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REVIEW

DRUG ADDICTION. *PART II.* NEUROBIOLOGY OF ADDICTION

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The drug addiction may be regarded as the disease of the brain reward system. This system, closely related to the system of emotional arousal, is located predominantly in the limbic structures of the brain. Its existence was proved by demonstration of the "pleasure centers," that were discovered as location from which electrical self-stimulation is readily evoked. The main neurotransmitter involved in the reward is dopamine, but other monoamines and acetylcholine may also participate. The anatomical core of the reward system are dopaminergic neurons of the ventral tegmentum that project to the nucleus accumbens, amygdala, prefrontal cortex and other forebrain structures. Several of those structures may be specifically involved in the reward produced by different substances, when anticipating the reward. The recent discovery of CART peptides may importantly expand our knowledge about the neurochemistry of reward. Natural rewarding activities and artificial chemical rewarding stimuli act at the same locations, but while natural activities are controlled by feedback mechanisms that activate aversive centers, no such restrictions bind the responses to artificial stimuli. There are several groups of substances that activate the reward system and they may produce addiction, which in humans is a chronic, recurrent disease, characterized by absolute dominance of drug-seeking behavior. The craving induced by substances of addiction inhibits other behaviors. The adaptation of an organism to a chronic intake of drugs involves development of adaptive changes, sensitization or tolerance. It is thought that the gap between sensitization developing for the incentive value of the drug and tolerance to the reward induced by its consumption underlies the vicious circle of events leading to drug dependence. The vulnerability to addiction is dependent not only on the environment, but also on genetic factors.

Key words: *addiction, reward, dopamine, CART peptides, addiction vulnerability*

Humanity successfully searched for pleasure-giving substances from the beginning of its history, and in the present days they are still used extensively. While the number of widely used substances of addiction was reduced, their power and availability still increase. This indicates that the search for substances altering the consciousness and improving mood is an important human trait. The abused substances are generally regarded as harmful both from medical and social point of view, but in spite of their use, in most cases they did not impair the competitiveness of various human tribes, and did not harm the evolutionary success of the human species. However, as described earlier [123], the recent changes in the use of addictive substances and the change in the attitude of society to this problem resulted in regarding the addiction as a serious social plague. Therefore, discovery of biological basis of the need to use psychoactive substances is of crucial importance.

The most dangerous characteristic of psychoactive substances appears to be their ability to evoke addiction. Drug addiction should be considered a complex disease of the central nervous system, characterized by compulsive, uncontrolled craving for a drug, its seeking and striving to get it at all cost, and its use despite obvious, serious health- and life-threatening consequences. For many persons addiction became a chronic disease, with relapses occurring even after long abstinence periods. The development of addiction and emergence of craving is connected with direct disturbance of one of large functional brain systems, the reward system, while indirectly it impairs also remaining systems – arousal system, especially its part related to emotions, and cognition system.

Functional systems of the brain

Behavior of mammals (and presumably lower animals) is a resultant of action of three large functional systems of the brain: arousal, reward and cognition system. These systems are closely interconnected and are necessary for proper functioning of the organism in the environment. They all are also engaged in the development of drug addiction and drug seeking behavior. The cognitive system is often the ultimate victim of addiction, as in several cases of chronic drug addiction cognitive impairments of various type ensue. The discussion of the involvement of cognitive system in addiction is, however, beyond the scope of this review.

Arousal system

The brain must be aroused to play its most essential function: to adapt the organism to the environment in order to secure its life and reproduction. The basic arousal system regulates waking and sleeping. There is a variety of awaking states, and definition of wakefulness still remains controversial. Yet wakefulness is a useful term, though it embraces a number of different states of nervous activity, connected with excitation of diverse anatomical and functional subsystems.

The arousal system comprises three tightly connected subsystems: general, directed, and peripheral. The anatomical basis for the subsystem responsible for general arousal, constituting the basis for regulation of the central nervous system excitability, is the ascending reticular system [115]. The subsystem of directed or goal-oriented arousal is concerned with motivations and emotions and the brain structures involved are the hypothalamus and the structures of the limbic system, proposed by Papez [85]. The further studies extended the number of structures regarded as constituents of the limbic system. The most important anatomical structures involved in emotions are the prefrontal cortex and amygdala [25]. The third subsystem links the brain with the periphery: this is the system of peripheral arousal, which enables the interaction of the central nervous system with peripheral organs both through the autonomic nervous system and hormonal systems *via* the hypothalamus [97]. This system is necessary for expression of emotional states.

When drug addiction is concerned, the most involved is the system of directed arousal. It provides cortical responses with emotional quality, such as anxiety or curiosity, anger, pleasure, aversion, etc. Existence of the system of directed arousal implies the existence of the mechanism governing a choice of appropriate goals, which initiates behavioral reactions necessary to attain these goals and which signals that the goals have been attained. If these goals are important for subject's survival or for increasing its reproductive success, such behavioral reactions should be reinforced by proper reward. If they are not beneficial, they should be inhibited in the future by proper punishment. The behavior is thus regulated by the special reward system.

Reward system

The reward system, which can "praise what is good and punish what is wrong" was discovered at the beginning of the fifties. Earlier experiments on the influence of electrical stimulation of different brain structures on cognitive functions prompted James Olds and his postgraduate student Peter Milner to examine the effect of electrical stimulation on learning. Olds wanted to examine whether stimulation of the reticular substance could facilitate learning. Due to technical mistake, probably a bending of the stimulation electrode during its insertion, it landed quite far from its destination, in the hypothalamus. It appeared that the animal evidently enjoyed passing the current and willingly returned to the experiment. Olds and Milner modified the experiment in this way that a rat could deliver itself the current by pressing a lever located in the cage [67]. This self-stimulation was particularly pronounced when electrodes were placed in certain brain regions [83]. At the same time, Delgado et al. [26] showed that activation of some brain structures in the cat produced vigorous escape responses and appeared to have strongly aversive effects. At present, we know fairy precisely the map of pleasure--affording regions of the brain [82]. The pleasure centers are connected mostly with the ascending dopaminergic and noradrenergic projections in the median forebrain bundle [39] and the terminals in the prefrontal cortex [77], the seats of mechanisms of directed stimulation, and regions responsible for general arousal. On the other hand, aversive centers are located mainly in the periventricular system, and are modulated by GABA and serotonin [45].

Electrical self-stimulation has been later described in many vertebrates, beginning from goldfish, across guinea-pigs, dogs, cats to dolphins, monkeys and humans. The places, stimulation of which produced aversive sensations, have also been identified [84]. Humans can report quality of their experiences. Stimulation of the sites evoking pleasure elicited general feeling of bliss, happiness and unusual well-being. Stimulation of aversive sites caused a feeling of anxiety, approaching danger, isolation and abandonment.

There are numerous bliss centers, and stimulation of different centers appears to generate different feelings. If electrodes are placed simultaneously in several brain regions and a rat can choose the stimulation site, it changes them frequently, switching from one to another. Also, animal's condition can modify its preferences: a hungry rat stimulates other regions than a thirsty one.

Under normal conditions, the reward system obviously is not stimulated by electric current but by appropriate neurotransmitters. Stimulation of this system depends on the action of catecholamines, particularly dopamine, and of serotonin, while opioid peptides exert modulatory effects. Addiction-forming substances can stimulate release of certain neurotransmitters or mimic their action at the receptor level in the reward system.

The reward system is engaged in all basic types of behavior: food and water intake, sexual activity, aggression, etc. A decrease in blood glucose level, induced by food deprivation, causes hunger, which strongly motivates an animal to seek food, since in this state eating strongly stimulates the reward system, and becomes pleasurable. Certain ionic changes, induced by lack of drinkable liquids, cause thirst, which in the same way motivates an animal to seek water. However, when an animal has consumed enough food, a satiety center suppresses the reward system connected with feeding, and when thirst is satisfied, stimulating effect of drinking on the reward system is inhibited. Also sexual drive stimulates the reward system only to certain extent, so after sexual activity, assuring reproductive success, pleasure disappears. Subtleness of such regulation is illustrated by Coolidge's effect, showing that a male not attempting to copulate again with the same female, readily copulates with a new partner, which certainly increases his chance for reproductive success [1].

