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Neurobiological mechanisms of motor and motivation deficits of dopamine

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Abstract

Dopamine (3,4-dihydroxyphenethylamine) together with adrenaline and noradrenaline belong to the group of catecholamines present in different tissues, predominantly in the nervous system, where they function as neurotransmitters. Our choice of the genetic determinants of the dopaminergic system disorders for the main topic of our project study was influenced by a wide spectrum of influence which the system has on the functions of an organism connected with, for example, its adaptive response to physical effort (it is the very adrenergic system that physiologists call the "work and fight" and even the "fight and flight" system). It is, for example, proven by the confirmed influence of dopaminergic mechanisms on blood pressure, widening of bronchi and a mobilization of energetic substrates. On the other hand, it is worth mentioning another importance of dopamine recognized by psychologists and psychiatrists as the hormone of "motivation, thrill and adventure seeking", which in sport can be of key importance. That is why we would like to link these two areas – genetic and psychological.

KEYWORDS: dopamine, sports, motivation, reward system, methylation.

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Introduction

Competition and dopamine

It is common knowledge that it is the head, not muscles, which is behind winning a sport competition. Success or failure are most often determined by the will to fight, determination, courage and motivation to reach a goal – in other words it is the above mentioned personality qualities and temperament. Additionally, it is worth mentioning the importance of dopamine recognized by psychologists and psychiatrists as the hormone of "motivation, thrill and adventure seeking" [4]. In this context dopamine has a considerable influence on

making the so called "risky decisions". What is also worth mentioning is the so called "mesolimbic reward system" which mediates in reward psychopharmacology caused by a physical effort and other factors. Nevertheless, in this case the brain region of the ventral tegmental area, where neurons of the dopaminergic system are situated, and the nucleus accumbens, which is functionally connected to it, are called the "pleasure centre" and dopamine itself is called the "pleasure neurotransmitter". Therefore, what can be assumed in this context is that that the above mentioned system may be one of the key determinants in taking up and continuing an athletic training.

In this case ontogenetic differences are, for example, expressed by a modulating influence of the neurotransmitter system on the expression of particular personality traits. A good example is "novelty seeking", which is expressed by a "hunger" for experiencing thrills, which results from the dopaminergic system functioning, i.e. dopamine deficiency to be precise.

It is also worth mentioning additional, physiological reasons to start studies into genetic mechanisms determining operations of the dopaminergic system in the context of physical effort and sport. Bearing in mind the fact that dopamine, as a neurotransmitter, is also involved in neural transmitting, e.g. in the extrapyramidal system, one could argue that it could also be of fundamental importance to the level of motor coordination. Studies using animal models have shown, that in extreme cases of dopamine stimulation deficiency mammals become immobile (akinetic), whereas an increase in dopamine stimulation over the primary level results in greater mobility [26].

Another, and probably not the last argument for the importance of dopamine in sport achievements is its influence on visual perception, which, in the case of martial arts, is one of the key determinants of a possible success. Since it is in the retina where dopamine plays a role of a paracrine neurotransmitter, a "chemical analog to light", and the receptors D2 and D4 situated on photoreceptor cells control illumination-related processes including melatonin biosynthesis, opsin expression in the cone cells or the levels of cAMP inside the photoreceptor [26].

Animal research

Critical decisions in life often require weighing a given option's costs against its associated benefits, and virtually every severe mental illness is associated with difficulties in such cost/benefit decision making [7, 18]. For one such cost, the effort to obtain a reward, a number of animal models have been developed: rats are given the option to climb a barrier in a T-maze in one task, or to make a higher number of responses on a lever in another, to obtain a larger food reward [17, 32]. To account for the discrepancy in the literature, human studies have begun to incorporate physical costs in decision-making paradigms [41] and have shown a similar involvement of dopamine in human decision making involving physical effort [40, 43]. The converse approach, applying cognitive effort costs to animal models, allows for examination of mental effort in ways inaccessible to human studies. The study Hosking et al. – wherein animals can choose to allocate greater visuospatial attention for a greater reward, and shown that amphetamine's effects on the task are mediated by animals' individual sensitivity [19].

