REVIEW PAPER Curr Probl Psychiatry 2022;23(4)

DOI:10.2478/cpp-2022-0016

Czasopismo indeksowane na liście MNiSW - 70 pkt.

Cellular and neuronal mechanisms that underlie addiction - literature review

Mechanizmy komórkowe i neuronalne, które leżą u podstaw uzależnienia - przegląd literatury

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Abstract

Introduction: Addictive substances act on a number of neurotransmitter systems, and the end result of this action is the activation of the reward system in the brain. The cellular and neuronal mechanisms that underlie addiction have long been searched for. One of such neurotransmitters is dopamine, a catecholamine synthesized in neurons located mainly in the midbrain.

Material and method: The available literature was reviewed on the Pubmed platform and from other sources. The analysis included original studies, reviews.

The aim of the study was to review the literature on the relationship between the *DRD2* gene and the occurrence of substance addiction.

Discussion: This work presents several currently discussed biological mechanisms, especially at the molecular and genetic level, involved in the process of addiction to various psychoactive substances. They discovered the brain structures that are most at risk, as well as other neurotransmitter systems and receptor proteins through which they can exert their pathological effects. It has also been established that exposure to psychoactive substances causes significant changes in expression in over 100 genes (including genes for dopaminergic, serotonergic and signaling pathways). The DRD2 receptor (present, among others, in the nucleus accumbens) plays an important role in the reward system, in the transmission of information. The weakening of this conductivity is a significant risk factor for the onset of clinical features that are associated with reward system deficiency syndrome. The expression of the D2 receptor gene may take up to 2 isoforms: short D2S and long D2L.

Conclusions: Further research at the molecular level may result in the modification of psychotherapy and pharmacotherapy in terms of their personalization.

Keywords: reward system, *DRD2* gene, DAT, dopamine

Streszczenie

Wstęp: Substancje uzależniające działają na szereg układów neuroprzekaźników, a końcowym rezultatem tego działania jest aktywacja układu nagrody w mózgu. Od dawna poszukiwano mechanizmów komórkowych i neuronalnych, które leżą u podstaw uzależnienia. Jednym z takich neuroprzekaźników jest dopamina, katecholamina syntetyzowana w neuronach zlokalizowanych głównie w śródmózgowiu.

Materiał i metoda: Przegląd dostępnej literatury dokonano na platformie Pubmed oraz z innych źródeł. Analiza obejmowała opracowania oryginalne, recenzje. Celem pracy był przegląd literatury dotyczącej związku genu *DRD2* z występowaniem uzależnienia od substancji psychoaktywnych.

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Dyskusja: W tej pracy przedstawiono kilka obecnie dyskutowanych mechanizmów biologicznych szczególnie na poziomie molekularnym i genetycznym uczestniczących w procesie uzależnień od różnych substancji psychoaktywnych. Praca koncentruje się na charakterystyce dopaminy, która jest neuroprzekaźnikiem zaangażowanym w takie procesy, jak skoordynowana kontrola ruchu, nagroda, uzależnienie, wydzielanie hormonów i metabolizm. Odkryto struktury mózgu, które są najbardziej narażone na jej działanie, a także inne układy neuroprzekaźników i białka receptorowe, poprzez które mogą wywierać swoje patologiczne działanie. Ustalono również, że ekspozycja na substancje psychoaktywne wywołuje istotne zmiany ekspresji w ponad 100 genach (w tym genach szlaków dopaminergicznych, serotoninergicznych, sygnałowych). Receptor DRD2 (obecny m.in. w jądrze półleżącym) odgrywa ważną rolę w układzie nagrody, w przekazywaniu informacji. Osłabienie tego przewodnictwa jest istotnym czynnikiem ryzyka wystąpienia objawów klinicznych związanych z zespołem niedoboru układu nagrody. Ekspresja genu receptora D2 może zajmować do 2 izoform: krótkiej D2S i długiej D2L. Efekt pominięcia eksonu 6 genu *DRD2* w trakcie transkrypcji, produkującej białko o 29 aminokwasów krótsze („short" – S).

Wnioski: Dalsze badania na poziomie molekularnym mogą skutkować modyfikacją psychoterapii i farmakoterapii pod kątem ich spersonalizowania.

Słowa kluczowe: system nagrody, gen *DRD2*, DAT, dopamina,

Introduction

Addictive substances act on a number of neurotransmitter systems, and the end result of this action is the activation of the reward system in the brain. The cellular and neuronal mechanisms that underlie addiction have long been searched for. One of such neurotransmitters is dopamine, a catecholamine synthesized in neurons located mainly in the midbrain. Dopamine works on many levels related to the control of emotions and behavior. The dopaminergic system is responsible for modulating neuronal processes such as: mood, motor control, reward systems, sexual behavior and pain sensation [1,2].