Aggression is associated with the reward system as well [6]. It has to give pleasure since it occurs in spite of its dangerous consequences, and if it did not bring about such pleasure, aggressive behavior, anyhow very helpful in struggle for existence and finding sexual partner, would be uncommon. However, excessive, uncontrolled aggression is blocked by pain caused by victim's reaction to aggression. If an aggressor meets a stronger individual, aggression disappears. Even a very aggressive dog usually flees after welting.

Precisely because the reward system is composed of pleasure and punishment systems, it can function efficiently, and seeking a pleasure does not hinder natural adaptation to the environment. Unfortunately, similarly as most of systems in living organisms, particularly in humans, the reward system can be a subject to disturbances. Such lack

of balance is accompanied by behavioral disturbances: bulimia or anorexia, psychosexual disturbances or excessive aggressiveness.

The reward system can be stimulated by certain psychotropic substances. It appears that mere seeking pleasurable drugs, which stimulate reward system, is not an aberrant behavior, and even can have adaptive value. Only when drug addiction occurs it can be considered the reward system disease.

Dopamine and reward system

It is unquestionable at present that dopamine plays the key role in motivational behavior and addiction. Dopaminergic theory of reward has been challenged many times but a general role of dopamine in the reward system was never denied altogether. It has been reviewed in an excellent recent article by Kostowski [68].

Dopaminergic theory was put forward when the structures which could be electrically self-stimulated were shown also to be sensitive to dopamine [47], and mesencephalic dopaminergic system, beginning in the ventral tegmental area and sending its projections to the limbic system structures, especially to the shell of the nucleus accumbens and prefrontal cortex, was assumed to be the anatomical basis of the reward system [129]. Synaptic dopaminergic transmission in the nucleus accumbens septi increases as well during natural rewarding actions, such as feeding, drinking, sexual activity as after the administration of substances inducing addiction [31, 93]. It is believed that chronic administration of such substances evokes long-term adaptive changes in dopaminergic transmission, leading both to disturbance and desensitization of the reward system to some drug effects [66], and its sensitization to the others [102].

Till mid nineties, an opinion prevailed that rewarding activity was connected with direct stimulation of dopamine release by a drug or satisfaction-affording behavioral stimulus. However, recently it has been noticed that dopamine is released rather in the first phase of the contact with reward. Schultz [106] observed that although dopamine release increased during pleasurable activities, it was high mainly at the beginning, when pleasurable experience was anticipated. Unexpected reward causes strong dopaminergic stimulation, which diminishes upon repetition and learning, until reward presentation does not evoke dopaminergic stimulation. On the contrary, the lack of expected reward causes reduction of dopaminergic signal. It suggests that response of mesencephalic dopaminergic neurons is a sign of learning, encoding anticipated error in the expectation of a reward [50].

An alternative theory, called “switch hypothesis”, was postulated by Redgrave et al. [98]. This hypothesis assumes that dopaminergic signal detects unexpected but salient events, including but not limited to a reward. Therefore, dopaminergic system would be significant for associative learning, not necessarily connected with evoked pleasure. Indeed, it was shown that dopaminergic system of the nucleus accumbens was stimulated during learning [120].

Another hypothesis, fairly similar in general, was proposed by Di Chiara [30]. It attributes an important role in reward-associated learning processes to mesolimbic dopaminergic transmission, and suggests that drug addiction is a disease of dopamine-related associative learning. Di Chiara postulates that associative learning and activation of dopaminergic neurons evoked by natural rewarding factors, are different from abnormal associative learning and dopaminergic activity induced by drugs of abuse. According to this hypothesis, dopaminergic activation in the nucleus accumbens septi by natural events is subject to habituation. On the other hand, addiction-forming drugs produce effects that are not subject to habituation, which causes non-adaptive, and even progressively enhanced dopamine release after repeated administration of addictive drugs. These neurochemical consequences of addictive drugs would strengthen association between a salient stimulus and reward, which could be the basis for drug-seeking behavior.

All these theories confirm the hypothesis developed by Di Chiara and North as early as in 1992 [32], suggesting that reward consists of two phases: the incentive phase, in which a pleasure is anticipated, and the consummatory phase, involving experience of a pleasurable stimulus. It appears that dopamine contribution dominates in the first phase. Our common human experience indicates that waiting for the expected reward may be equally, if not more, pleasurable than the reward itself (*catching a bunny is not important, what matters is chasing it*). Universal significance of anticipation is confirmed by sexual behavior: most animals, including certain invertebrates, engage in prolonged nuptial rituals before copulation. In all human so-

cieties, pleasure connected with flirting is highly appreciated.

The fact that reward associated with the anticipation of pleasure is very high can explain a number of aspects of addiction, particularly craving induced by cues related with drug use (watching films showing crack smoking, by cocaine abusers or inspecting paraphernalia for drug use, e.g. pipe collection by a smoker).

Dopamine receptors undoubtedly play a crucial role in rewarding behaviors, and abnormal seeking of the objects that stimulate the reward system. Behaviors such as gluttony, hypersexuality, gambling, risky behavior or, finally, taking addiction-forming drugs, may be a compensation for congenital underdevelopment of the reward system, which has to be stimulated stronger to afford the normal level of well-being. Such deduction may be substantiated by a large body of evidence, and the most recent and convincing of them has indicated that methylphenidate evoked feeling of pleasure in those subjects (not drug abusers) whose D2 dopamine receptor level in the brain was low, while in those with high level of D2 dopamine receptor, intravenous administration of methylphenidate was aversive [124].

It should be noted that, possibly, dopamine is not the only neurotransmitter engaged in rewarding behavior and addiction, since it was shown that in mutant dopamine-transporter knockout mice, whose synaptic dopamine level was much higher in comparison with normal animals, and which exhibited hyperactive behavior, cocaine still evoked addiction (mice self-administered cocaine) despite that obviously nonexistent dopamine transporter could not be further blocked [103]. As cocaine influences also serotonin transporter, this implicates that serotonergic system also contributes to the development and maintenance of addictions.

CART peptides

New prospects to approach the problems related to the mechanism of drug addiction and even searching the methods for their control, opened after discovery of specific neuropeptides, termed CART peptides [70].

In 1995, Douglass et al. detected a unique mRNA in the rat striatum, whose expression increased five times after the administration of psychostimulants, cocaine and amphetamine [35]. These transcripts were named CART (cocaine- and amphetamine-regulated transcripts), and the peptides encoded by them were designated CART peptides. The presence of CART was demonstrated in different regions of the rat brain and in endocrine organs, but CART expression increased after psychostimulant treatment only in the striatum. Following the preparation of appropriate cDNA, CART protein was cloned, and the presence of both the peptide and its fragments was demonstrated in the rat neurons by immunohistochemical methods. CART, CART cDNA and CART proteins have also been discovered in humans, and a part of human CART responsible for encoding the propeptide showed 95% homology with rat CART [53]. At present, CART peptides are believed to reside in certain groups of neurons in the brain.

A rise in CART expression after psychostimulant treatment suggests that they can be associated with the reward system and processes implicated in drug addiction. Location of the neurons containing CART peptides, which appear to be secreted by neurons, indicates their extensive physiological functions: they seem to play a role in feeding, stress, processing of sensory data, regulation of central autonomic functions [70]. Contribution of CART peptides to rewarding behavior and addictions was supported by their distribution in the nucleus accumbens, ventral tegmental area and amygdala. As CART peptides were also found in the myenteric plexus, they may be classified as brain-gut peptides [20].

The first physiological role ascribed to CART peptides consisted in the inhibition of feeding [69, 71]. Intracerebroventricular administration of active CART 89-103 peptide fragment was reported later not only to inhibit feeding but also to intensify fear reactions in the elevated plus maze test. These results suggest that CART proteins can be endogenous regulators of stress effects on appetite [58].