A very interesting study regarding this issue is the study carried out by Pasquereau and Turner where the authors researched the spiking activity of dopamine neurons in the substantia nigra pars compacta of monkeys (Macaca mulatta) during a reaching task in which the energetic costs incurred (friction loads) and the benefits gained (drops of food) were manipulated independently. Their results may explain the oft-hypothesized role for dopamine in the regulation of the balance in natural behaviours between the energy expended and the benefits gained, which could explain why dopamine disorders, such as Parkinson's disease, lead to a breakdown of that balance [28].

The function of dopamine and physical fitness

This may be easily translated into a human model. Why don't we make more effort? Is it because we don't want to, or just because we can't? This question is particularly hard to address in the case of patients with pathological conditions that combine motivational and motor deficits, such as Parkinson's disease (PD).

Candidate neurobiological mechanisms underlying motor and motivational deficits both involve dopamine. Motor symptoms are primarily caused by the degeneration of dopaminergic neurons in the substantia nigra pars compacta that project on dorsal parts of the striatum [15, 20]. Apathy, one of the most frequent nonmotor symptoms in PD [5, 36], might also relate to dopamine depletion [8, 39], but more specifically to the degeneration of dopaminergic projections to the ventral striatum arising from the ventral tegmental area [6, 30]. Thus, motor and motivational deficits in PD could arise from dopamine depletion in distinct territories. Capturing this dissociation requires a proper articulation of motivational and motor functions, an

issue that has only recently received consideration in theoretical neuroscience [31, 35].

In their study Le Bouc et al. [24] assessed the effects of dopamine depletion (comparing Off-PD patients to healthy controls) and dopamine repletion (comparing Off-PD to On-PD patients) on effort allocation, using both binary choice and incentive force tasks. Model-free analyses showed that dopamine is causally involved in (1) amplifying the boosting effect of potential rewards on force production and (2) speeding up force rise to the peak, regardless of expected rewards. They developed a computational model of effort production to further characterize the dissociation of motivational and motor effects, focusing on the effect of dopaminergic medication in PD patients. Model-based analyses showed that dopamine enhancers increase reward sensitivity and increase motor activation rate, while leaving unaffected other parameters such as cost sensitivity, fatigability, or choice temperature [24].

Another interesting piece of work was carried out by Gepshtein et al. [16] who claimed that although activity of dopamine cells does not specify movements themselves, a recent study in humans has suggested that tonic levels of dopamine in the dorsal striatum may in part enable normal movement by encoding sensitivity to the energy cost of a movement, providing an implicit "motor motivational" signal for movement. They investigated the motivational hypothesis of dopamine by studying motor performance of patients with Parkinson disease who have marked dopamine depletion in the dorsal striatum and compared their performance with that of elderly healthy adults. All participants performed rapid sequential movements to visual targets associated with different risk and different energy costs, countered or assisted by gravity. In conditions of low energy cost, patients performed surprisingly well, similar to prescriptions of an ideal planner and healthy participants. As energy costs increased, however, performance of patients with Parkinson disease dropped markedly below the prescriptions for action by an ideal planner and below performance of healthy elderly participants. The results indicate that the ability for efficient planning depends on the energy cost of action and that the effect of energy cost on action is mediated by dopamine [16].

Methylation

In the era of contemporary studies it is impossible not to mention DNA methylation and translation of this process into a research on the genetics of sport and motivation to act.

DNA methylation is generally thought to be mitotically stable. Consequently, environmental factors have been disregarded as driving substantial and sustained changes in DNA methylation patterns in adult tissues. However, several studies support the notion that environmentally induced changes in DNA methylation patterns throughout life influence gene-expression signatures. For example, the naturally occurring short-chain fatty acid butyrate acutely alters histone deacetylase activity and DNA methylation status in normal [27] and cancer cell lines [9, 37]. Moreover, acute exposure of cultured human myotubes to either palmitate or oleate increases promoter methylation of the mitochondrial protein peroxisome proliferator-activated receptor gamma, coactivator 1 a (PGC-1a) [1]. Evidence is emerging that epigenetic modifications through DNA methylation contribute to the increased risk and development of metabolic disease by modifying the expression of genes controlling whole body energy and glucose homeostasis [1, 21].

