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PHYSIOLOGY

Physiology and Pharmacology of Positive Reinforcement

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An original concept of a two-stage mechanism of positive reinforcement is proposed. The first stage, "virtual" reinforcement, is formed in parallel with the action result acceptor when the result is still not achieved. At this stage, the importance of the planned result and the probability of its achievement are assessed. The greater are these indices, the stronger is "virtual" reinforcement. Hypothetically, the "virtual" reinforcement is mediated by dopamine release from nerve terminals in the mesencephalon. The "real" reinforcement (the second stage) occurs after achievement of the result. Probably, an important role in the mechanisms of the "real" reinforcement is given to endogenous opioids, cannabinoids, and GABA. Based on the advanced hypothesis on interaction between the central and peripheral subdivisions of the corresponding neurochemical systems, the review focuses on possibility of pharmacological intervention into the mechanisms of positive reinforcement by modifying activity of the peripheral opioid and dopamine receptors with the ligands that cannot cross blood—brain barrier.

Key Words: *action result acceptor; mesocorticolimbic dopamine system; endogenous opioid system; β-endorphin; "virtual" reinforcement*

This study considers the positive reinforcement as a process culminating in the state of pleasure consequential to achievement of biologically or socially important result. Satisfaction of any need results in positive reinforcement.

There is consensus in the view that the key role in positive reinforcement is played by interaction between the neurotransmitters and various receptors for dopamine, serotonin, nicotine, opioids, and cannabinoids. In this interaction, the most important participant is mesocorticolimbic systems [21]. The dopamine-synthesizing neurons, whose somata are located in ventral tegmental area, are persistently bombarded by the inhibitory impulses from GABAergic neurons. During natural physiological reinforcement, the GABAergic neurons are inhibited by opioid peptides, which results in activation of dopamine-synthesizing neurons, release of dopamine from their terminals projecting to various brain subdivisions such as the cortex and nucleus accumbens. The same subdivisions incorporate other neurochemical systems that can modulate the dopaminergic neurotransmission during reinforcement.

Here, a hypothesis is proposed on a two-stage reinforcement mechanism, which does not consider the described activation of the mesocorticolimbic dopamine system as the real mechanism of reinforcement. It postulates that reinforcement mechanisms merely accompany the formation of the action result acceptor (ARA) in the central architectonics of the functional system of goal-directed behavior [2]. At this, not only the parameters of expected result are evaluated, but also the probability of its achievement. The more important the result and the higher subject-assessed probability of its achievement, the larger amount of dopamine is released and the stronger are the pleasant sensations evoked during assessment of the perspective. However, the expected result has not been

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achieved yet, so the real reinforcement is absent at this stage, which can be considered as the first reinforcement stage or "virtual" reinforcement (Fig. 1). The release of dopamine in nucleus accumbens and cerebral cortex results in psychostimulation and mobilization of organismal resources aimed to achieve the result [22].

To test this hypothesis, we examined the level of monoamines in the microdialysate obtained from the anterior cingulate cortex of the rats during forced or self-administration [14]. It was assumed that in preliminarily trained rats, self-administration of morphine would form the respective ARA manifested by the release of monoamines. In contrast, the forced administration of morphine should not induce the "virtual" reinforcement despite its positive reinforcement potency. Actually, the intraperitoneal injection of morphine to rats did not significantly change the level of monoamines in dialysate. In contrast, self-administration of morphine resulted in significant and pronounced elevation of monoamines in the intercellular space of the anterior cingulate cortex. The levels of dopamine and norepinephrine determined during the first 20 min of self-administration were higher than the baseline values by 2.5 and 1.7 times, respectively. Moreover, these levels increased further during the following 40 min of self-administration [11]. Elevation of catecholamines in the intercellular space of the anterior cingulate cortex positively correlated with the amount of self-administered morphine. Thus, the release of catecholamines results not from the direct action of morphine on the cerebral structures, but it occurs only during conscious and intentional behavior, which forms expectation of future reinforcement.

