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How Drugs and Stress Alter the Human Metabolism: A Mini Review

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Abstract

Humans are born with the metabolic ability to adapt to various different conditions and threats in order to secure survival. Thereby the continuous aim is to maintain homeostasis, to keep the body in a functional state. This review paper aims to discuss metabolic alterations when the body's homeostasis is disturbed by environmental or chemical factors. Different research papers revealed a high metabolic suggestibility initiated from different influences, especially alcohol, cannabis, 3, 4-Methyl enedioxy methamphetamine (MDMA) and stress as discussed in the following. Alcohol, known for disrupting neurotransmitter pathways, leads to alterations in hormone production, as well as impaired motor functions and pain recognition. Furthermore, its metabolic end-products disturb metabolic energy pathways and result in increased fat storage. Cannabis' active molecules, Δ9-trans-tetrahydrocannabinol (THC) and Cannabidiol (CBD), interact with receptors resulting in psychoactive effects such as a mental high, pain relief and paranoia, but not altering the metabolism to a great extent, unless abused by individuals. MDMA, a psychoactive drug, enhances pro-social behavior by altering hormone levels. Stress, a metabolic response to mental or physical threats, is known to have beneficial effects, in order to help the body resist threats. Chronic stress is known to depress the immune system, causing brain damage, as well as diabetes or even cancer, and the same applies to traumatic stress, which is defined by severe acute stress.

Keywords

Homeostasis, Trauma, Chronic Stress, MDMA, Alcohol, Cannabis

1. Background

Metabolism is an integrated network of catabolic and anabolic reactions, which maintain the balance between energy consumption and the construction of new cell components. It enables the body to keep living, growing and dividing. There are many metabolic pathways in the human body, that all interact with each other in a complex way, to ensure an adequate regulation and maintenance of the bodies' homeostasis. The main metabolic reaction is the conversion of nutrients to energy which will be used for the cellular processes or to form lipids, proteins, nucleic acids, and carbohydrates from available building blocks, but also the elimination of wastes such as ammonium, in the form of urea and uric acid. When the environmental or physiological conditions change, the metabolism of the individual will change accordingly, in order to enable the individuals body to maintain homeostasis. These changes may include cold or hot temperatures, dietary changes, drug consumption, stress, diseases and more. Usually these metabolic changes cannot be sustained for a long period of time, which can result in harmful and permanent alterations of body functions, if conditions are persistent [1].

Various factors affect the human metabolism, from changes in the surroundings, to emotional and physical stress, to various drugs. The effects of various conditions and substances on the human metabolism are of great importance today, as with each year there is an increase in drug use and abuse as well as stress levels being observed in the modern world.

1.1. Alcohol Effects on Human Metabolism

With millions of liters flowing each year and entire

festivals dedicated to drinking it, alcohol is one of the most commonly used drugs in the world. But like every other natural stimulant, alcohol has a huge influence on the human body, thus also affecting its metabolism.

Alcohol is a water-soluble molecule that can easily enter the blood circulation and even pass through the blood brain barrier. The most commonly consumed alcohol is ethanol, consumption is believed to alter the release of inhibitory neurotransmitters - serotonin, dopamine and γ-amino butyric acid (GABA), as well as the excitatory – glutamate, that will influence the several areas in the brain, which in turn will result in the production of a sense of euphoria or relaxation, stimulation of stress response, pain relief, impact the menstrual cycle, decrease growth hormones secretion, increased appetite and more. In case of chronic alcohol abuse, neurotransmitter pathways are altered in the brain. This will result in alcoholism. Its effects include blunted stress response, alcohol use disorder, immune dysfunction, decreased fertility, hypogonadism, a decrease in thyroid hormones, growth retardation, type two diabetes, fatty liver and more.

Since alcohol is a toxin, it is metabolized in the body by the enzyme aldehyde dehydrogenase, needed in the oxidative pathways that will results in the formation of acetyl CoA. In this reaction NAD^+ is reduced to NADH and the cellular NAD^+/NADH ratio is lowered. Excessive levels of NADH inhibit important metabolic pathways, such as glycolysis, gluconeogenesis or the citric acid cycle. It will lead to an increased fat storage which will result in weight gain [2−6].

There are however different factors that can modify the elimination of alcohol in the human body, such as a person's sex, age or even race. Whether a person is physically active also contributes to the blood alcohol concentration, as well as being either in a fed or a fasted state [4].

1.2. Cannabis Effects on Human Metabolism

Alcohol is not the only "drug" to be commonly abused by people in our days. There are also drugs like cannabis and MDMA that are progressively being used by the youth of today.