The studies providing a direct proof of a possible role of CART proteins in addiction have been conducted recently. They demonstrated that a single administration of CART 55–102 peptide fragment (that occurs naturally) into the ventral tegmental area elevated locomotor activity of rats, while its fourfold administration evoked strong place preference, indicating its reinforcing properties. In contrast to the action of exogenous rewarding stimuli, CART protein-induced locomotor effects did not show sensitization or tolerance. They did not cause sensitization to amphetamine and co-

caine, and *vice versa*, neither cocaine nor amphetamine evoked sensitization to CART proteins. CART effect appears to be associated with the stimulation of the reward system, since their administration into the substantia nigra did not elicit any changes in locomotor activity [61].

An interesting aspect of CART physiology is the existence of gender differences in CART expression. Under natural conditions CART mRNA expression in the nucleus accumbens septi in males is higher than in females, but after several cocaine doses CART expression increases in the amygdala of males but not females, while in the nucleus accumbens septi the situation is opposite. These results may shed new light on gender differences in addiction and drug abuse [37, 53].

The important feature of CART peptides and their analogues is their ability to cross rapidly the blood-brain barrier [59]. It appears that future studies will be focused on searching for low molecular weight agonists and antagonists of CART peptides that might find their place in clinical practice as agents of addiction control and treatment of reward system deficits leading to bulimia or anorexia.

Moreover, the discovery of CART proteins can change our views on the mechanism of rewarding action of psychostimulants.

Craving

Craving, the compulsive desire to seek for and take a drug, is a complex phenomenon present in addicted animals or humans. It can appear after withdrawal from drug use [38], which leads to a depression of the activity of dopaminergic system that may evoke a feeling of anhedonia [65], or it can develop in drug-free addicts in response to a single drug administration (priming effect) [56] or to signals presaging this possibility (cue-induced craving) [15, 36]. Activation of dopaminergic system was observed both following addictive drug administration [117] and presentation of cues associated with drug use to addicted animals [33, 64]. Therefore, craving can be induced equally well by excessive and by insufficient dopaminergic stimulation. It can be evoked by agonists conveying dopaminergic signals and antagonists such as neuroleptics, despite that the latter block cocaine seeking behavior [99, 126] and elicit dysphoria [51], thus being reluctantly taken by the patients.

Craving is the main cause of relapse among drug addicts and its control is a goal of the present-day pharmacotherapy of drug addiction and will be discussed in the next part of this review.

Studies on addiction liability

Addiction liability can be studied in animal models since the mechanisms of addiction are universal, and the results can easily be adopted for humans. If any substance evokes addiction in a rat or mouse, we can be almost sure that it will be liable to produce addiction in humans as well.

Animal studies can employ indirect methods, the most commonly used being: investigation of place preference (a rat prefers the place in a cage associated with previously experienced pleasure) and facilitation of electric self-stimulation (activation of rewarding centers increases the pleasure of self-stimulation of the brain with electric current, and produces responses even at so weak currents that the control animals do not react to them). These methods were described in literature in detail [119, 122].

It seems that addiction liability or the effectiveness of agents alleviating craving in drug addicted individuals can be easily examined in humans. As mentioned above, simple watching video tapes which show cocaine taking evokes symptoms of craving in cocaine addicts, and physiological correlates of these symptoms are easily measurable [15, 36]. This model can enable to assess the degree of addiction and whether the proposed pharmacological treatment increases or decreases cue-induced drug craving.

Direct investigation of addiction liability involves determination if an animal self-administers a substance upon the free choice paradigm. When orally taken substances are tested, an animal chooses between a bottle with a solution of the tested substance and a control liquid (in this way alcohol preference is tested: an animal has an access to a bottle with water and the one with alcohol, and the consumed volumes of both liquids are measured and compared).

In other tests, an animal is introduced to an apparatus provided with a lever or a switch which after activation starts an infusion pump, which delivers appropriate amount of a solution of the tested substance [119]. The substance is most frequently administered by the intravenous catheter, but a si-

milar device can be used either to opening the access to the container with the substance to be taken orally, or to administer the substance under examination into the brain ventricles or structures to elucidate anatomical targets of addictive substance action.

Anatomical targets of addictive substances

The reward system comprises a number of brain structures, and self-stimulation can be initiated after activation of many regions [82]. Nevertheless, an essential role in addiction process has been ascribed to the mesolimbic dopaminergic system, encompassing the ventral tegmental area, where dopaminergic neurons projecting to the nucleus accumbens septi and prefrontal cortex are located.

The nucleus accumbens, which is a heterogenous structure, can be considered a switch between emotional and locomotor systems. The cells of its ventromedial region, called the shell, and believed to constitute a part of the extended amygdala, project more strongly to the ventral tegmental area, whereas the cells of the more dorsal and lateral region of the amygdala, the so-called core, projects more strongly to the zona compacta of the substantia nigra [132]. The D2 receptors are highly expressed in the shell while D3 receptors are more abundant in the core [73].

Despite the fact that final rewarding effect is connected with an elevation of dopamine release in the nucleus accumbens [cf. 68], different parts of the limbic system seem to be a target of addictive drug action. It was demonstrated upon observation of animals exhibiting a tendency to drug self-administration directly into the abovementioned structures.

Addictive drug actions localized in the ventral tegmental area

The ventral tegmental area is the place, where rewarding actions of morphine are localized [8, 89]. Both μ- and δ-opid receptor agonists exert their reinforcing effects *via* this region [3, 28]. μ-Opioid receptor agonists block GABA receptors located on dopaminergic neurons and cause disinhibition of the latter [57]. Dopaminergic neuron disinhibition results in the increased dopamine release in the nucleus accumbens [29, 75]. Mechanisms of action of δ-opioid receptor agonists still remain unclear, but we know that their rewarding actions are 100-fold weaker than those of μ-receptor agonists. Agonists of κ-opioid receptors, which evoke aversive reactions after peripheral administration, have no effects whatsoever following administration into the ventral tegmental area [78].

Nicotine addiction appears also to be associated with the ventral tegmental area. Nicotine receptors are reportedly located on dopaminergic neurons in this region [16]. Systemic nicotine administration increases dopaminergic neuron firing [76]. Dopamine antagonists injected into the ventral tegmental area inhibit nicotine self-administration [17–19]. As such effect is not caused by neuroleptics administered into the nucleus accumbens [88], the ventral tegmental area is believed to trigger nicotine addiction. Its neurons form synapses with cholinergic neurons of the laterodorsal tegmental nucleus and pedunculopontine nucleus.

Addictive drug actions localized in the nucleus accumbens

The nucleus accumbens is the structure, where the actions of addictive psychostimulants, cocaine and amphetamine, are localized, as upon peripheral administration they elevate dopamine level in this brain region [54, 88, 96]. Studies of various authors have not produced an unequivocal answer whether an increase in dopamine release is dependent on consumption and remains tonically enhanced over whole self-administration period [128], or the release is triggered by anticipation of each consecutive injection [46, 62, 63]. It appears that a part of dopaminergic system activation is associated with consummatory phase, while another part depends on awaiting a reward [9, 10, 14, 107].

It is very interesting that two stimulatory substances believed to have similar mechanisms of action, amphetamine and cocaine, differ with respect to the targets for their addiction-evoking action. Rats readily self-administer amphetamine into the nucleus accumbens [49, 90], while cocaine self-administration is observed only when the drug is given here at high concentrations and for longer periods [43]. Nomifensine, which also blocks dopamine uptake and, similarly as amphetamine, does not possess local anesthetic properties, was self-administered into the nucleus accumbens equally eagerly as amphetamine [11].

Morphine and met-enkephalin are readily self-administered into the nucleus accumbens as well [42, 81], and their actions in this structure seem independent of the effects in the ventral tegmental area. Reinforcing effects of peripheral cocaine and heroin administration are blocked by intra-caudate treatment with pertussis toxin, the substance that blocks G_i and G_o proteins, suggesting the involvement of dopamine D_2 receptor [111, 120].

Besides, phencyclidine and NMDA receptor antagonists, MK-801 and CPP, elicit reinforcing effect after their administration into the nucleus accumbens [12]. As mentioned above, it appears that the shell, and not the core, is a target for all compounds evoking self-stimulation from the nucleus accumbens.

