ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN – POLONIA
VOL. XXIV, N 1, 18 SECTIO DDD 2011

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Psychostimulant drugs – pharmacology and pharmacotherapy of addiction

Środki psychostymulujące – farmakologia i farmakoterapia uzależnienia

INTRODUCTION

Psychostimulants are psychoactive drugs which induce temporary improvements in either mental or physical function. Psychostimulants include a diverse class of drugs exhibiting central nervous system (CNS) stimulant properties, and have a high abuse potential. The most popular are following: amphetamine, methamphetamine, cocaine, methylphenidate and ecstasy. They are widely used throughout the world as prescription medicines, e.g. methylphenidate in the attention deficit hyperactivity disorder (ADHD) syndrome at children, and as illicit substances of recreational use or abuse. They produce a variety of different effects by enhancing the activity of the central and peripheral nervous system. Common effects, which vary depending on the substance used, may include enhanced alertness, awareness, wakefulness, endurance, productivity and motivation, increased arousal, locomotion, heart rate and blood pressure, as well as the perception of a diminished requirement for food and sleep. Many stimulants are also capable of improving mood and relieving anxiety, and some can even induce feelings of euphoria. It should be noticed, however, that many of these drugs have ability to cause anxiety, even the ones that may paradoxically reduce it to a degree at the same time [5,9,16].

Nowadays, derivatives of amphetamine are one of the most often used illegal stimulant substances in the world. Psychostimulant-induced dependence constitutes really important health and social problem for which no effective treatments currently exist. As it was mentioned above, these compounds may lead to psychological dependence and to serious threat for the proper functioning of the body and even death. That is why, understanding of the pathological processes underlying addiction is essential for effective treatment [16].

MECHANISMS OF ACTION OF PSYCHOSTIMULANTS

Neurological mechanisms underlying stimulant drugs' dependence aren't fully elucidated. Drugs of abuse, including cocaine and amphetamine, elevate extracellular dopamine levels in the brain,

thereby altering the activity or plasticity of reward circuits and precipitating addiction. Dopamine transporter and vesicular monoamine transporter play pivotal role in the action of amphetamine. Due to structural similarity, methamphetamine, one of the most commonly used psychostimulants, substitutes for monoamines at membrane-bound transporters, namely the dopamine transporter (DAT), noradrenaline transporter (NET), serotonin transporter (SERT) and vesicular monoamine transporter-2 (VMAT-2). VMAT-2 is situated in vesicular membranes, while active DAT, NET and SERT are cell surface integral membrane proteins [24,30]. Methamphetamine redistributes monoamines from storage vesicles into the cytosol by reversing the function of VMAT-2 and disrupting the pH gradient that otherwise drives accumulation of monoamine in the vesicles. The endogenous function of DAT, NET and SERT is reversed, resulting in release of dopamine, noradrenaline and serotonin from the cytosol into synapses. Synaptic monoamines are then available to stimulate postsynaptic monoamine receptors. Methamphetamine increases monoamine metabolism by inhibiting monoamine oxidase [30]. Major CNS dopaminergic circuits include the mesocorticolimbic circuit and the nigrostriatal pathways [33]. Noradrenergic regions of particular interest include the medial basal forebrain, which mediates arousal; the hippocampus, involved in memory consolidation; and the prefrontal cortex (PFC), which processes cognitive functions [2]. Serotonin neurones are distributed widely throughout the brain and regulate variety of functions including reward, hyperthermia, respiration, pain perception, sexual behaviour, satiety, impulsiveness, anxiety and higher cognitive functions [14,34]. The processes mentioned above are much more complicated than it seems. There are several factors adding essential complexity to understanding psychostimulant effects upon monoamines. First of all, multiple receptor subtypes exist for noradrenaline, dopamine and serotonin, with distinct binding affinities, second-messenger effects and CNS distribution. Secondly, neuronal pathways interact with each other [e.g. monoamine neurones modulate excitatory glutamate neurones and inhibitory gama-aminobutyric acid (GABA) neurones]. Finally, some effects of amphetamines are mediated peripherally. Basic dopamine function also appears to influence the response to amphetamines. Low D2-receptor density is associated with a pleasant response to exogenous stimulants while high baseline D2-receptor density may produce unpleasant responses [3,31].

