed in almost all cells, has been implicated in some of the neurotoxic effects of methamphetamine in striatal regions (Asanuma and Cadet 1998).

8. Medical treatment of amphetamine use disorder

When IAAs are abstinent from amphetamine, the function of the dopaminergic system is depressed, and they suffer from withdrawal

symptoms. During the withdrawal period, IAAs are sensitized to amphetamine; therefore, the reaction of the dopaminergic system to amphetamine is enhanced. Pharmacologically, a partial dopamine agonist is suitable for maintaining homeostasis of the dopaminergic system, because partial agonists act as dopamine agonists in the dopamine-depleted period, i.e., the abstinent and withdrawal period. Alternately, when release of dopamine is accidentally enhanced by reuse or stress, partial agonists act as dopamine receptor antagonists. However, they failed to ease the withdrawal symptoms, as well as ordinary antipsychotics (Coffin et al. 2013, Kishi et al., 2013). Medical treatment for hallucinations and delusions in amphetamine-induced psychotic disorders, however, is the same as for idiopathic psychotic disorders. Antipsychotics are effective for them. Amphetamine-induced depression and anxiety disorders are also treated with antidepressants and anxiolytics, respectively. Tamoxifen, a selective estrogen receptor modulator, as well as a PKC inhibitor, has been proposed to be effective for amphetamine addiction (Mikelman et al. 2017).

Because no successful drug therapy has appeared for treating amphetamine addiction thus far (Bhatt et al. 2016, Lee et al. 2018, Chan et al. 2018, Siefried et al. 2020), the main treatment is counseling, group psychotherapy, cognitive behavioral therapy, and joining in local mutual self-help groups. IAAs who engaged in a physical exercise program exhibited better fitness measures (gauged by substantial improvements in aerobic capacity, muscle strength and endurance, body composition, and increased heart rate variability)

and showed less depression and anxiety symptoms, lower relapse rates, and sustained abstinence when compared to nonexercised individuals (Morais et al. 2018). As the brain's anatomical structure has been altered, it is impossible to restore these anatomical alterations by social therapy. Therefore, the most important thing for them is to continue refraining from amphetamine use.

9. Closing remarks

Amphetamine is an intriguing drug. Amphetamine changes the functions of the CNS permanently through the glutamatergic system. This feature is a suitable model for studying neural plasticity. Amphetamine enhances and depresses the functions of the dopaminergic system, which is involved in many functions in the brain. High or sustained use of the drug induces neuronal death of dopaminergic neurons, which is a valuable model of patients with schizophrenia. Many molecules that are related to amphetamine's action have been reported. Scientists are becoming interested in the effects of amphetamine on psychological and high-order brain functions. I believe that studies of amphetamine are contributing to unveiling the function of the human brain.

GLOSSARY

Associative memory

Associative memory is defined as the ability to learn and remember the relationship between unrelated items. Processes to form associative memory are operant conditioning and classical

conditioning. Operant conditioning is involved in relapse in IAAs. Although the cardinal brain regions that are involved in associative memory are the hippocampus and its surrounding structures, other regions e.g., the PFC, the parietal cortex, and the striatum, are also needed to form associative memory.

Immediate early gene

Immediate early genes (IEGs) are genes that are rapidly transcribed to mRNA in response to cellular stimuli without any new protein synthesis. Coding proteins by these genes include transcription factors, DNA-binding proteins, secreted proteins, cytoskeletal proteins, and receptor subunits. Approximately 40 IEGs have been identified so far. Some IEGs are implicated in learning, memory, and neural plasticity. They are c-fos, Egr1, Arc, and Homer1a/Vesl-1s; c-fos and Egr1 are transcription factors belonging to the bZIP family and Zinc finger protein, respectively. Arc is a modifying factor of AMPA receptors, and Homer1a is an induced EVH domain protein.

Although the mechanism of induction of IEGs responding to stimuli is different for each IEG, a common pathway has been elucidated. CaMK and MAPK are activated by Ca²⁺ entering through NMDA receptors or voltage-gated Ca²⁺ channels. CREB, serum response factor (SRF), and myocyte enhancer factor-2 (MEF2) are phosphorylated, and then transcription of IEGs is started.