Materials and methods

The available literature was reviewed on the Pubmed platform and from other sources. The analysis included original studies, reviews, meta-analyzes and internet sources. The aim of the study was to review the literature on the relationship between the *DRD2* gene and the occurrence of substance addiction.

Discussion

Award layout

Various psychoactive substances act at different places in the brain through different neurotransmitters that are secreted and taken up by nerve cells into synapses, which are connections between neurons. For all psychoactive substances, the reward system in the brain is a very important, if not the most important place. In this system, dopamine is a key neurotransmitter. This system includes the ventral tegmental nucleus (VTA), which, in turn, connects with the nucleus accumbens (NAc), from where it extends to the cortex of the brain. These nuclei are part of the subcortical nuclei, which, in turn, form the mesolimbic system. As a result of stimulation of the VTA nuclei, dopamine is transferred to the synapse, which connects the abdominal tegument neurons with the NAc nucleus. The stimulated projections of the NAc nucleus project up to the prefrontal cortex, which, in turn, is responsible for a specific feeling and action in humans. In order to avoid too strong stimulation, the NAc accumbens nucleus feedback inhibits the ventral tegmental nuclei.

On the other hand, if psychoactive substances have a strong effect on the NAc nucleus, they will also strongly inhibit the abdominal teguments, which, with prolonged use of psychoactive substances, may lead to the fact that the abdominal teguments begin to systematically reduce their activity, which may lead to their partial degradation. There will be a situation where, in the case of stopping the use of a psychoactive substance, the VTA nuclei will no longer be able to stimulate the nucleus accumbens, i.e. the expected level of pleasure associated with various activities will not be achieved. This will result in the search for such situations that will be able to stimulate the NAc nucleus to the appropriate level of activity [3].

Due to the knowledge of the principle of the reward system, a person looks for such behaviors or things that will contribute to the achievement of pleasure. There are two phases of experiencing pleasure: 1.) The appetitive phase, consisting in the human search for a source through which pleasure will be satisfied, where in some cases the very search by increasing tension causes the feeling of pleasure. 2.) The consumption phase is associated with achieving satisfaction with the satisfaction of the needs and reducing tension. The reward system is an extensive neural network that covers part of the limbic system, which includes the cortical, forebrain and trunk centers. The central center of the described system is the ventral tegmental area, which sends dopaminergic projections to the lateral olfactory stripe, septum and olfactory cusp, as well as to the prefrontal region, the ventro-anterior caudate, to the nucleus accumbens and the amygdala. From the above-mentioned structures, there are reciprocal connections to the ventral tegmental area, where the interaction of dopaminergic and opioidergic neurons takes place. The reward system is an element that controls the drive-motivational behavior by being associated with emotional reactions that trigger the satisfaction of aversive and appetitive drives (arousal is transmitted through the cholinergic system) [3,4].

Receptors and transporters

Dopamine is an organic chemical compound from the catecholamine group. It works through specific receptors that are located in the postsynaptic and presynaptic membranes. The synthesis of such an important neurotransmitter takes place in peripheral tissues as well as in the central nervous system by dopaminergic neurons. Depending on where it acts, dopamine has many functions in the body. It is responsible for higher mental activities, motor coordination, emotional processes and muscle tension. It also regulates the secretion of hormones such as gonadotropin and prolactin. It also functions as a so-called "pleasure relay". Dopamine interacts by binding to its specific receptors. They are glycoproteins belonging to the α group of the rhodopsin family of membrane receptors coupled to heterotrimeric G regulatory proteins, and their structure is composed of α, β and γ subunits [5-7]. Five types of dopamine receptors have been identified in mammals and are defined as D1 through D5. These receptors belong to the metabotropic receptors that are closely related to the G protein [8]. The proper functioning of ion channels depends on these metabotropic receptors, which are located in the cell membrane. The extracellular neurotransmitter activates a secondary cascade of signals inside the cell. As a result, the ion channels located in the vicinity are affected. Metabotropic receptors in mammals have been divided into two families: D1 and D2 [8,9].

The opening of sodium channels takes place thanks to the stimulation of receptors that have been activated in the nervous system by D1. Inhibition in the nervous system occurs due to the opening of potassium channels. In such a situation, inhibition of the target neuron is the result of activation of receptors belonging to the D2 family. The effect of dopamine on a given neuron is conditioned by the type of receptor located on the cell membrane, which determines the increase or decrease of cAMP. The frequency of the individual types of receptors in the human nervous system is as follows: the most common are D1 receptors, followed by D2. The remaining D3, D4 and D5 repeaters are identified the least frequently [8].