Addictive drug actions in the frontal cortex

The frontal cortex constitutes also a part of the reward system, but in some aspects it differs from the nucleus accumbens. Thus, rats readily self-administer cocaine into the medial region of the frontal cortex, but, as mentioned above, they do not exhibit this tendency when cocaine is administered into the nucleus accumbens [44]. Interestingly, amphetamine has no reinforcing properties in the frontal cortex [41], whereas it is eagerly self-administered into the nucleus accumbens. However, there is no mutual exclusion of these two structures, since phencyclidine, MK-801 and CPP have reinforcing effects both in the prefrontal cortex and nucleus accumbens [12].

Addictive drug actions in the hippocampus

The hippocampal formation has been linked rather with memory processes than addictions, but opioids, morphine and α-dynorphin are readily self-administered by rats into CA3 region of the hippocampus [110, 116].

Addictive drug actions in the pedunculopontine nucleus

Contribution of the pedunculopontine nucleus to addiction-forming processes is corroborated by experiments showing the blockade of morphine- and amphetamine-induced place preference by lesions to this structure [5]. It also seems that cholinergic neurons of this nucleus activate nicotinic receptors on dopaminergic neurons in the ventral tegmental area, which leads to dopamine release [7, 72].

Drug-induced adaptive changes

Dependence on a drug (and also on other rewarding stimuli) can be defined as a condition in which such changes in psyche have occurred that seeking a drug or other rewarding stimulus becomes the main focus of an addict's life. Undoubtedly, dependence develops as a result of adaptive changes evoked by chronic drug use. Exactly these changes lead to the destruction of addicts' personality.

Drug-induced adaptive changes can be divided into two basic categories: sensitization and tolerance.

Initially, tolerance that accompanies the use of a majority of addiction-forming substances, and that consists in progressively weaker drug action, including diminishing the rewarding effect, was believed to play the primary role in drug addiction. However, currently it is assumed that sensitization, i.e. enhancement of the response to consecutive drug doses, is equally, if not more important. Sensitization is evoked by many psychostimulants (cocaine, amphetamine, and also nicotine), and the way of drug administration is crucial for its development [101]. Sensitization could be responsible for priming effect, i.e. drug craving induced in a drug-free addict by a single drug dose.

Problems connected with tolerance have been detailed elsewhere [122]. Tolerance is defined as a need to increase drug doses to experience the same reaction. Tolerance can develop not only in response to addictive substances, since pharmacokinetic and metabolic tolerances are important categories of tolerance as well. One of the causes of tolerance is enzymatic induction, due to which a drug is eliminated more rapidly from the organism, and even when its maximum effect remains unchanged, its total effect is weaker, as it acts for a shorter period of time. Out of addictive substances capable of evoking enzymatic induction, barbiturates, certain tranquillizers, such as meprobamate, and nicotine should be mentioned.

It is also necessary to mention pharmacokinetic sensitization, causing progressively stronger drug action as it continues to be used. It is connected with liver damage and impairment of drug metabolism. Ethanol is the most commonly known sub-

stance which can elicit this phenomenon. Due to liver damage, an alcoholic metabolizes ethanol less efficiently and intoxication can be caused by lower alcohol doses, and lasts longer. Pharmacokinetic sensitization has entirely different basis than the sensitization mentioned earlier, which is associated with elevated reactivity of dopaminergic system.

Functional, i.e. pharmacodynamic tolerance is another type of tolerance. This tolerance can be acute or chronic. Three mechanisms are believed to be involved: rapid desensitization, linked with receptor phosphorylation, internalization of the receptor, and induction of genomic changes leading to a decrease in the rate of synthesis of receptor and in synthesis of defective forms of the receptor.

Some addiction-forming substances cause very quick development of tolerance. Benzodiazepines, barbiturates, nicotine and alcohol can be included into this category. It is sometimes connected with tachyphylaxis caused by receptor occupancy or depletion of neurotransmitter stores, due to drug-induced neurotransmitter release.

Chronic administration of addictive substances leads to slow, but much longer-lasting tolerance. An array of adaptive changes occur in an organism trying to preserve homeostasis. The mechanisms involved can be very diverse. As mentioned earlier, they can embrace receptors, their coupling with G proteins and second messengers-generating enzymes, membrane channels, intracellular calcium distribution, and genomic changes. As a result of adaptation, and in spite of permanent presence of a drug attacking its structures, an organism functions almost normally, compensating for drug effects.

To assess a degree of tolerance, the tolerance index was introduced. It is defined as a ratio of a drug dose acting in an animal with full tolerance to a dose evoking the same response in an animal coming into contact with a drug for the first time. The tolerance index of LSD and other hallucinogens, and also some opioids, was estimated at 10–100 while the respective value for pentobarbital is 2–3. Tolerance to LSD also develops rapidly [125].

Development of tolerance to a drug is a complex phenomenon, and environmental factors play an important role in this process, which can be experimentally demonstrated not only in humans but also in laboratory rodents. Tolerance development and degree can depend for example on whether an animal is tested in the cage in which it was administered the drug or in another place. A number of experiments of Siegel showed that development of tolerance to antinociceptive morphine action in rats or morphine abstinence effects in mice were dependent on the environment where the drug was given and the tests were performed [4, 48, 113]. For instance, rats that received morphine for four days and were tested for antinociceptive response in the same cage developed tolerance to antinociceptive drug effect. However, if fourth drug dose was administered in another environment, antinociceptive morphine action was much stronger [114].

Furthermore, the fact whether the test is performed under drug influence or not, can be consequential during tolerance development. Carlton and Wolgin [13] examined anorexic effect of amphetamine in starving rats, which were allowed only short access to food during the day. If amphetamine was administered before food availability, tolerance to anorexic action developed over four days. However, if amphetamine was given after feeding, the drug administration on fifth day before feeding evoked full anorexic effect.

Similar dependence on the schedule of drug administration was observed for LSD-induced disruption of operant behavior [79].

The significance of environmental conditions for development of amphetamine-induced tolerance and sensitization has been discussed by Wolgin [130]. If environmental factors play such critical a role in animals, unquestionably they can be even more crucial in humans.

Physical dependence

Dependence was believed to be one of the consequences of tolerance development. Physical dependence is characterized by emergence of specific behavioral syndrome and symptoms following sudden discontinuation of drug administration in animals and humans who previously had been under its chronic influence, or after the treatment of an addicted individual with an addictive drug antagonist. It is undeniably the result of activation of homeostatic mechanisms, responsible for tolerance development, which in this situation miss their aims without inhibition by the drug.

It should be noted that symptoms of drug withdrawal can be observed also in the case of drugs, with no addiction liability, and even those exerting

aversive action. For example, abstinence symptoms were reported after chronic neuroleptics administration [2, 34].

Tolerance and physical dependence are particularly dangerous aspects of action of some drugs since:

1. When tolerance begins to develop, progressively higher drug doses are required to obtain the same therapeutic effect, which accelerates tolerance development leading to the vicious circle effect.

2. Abstinence symptoms are aversive, unpleasant for the patient, who starts to seek a drug not for its direct rewarding action but to avoid disagreeable abstinence symptoms.

3. Long-term use of addiction-forming drugs evokes so called chronic tolerance, connected with permanent changes in the brain, which lead to drug abuse relapse after detoxification, and constitute a personality trait that predisposes an addict to seeking a comforting drug.

The degree of physical dependence is different for different addictive substances. Opioids, ethanol, barbiturates and anxiolytics evoke relatively strong physical dependence. Cannabinoids cause rapid tolerance development but weak physical dependence. Hallucinogens, such as LSD, despite the rapid tolerance, elicit no physical dependence. Also, amphetamine withdrawal does not cause physical abstinence signs.