As it was said at the beginning of the article, psychostimulants powerfully activate the dopamine system and have serious abuse potential. Repeated psychostimulant intake induces neuronal plasticity within the mesolimbic dopamine system. There are numbers of evidences that repeated amphetamine exposure results in a suppression of intrinsic neuronal excitability in the ventral subiculum, the hippocampal region that activates dopamine neurotransmission. The mesocorticolimbic dopaminergic pathway, which originates from the ventral tegmental area (VTA) and projects to the nucleus accumbens (NAC), amygdala, (PFC) and other forebrain regions, plays an essential role during the development of behavioural sensitization [17]. What is more, abuse of psychostimulant drugs may lead to tolerance that is exhibited by the need of higher doses of the drug to produce the same desired effects. Therefore, users may try to intensify the drug's positive effects by increasing the drug dosage, taking it more often or changing the route of administration leading to the possibility of drug abuse, toxicity or misuse. In toxic doses, the psychostimulants begin to produce unpleasant CNS symptoms including anxiety, agitation, hallucinations, delirium, seizures, and death. High-dose, long-term use of stimulants can induce an acute psychotic state in previously healthy individuals.

CNS-related abnormalities, seizures, or muscular hyperactivity may induce hyperthermia. Secondary rhabdomyolysis may also occur. Cardiovascular manifestations include hypertension, tachycardia, arrhythmias, and myocardial ischemia. Cerebrovascular accidents are precipitated by elevated blood pressure or drug-induced vasospasms. And when it comes to psychiatric symptoms of intoxication, schizophrenic symptoms, maniac-like states, psychoses, depressions (especially during withdrawal), and various types of anxiety conditions including panic states can be seen [20,21]. Psychotic symptoms usually arise with chronic abuse but may also appear acutely with large doses of stimulants. All these adverse effects of psychostimulants intake lead to serious complications, that is why treatment of stimulants abuse is so necessary.

USE OF PSYCHOSTIMULANTS IN MEDICAL PURPOSES

It is important to emphasize that a number of synthetic stimulants, including amphetamines, are useful medications in the treatment of some diseases. They include ADHD, obesity, narcolepsy, excessive daytime sleepiness. Cocaine is still used clinically as a local anaesthetic, primarily for eye, ear, nose or throat procedures. Nowadays they are prescribed in palliative care, as opioid induced sedation, cognitive dysfunction and fatigue are very frequent and severe symptoms in patients with cancer. The psychostimulants are becoming increasingly important as pharmacological options in the treatment of these symptoms. They are well tolerated with prudent dosing and attention to response. Furthermore, psychostimulants are drugs of choice for treating depression in patients with prognosis of less than 3 months because they may not live long enough to benefit maximally from a conventional antidepressant [4]. It is possible to achieve a response in a few days by increasing the dose gradually until undesirable effects or benefit occur. Stimulants may relief drowsiness related to opioid intake. They improve psychomotor performance and allow opioid dose escalation to a higher level than would otherwise be possible. This can be particularly helpful for patients experiencing breakthrough pain [15].

Commonly accepted indications for psychostimulants include ADHD and narcolepsy. ADHD is characterized by attention deficit, impulsivity, and sometimes overactivity (“hyperactivity”). It seems that at least part of these mechanisms is regulated by the activity of the dopaminergic system in the PFC. Most of the drugs, which are characterized by their effectiveness in reducing symptoms of ADHD, impact on this circuit [18]. As already mentioned, psychostimulant substances act by increasing dopamine release from nerve terminals and inhibiting reuptake of the neurotransmitter by the presynaptic neurons. In general, these kinds of drugs, which can be divided into amphetamines and methylphenidate, are effective in reducing the severity of axial symptoms of ADHD in 65% -75% of people with this disorder. In a significant, although slightly lower percentage of patients have improvement of impaired functioning associated with ADHD, such as aggressive behaviour and learning difficulties. Methylphenidat is drug of choice in this case [18,32].

POSSIBILITIES OF PSYCHOSTIMULANT DEPENDENCE TREATMENT

Psychostimulant abuse is a serious social and health problem and currently there is no effective treatment. Cognitive behavioural therapies, alone or in combination with psychotropic medication,

are accepted as therapeutic approaches for cocaine dependence. It is also accepted that over the long term the combination of psychotherapeutic treatments is usually more effective than any single approach, they have not been approved by health authorities as treatment for addictions. However, pharmacological treatments are under investigation. Substitution therapy involves the replacement of abused drug, which is often illegal, used several times a day, by a legal, orally administered one. A substitutive drug has similar effects to the abused one, but with a lower addictive potential therefore leading to drug abstinence and involving patients to follow medical and psychological assistance. Most of the clinical progresses in addiction treatment are focused on the elimination of physical dependence and withdrawal syndromes and don't target the psychological symptoms of addiction including drug craving and relapse during abstinence. Unfortunately, at present there is not any available method to treat psychostimulant craving and relapse through the known molecular mechanism [26]. Taking into account the general concept that midbrain dopamine is essential for the development of drug addiction, several dopamine agonists and antagonists have been tested [6]. The results demonstrate that although dopamine antagonists can block acute drug-induced behavioural activation, they cannot limit drug craving. There are several studies where D1 receptor agonists or D2 partial agonists were able to reduce cocaine craving and relapse. As that a thorough understanding of the molecular mechanism in behavioural sensitization to psychostimulants could be effectively used in a therapeutic drug program against drug addiction [25,34].