LTP and LTD

LTP and LTD are mechanisms of amphetamine addiction and sensitization (Baptista

et al. 2016). LTP is a persistent enhancement of synaptic transmission, which is a molecular mechanism of learning and memory, and induced at all excitatory synapses in the mammalian brain (Malenka and Bear 2004, Cooke and Bliss 2006). Several mechanisms are considered in LTP, and their types depend on the features of each synapse, even in the same brain region.

LTP has four features. The first one is input specificity. LTP is confined to a specific synapse. LTP does not always occur on the rest of the synapses belonging to the same neuron, since the mechanism is due to synaptic tagging (Frey and Morris 1997, Martin et al. 1997). Only the postsynaptic membrane that receives LTP-inducing stimulation develops LTP. When the postsynaptic membrane receives LTP-inducing stimulation, it sends a message to the nucleus of the neuron. The neuron produces molecules that are necessary to induce LTP and sends these molecules to all dendrites of the neuron. Only the postsynaptic membrane that has received the LTP-inducing stimulation can bind these molecules, as though the postsynaptic membrane has a tag to attract these molecules. The second feature is associativity. Simultaneous stimulation, which is strong enough to induce LTP on a certain synapse, establishes another LTP in associated synapses, where only weak stimulation is given. The third is cooperativity. Weak stimulation from many presynaptic terminals that converge on a single postsynaptic membrane can induce LTP. The fourth one is persistence.

A representative type of LTP is as follows. In regular transmission in glutamatergic

synapses, glutamate binds postsynaptic AMPA receptors because NMDA receptors are blocked by magnesium. NMDA receptors are co-localized with AMPA receptors. In the induction phase, repetitive stimulation of the presynaptic membrane induces the summation of EPSP in the postsynaptic membrane, which induces strong depolarization. Magnesium is released by the strong depolarization, and then extracellular Ca^{2+} enters the postsynaptic neuron through activated NMDA receptors. Many Ca^{2+} -dependent protein kinases, especially CaMKII and PKC, are activated, which are co-localized with NMDA receptors. The maintenance phase follows the induction phase. When the Ca^{2+} level in the postsynaptic neuron returns, Ca^{2+} -independent protein kinases are activated in turn, e.g., protein kinase ζ . Proteins that are necessary to maintain the LTP can be phosphorylated by protein kinase ζ . In an expression phase, AMPA receptors in the postsynaptic membrane are recruited on the surface of the postsynaptic membrane without any AMPA receptor synthesis. More postsynaptic AMPA receptors enhance EPSP. In a late phase, protein synthesis occurs in the postsynaptic neuron. Anatomically, the number and surface area of dendrites increase in this phase. In addition to the alteration of postsynaptic neurons, alteration of the presynaptic membrane, e.g., increased number of synaptic vesicles, occurs in the late phase.

LTD is another synaptic plasticity in which transmission efficiency is depressed for a long period. LTD is one of the mechanisms to maintain neural homeostasis (Turrigiano et al. 1998). If a

neuron were consistently activated, the coming input would be peaked and would not be recognized by the neuron. To reset the input range of a neuron is called scaling (Pérez-Otaño and Ehlers 2005). Synaptic scaling is a form of homeostatic plasticity, in which the brain responds to chronically elevated activity in a neural circuit with negative feedback, allowing individual neurons to reduce their overall action potential firing rate (Siddoway et al. 2014). Synaptic scaling not only depresses, but also activates the synapse. Neurons have a homeostatic autonomous mechanism that adjusts average synaptic strength (neurotransmitter amount) to bring the average level of their postsynaptic response to within an appropriate range (Turrigiano and Nelson 2004, Lisman 2017). Although LTD is well-known in the hippocampus and cerebellum, most brain systems use LTD (Massey and Bashir 2007). As a representative example, the mechanism of LTD in the cerebellum is described. LTD in the cerebellum is a decreased ratio of synaptic transmission from parallel fibers to Purkinje cells. This decrease is induced when parallel and mossy fibers are simultaneously activated and is caused by less postsynaptic AMPA receptors. Both fibers are excitatory inputs to Purkinje cells. Excitatory inputs from parallel fibers activate mGluR1 in the Purkinje cells. Stimulating mGluR1 activates phospholipase C, which then produces inositol 1,4,5-trisphosphate (IP3) and diacyl glycerol. IP3 opens calcium channels in the endoplasmic reticulum, which increases Ca^{2+} concentration in Purkinje cells. In addition, the excitation of the mossy fibers opens the voltage-gated Ca^{2+} channel in the Purkinje