It appears that strong abstinence symptoms are observed after withdrawal from chronic use of those addiction-forming substances which inhibit neuronal activity: opioids do that by increasing potassium ion influx and decreasing calcium ion influx into neurons, while barbiturates and anxiolytics enhance GABAergic transmission, and elevate chloride ion influx. The abovementioned inhibitory systems are interspersed throughout the central nervous system, thus no wonder that the disturbance of their function causes very complex and diverse abstinence symptoms. It seems that clinically important kinds of physical dependence are associated with brain effort to adapt central inhibitory processes.

Psychical dependence

Substances which elevate stimulatory neurotransmitter actions do not cause strong physical dependence, inducing, however, very potent psychical dependence.

Dysphoria after drug withdrawal is caused by depression of the reward system. It was first reported by Leith and Barrett [74], who reported that electric stimulation of the brain was less effective after withdrawal from chronic amphetamine administration. It was later confirmed by Wise and Munn [127], and similar effect was observed following ethanol withdrawal [105]. Dackis and Gold [23] were the first who postulated that this was an effect of the decreased dopamine level, which was further substantiated by the studies into cocaine [55, 86, 100, 104], amphetamine [87, 104], opiate [94, 104] and alcohol [104] action using microdialysis technique.

This approach differs from that adopted earlier, which linked dependence with abstinence symptoms and the whole constellation of accompanying aversive effects. A decrease in dopaminergic activity after drug withdrawal is a phenomenon common for a variety of addictive substances, such as stimulants, opioids, alcohol, nicotine, evoking diverse, sometimes negligible symptoms upon withdrawal.

The mode of drug intake – active or passive – may be critical for the biochemical and behavioral consequences. It is a common observation that people treated with morphine as an analgesic and receiving it according to the doctor-controlled schedule develop morphine-dependence much more rarely than persons actively self-administering morphine for recreational purposes. The studies on the effect of ethanol in rats demonstrated that the effects of the drug in rats actively working for alcohol reward were different than those in yoked controls (cf. [68]).

Pharmacological history can also influence dependence development, which is authenticated by the fact that animals previously receiving addictive substances learn more quickly to self-administer drugs than those which never encountered them earlier [52, 91].

A growing number of studies have focused on a role of stress in triggering drug abuse [92, 112]. Stress plays a crucial and complex role in drug self-administration and self-administration reinstatement. Relapse and violent craving can be initiated both in animals and humans by a stressful stimulus, and it can be blocked by CRF administration [108]. The mechanism of stress-induced craving attack differs from the mechanism of relapse precipitation by priming effect or drug-associated cues, as the former engages noradrenergic system [118].

Recently, molecular biology techniques have been employed in the studies of drug addiction.

Addictive drug-induced secondary messenger responses [109], self-administration effect on the expression of early response genes coding for neurotransmitter receptors [80], and the influence of antisense nucleotides on the action of addictive substances [40, 60, 95] have been investigated from mid nineties. The forecasts presaging a surge in cellular neurobiological studies of drug addiction [24, 109] has proven fully correct.

Addiction and heredity

The hereditary base for drug addiction has been hypothesized long ago, and breeding strains of rats preferring or avoiding alcohol (cf. [68]) confirms this notion. However, in humans it was difficult to ascertain whether environmental and family factors were indeed consequential. Especially in alcoholic environments, drinking could be regarded as a cultural pattern, not connected directly with heredity. Only in the last decade, the role of inherited factors has been proven with certainty as a result of intensive examination of twins and families.

High variability of dopamine D2 receptor in the human brain is certainly determined genetically. Individual differences in vulnerability to addiction are based, *inter alia*, on variations in the activity of dopaminergic neurotransmission, which partly can be attributed to genetic differences. It has been shown that in white population, Taq1A1 and B1 markers of restriction length fragment polymorphisms (RLFP) of D2 receptor gene are linked with vulnerability to drug addiction, and their incidence is higher in alcoholics and addicts abusing several drugs (polyusers), especially those who prefer cocaine and amphetamine [121]. It can be expected that dopamine receptor expression is weaker in the subjects bearing the gene with these polymorphism, which, as mentioned above, can be associated with higher sensitivity to rewarding drug action [124].

Individual differences in vulnerability to addiction-forming drugs are graded, and the genes responsible for the strength of tendency toward drug addiction are minor genes. Their loci were called quantitative trait loci (QTL). Therefore, QTL are such loci in which the genes connected with phenotypic differences in vulnerability are located. Although individual QTL have slight effect, their groups can be responsible for genetic determinants of addiction.

Over the last decade, a number of specific loci have been identified, that regulate different aspects of drug response: initial sensitivity, tolerance and sensitization development. In mid nineties, 50 loci potentially involved in the regulation of response to alcohol, morphine, NO, amphetamine and haloperidol were identified using recombinant inbred mice [21]. Although initially many results were suspected to be falsely positive, in the last years, loci responsible for 24 responses to addictive substances, mainly alcohol, cocaine and barbiturates, were established beyond any doubt [22].

Discovery of QTL not necessarily has to conclusively resolve whether indeed a gene responsible for certain trait (e.g. morphine preference) resides in these loci, since QTL may constitute a regulatory sequence, which modifies expression of other functional genes. If unknown genes are to be discovered on the basis of their expression, it is necessary to review all mRNA transcripts to determine, which genes are induced or repressed by a drug. These genes can be cloned, sequenced and identified by comparison with the sequences already published in databases. Such identification can be performed by differential display method. This method was applied to identify the abovementioned CART gene encoding new neuropeptide, induced by cocaine and amphetamine [35]. Identification of the genes implicated in drug addiction will certainly be facilitated by the technology involving automatic preparation of micromatrices called DNA chips [27].

REFERENCES

1. Ago A.: Sexual motivation – an inquiry into events determining the occurrence of sexual behavior. Behav. Brain Res., 1999, 105, 129–150.
2. Amore M., Zazzeri N.: Neuroleptic malignant syndrome after neuroleptic discontinuation. Prog. Neuropsychopharmacol. Biol. Psychiat., 1995, 19, 1323–1334.
3. Bals-Kubik R., Ableitner A., Herz A., Shippenberg T.S.: Neuroanatomical sites mediating the motivational effects of opioids as mapped by the conditioned place preference paradigm in rats. J. Pharmacol. Exp. Ther., 1993, 264, 489–495.
4. Baptista M.A., Siegel S., MacQueen G., Young L.T.: Pre-drug cues modulate morphine tolerance, striatal c-Fos, and AP-1 DNA binding. NeuroReport, 1998, 9, 3387–3390.
5. Bechara A., Van der Kooy D.: The tegmental pedunculopontine nucleus: a brain-stem output of the limbic system critical for the conditioned place preferences