It seems reasonable to postulate that the stage of "virtual" reinforcement is characterized by the release of dopamine into the mesocorticolimbic structures, where it evokes emotional excitation and euphoria. This mechanism is the target for psychostimulants such as amphetamine, cocaine, nicotine, cathinone, *etc*. as well as ethanol, opiates, and cannabinoids used in small doses. Probably, the release of monoamines in the mesocorticolimbic structures is necessary for formation of the advanced stages of psychological dependence, addiction for the computer games included.

The "real" reinforcement occurs after achievement of the result. Seemingly, it relates to the action of inhibitory neurotransmitters and activation of endogenous opioid system resulting in relaxing and tranquilizing effects. The mechanisms of "real" reinforcement are little studied. Probably, the stage of "real" reinforcement is characterized with termination of dopamine release in the mesocorticolimbic structures resulting in sedation, relaxation, and euphoria. The mechanisms of "real" reinforcement are the substrates for the large doses of ethanol and opiates as well as for the formation of tolerance and physical dependence to psychoactive substances.

A challenging problem related to the mechanisms of "real" and "virtual" reinforcements is assessment of visibility to affect these mechanisms in order to correct the functions, in which the positive reinforcement is essential. Actually, activation of "virtual" reinforcement could induce the psychostimulating effects thereby affecting such pathological processes as anorexia, behavioral sexual abnormalities, and cognitive disorders, whereas triggering the "real" reinforcement could promote sedation, thereby inhibiting food overconsumption, abuse of drugs and alcohol, game addiction, and pathological sexual behavior. Unfortunately, the direct pharmacological activation of central mechanisms implicated in the positive reinforcement is possible only with the remedies that provoke dependence.

It is logically to hypothesize that any action on endogenous opioid system could predominantly affect the mechanisms of "virtual" and "real" reinforcement. Based on our previous hypothesis on reciprocal inter-

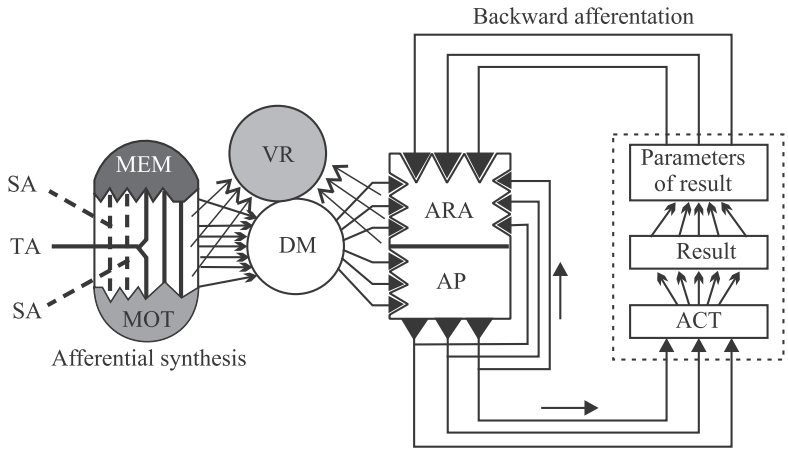

Fig. 1. Central architectonics of behavioral act. SA: situational afferentation; TA: triggering afferentation; DM: decision-making; VR: virtual reinforcement, ARA: action result acceptor; AP: action program; ACT: action; MEM: memory; MOT: motivation.

action between the central and peripheral branches of endogenous opioid system [17], a possibility became visible of indirect action on the central mechanisms of positive reinforcement by affecting the opioid receptors in the gastrointestinal tract with the ligands that cannot cross blood—brain barrier (BBB). At this, we demonstrated that intragastric administration of loperamide, a BBB-impermeable agonist of μ-opioid receptors, modified the release of β-endorphin into the perineural space of ventral tegmental area and the anterior cingulate cortex [16,23]. These changes were accompanied by a decrease in the number of active μ-opioid receptors in these structures [4,23]. Expectedly, the intragastric administration of loperamide provoked hyperalgesia [17,18].