cell. This accumulated Ca^{2+} activates PKC. PKC phosphorylates GluA2 of AMPA receptors; it then unbinds AMPA receptors from GRIP. GRIP is an anchor protein to the postsynaptic membrane. The unbound AMPA receptors are endocytosed, then inactivated. LTD is also induced in the midbrain dopaminergic neurons, triggered by the activation of non-L-type voltage-dependent Ca^{2+} channels (Thomas et al. 2000).

The term “metaplasticity” is proposed, which means a synapse’s previous history of activity determines its current plasticity (Abraham and Bear 1996). This term contains both LTP and LTD.

Reward system

A reward is an essential factor for organisms for their survival. Rewards are classified into intrinsic and extrinsic. The intrinsic reward is inherently pleasurable, e.g., food in the hungry condition. On the other hand, the extrinsic reward is a learned reward that has no feature of intrinsic pleasure, e.g., money. The extrinsic reward is formed by conditioning with an intrinsic reward. Functions of the reward system are producing associative learning, giving motivational salience to a certain thing, and turning this motivational salience into pleasure. The reward system per se functions to survive for organisms, but under the condition of drug addiction, the purpose of this system is changed to obtain only pleasure or avoid withdrawal symptoms. Initially, the reward system is activated when a reward is obtained, but after learning an associative cue as the reward, this system is activated before acquisition, i.e., expecting the reward.

Although the reward system is involved in the PFC, the basal ganglia, and the thalamus, the most important role resides in the mesolimbic dopaminergic system that projects to the amygdala, the NAc, the ACC, the orbitofrontal cortex, and the PFC (Olds and Milner 1954, Hyman et al. 2006). The amygdala and the orbitofrontal cortex link a reward cue to a pleasurable reward. The orbitofrontal cortex revises this linkage. In the hippocampus, this linkage and circumstantial conditions are memorized, which strengthens addiction. The primary rewarding effects of direct dopamine receptor stimulation is dissociable from hedonic responses in animals, and D1 receptors contribute to drug-induced euphoria in humans. Glutamatergic inputs from the orbitofrontal cortex, the amygdala, and the hippocampus to the NAc are involved in the expression of cue-induced craving (Volkow et al. 2011a).

Salience

Functions of the brain are neurobehaviorally classified into the executive-control network and the salience network (Seeley et al. 2007). Both belong to the default mode network. The default mode network is initially recognized as brain regions that are deactivated during a certain goal-oriented task, but recently it has been found to be active when individuals are not focused on the outside world and the brain is at wakeful rest, such as daydreaming (Raichle et al. 2001). The term “salience” is an important concept to understand the symptoms of amphetamine addiction (Berridge 2012, Puglisi-Allegra and

Ventura 2012, Edwards 2016). Salience means features of things outstanding from others. It arises from contrasts between things and their surroundings. When attention development is driven by salient stimuli, it is considered to be bottom-up. Conversely, top-down means memory-dependent or anticipatory mechanisms to be salient, e.g., when we look at a moving object, we look ahead of the object anticipating the course of the moving object. Salience was first introduced in the field of neuroscience by Kapur et al. (2003). Kapur linked the psychological concept “salience” with psychiatric symptoms such as delusions and hallucinations in patients with schizophrenia and explained the mechanism of antipsychotics to sedate these symptoms through salience. The role of dopamine in the brain is to assign salience to environmental events. Patients with schizophrenia, whose dopaminergic system is hyperactive, have aberrant assignment of salience to elements of their experience, e.g., patients with delusions of reference believe that mere coincidences (non-salient) have strong personal significance (become salient). Antipsychotics dampen their abnormal assignment of salience by reducing dopaminergic activity.