European scientists under Professor Barrès from Copenhagen [2] looked into this issue from the epigenetic point of view. They succeeded in employing 14 volunteers who had declared they had a sedentary lifestyle. Prior to physical effort the volunteers had undergone a skeletal muscle biopsy procedure. Then they were put on an acute "physical strain" and underwent a skeletal muscle biopsy procedure once more. The general level of methylation was determined in the studied samples. As it turned out it was significantly different between the state before their effort and after effort.

The studies were also carried out on a bigger group of laboratory animals, which confirmed the results obtained from the studies on humans. What is interesting, a similar result was also observed when mice were administered a high dose of caffeine. The scientists speculated that a decrease in genome methylation may be related to the intensity of the calcium transport mechanism between cellular compartments. In people with a reduced cellular sensitivity to insulin the results were contrary to those observed by the Barres's team. Therefore a hypothesis was formed that if an increase in methylation may result in disordered metabolism in muscle cells and result in diabetes, similarly, a decrease in methylation, as a contrary phenomenon, may confirm a beneficial influence of exercise on myocytes [2].

Experiencing pleasure and dopamine

Two stages of experiencing pleasure related to reward may be distinguished: preparatory stage and

consumption stage. It is very often that much more pleasure is experienced in the first stage of waiting for a reward, which is related to dopamine secretion. Ultimately, repetitive triggering circumstances lead to adaptive changes and a reduced dopamine level with the reward itself. However, the level is still high in the first stage [22]. A conjecture was made on the basis of this observation that dopamine is related to associative learning. Several hypotheses are an attempt to explain how dopamine act in response to the rewarding task. On the basis of the above correlations and the fact that dopamine secretion is reduced when an anticipated reward is passed over Schutlz (1997) suggested that the response of dopamine neurons of the midbrain is a learning signal encoding the predicted error in anticipation of reward [34].The Redgrave, Prescott and Gurney's theory (1999) [29] holds that the dopamine signal function is to draw attention to significant, unexpected effects, including reward, but not only. Therefore, the dopamine system would be of importance in associative learning not necessarily related to reward [29]. It should be emphasized that the dopamine system of the nucleus accumbens is genuinely stimulated in the process of learning [44].

Di Chiara is of the opinion that addiction should be regarded as an associative process disorder because behaviour is recurrent, permanent and compulsively concentrated on obtaining a psychoactive substance [10, 11, 12, 13]. Novelty seeking is a temperament quality implying a tendency for responding actively to new stimuli, and what is most interesting, it remains in relation to the dopaminergic system. The DRD4 gene encoding the dopamine receptor D4 is considered a genetic marker for novelty seeking [25]. The DRD4, also known as the gene of "risk taking" or "thrill seeking" is expressed in the frontal and prefrontal cortex, amygdala, hypothalamus and hippocampus. The polymorphism of particular influence on the quality in question is a VNTR (variable number tandem repeat) type variation with 2-11 repetitions and 48 base pairs [42]. An association was observed of a higher number of repetitions (more than 7) with higher numbers of values on the novelty seeking scale, which may be related to a predisposition to reward seeking, for example as an increased consumption of an addictive substance [23, 33]. What is especially important is the fact that the presence of alleles including more than 7 repetitions is related to a reduced receptor affinity with the dopamine molecule. Therefore, maintaining an optimal mental state requires that bigger amounts of dopamine are secreted [3, 14, 38].

Conclusions

Change substances into sport? Dopamine as a molecule of motivation

It is because of dopamine that we are able to reach our objectives. All aspirations, competition, rivalry in various aspects of life (love, business, sport) are dependent on the level of dopamine. The so called reward system is based on it, which allows to feel satisfaction, happiness, fulfilment and even euphoria. However, if the level of dopamine is too low it can result in drowsiness, unwillingness to act, lack of motivation, and in extreme cases it may lead to severe depression. People with a low level of dopamine are often addicted to artificial stimulants of good mood and energy, including coffee, nicotine, sugar, gambling, medications, games, alcohol, sex, etc., because this is the way in which they want to boost their energy and compensate deficiencies.

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