Peripheral administration of loperamide significantly moderated the natural food consumption in rats [8,20]. Interesting data were harvested in the experiments with the rats conditioned to press the lever to get a food pellet as a reward [20]. The conditioned rats were further trained every day to get a food reward after greater number of lever pressings, which was increasingly set to 2, 4, 8, 16, 32, 64, and 128 ones. Administration of loperamide to these rats reduced food consumption when it was rather easily to get a pellet by 1-8 lever pressings. The effect of loperamide discontinued with further elevation of operating expenses [20], which probably attests to implication of μ-opioid system in the mechanisms of "virtual" reinforcement. This hypothesis is corroborated by loperamide-induced suppression of morphine self-administration in rats trained to get a certain portion of the drug via implanted intravenous catheter after pushing the lever in the operant chamber [15,17].

The changes in the state of cerebral opioid system induced by intragastric loperamide were accompanied by a drop of anxiety level. Loperamide increased the time spent by the rats in open arms of elevated plus-maze [7,8]. The anti-anxiety effect of loperamide was annihilated by partial vagotomy, which however did not completely suppress the anorexic action [8].

We also examined the effects of agonists at μ-, δ-, and κ-opioid receptors as well as the action of caffeine, ethanol, and nicotine on behavioral parameters of rats. To this end, the peptide agonists were administered directly into the stomach via a special gastric tube. These agonists could activate the gastric receptors for a certain time, but then they were degraded by gastrointestinal peptidases. In these studies, we examined implication of gastric μ-, δ-, and κ-opioid receptors in the control of natural feeding behavior, the level of metabolism, and motor activity in rats [10]. To this end, the rats were placed into a standard "home" cage of Phenomaster system (TSE). The following parameters were recorded every 40 min over 24 h: motor activity (the number of crossed squares), the amount of consumed food, water, and oxygen, as well as production of carbon dioxide. Administration of μ-opioid agonist DAMGO suppressed the feeding behavior during daytime, but did not significantly modify motor activity and metabolism. In contrast, δ-opioid agonist DADLE activated metabolism over 24 h. In addition, it suppressed the motor activity during the day time and up-regulated feeding behavior during day/night transition time. Finally, administration of κ-opioid agonist ICI204,448 suppressed feeding behavior, metabolism, and motor activity of the rats only during the nighttime. Probably, the opioid peptides formed in the stomach during gastrointestinal digestion play an important role in the control of foraging motivation and intensity of metabolism in mammals. At this, the different subtypes of opioid receptors can control the feeding behavior and the level of metabolism during various phases of animal life.

Important data were obtained in studies focused on the effect of intragastric μ-opioid agonist DAMGO and δ-opioid agonist DADLE on food consumption and feeding motivation in conditioned instrumental food-procuring behavior of various intensity and effectiveness. At this, the trained rats should receive 1 pellet of food when they press the lever 1, 2, 4, 8, 16, and 32 times on the experimental days 1, 2, 3, 4, 5, and 6, respectively. Activation of gastric δ-opioid receptors suppressed the feeding behavior and pronouncedly diminished the energy expenditure for its realization. At this, the level of food-procuring motivation virtually coincided with the control one. Activation of gastric μ-opioid receptors suppressed the energy-intensive feeding behavior, but increased the level of food-procuring motivation [3].

In special studies, we examined the effect of intragastric administration of μ-opioid agonist DAMGO, δ-opioid agonist DADLE, and κ-opioid agonist ICI204,448 on anxiety and motor activity of rats in elevated plus-maze. In these experiments, ICI204,448 exerted the anxiolytic action, but produced no effect on motor activity. In contrast, DAMGO and DADLE diminished motor activity and augmented anxiety [1,11].

Interestingly, intragastric administration of μ-opioid agonist DAMGO to the rats eliminated the effect of caffeine. After DAMGO, caffeine did not stimulate motor activity and metabolism. In addition, intragastric DAMGO prevented the development of caffeine-induced anxiolytic effect tested in elevated plus-maze [13].

A single intraperitoneal injection of ethanol (2 g/kg) exerted an essential depressive effect manifested by moderation of horizontal motor activity and down-regulation of metabolism. Both μ-opioid agonist DAMGO and κ-opioid agonist ICI204,448 partially al-

leviated the effect of ethanol on motor activity in rats, the effect of ICI204,448 being most pronounced. In contrast to DAMGO, ICI204,448 prevented ethanol-induced down-regulation of metabolism. Thus, the present data showed that κ-opioid agonist ICI204,448 significantly ameliorated the ethanol-induced depression and probably exerted the sobering effect. Under experimental conditions, similar effects of DAMGO were less pronounced [19].