The clinical feature of drug addiction is that not only a drug itself, but also the neutral elements become motivationally salient. Initially, individuals take amphetamine for positive reinforcement. However, after repeated usage, various things and situations become associated with amphetamine (associative learning). For example, a syringe gets incentive salience after repeated injections of amphetamine. Individuals

with amphetamine addiction can relapse when they see syringes.

A certain stimulation is allotted to incentive salience, which is involved in the NAc shell (Berridge 2012). This system is responsible for both pleasurable incentive salience and aversive salience (Salamone and Correa 2012, Baliki et al. 2013). MSNs expressing D1 receptors in the NAc shell assign incentive salience to reward stimuli, whereas MSNs expressing D2 receptors in the NAc shell assign aversive salience to aversive stimuli. Motivational salience is a cognitive process and a form of attention that motivates an individual's behavior toward or away from a particular object (Puglisi-Allegra and Ventura 2012), which is composed of two processes: incentive salience and aversive salience. Incentive salience is the psychological power to go close to this salience. Conversely, aversive salience is the salience to avoid this salience. Individuals take amphetamine because of its pleasurable effect (incentive salience of motivational salience) or to avoid unpleasant withdrawal symptoms (aversive salience of motivational salience).

Robinson and Berridge (1993) present a biopsychological theory of drug addiction, the incentive-sensitization theory. Repeated intake of amphetamine induces extraordinary incentive salience, i.e., the ordinary wanting state is changed into excessive drug craving. We should discriminate between “wanting” and “liking” of incentive salience. Individuals initially use amphetamine by “liking” of incentive salience. However, after repeated intake of amphetamine when they develop amphetamine dependence,

they take amphetamine by “wanting” incentive salience.

VMAT2

VMAT2 is a transmembrane protein and uses a proton gradient generated by vacuolar ATPase in the vesicle membrane to import monoamines. Monoamines are stored and protected from degradation. Methamphetamine decreases Vmax, whereas cocaine increases it. Methamphetamine binds a specific site of VMAT2. Repeated amphetamine administration increases VMAT2 mRNA (Lu and Wolf 1997). TH and amino acid aromatic decarboxylase are coupled with VMAT2, which help to synthesize dopamine effectively. Amphetamine binds VMAT2 directly (Gonzalez et al. 1994, Peter et al. 1994, Teng et al. 1998, Partilla et al. 2006) and elicits dopamine release into the cytosol. VMAT2 has two distinct but overlapping ligand binding sites, a reserpine binding site and a tetrabenazine binding site (Schuldiner et al. 1993).

Brain regions involved in the action of amphetamine

ACC

The ACC is involved in the function of decision-making considering risk and benefit (Kennerley et al. 2011).

The ACC is divided into three areas, the dorsal ACC, the pregenual ACC, and the subgenual ACC (Vogt 2005, Amodio and Frith 2006). The dorsal ACC regulates attentional processing (Pardo et al. 1990), reward-based decision-making (Bush et al. 2000, 2002), behavioral monitoring (Ridderinkhof et al. 2004), and morale (Sevinc et al. 2017). The

pregenual ACC is involved in social recognition (Amodio and Frith 2006). Emotion is involved in each ACC depending on the sort of emotion, e.g., activity of the dorsal ACC increases responding to fear (Dolan et al. 2001).

Amygdala

The function of the amygdala is processing of memory, decision-making, and emotional responses. Hemispheric specializations are reported. Right amygdala stimulation induces negative emotions. Left amygdala stimulation induces either negative or positive emotions (Lanteaume et al. 2007). The left amygdala contributes to the reward system. The volumes of the hemispheric amygdalas are different (Hines et al. 1992).

In general, formation and storage of memories are strengthened with concomitant emotional events. This mechanism, which is a kind of LTP, is involved in the amygdala (Maren 1999, Blair et al. 2001). Motivational salience is produced in the amygdala, especially in the basolateral amygdala (Nieh et al. 2013).