produced by morphine and amphetamine. J. Neurosci., 1989, 9, 3400–3409.
6. Berkowitz L.: Some determinants of impulsive aggression: role of mediated associations with reinforcements for aggression. Psychol. Rev., 1974, 81, 165–176.
7. Blaha C.D., Allen L.F., Das S., Inglis W.L., Latimer M.P., Vincent S.R., Winn P.: Modulation of dopamine efflux in the nucleus accumbens after cholinergic stimulation of the ventral tegmental area in intact, pedunculopontine tegmental nucleus-lesioned, and laterodorsal tegmental nucleus-lesioned rats. J. Neurosci., 1996, 16, 714–722.
8. Bozarth M.A., Wise R.A.: Intracranial self-administration of morphine into the ventral tegmental area in rats. Life Sci., 1981, 28, 551–555.
9. Carelli R.M., Deadwyler S.A.: A comparison of nucleus accumbens neuronal firing patterns during cocaine self-administration and water reinforcement in rats. J. Neurosci., 1994, 14, 7735–7746.
10. Carelli R.M., King V.C., Hampson R.E., Deadwyler S.A.: Firing patterns of nucleus accumbens neurons during cocaine self-administration in rats. Brain Res., 1993, 626, 14–22.
11. Carlezon W.A. Jr., Devine D.P., Wise R.A.: Habit-forming actions of nomifensine in nucleus accumbens. Psychopharmacology, 1995, 122, 194–197.
12. Carlezon W.A. Jr., Wise R.A.: Rewarding actions of phencyclidine and related drugs in nucleus accumbens shell and frontal cortex. J. Neurosci., 1996, 16, 3112––3122.
13. Carlton P.L., Wolgin D.L.: Contingent tolerance to the anorexigenic effects of amphetamine. Physiol. Behav., 1971, 7, 221–223.
14. Chang J.Y., Sawyer S.F., Lee R.S., Woodward D.J.: Electrophysiological and pharmacological evidence for the role of the nucleus accumbens in cocaine self-administration in freely moving rats. J. Neurosci., 1994, 14, 1224–1244.
15. Childress A., Ehrman R., McLellan A.T., O'Brien C.: Conditioned craving and arousal in cocaine addiction: a preliminary report. NIDA Res. Monogr., 1988, 81, 74–80.
16. Clarke P.B.S., Pert A.: Autoradiographic evidence for nicotine receptors on nigrostriatal and mesolimbic dopaminergic neurons. Brain Res., 1985, 348, 355–358.
17. Corrigall W.A., Coen K.M.: Selective dopamine antagonists reduce nicotine self-administration. Psychopharmacology, 1991, 104, 171–176.
18. Corrigall W.A., Coen K.M., Adamson K.L.: Self-administered nicotine activates the mesolimbic dopamine system through the ventral tegmental area. Brain Res., 1994, 653, 278–284.
19. Corrigall W.A., Franklin K.B.J., Coen K.M., Clarke P.: The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine. Psychopharmacology, 1992, 107, 285–289.
20. Couceyro P., Paquet M., Koylu E., Kuhar M.J., Smith Y.: Cocaine- and amphetamine-regulated transcript (CART) peptide immunoreactivity in myenteric plexus neurons of the rat ileum and co-localization with choline acetyltransferase. Synapse, 1998, 30, 1–8.
21. Crabbe J.C., Belknap J.K., Buck K.J.: Genetic animal models of alcohol and drug abuse. Science, 1994, 264 1715–1723.
22. Crabbe J.C., Phillips T.J., Buck K.J., Cunningham C.L., Belknap J.K.: Identifying genes for alcohol and drug sensitivity: recent progress and future directions. Trends Neurosci., 1999, 22, 173–179.
23. Dackis C.A., Gold M.S.: New concepts in cocaine addiction: the dopamine depletion hypothesis. Neurosci. Biobehav. Rev., 1985, 9, 469–477.
24. Daunais J.B., Roberts D.C.S., McGinty J.F.: Short--term cocaine self administration alters striatal gene expression. Brain Res. Bull., 1995, 37, 523–527.
25. Davidson R.J., Irwin W.: The functional neuroanatomy of emotion and affective style. Trends Cogn. Sci., 1999, 3, 11–21.
26. Delgado J.M.R., Roberts W.W., Milner N.: Learning motivated by electrical stimulation of the brain. Amer. J. Physiol., 1954, 587–593.
27. DeRisi J.L., Iyer V.R., Brown P.O.: Exploring the metabolic and genetic control of gene expression on a genomic scale. Science, 1997, 78, 680–686.
28. Devine D.P., Leone P., Pocock D., Wise R.A.: Differential involvement of ventral tegmental mu, delta, and kappa opioid receptors in modulation of basal mesolimbic dopamine release: in vivo microdialysis studies. J. Pharmacol. Exp. Ther., 1993, 266, 1236–1246.
29. Devine D.P., Wise R.A.: Self-administration of morphine, DAMGO, and DPDPE into the ventral tegmental area of rats. J. Neurosci., 1994, 14, 1978–1984.
30. Di Chiara G.: A motivational learning hypothesis of the role of mesolimbic dopamine in compulsive drug use. J. Psychopharmacol., 1998, 12, 54–67.
31. Di Chiara G., Imperato A.: Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc. Nat. Acad. Sci. USA, 1988, 85, 5274–5278.
32. Di Chiara G., North R.A.: Neurobiology of opiate abuse. Trends Pharmacol. Sci., 1992, 13, 185–193.
33. Di Ciano P., Blaha C.D., Phillips A.G.: The relation between dopamine oxidation currents in the nucleus accumbens and conditioned increases in motor activity in rats following repeated administration of d-amphetamine or cocaine. Eur. J. Neurosci., 1998, 10, 1113––1120.
34. Dixon L., Thaker G., Conley R., Ross D., Cascella N., Tamminga C.: Changes in psychopathology and dyskinesia after neuroleptic withdrawal in a double-blind design. Schizophr. Res., 1993, 10, 267–271.
35. Douglass J., McKinzie A.A., Couceyro P.: PCR differential display identifies a rat brain mRNA that is transcriptionally regulated by cocaine and amphetamine. J. Neurosci., 1995, 15, 2471–2481.
36. Ehrman R.N., Robbins S.J., Childress A.R., O'Brien C.P.: Conditioned responses to cocaine-related stimuli

