Evidence for the similar biochemical background for psychiatric disorders and psychoactive substances addiction

Dowody na wspólne biochemiczne podłoże zaburzeń psychicznych oraz uzależnień od substancji chemicznych

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Abstract

Nowadays, the effects of psychoactive substances dependence are becoming more severe and acute on the social level, so this topic of research appears in the orbit of interest to many sub-disciplines, such as psychiatry, neuropsychology, neurosciences and biochemistry. The authors conducted a literature review devoted to psychiatric disorder and addiction to alcohol and other psychoactive substances in order to present evidence for the similar biochemical and neurophysiologic background for both of the mentioned above disorders. In this paper there are presented data of animal models, neuroimaging techniques and neuropsychological tests. Moreover, the authors of this paper try to identify the possible link between personality traits (e.g. impulsivity or novelty seeking) or inborn properties of the central nervous system and the development of addiction that can gradually lead to irreversible brain changes. The authors also address the phenomena of self-medication among schizophrenic patients using regularly tobacco. In the article there is also discussed the potential application of psychostimulants in the treatment of disorders such as Attention Deficit Hyperactivity Disorder (ADHD) or narcolepsy.

Keywords: addiction, psychiatric disorders, neuroimaging techniques

Streszczenie

Współcześnie skutki uzależnienie od substancji psychoaktywnych stają się coraz bardziej dojmujące na poziomie społecznym, dlatego ta tematyka badań pojawia się w orbicie zainteresowań wielu dyscyplin, takich jak: psychiatria, neuropsychologia, neuronauki czy biochemia. Autorzy dokonali przeglądu literatury poświęconej zagadnieniom genezy zaburzeń psychicznych, jak również uzależnienia od alkoholu oraz substancji psychoaktywnych, w poszukiwaniu dowodów świadczących o podobieństwach w etiologii na poziomie biochemicznym oraz neurofizjologicznym. W poniższym artykule przedstawione zostaną dane pochodzące z modeli zwierzęcych, technik neuroobrazowania oraz testów neuropsychologicznych. Ponadto omawiane są także związki pomiędzy niektórymi cechami osobowości takimi jak impulsywność czy poszukiwanie nowości a wrodzonymi właściwościami ośrodkowego układu nerwowego, które mogą wpływać na rozwój uzależnienia. Autorzy pochylili się także nad zagadnieniem używania wyrobów tytoniowych przez osoby chorujące na schizofrenie w kontekście samoleczenia. W poniższym artykule zostało omówione także zastosowanie substancji psychoaktywnych w leczeniu zaburzeń takich jak: zespół nadpobudliwości psychoruchowej z deficytem uwagi (ADHD) czy narkolepsja.

Słowa kluczowe: uzależnienie, zaburzenia psychiczne, techniki neuroobrazowania

Introduction

All organisms strive to maintain homeostasis, a process that is defined as a tendency of equilibrium in all their systems, including the brain reward system, which is crucial in the drug addiction [1]. When a threatening environmental factor occurs, such as e.g. stress or a psychoactive substance, the body activates the allostatic process (by varying internal parameters) to regain stability. This, in turn, may lead to profound energy loss if the factor keeps impacting on the organism, and 'the system is at the limit of its capability, and thus a small challenge can lead to breakdown, which is the beginning of spiralling distress and the addiction cycle' [1, p. 56]. In light of this theory, the authors would like to prove that drug addiction, like all illnesses, with the particular emphasis on mental disorders, is the result of imbalanced homeostasis**.** To support this view, there will be presented data of animal models, neuroimaging techniques and neuropsychological tests. The other goal of this paper is to identify the possible link between personality traits (e.g. novelty seeking) or inborn properties of the central nervous system and the development of addiction that can gradually lead to irreversible brain changes. Moreover, the emphasis will also be placed on selected modes of addmedical use of particular drugs applied in the treatment of various disorders.