In substance addiction, the amygdala is a region responsible for anhedonia (Volkow et al. 2002), craving, cue-induced craving (Quirk et al. 2003), reward prediction errors (Schultz 2016a, b), and sensitization (Bijou et al. 2002). The VTA-amygdala dopaminergic system input and glutamatergic output to the PFC and the NAc are involved in these phenomena.

NAc

The NAc is involved in reward prediction

errors (Schultz 2016a, b), goal-directed behavior (Burton et al. 2015), and incentive salience (Berridge 2012). As to addiction and sensitization, the NAc plays an important role in cue-induced craving (Dackis and O'Brien 2001) and the expression of amphetamine sensitization. NAc is responsible for the expression of behavioral sensitization, whereas the dopaminergic cell bodies in the VTA are responsible for the initiation of the sensitization.

The NAc is divided into two parts: the core and the shell. The core is a part of the ventral striatum, and the shell is a part of the extended amygdala, which indicates that the NAc is an interface between the limbic system and the motor system (Mogenson et al. 1980, Hart et al. 2014).

The core is involved in motivation that elicits real behavior in the conditioned response. GABAergic MSNs, which occupy 95% of all neurons in the core, have either D1 or D2 receptors (Geldwert et al. 2006), and they send their axons to other subcortical areas, i.e., the globus pallidus and the SN.

On the other hand, the shell is related to an unconditioned response, e.g., orienting response, which is an organism's immediate response to a change in its environment (Heimer and Van Hoesen 2006). Most neurons in the shell are MSNs expressing D1 receptors. A subpopulation of MSNs in the shell expresses both D1 and D2 receptors. The shell neurons are involved in the cognitive processing of reward, i.e., subjective "liking" links to pleasurable stimuli, motivational salience, and positive reinforcement (Berridge 2003). MSNs expressing D1 receptors in the shell mediate

reward-related cognitive processes (Nestler 2013, Sadoris et al. 2015), whereas MSNs with D2 receptors in the shell mediate aversion-related cognition in cocaine addiction (Calipari et al. 2016). An addictive drug has a larger effect on dopamine release in the shell than in the core.

GABAergic MSNs in the NAc receive dopaminergic inputs from the VTA (Ikemoto 2010). Major glutamatergic inputs come from the PFC (the prelimbic cortex and the infralimbic cortex), the basolateral amygdala, the ventral hippocampus, the thalamic nucleus (the midline thalamic and the intraventricular nuclei), and the VTA (Yager et al. 2015). The output from the NAc is to the basal ganglion, including the globus pallidus, which makes a circuit: the NAc to the globus pallidus to the medial dorsal nucleus of the dorsal thalamus to the PFC to the striatum. Other efferents are to the VTA (Barrot et al. 2012), the SN, and the reticular formation of the pons.

PFC

The PFC is a part of the frontal cortex that is not involved in motor function. Anatomically, the PFC is divided into three regions, the lateral PFC (BA10, 46, 44, 9, 8), the orbital PFC (BA10, 11, 12), and the medial PFC (BA10, 9, 32, 8). The medial PFC is further divided into the dorsal part and the ventral part; the former innervates the NAc core, and the latter innervates the NAc shell. BA10 is specific to humans and primates, from and to where neural networks are confined in other regions of the PFC, though the rest of the PFCs have various neural connections to other PFCs and other brain regions. The lateral PFC

is involved in working memory. The orbital PFC and the medial PFC are involved in emotion and volition and have an intense connection with the limbic brain regions.

VTA

The VTA is not a nucleus but an area because of heterogeneous cytoarchitectonic features of the region and the lack of clear borders that separate it from adjacent regions (Björklund and Dunnett 2007). The VTA is subdivided into the paranigral nucleus, the parabrachial pigmented area, the parafasciculus retroflexus area, and the rostromedial tegmental nucleus. The paranigral nucleus and the parabrachial pigmented area are rich in dopaminergic neurons, and the rostromedial tegmental nucleus is composed of GABAergic neurons (Kaufling et al. 2009, Jhou et al. 2009).