in cocaine abuse patients. Psychopharmacology, 1992, 107, 523–529.
37. Fagergren P., Hurd Y.L.: Mesolimbic gender differences in peptide CART mRNA expression: effects of cocaine. NeuroReport, 1999, 10, 3449–3452.
38. Fuller R.K., Hiller-Sturmhofel S.: Alcoholism treatment in the United States. An overview. Alcohol Health Res. World, 1999, 23, 69–77.
39. Gallistel C.R.: The role of the dopaminergic projections in MFB self-stimulation. Behav. Brain Res., 1986, 22, 97–105.
40. Gawin F.H., Kleber H.D.: Abstinence symptomatology and psychiatric diagnosis in cocaine abusers. Clinical observations. Arch. Gen. Psychiat., 1986, 43, 107–113.
41. Goeders N.E., Dworkin S.I., Smith J.E.: Neuropharmacological assessment of cocaine self-administration into the medial prefrontal cortex. Pharmacol. Biochem. Behav., 1986, 24, 1429–1440.
42. Goeders N.E., Lane J.D., Smith J.E.: Self-administration of methionine enkephalin into the nucleus accumbens. Pharmacol. Biochem. Behav., 1984, 20, 451–455.
43. Goeders N.E., Smith J.E.: Cortical dopaminergic involvement in cocaine reinforcement. Science, 1983, 221, 773–775.
44. Goeders N.E., Smith J.E.: Reinforcing properties of cocaine in the medial prefrontal cortex: primary action on presynaptic dopaminergic terminals. Pharmacol. Biochem. Behav., 1986, 25, 191–199.
45. Graeff F.G., Brandao M.L., Audi E.A., Schutz M.T.L.: Modulation of the brain aversive system by GABAergic and serotonergic mechanisms. Behav. Brain Res., 1986, 22, 173–180.
46. Gratton A., Wise R.A.: Drug- and behavior-associated changes in dopamine-related electrochemical signals during intravenous cocaine self-administration in rats. J. Neurosci., 1994, 14, 4130–4146.
47. Hall R.D., Bloom F.E., Olds J.: Neuronal and neurochemical substrates of reinforcement. Neurosci. Res. Program Bull., 1977, 15, 131–134.
48. Hinson R.E., Siegel S.: Anticipatory hyperexcitability and tolerance to the narcotizing effect of morphine in the rat. Behav. Neurosci., 1983, 97, 759–767.
49. Hoebel B.G., Monaco A.P., Hernandez L., Aulisi E.F., Stanley B.G., Lenard L.: Self-injection of amphetamine directly into the brain. Psychopharmacology, 1983, 81, 158–163.
50. Hollerman J.R., Schultz W.: Dopamine neurons report an error in the temporal prediction of reward during learning Nat. Neurosci., 1998, 1, 304–309.
51. Hollister L.E.: Neuroleptic dysphoria: so what's new? Biol. Psychiat., 1992, 31, 531–532.
52. Horger B.A., Shelton K., Schenk S.: Preexposure sensitizes rats to the rewarding effects of cocaine. Pharmacol. Biochem. Behav., 1990, 37, 707–711.
53. Hurd Y.L., Svensson P., Ponten M.: The role of dopamine, dynorphin, and CART systems in the ventral striatum and amygdala in cocaine abuse. Ann. NY Acad. Sci., 1999, 877, 499–506.
54. Hurd J.L., Weiss F., Koob G.F., Andén N-E., Ungerstedt U.: Cocaine reinforcement and extracellular dopamine overflow in rat nucleus accumbens: an in vivo microdialysis study. Brain Res., 1989, 498, 199–203.
55. Imperato A., Mele A., Scrocco M.G., Puglisi-Allegra S.: Chronic cocaine alters limbic extracellular dopamine. Neurochemical basis for addiction. Eur. J. Pharmacol., 1992, 212, 299–300.
56. Jaffe J.H., Cascella N.G., Kumor K.M., Sherer M.A.: Cocaine-induced cocaine craving. Psychopharmacology, 1989, 97, 59–64.
57. Johnson S.W., North R.A.: Opioids excite dopamine neurons by hyperpolarization of local interneurons. J. Neurosci., 1992, 12, 483–488.
58. Kask A., Schioth H.B., Mutulis F., Wikberg J.E., Rago L.: Anorexigenic cocaine- and amphetamine-regulated transcript peptide intensifies fear reactions in rats. Brain Res., 2000, 857, 283–285.
59. Kastin A.J., Akerstrom V.: Entry of CART into brain is rapid but not inhibited by excess CART or leptin. Amer. J. Physiol., 1999, 277, E901–E904.
60. Kest B., Lee C.E., McLemore G.L., Inturrisi C.E.: An antisense oligodeoxynucleotide to the delta opioid receptor (DOR-1) inhibits morphine tolerance and acute dependence in mice. Brain Res. Bull., 1996, 39, 185–188.
61. Kimmel H.L., Gong W., Vechia S.D., Hunter R.G., Kuhar M.J.: Intra-ventral tegmental area injection of rat cocaine and amphetamine-regulated transcript peptide 55–102 induces locomotor activity and promotes conditioned place preference. J. Pharmacol. Exp. Ther., 2000, 294, 784–792.
62. Kiyatkin E.A., Stein E.A.: Biphasic changes in mesolimbic dopamine signal during cocaine self-administration. NeuroReport, 1994, 5, 1005–1008.
63. Kiyatkin E.A., Stein E.A.: Fluctuations in nucleus accumbens dopamine during cocaine self-administration behavior: an in vivo electrochemical study. Neuroscience, 1995, 64, 599–617.
64. Kiyatkin E., Stein E.A.: Conditioned changes in nuclues accumberns dopamine signal established by intravenous cocaine in rats. Neurosci. Lett., 1996, 211, 73–76.
65. Koob G.F.: Drug addiction: the yin and yang of hedonic homeostasis. Neuron, 1996, 16, 893–896.
66. Koob G.F., Le Moal M.: Drug abuse: hedonic homeostatic dysregulation. Science, 1997 278, 52–58.
67. Kornetsky C.L.: Functional, anatomical and pharmacological aspects of central motivational systems: a tribute to James Olds. Introduction. Fed. Proc., 1979, 38, 2445.
68. Kostowski W.: Involvement of dopamine in reward mechanisms and development of addictions: facts and hypotheses (Polish). Alkohol. Narkoman., 2000, 13, 9–32.
69. Kristensen P., Judge M.E., Thim L., Ribel U., Christjansen K.N., Wulff B.S., Clausen J.T., Jensen P.B., Madsen O.D., Vrang N., Larsen P.J., Hastrup S.: Hypothalamic CART is a new anorectic peptide regulated by leptin. Nature, 1998, 393, 72–76.

70. Kuhar M.J., Dall Vechia S.E.: CART peptides: novel addiction- and feeding-related neuropeptides. Trends Neurosci., 1999, 22, 316–320.
71. Lambert P.D., Couceyro P.R., McGirr K.M., Dall Vechia S.E., Smith Y., Kuhar M.J.: CART peptides in the central control of feeding and interactions with neuropeptide Y. Synapse, 1998, 29, 293–298.
72. Lanca A.J., Adamson K.L., Coen K.M., Chow B.L., Corrigall W.A.: The pedunculopontine tegmental nucleus and the role of cholinergic neurons in nicotine self-administration in the rat: a correlative neuroanatomical and behavioral study. Neuroscience, 2000, 96, 735–742.
73. Larson E.R., Ariano M.A.: D3 and D2 dopamine receptors: visualization of cellular expression patterns in motor and limbic structures. Synapse, 1995, 20, 325–337.
74. Leith N.J., Barrett R.J.: Amphetamine and the reward system: evidence for tolerance and post-drug depression. Psychopharmacology, 1976, 46, 19–25.
75. Leone P., Pocock D., Wise R.A.: Morphine–dopamine interaction: ventral tegmental morphine increases nucleus accumbens dopamine release. Pharmacol. Biochem. Behav., 1991, 39, 469–472.
76. Mereu G., Yoon K-W.P., Boi V., Gessa G.L., Naes L., Westfall T.C.: Preferential stimulation of ventral tegmental area dopaminergic neurons by nicotine. Eur. J. Pharmacol., 1987, 141, 395–400.
77. Mora F., Ferrer J.M.: Neurotransmitters, pathways and circuits as the neural substrates of self-stimulation of the prefrontal cortex: facts and speculations. Behav. Brain Res., 1986, 22, 127–140.
78. Mucha R.F., Herz A.: Motivational properties of kappa and mu opioid receptor agonists studied with place and taste preference conditioning. Psychopharmacology, 1985, 86, 274–280.
79. Murray T.F., Craigmill A.L., Fischer G.J.: Pharmacological and behavioral components of tolerance to LSD and mescaline in rats. Pharmacol. Biochem. Behav., 1977, 7, 239–244.
80. Nestler E.J., Hope B.T., Widnell K.L.: Drug addiction: a model for the molecular basis of neural plasticity. Neuron, 1993, 11, 995–1006.
81. Olds M.E.: Reinforcing effects of morphine in the nucleus accumbens. Brain Res., 1982, 237, 429–440.
82. Olds M.E., Fobes J.L.: The central basis of motivation: intracranial self-stimulation studies. Annu. Rev. Psychol., 1981, 32, 523–574.
83. Olds J., Milner P.M.: Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. J. Comp. Physiol. Psychol., 1954, 47, 419–427.
84. Olds M.E., Olds J.: Approach-avoidance analysis of rat diencephalon. J. Comp. Neurol., 1963, 120, 259–295.
85. Papez J.W.: A proposed mechanism of emotion. Arch. Neurol. Psychiat., 1937, 38, 725–743.
86. Parsons L.H., Smith A.D., Justice J.B.: Basal extracellular dopamine is decreased in the rat nucleus accumbens during abstinence from chronic cocaine. Synapse, 1991, 9, 60–65.
87. Paulson P.E., Camp D.M., Robinson T.E.: Time course of transient behavioral depression and persistent behavioral sensitization in relation to regional brain monoamine concentrations during amphetamine withdrawal in rats. Psychopharmacology, 1991, 103, 480–492.
88. Pettit H.O., Justice J.B.: Dopamine in the nucleus accumbens during cocaine self-administration as studied by in vivo microdialysis. Pharmacol. Biochem. Behav., 1989, 34, 899–904.
89. Phillips A.G., LePiane F.G.: Reinforcing effects of morphine microinjection into the ventral tegmental area. Pharmacol. Biochem. Behav., 1980, 12, 965–968.
90. Phillips G.D., Robbins T.W., Everitt B.J.: Bilateral intra-accumbens self-administration of D-amphetamine: antagonism with intra-accumbens SCH-23390 and sulpiride. Psychopharmacology, 1994, 114, 477–485.
91. Piazza P.V., Deminiere J.M., Le Moal M., Simon H.: Factors that predict individual vulnerability to amphetamine self-administration. Science, 1989, 245, 1511–1513.
92. Piazza P.V., Marinelli M., Jodogne C., Deroche V., Rouge-Pont F., Maccari S., Le Moal M., Simon H.: Inhibition of corticosterone synthesis by metyrapone decreases cocaine-induced locomotion and relapse of cocaine self-administration. Brain Res., 1994, 658, 259–264.
93. Pontieri F.E., Tanda G., Di Chiara G.: Intravenous cocaine, morphine, and amphetamine preferentially increase extracellular dopamine in the "shell" as compared with the "core" of the rat nucleus accumbens. Proc. Nat. Acad. Sci. USA, 1995, 92, 12304–12308.
94. Pothos E., Rada P., Mark G.P., Hoebel B.G.: Chronic morphine increases synaptic dopamine in the nucleus accumbens and naloxone decreases it unless withdrawal is blocked with clonidine. Brain Res., 1991, 566, 348–350.
95. Raffa R.B., Goode T.L., Martinez R.P., Jacoby H.I.: A Gi2alpha antisense oligonucleotide differentiates morphine antinociception, constipation and acute dependence in mice. Life Sci., 1996, 58, 73–76.
96. Ranaldi R., Pocock D., Zereik R., Wise R.A.: Dopamine fluctuations in the nucleus accumbens during maintenance, extinction, and reinstatement of intravenous D-amphetamine self-administration. J. Neurosci., 1999, 19, 4102–4109.
97. Ranson S.W.: The hypothalamus: its significance for visceral and emotional expression. Trans. Coll. Physicians Phila., 1934, 2, 222–242.
98. Redgrave P., Prescott T.J., Gurney K.: Is the short-latency dopamine response too short to signal reward error? Trends Neurosci., 1999, 22, 146–151.
99. Roberts D.C.S., Ranaldi R.: Effect of dopaminergic drugs on cocaine reinforcement. Clin. Neuropharmacol., 1995, 18, S84.
100. Robertson M.W., Leslie C.A., Bennett J.P. Jr.: Apparent synaptic dopamine deficiency induced by with-