Use of cannabis among patients with schizophrenia

Recent research has proven the hypothesis of a possible link between drug addiction and mental disorders, because both may reflect improper functioning of specific brain neurotransmitters systems. This statement was proposed, since drugs mimic the action of neurotransmitters at postsynaptic receptors, which leads to either releasing them or behaves as antagonists. Moreover, both drug addiction and psychiatric disorders may be manifested in similar behavioural actions, such as psychosis, delusions or auditory hallucinations, the major components for both amphetamine abuse and schizophrenia [2]. In light of the dopamine theory of schizophrenia, the tie between these two, i.e.\ drug addictions and mental illness, seems to be even more discernible. Psychostimulants, such as cocaine and amphetamine, increase dopaminergic transmission in the nucleus accumbens, while schizophrenia is manifested by significant dopaminergic innervations of the prefrontal cortex and other limbic regions [3].

In this article, authors wish to substantiate the cannabis effect on the potentiality of mental disorder development, as well as to show the link between deterioration among schizophrenic patients and use of marihuana in their adolescence. A study conducted on mice [4] has proven that activation of CB1 receptors in the amygdala (particularly basal – lateral complex) leads to reduction of GABAnergic response, which results in the excitation of pyramid cell in the amygdala. GABA inhibition of the inhibition of pyramid cell is manifested in increased activation of dopaminergic receptors and decrease in corticotrophin-releasing hormone in the central nuclei of amygdala. It was also discovered that knock-out mice did not develop cannabis dependence. These two findings seem to be of priority, given their reference to disorders like schizophrenia. A supposition can be hence stated that psychiatric patients, who suffer from all negative symptoms, like e.g. lack of emotional reactivity, inability to experience pleasure (anhedonia) or anxiety, will experience mild euphoria after smoking cannabis (it is also relevant to smoking tobacco, which will be discussed later). However, a longitudinal study [5] proved that first-episode schizophrenia patients, who use cannabis showed a more pronounced brain volume reduction, particularly over a 5-year follow-up than patients with schizophrenia who do not use cannabis. Another longitudinal research (15 years) revealed that the relative risk for schizophrenia among high consumers of cannabis was 6.0 compared with non-users [6]. It was also observed that the endogenous cannabinoid system is altered in schizophrenia; the enhanced cerebrospinal fluid anandamide levels were documented [7].

The link between the use of tobacco and alcohol and psychiatric disorders

An unusually high ratio of smokers has been noticed among schizophrenic patients. It can be triggered by stimulating qualities of nicotine [8]. Nicotine increases mesolimbicocorticol dopaminergic activity in the nucleus accumbens and the prefrontal cortex. Reduction of brain activity in the area of prefrontal cortex is associated with apathy, anhedonia and lack of motivation, one of the core symptoms of schizophrenia. Nicotine is released in the nucleus accumbens, likewise in the prefrontal areas, thus working as reinforcement, as well as other known addiction like cocaine or amphetamine. In light of this evidence, it is highly probable that schizophrenic patients gain a kind of alleviation, while smoking. So, becoming addicted seems to be a subconscious way of self-medication. To show patients' urge to smoke [9] it is worth citing the result of the study conducted at the one of psychiatric wards reporting that 'significantly more verbal assaults and prescribing of medications for anxiety occurred immediately after the smoking ban.'

A study has also shown that alcohol abuse can contribute to psychosis and delusions, labelled as the Korsakoff's syndrome, which is manifested in anterograde and retrograde amnesia, severe memory loss and confabulation. High alcohol consumption leads not only to irreversible brain changes, such as damage to neural cells, but it also alters an individual's behavior, even after a long time of abstinence. A study [10] conducted on rats showed that ethanol-vapor-exposed animals experiencing acute withdrawal and protracted abstinence spent a significantly lower amount of time exploring the open arm of elevated plus maze, compared to control rats. The above-mentioned effect is likely due to the behavioral changes associated with negative symptoms of withdrawal. The same paper also demonstrated that rats injected with CRF receptor antagonist proved attenuation of increase in ethanol self-administration. It suggests that CRF plays a key role in the stress response. Neuropsychological tests conducted on Korsakoff's syndrome patients revealed profound deficits in short term memory and implicit learning [11]. The same study, thanks to neuroimaging techniques, showed brain volume shrinkage, especially in the regions such as mammillary bodies, thalamus, pons and anterior superior vermis. Scientists also noted bilateral deficits in a hippocampus, which is believed to be the cause of poor performance in the memory tasks. What occurred to be a really riveting finding was that deficits in hippocampal volumes bilaterally were equivalent to those among Alzheimer's disease patients. It supports the clinical knowledge about deep amnesia among Korsakoff's syndrome patients. Although during the protracted abstinence some brain abnormalities may be partially reversible, it is highly unlikely for the individual to gain full recovery.