Almost all areas receiving projections from the VTA project back to it. The VTA receives glutamatergic inputs from the PFC, the pedunclopontine tegmental nucleus, the laterodorsal tegmental nucleus, the subthalamic nucleus, the bed nucleus of the stria terminalis, the superior colliculus, the periaqueductal gray, the lateral habenula, the dorsal raphe nucleus, and the lateral hypothalamic and preoptic areas (Morikawa and Paladini 2011, Morales and Margolis 2017). Glutamate released from these terminals increases activity of dopaminergic neurons in the VTA. This characteristic is critical to drugs of abuse. The VTA receives GABAergic inputs from the NAc, the ventral pallidum, the dorsal raphe nucleus, the lateral hypothalamus, the periaqueductal

gray, the bed nucleus of the stria terminals, and the rostromedial tegmental nucleus. The lateral habenula exerts an inhibitory effect on dopaminergic neurons in the VTA by exciting the rostromedial tegmental nucleus GABAergic neurons, which is important for reward prediction errors (Watabe-Uchida 2017). The VTA receives cholinergic inputs from the pedunculopontine tegmental nucleus and the laterodorsal tegmental nucleus, which increases the activity of dopaminergic neurons and modulates the reward system (Dautan et al. 2016).

The VTA output is to the PFC and the NAc. Most of them are dopaminergic. GABAergic outputs are to the PFC, NAc, and locus coeruleus.

Three neural circuits related to the VTA have been identified: the limbic loop controls cognitive and affective functioning; the CA3 loop is important for reward-seeking (Luo et al. 2011); and the posterior VTA-the NAc shell is involved in the reward system.

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覚醒剤の薬理

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覚醒剤は本邦で最も深刻な影響を及ぼしている薬物であるが、それとは別に、それが引き起こす依存、嗜癖、逆耐性は神経科学的に興味を惹かれる現象である。それらについての最近の知見を踏まえて私見を述べた。

覚醒剤による精神障害はDSM-5では、覚醒剤関連嗜癖障害と命名されている。それは覚醒剤使用障害と覚醒剤誘発性障害に分けられる。覚醒剤使用障害の本質は覚醒剤への渴望にある。覚醒剤誘発性障害は覚醒剤中毒、覚醒剤離脱に分けられる。日本では覚醒剤により統合失調症と判別が不可能な精神障害を起こすと認識されている。しかし、DSM-5ではその場合、覚醒剤使用が統合失調症を誘発しただけであり、それは統合失調症と何ら変わることはない結論している。しかし、日本では症状の差異、発症年齢などから覚醒剤が統合失調症を起こすことはあると考えられている。DSM-5ではdependenceという用語は消えaddictionに包括されたが、DSM-5はあくまでも疾患分類であるので、両者の言葉に明らかな違いがないならばどちらかの用語は採用して他方はしないということは納得できる。しかし、覚醒剤依存とは覚醒剤がないとホメオスタシスが保てない状態であり、嗜癖とは覚醒剤への制御不能の渴望であり、両者は異なる。渴望には2種類あり、覚醒剤から得られる高揚感などが好き「liking」で摂取するものと、退薬症状から逃れるために必要とする場合「wanting」がある。

急性効果として覚醒剤は覚醒作用や疲労感を麻痺させる作用がある。その作用機序はドパミントランスポーター (DAT) の抑制によるシナプス間隙のドパミン上昇と DAT の逆輸送によるシナプス間隙のドパミン上昇である。前頭前野のドパミン神経終末には DAT が存在せず、代わりにノルアドレナリントランスポーターがドパミンを取り込んでいるので、前頭前野のアムフェタミンの効果の機序は他の部位と同様ではないと思われる。