In the brain's dopaminergic system, the dopaminergic signal is mainly modulated by the dopamine active transporter (DAT) protein, which actively carries dopamine from the synaptic space back to dopaminergic neurons. The high dynamics of proteins and the speed of penetration through the cytoplasmic membrane of the dopamine transporter may have a significant impact on the regulation of the activity of the dopaminergic system by changing the number of transporters present on the cell surface. Various psychostimulants, which are DAT ligands, affect the speed of penetration of the transporter, which causes rapid penetration or removal of plasma DAT [10].

Neurotransmitters

There are two types of synaptic transmission in the nervous system. When a nerve impulse is transferred from one cell to another by an electrical impulse, there is electrical transmission which occurs mainly during development. A characteristic feature of an electrical synapse is very high speed, two-way action and high transmission fidelity. On the other hand, when a nerve impulse is transferred from one cell to another with the participation of substances acting as a neurotransmitter, we are dealing with chemical transmission. Most of the cells have chemical synapses, and the release of the neurotransmitter requires the presence of ATP

(adenosine-5'-triphosphate), ATPase (adenosine-5'-triphosphatase) and increasing the concentration of Ca2+ (calcium ion). The released neurotransmitter diffuses through the synaptic cleft and binds to dedicated receptors on the postsynaptic membrane [11]. Despite the fact that chemical synapses are slower, they enable signal amplification, they can have an inhibitory or stimulating effect, they are susceptible to modulating factors, and they themselves have the ability to modulate the activities of other cells by releasing substances that activate the secondary messenger cascade. Neurotransmitters are chemical compounds whose molecules carry signals between the neurons of nerve cells, through synapses, and from nerve cells to muscle cells or to glands. A neurotransmitter is used to convert an electrical signal into a chemical signal at the synapse and to transmit this signal from a presynaptic cell to another postsynaptic cell. There are two main classes of neurotransmitters in the nervous system. The first is small-molecule messengers that mediate rapid synaptic conduction and are stored in small vesicles. These include dopamine, glutamate, gamma-aminobutyric acid (GABA), glycine, acetylcholine, serotonin, epinephrine, norepinephrine, and histamine. The second, very numerous group are neuropeptides stored in large vesicles and modulating the transmission of information in the synapse. These include somatostatin, endorphins, opioids, and hypothalamic releasing hormones [12].

Transmission

The work focuses on the characteristics of dopamine, which is a neurotransmitter involved in processes such as coordinated movement control, reward, addiction, hormone secretion and metabolism. Dysregulation of the dopaminergic system is observed in schizophrenia, Parkinson's disease, depression, Attention-Deficit Hyperactivity Disorder (ADHD), nausea and vomiting [13]. Dopamine may also act autocrine and / or paracrine in peripheral tissues [14]. Dopamine is a monoamine. The main site of dopamine synthesis are the midbrain neurons, more specifically the substantia nigra neurons, the ventral tegmental area, and the neurons in the hypothalamus. Dopamine synthesis takes place in two stages. In the first stage, L-tyrosine transforms into L-DOPA (L - 3,4 - dihydroxyphenylalanine) with the participation of the enzyme tyrosine hydroxylase with oxygen, tetrahydrobiopterin and iron (Fe2 +) as a cofactor. On the other hand, in the second stage, L-DOPA is converted into the final dopamine. The above transformation is possible thanks to dopamine decarboxylase [15,16]. L-DOPA is stored in the vesicles of the presynaptic neuron, and after uptake by the vesicular monoamine transporter (VMAT). When the vesicles release dopamine in the synaptic cleft, they can bind to post- or presynaptic dopamine receptors to transmit neuronal signals to the postsynaptic neuron. Dopamine, which is present in the synaptic cleft, is eliminated by conversion (with the participation of the enzymes: monoamine oxidase (MAO) and catechol O methyltransferase (COMT)) to its metabolites: homovanillic acid (HVA), 3-methoxytyramine (3-MT) or acid 3,4-dihydroxyphenylacetic acid (DOPAC). Elimination of dopamine may also occur through uptake into the presynaptic neuron by the dopamine transporter. In the latter case, dopamine is stored in vesicles or broken down into DOPAC or HVA [17].