Findings from neuroimaging techniques and neuropsychological tests

Thanks to the neuroimaging techniques, it is also known that intoxication with substances like alcohol, cocaine, morphine and amphetamine results in lower glucose metabolism in many areas of the brain, particularly in the above mentioned prefrontal cortex and anterior cingulate gyrus [12]. Most research studies documented abnormalities in the brain functioning among alcohol and cocaine withdrawal subjects that presented lower striatal dopamine response. Lubman et al. [13] substantiated long lasting influence of cocaine and alcohol on the brain by presenting under-activity of orbitofrontal cortex and anterior cingulated cortex not only among addicts but also among people refraining from them for lengthy periods. What transcranial doppler studies examined was perfusion deficit in anterior and middle brain circulation in the group of cocaine addicts. This puts psychostimulants abusers at a higher risk of cerebrovascular disease, such as stroke and aneurism rapture. The same study has also shown hypoperfusion in the putament and temporal cortex among cocaine users. It seems to be crucial to mention learning and memory circuit in addiction. A study [14] has shown not only the habit learning was involved in the drug abuse, but also conditioned – incentive learning and declarative memory. Images obtained with fMRI showed changes in the activation of particular regions responsible for learning and memory processes, such as nucleus accumbence, amygdala, putamen and hippocampus. These findings seem to be promising, because they direct our attention to a still broader issue like the whole environment of the addicted person. In parallel to medical research devoted to substance abuse treatment, it may be reasonable to figure out the effective way to support an individual gradually coming back to society, in particular to the neighbourhood when he used to take drugs.

Moreover, it is worth mentioning that whatever biological changes take place in the organism, is the effect is also manifested at the psychological or behavioural level. Researchers investigated deficits both in the verbal memory and non-verbal one among two groups: chronic schizophrenics and drug addicts, although subjects from the former group performed worse in the Words Memory test [15]. Researchers [16] seem to confirm these results, outlining the neurocognitive impairments among cocaine users, such as deficits in verbal and visual memory tasks. Furthermore, to stress short time changes in the cognitive performance it is crucial to show results of neuropsychological tests conducted among opioid withdrawal patients. The results of the tests undertaken by research studies show the correlation between fluid intelligence and the days of withdrawal. It proves that the more days of withdrawal were noticed, the better scores in the fluid intelligent test the individual got [17]. It also indicated a similar correlation between time of withdrawal and complex working memory. Poor performance in the cognitive tasks among drug addicts can be explained by prefrontal cortical volume reduction, which is responsible for complex executive functions such as planning or problem solving, prominent components in many neuropsychological tests.

Similar biochemical background for addiction and obsessive-compulsive disorder

There is an idea in the field of latest research that there may be a link between addiction and obsessive–compulsive disorder (OCD). Some models of addictions claim that it starts with impulsively taking a given substance and then as one administers the substance, one gradually loses the ability to control. Thus, from that point on, the addiction becomes a compulsion. Many addicted people talk about intrusive urge to take the drug, so as ODC patients who cannot help the urge to do their rituals (e.g. checking if the oven is plugged in or pulling hair). Another similarity was noticed at the level of brain structures. In both disorders a key player seems to be ventral striatal ventral pallidal thalamic loop to be responsible for compulsive behaviors (such as washing hands, counting, but also drug seeking) A few studies also examined the neural basis for the link between OCD and addiction [18]. Similar to alcohol and cocaine craving, abnormalities in the activity in the orbitofrontal cortex were also observed in the pathology of obsessive-compulsive disorder. As mentioned above, striatal region may play a critical role in addictions, but as well in OCD.