覚醒剤を慢性投与すると嗜癖が形成される。嗜癖サイクルは最初に乱れ打ち期 (binge)、次に怠薬期 (withdrawal)、最後に囚われ期 (preoccupation) からなる。乱れ打ち期では報酬系を形成する側坐核が重要な役割を担う。繰り返される覚醒剤の投与で報酬系に異常が生じ、生理的な「快」刺激では簡単に報酬系が反応しなくなる。また、条件づけが成立し、注射器などの覚醒剤に関連する事物に反応するようになる。怠薬期では中脳辺縁系のドパミン放出が減少し、快感消失状態 (anhedonia) に陥る、これには扁桃体が関与している。ストレスはグルココルチコイドを放出し、グルココルチコイド受容体をもつドパミン神経細胞を興奮させる。これがストレス状態のヒトが覚醒剤依存に陥り易く、また、ストレスにより再燃が起こる機序である。囚われ期では理性を司る前頭前野の機能が低下し、遅延報酬機能が障害され、覚醒剤の再使用に贖えなくなってしまう。また、報酬セイリアンスが過剰に活性化され、覚醒剤に関連したちょっとしたことでも注意が集中するようになる。そして、脳内抑制系の機能低下と報酬系の機能亢進により渴望と再使用が誘発される。欲しい物を手に入れたとき生物は脳内報酬系が活性化され、連合学習により報酬セイリアンスが動員され「快」状態を形成する。覚醒剤は脳内報酬系を過剰刺激して制御不能となるので嗜癖が生じる。

覚醒剤による「liking」刺激がないとホメオスタシスが保てなくなり、「liking」により覚醒剤を欲するのではなく、好き嫌いに関係なく欲してしまう「wanting」に変質する。その「wanting」が渴望となってしまうのが嗜癖の機序であるというインセンティブ感作理論というものもある。

自分では対処不能な苦悩を自己治療するために覚醒剤嗜癖に陥ってしまうという説もある。

報酬予測誤差理論というのは一般には予測した報酬より多ければ報酬系は興奮するが、これは慣れが生じる。しかし、覚醒剤には慣れが生じないので報酬系は過剰に興奮し続けるのが依存のメカニズムであるという理論である。

覚醒剤による依存、嗜癖、逆耐性は神経の可塑的变化により誘発される。その分子機構として Ca^{2+} トリガーとしたリン酸化と cAMP の活性化によるリン酸化が想定されている。覚醒剤は DAT を介して、または単純拡散によりドパミン神経終末に取り込まれるが、DAT を利用した場合、細胞外の Na^{+} も同時に取り込まれ、神経終末は脱分極する。そして、DAT と共存している L 型電位依存性 Ca^{2+} チャネルが開いて、 Ca^{2+} が流入し、 Ca^{2+} 依存性の多機能リン酸化酵素である PKC と CaMK II を活性化する。PKC は DAT をリン酸化し、リン酸化された DAT はインターナリゼーションされ、不活化する。一方、細胞内に入った覚醒剤は TAAR1 を活性化して、細胞内 cAMP を増加する。cAMP によって活性化された PKA は DAT をリン酸化し DAT による逆輸送を亢進する。同時に DAT をリン酸化してインターナリゼーションを促進して、シナプス間隙からのドパミン消失を抑制して、シナプス間隙のドパミン濃度を上昇させる。一方、D2 受容体、syntaxin1、TAAR1 は DAT のインターナリゼーションを防いでいる。CaMK II は DAT をリン酸化して逆輸送を促進する。覚醒剤の作用自体はドパミンの増加によるが、神経の可塑的变化はグルタミン酸神経系の変化により生じ、それがドパミン神経系に作用することが逆耐性や嗜癖の機序である。

覚醒剤中毒者は大脳基底核の障害があり、ドパミン神経終末の障害は尾状核優位であるが、そのパターンはパーキンソン病と逆である。また、覚醒剤使用者では前頭前野の機能低下が認められており、自己制御機能の低下、遂行機能障害はそのためと考えられている。しかし、神経細胞は消失していないようである。

覚醒剤の作用には個人差があり、心理学的な状況依存性があり、行動薬理の実験の解釈も一筋縄ではない。さらに、生化学的変化は中脳大脳皮質系のドパミン神経系の機能亢進から一步も進んでおらず、細胞内情報伝達系の結果は収斂することがない。しかし、ヒトの機能画像から得られる治験は集積されつつあり、前頭前野、島などの異常が報告されており、今までブラックボックスであったヒト特有の機能との関連が判明しつつある。

キーワード：アンフェタミン、依存、逆耐性、嗜癖、メタアンフェタミン