TREATMENT OF ABUSE

Behavioural therapies are the standard treatment for methamphetamine abuse and dependence, although inpatient treatment is sometimes used. Cognitive behaviour therapy and contingency management programmes have been successfully used in treating cocaine addiction and may have some benefit in treating methamphetamine addiction [19,23]. The vast majority of clinical research has focused on cocaine rather than other psychostimulants such as amphetamines and methylphenidate, because cocaine abuse is the most known of other psychostimulants [11]. There are some strategies in the treatment of drug abuse, as following: (1) functional-antagonists treatments which block the euphoric effects of cocaine and extinguish illicit drug use; (2) functional-agonists treatments which replace some of the pharmacological effects of cocaine, thereby stabilizing neurochemistry and behaviour; and (3) treatments that attenuate symptoms of cocaine toxicity or withdrawal [11,13]. There are studies suggesting that the GABAergic systems may be a useful pharmacological target for cocaine medications development, although additional, larger scale clinical trials are clearly warranted [29]. For example, baclofen is an antispasticity agent that is a nonselective $GABA_{\beta}$ agonist. In a placebo-controlled study in cocaine dependent subjects, baclofen treatment enhanced cocaine abstinence in comparison to placebo [27]. Tiagabin is a drug that increases synaptic levels of GABA by inhibiting GABA transporters. A recent placebo-controlled study reported that tiagabine attenuated cocaine use [10]. Tricyclic antidepressants are the best-characterized class of medications for the treatment of cocaine dependence. It turned out that desimipramine was effective in reducing relapse to cocaine use. Numerous medications have been evaluated for treatment of cocaine dependence that includes a wide range of pharmacological targets. Reviews of the clinical literature have reported no significant benefit from antidepressants or dopamine agonists for cocaine dependence [7,28].

Antagonists' strategies designed to block the euphoric or positive effects of psychostimulants with antipsychotic medications have included risperidone[12], flupenthixol [8] and olanzapine [22] and have yielded negative clinical outcome. Several novel approaches that have shown some clinical promise include disulfiram, a well-established medication for treatment of alcoholism. A recent review also reported promising results for agonist-like stimulant medications in the treatment of cocaine and amphetamine dependence [7,13,28].

TREATMENT OF ACUTE INTOXICATION

In terms of acute intoxication, symptomatic treatment should be taken into consideration. Benzodiazepines are indicated for seizures or agitation, and antipsychotics may be necessary in patients with paranoia. In case of sympathetic system stimulation (high blood pressure, tachycardia), alpha- and beta-blockers (e.g. labetalol, propranolol) are used with great care. Cooling measures may be required when hyperthermia occurs [1,19].

SUMMARY

Currently, no effective pharmacotherapy for psychostimulant abuse has indicated efficacy for long-term use. A better understanding of the neuropharmacological effects of cocaine and related psychostimulants has supported efforts to develop and improve useful medications for psychostimulant abuse and dependence. Functional agonist treatments may be used effectively to stabilize neurochemistry, influence behaviour and lead to long-term abstinence. Similarly, medications that target glutamatergic and GABAergic function are reasonable candidates that have received significant attention, and some have demonstrated effectiveness in reducing cocaine use and enhancing cocaine abstinence. However, these encouraging results will require additional clinical studies in order to identify safe and efficacious pharmacotherapies. Pharmacological mechanisms that may underline stimulants dependence were presented in this article. Furthermore, advances in pharmacotherapy were discussed.

Keywords: psychostymulants, drug of abuse, addiction, amphetamine, cocaine.

STRESZCZENIE

Obecnie nie ma efektywnego leczenia farmakologicznego uzależnienia od środków psychostymulujących, które wykazałoby skuteczność przy długotrwałym stosowaniu. Lepsze zrozumienie działania kokainy i jej podobnych substancji przyczynia się w znacznym stopniu do znalezienia leków skutecznych w leczeniu uzależnienia. Wykorzystanie agonistów różnych typów receptorów może być skuteczne do stabilizacji procesów neurochemicznych, może mieć wpływ na zachowanie oraz doprowadzić do długotrwałej abstynencji. Natomiast leki, które wpływają na funkcjonowanie układu glutaminianergicznego wykazały skuteczność w zmniejszaniu użycia kokainy i sprzyjały abstynencji. Jednak te obiecujące wyniki wymagają dodatkowych badań klinicznych w celu określenia bezpiecznej i skutecznej farmakoterapii. W artykule przedstawiono

neurobiologiczne mechanizmy leżące u podstawy uzależnienia od środków psychostymulujących. Przedyskutowano także postępy w farmakoterapii.

Słowa kluczowe: psychostymulanty, środki uzależniające, uzależnienie lekowe, amfetamina, kokaina.

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