drawal from chronic cocaine treatment. Brain Res., 1991, 538, 337–339.
101. Robinson T.E.: Stimulant drugs and stress: factors influencing individual differences in the susceptibility to sensitization. In: Sensitization in the Nervous System. Eds. Kalivas R.W., Barnes C.B., Telford Press, Caldwell NJ, 1978, 145–173.
102. Robinson T.E., Berridge K.C.: The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res. Brain Res. Rev., 1993, 18, 247–291.
103. Rocha B.A., Fumagalli F., Gainetdinov R.R., Jones S.R., Ator R., Giros B., Miller G.W., Caron M.G.: Cocaine self-administration in dopamine-transporter knockout mice. Nat. Neurosci., 1998, 1, 132–137.
104. Rossetti Z.L., Hmaidan Y., Gessa G.L.: Marked inhibition of mesolimbic dopamine release: a common feature of ethanol, morphine, cocaine, and amphetamine abstinence in rats. Eur. J. Pharmacol., 1992, 221, 227–234.
105. Schulteis G., Markou A., Cole M., Koob G.F.: Decreased brain reward produced by ethanol withdrawal. Proc. Nat. Acad. Sci. USA, 1995, 92, 5880–5884.
106. Schultz W.: Dopamine neurons and their role in reward mechanisms. Curr. Opin. Neurobiol., 1997 7, 191–197.
107. Schultz W., Apicella P., Ljungberg T.: Responses of monkey dopamine neurons to reward and conditioned stimuli during successive steps of learning a delayed response task. J. Neurosci., 1993, 13, 900–913.
108. Self D.W.: Neural substrates of drug craving and relapse in drug addiction. Ann. Med., 1998, 30, 379–389.
109. Self D.W., Nestler E.J.: Molecular mechanisms of drug reinforcement and addiction. Annu. Rev. Neurosci., 1995, 18, 463–495.
110. Self D.W., Stein L.: Pertussis toxin attenuates intracranial morphine self-administration. Pharmacol. Biochem. Behav., 1993, 46, 689–695.
111. Self D.W., Terwilliger R.Z., Nestler E.J., Stein L.: Inactivation of Gi and Go proteins in nucleus accumbens reduces both cocaine and heroin reinforcement. J. Neurosci., 1994, 14, 6239–6247.
112. Shaham Y., Stewart J.: Stress reinstates heroin-seeking in drug-free animals: an effect mimicking heroin, not withdrawal. Psychopharmacology, 1995, 119, 334–341.
113. Siegel R.K., Gusewelle B.E., Jarvik M.E.: Naloxone-induced jumping in morphine dependent mice: stimulus control and motivation. Int. Pharmacopsychiat., 1975, 10, 17–23.
114. Siegel S.: Opioid expectation modifies opioid effects. Fed. Proc., 1982, 41, 2339–2343.
115. Starzl T.E., Taylor C.W., Magoun H.: Collateral ascending excitation of the reticular formation of the brain stem. J. Neurophysiol., 1951, 14, 479–496.
116. Stevens K.E., Shiotsu G., Stein L.: Hippocampal μ-receptors mediate opioid reinforcement in the CA3 region. Brain Res., 1991, 545, 8–16.
117. Stewart J.: Conditioned and unconditioned drug effects in relapse to opiate and stimulant drug self--administration. Prog. Neuro-Psychopharmacol. Biol. Psychiat., 1983, 7, 591–597.
118. Stewart J.: Pathways to relapse: the neurobiology of drug- and stress-induced relapse to drug-taking. J. Psychiat. Neurosci., 2000, 25 125–136.
119. Stolerman I.: Drugs of abuse: behavioural principles, methods and terms. Trends Pharmacol. Sci., 1992, 13, 170–176.
120. Terwilliger R.Z., Beitner-Johnson D., Sevarino K.A., Crain S.M., Nestler E.J.: A general role for adaptations in G-proteins and the cyclic AMP system in mediating the chronic actions of morphine and cocaine on neuronal function. Brain Res., 1991, 548, 100–110.
121. Uhl G., Blum K., Noble E., Smith S.: Substance abuse vulnerability and D2 receptor genes. Trends Neurosci., 1993, 16, 83–88.
122. Vetulani J.: Pharmacological aspects of drug addictions. In: Drug Addictions (Polish). Ed. Przewłocka B., XII Szkoła Zimowa Instytutu Farmakologii PAN, Mogilany, 1995, 27–36.
123. Vetulani J.: Drug addiction. Part I. Psychoactive substances in the past and presence. Pol. J. Pharmacol., 2001, 53, 201–214.
124. Volkow N.D., Wang G.J., Fowler J.S., Logan J., Gatley S.J., Gifford A., Hitzemann R., Ding Y.S., Pappas N.: Prediction of reinforcing responses to psychostimulants in humans by brain dopamine D2 receptor levels. Amer. J. Psychiat., 1999, 156, 1440–1443.
125. Winter J.C.: Tolerance to a behavioral effect of lysergic acid diethylamide and cross-tolerance to mescaline in the rat: absence of a metabolic component. J. Pharmacol. Exp. Ther., 1971, 78, 625–630.
126. Wise R.A.: Neurobiology of addiction. Curr. Opin. Neurobiol., 1996, 6, 243–251.
127. Wise R.A., Munn E.: Withdrawal from chronic amphetamine elevates baseline intracranial self-stimulation thresholds. Psychopharmacology, 1994, 117, 130–136.
128. Wise R.A., Newton P., Leeb K., Burnette B., Pocock D., Justice J.B. Jr.: Fluctuations in nucleus accumbens dopamine concentration during intravenous cocaine self-administration in rats. Psychopharmacology, 1995, 120, 10–20.
129. Wise R.A., Rompre P.P.: Brain dopamine and reward. Annu. Rev. Psychol., 1989, 40, 191–225.
130. Wolgin D.L.: Contingent tolerance to amphetamine hypophagia: new insights into the role of environmental context in the expression of stereotypy. Neurosci. Biobehav. Rev., 2000, 24, 279–294.
131. Young A.M., Ahier R.G., Upton R.L., Joseph M.H., Gray J.A.: Increased extracellular dopamine in the nucleus accumbens of the rat during associative learning of neutral stimuli. Neuroscience, 1998, 83, 1175––1183.
132. Zahm D.S., Brog J.S.: On the significance of subterritories in the 'accumbens' part of the rat ventral striatum. Neuroscience, 1992, 50, 751–767.

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