A recent study [19] conducted on rats showed that temporary inactivation of the central striatum has an anticompulsive effect in the rat model of OCD. The intrastriatal disconnection procedure (selective, unilateral lesion of the nucleus accumbens core and infusion of a dopamine receptor antagonist into the contralateral dorsolateral striatum) that was performed on rats taught to press the lever to obtain cocaine, led to diminish compulsive behaviour [20]. Undoubtedly, there are some similarities in the drug addiction and OCD, but it is worth remembering that obsessions in OCD patients generate anxiety and fear, while among drug addicts there is the same effect. Moreover, although both in the case of drug abuse and OCD, similar areas in the brain seem to be struck, like prefrontal cortex and anterior cingulate gyrus, the first study showed lower glucose metabolism [21]. As far as OCD is concerned, researchers discovered increased glucose metabolism [22]. Nevertheless, prefrontal cortex appears to be hypoactive mostly during withdrawal, while during exposure to drug related cues, an activation of this region was discerned. This finding seems to be of particular

importance, especially for psychologists and social workers who aim at helping addicted people realize that even a thought of a drug can lead to an activation of the brain area responsible for the decision-making process.

Relation between traits of personality – novelty seeking and addiction

Impulsivity, viewed as a trait of personality, has been studied in many papers. There has been a hypothesis that people characterized by novelty seeking can be more prone to the addiction then others. Studies also tried to bind different levels of impulsivity and substance abuse, especially in animal studies. Belin et al. [23] proved that rats exhibiting high levels of novelty-induced locomotor activity showed increased sensitivity to the reinforcing effects of addictive drugs. Other animal models revealed that high impulsivity is linked to elevated alcohol self-administration among rats [24]. Human studies [25], in turn, proved that poor response inhibition predicted aggregate alcohol-related problems, the number of illicit drugs used and comorbid alcohol and drug use among adolescents. Bearing in mind the above, it is highly possible that disorders characterized by impulsive behavior, such as ADHD or OCD, can have similar origins as drug addiction.

To partially rebut the aforementioned arguments that drugs of abuse have mostly the harmful effect on the body, such as changing the dopaminergic or GABAinergic circuits in the brain, indeed, there are some medical usages of psychoactive substances. Psychostimulants, such as e.g. amphetamine, are used in the ADHD (Attention Deficit Hyperactivity Disorder) treatment among children. Admittedly, there seems to be no scientific basis to give already overactive children substance leading to increase motor activity, but it was demonstrated that amphetamine improves attention levels. To support this statement, authors will present data derived from the animal model of ADHD (the Spontaneously Hypertensive Rat) [26]. It was observed that striking impulsiveness, hyperactivity and poorer sustained attention during baseline conditions in the Spontaneously Hypertensive Rat (SHR) were improved by treatment with amphetamine isomers. The results of the mentioned above research present an interesting finding that the lowest dose of d-amphetamine and low-to-medium doses of l-amphetamine improved sustained attention, while the highest dose of d-amphetamine used interfered with SHR behaviour. It is also worth mentioning that amphetamine in high doses was used in the treatment of narcolepsy, a chronic sleep disorder, characterized by excessive daytime sleepiness.

Conclusion

In conclusion, this papers offers an insight into the relations between the molecular level of addiction, such as e.g. that of stimulant drugs on preventing dopamine reuptake, the structural level manifested in changes in the brain functions, and the product of these two: disruption of actions and cognition on the behavioural level. Further studies should be conducted to examine if these changes are long lasting and persist even in the period of abstinence. A considerable weakness of the quoted articles is undoubtedly the quantity of groups that varies from several to several dozens. It can severely diminish statistical power of the described results. What authors find genuinely interesting as a field for further studies is the link between higher response to novelty and vulnerability for drug addiction. In particular, authors would rather concentrate on individuals' disposition to seek novelty, which was studied, to establish if it is correlated with higher basal of corticosterone and higher level after amphetamine injection [27]. A study conducted on rats confirmed that several amphetamine injections have a similar effect as chronic stress, but scientists are not unanimous if it is possible to extrapolate it into humans. If this finding were also applicable with human beings, it would pave way for a new approach in the field of addiction prevention.

The next question to ponder is whether we can modulate inborn level of novelty seeking by changing an individual's environment. If this way of thinking is reasonable, we would be able to decrease human vulnerability of drug addiction in adult life, by depriving children of redundancy of stimuli, causing stress and elevating cortisol level. The chances are that this assumption would lead us to work with the youngest members of society, coming from a high-risk environment, who are constantly exposed to stressors, to help them refrain from taking drugs.

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