Molecular basis of addiction

Both nicotine and other substance addictions are serious public health threats worldwide. Research has shown that genetic factors contribute to susceptibility to addiction, but susceptibility genes and their variants remain largely unknown. It has been known for many years that addictions, regardless of the type of psychoactive substance, addiction type or addictive behavior, do not show a simple model of inheritance, but are multi-gene conditioned, which is another reason why one "addiction gene" has not yet been discovered, and the GWAS research genome wide association studies are so difficult in this case. Family, twinning, and adoption studies have shown moderate heritability from nicotine addiction. Estimates of heritability of nicotine dependence range from 54.6% to 69% [18-21]. In a meta-analysis of 17 twin studies, a weighted mean heritability for nicotine dependence was 59% for male smokers and 46% for female smokers (mean 56% for all smokers). Additional studies [19-22] revealed a similar degree of heredity to other smoking-related behaviors, including smoking initiation and cessation.

Many different determinants of addiction have been discovered. These include the influence of the environment, the social context of starting addictive substances, psychological conditions and genetic predisposition that may cause disturbed functioning of certain pathways in the brain. For many years, attempts have been made to explain the mechanism of addiction. The structures of the brain that are most exposed to their action, as well as the neurotransmitter systems and receptor proteins through which they can exert their pathological effects, have been discovered. It has also been established that exposure to psychoactive substances induces significant changes in expression in over 100 genes (including genes of the dopaminergic, serotonergic, signaling pathways) [23,24].

Genome wide association studies have shown promise in identifying causal genes in many diseases including breast cancer, obesity, diabetes or Crohn's disease [25-28]. Genome wide association studies help reveal genetic

variation that explains individual differences within complex phenotypes, including addiction [29].

They focus on the presence of addiction to a specific substance, for example nicotine, alcohol, psychoactive substances. Of the susceptibility genes studied, the *DRD2* gene has received a lot of attention.

The DRD2 gene

The *DRD2* dopamine receptor gene is located on chromosome 11q23; covers an area of 65.56 kb and consists of 8 exons transcribed into 2.713 kb mRNA. As a result of its translation, a receptor protein consisting of 443 amino acids is formed [30]. The expression of the D2 receptor gene may take up to 2 isoforms: short D2S and long D2L. The effect of skipping exon 6 of the *DRD2* gene in the course of transcription, producing a protein that is 29 amino acids shorter ("short" – S) [30]. In animal studies, Maldonado et al. observed that in mice lacking the D2 receptor (knockout), an abolished reward effect on administered morphine was characteristic, and in the site preference test, with a current response to searching for food [31]. The *DRD2* receptor (present, among others, in the nucleus accumbens) plays an important role in the reward system, in the transmission of information. The weakening of this conductivity is a significant risk factor for the onset of clinical features that are associated with reward system deficiency syndrome [32].

The study analyzed the following polymorphic sites in the *DRD2* gene:

1. The rs1076560 polymorphism

Single Nucleotide Polymorphism (SNP) located in intron 6; it comes in two allelic forms: adenine (A) and cytosine (C). Studies have found that this polymorphism is associated with addiction to opioids [33] and cocaine. [34,35]. In one of the studies devoted to the genetics of schizophrenia, the presence of the allelic form A was noticed, influencing the availability of the dopamine D2 receptor in the striatum, which was related to the predominance of the longer L form of the D2 receptor protein [36].

2. The rs1079597 polymorphism

It is located in the intron 1 of the gene; single nucleotide polymorphism. It is a splicing polymorphism [30]. There are two allelic forms of polymorphism: the adenine form (A) and the cytosine form (C). The above polymorphism is related to addiction, among others, to heroin [37,38] and alcohol [39].

3. The rs1799732 polymorphism

The rs1799732 polymorphism (also referred to as -141C Ins / Del) is a cytosine insertion / deletion (C) polymorphism located in the 5 'region of the *DRD2* gene. This variant has been shown to be a functional polymorphism that has the potential to alter the expression of the *DRD2* gene in vitro (Arinami et al., 1997) and to affect the binding of the striatal *DRD2* receptor [40,41]. It is related to nicotine addiction [42].

Conclusions

This work presents several currently discussed biological mechanisms, especially at the molecular and genetic level, involved in the process of addiction to various psychoactive substances. Further research at the molecular level may result in the modification of psychotherapy and pharmacotherapy in terms of their personalization. The *DRD2* polymorphisms can be used as diagnostic biomarker for susceptibility to addictive substances. The level of *DRD2* gene polymorphisms expression could be crucial in diagnostics of the addiction nature, whether it is behavioral, or the cause lies in neurotransmission, which will enable to establish individualized pharmacotherapy or psychotherapy. Further studies could provide answer if association of *DRD2* expression with addiction is causation or correlation.

Conflict of interest

The authors have declared no conflict of interest.

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Otrzymano: 09.08.2022
Zrecenzowano: 26.08.2022, 06.09.2022
Przyjęto do druku: 26.09.2022