The effects of peptide agonists at opioid receptors on the development of resistance to analgesic action of ethanol were examined with hot plate test. Activation of gastric κ-opioid receptors eliminated the analgesic action of ethanol and accelerated the development of resistance to this action. In contrast, activation of gastric μ-opioid receptors decelerated the development of such resistance [5].

Withdrawal of nicotine stimulated metabolism, motor activity, and food consumption in rats conditioned to its long-term (14 days) administration, which was observed in 24 h after the last injection. These withdrawal effects were completely eliminated by κ-opioid agonist ICI204,448 [12]. In addition, acute administration of caffeine (10 mg/kg) to nicotine-dependent rats at the stage of nicotine withdrawal resulted in pronounced psychostimulating and anxiolytic effects. Intragastric administration of κ-opioid agonist ICI204,448 to nicotine-dependent rats at the stage of nicotine withdrawal, which were subjected to a single caffeine probe (10 mg/kg), suppressed the psychostimulating and anxiolytic effects of caffeine [9]. It can be hypothesized that nicotine withdrawal syndrome is related to inhibition of dopamine release in nucleus accumbens probably resulted from up-regulated κ-opioid activity at the presynaptic terminals. Seemingly, activation of peripheral κ-opioid receptors reciprocally suppresses the central activity of such receptors and moderates the nicotine withdrawal symptoms in nicotine-dependent mammals via the vagal afferent pathways.

In contrast to agonists that cannot cross BBB, opioid receptor antagonist methyl-naloxone after intragastric administration activates the central subdivision of endogenous opioid system, which is manifested by enhanced release of β-endorphin and increased density of μ-opioid receptors in the brain cortex [4,16,23]. Consequently, methyl-naloxone exerts analgesic and antistress effects [7,17]. In addition, intraperitoneal injections of methyl-naloxone (2 mg/kg) to morphine-dependent rats over 3 days after morphine withdrawal alleviate symptoms of abstinence [15].

Peripheral administration of ICI 174,864 (an antagonist of δ-opioid receptors) increased the time spent in the open arms of elevated plus-maze, but produced no effect on the motor activity of rats. These phenomena make it possible to consider this antagonist of δ-opioid receptors as a potential drug with original mechanisms of anxiolytic action [11].

Similar peripheral administration of μ-opioid or δ-opioid antagonists respectively decelerated or accelerated the development of resistance to analgesic effect of ethanol [5].

As mentioned in the above, an important role in "virtual" reinforcement is given to mesocorticolimbic dopaminergic system. The dopamine concentration can be increased at the terminals of neurons located in ventral tegmental area with various psychostimulators (amphetamine, cocaine, nicotine, *etc*.), which provoke the narcotic dependence after repetitive use.

The advanced conception on interaction between the central and peripheral elements of analogous neurochemical systems was employed as a guide in the attempts to affect the central dopamine system via D2 dopamine receptors using their antagonist domperidone that cannon cross BBB. Examination of rats in Phenomaster system showed that intragastric domperidone (0.1 mg/kg) significantly inhibited the food-procuring behavior, up-regulated basic metabolism, but produced virtually no effect on motor activity characteristic of the action of various psychostimulators that promote dopamine release from the nerve terminals located in nucleus accumbens and some regions of the cerebral cortex [6].

Thus, the data harvested in a series of works highlighted the visibility to affect the physiological functions related to central opioid and dopamine systems via peripheral opioid and dopamine receptors. These data corroborate the paradigm on interaction between the central and peripheral elements of analogous neurochemical system. In this paradigm, activation of peripheral receptors inhibits the analogous central element, whereas inhibition of peripheral receptors activates the central part of analogous neurochemical system. These reciprocal effects are echoed by the behavioral manifestations. However, the interrelations between the central and peripheral elements of the integral neurochemical system can be modified during altered states of the organism. Importantly, both agonist and antagonist of opioid receptors up-regulates the release of β-endorphin from the nerve terminals in the anterior cingulate cortex in emotionally stressed rats, although both agents exert the antistress effect [23].

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