The mechanism by which cannabis exactly affects the human body is still only vaguely understood. One of the common interactions that the plant derivative tetrahydrocannabinol (THC) seems to have in the human body, is with the two cannabinoid (CB) receptors – receptors Type 1 and Type 2, which are currently targeted for therapeutic drug development [7]. The CB receptors are a type of G-coupled cell membrane receptor in the human body that is responsible for feeling hunger, memory, mood and other sensations. These receptors seem to be present in the lungs, liver and kidneys and similarly structured cannabinoid receptors, also found in the human brain.

Cannabidiol (CBD) on the other hand interacts mostly with non-cannabinoid sites of CB1 and CB2, due to this they often allosterically inhibit the binding of THC in a process of negative allosteric modulation (NAM) [8].

Cannabis, more commonly known as Marijuana, is part of the Cannabaceae family. This plant is of particular interest for multiple reasons: it has psychoactive and cognitive effects on the human body and is widely used in treating developing neurological diseases. It contains various molecules of phytocannabinoids [9]. The two previously mentioned active molecules are of special interest as Δ9-trans-tetrahydrocannabinol is psychoactive, commonly used by large groups of the community, while CBD is non-psychoactive.

Cannabis and its derivatives serve as anticonvulsants that are commonly used in the treatment of epilepsy. Cannabis extracts have been known to have analgesic and anti-inflammatory effects, reduce seizures improve speech, behavior, understanding and attention [9]. They have also been used to stimulate appetite and pain relief in HIV patients [10]. Studies performed on mice showed a decreased locomotor activity after being administered THC which is a feature of the molecule that can be used in the future [11].

Recent studies have not portrayed any serious, physically impairing effects of the substances contained in cannabis. The long term effects of heavy marijuana use by adolescents may lead to an increased risk of financial instability and anxiety later in life [12].

1.3. MDMA Effects on Human Metabolism

The other drug of particular interest is 3, 4-Methylenedioxymethamphetamine (MDMA), which has significantly more adverse effects on the human metabolism. MDMA (ecstasy) is a psychoactive drug consisting of 3, 4-Methylenedioxymethamphetamine and referred to as a common "club-drug" (Emphatogen) in young adults. Although the composition of MDMA varies greatly, due to its origin from different producers, it is associated with a greater response to positive emotions and communicational availability. In certain cases MDMA is used for treatment in patients with social dysfunctions and has shown to be mainly effective in women (85%).

Depending on gender, MDMA has a wide range of different effects.

In men the drug induces pro-social behavior (SVO) and enhanced emotional empathy (MET). Up to a level women were able to reach in placebos and overall less competitive behavior. These outcomes were assessed via Emotional tests.

This could not be observed in women to the same extend. One main difference is the impaired recognition of negative emotions, which was not detected in men, as the FERT test determined. Furthermore the threshold level for detecting emotions like fearfulness, sadness and disgust was elevated in women and decreased evaluation of the severity of these negative emotions, was detected.

Both groups did not show altered cognitive empathy, only emotional recognition as described in [13].

The use of MDMA can cause long-term impairments. It is associated with decreased cerebrospinal fluid and SERT binding sites. Furthermore serotonergic neurotransmission is often altered and myocardial damage as well as valvular diseases, are known to be caused by MDMA. Investigators

reported, that these defects may lead to impaired decision making, short-term memory and attention difficulties.

All the named social effects are highly related to metabolic pathways MDMA interferes with. The intake of MDMA results in increased serotonin and norepinephrine, thus mediating psychotropic effects, increasing the levels of cortisol and prolactin in plasma. Especially the pro-social behavior is promoted by MDMA, as it acts similar to Oxytocin. Moreover MDMA acts in the same place as certain anti-depressant drugs such as Citalopram and Reboxetine. Citalopram inhibits serotonin transporters, enhancing serotonin concentration and leading to enhanced recognition of positive feelings and social behavior. Reboxetine has a similar mechanism, only it is enhancing the norepinephrine transporters leading to an increased recognition of happy feelings [14].

1.4. Stress Effects on Human Metabolism

Another factor that may affect the human metabolism is stress, unlike drugs, stress is an internal response which is part of everyday life for the majority of the population.

When the body senses a threat, whether it is psychological or physical, it is stressed. In order to face this threat, the brain receives a stress single and initiates neuroendocrine pathways, first the sympathetic autonomic nervous system – "flight or fight" results in releasing mostly of noradrenaline that will affect the cardiovascular system and other metabolic functions. Secondly, the hypothalamic–pituitary–adrenal axis (HPA) is activated and causes a cascade that will result in cortisol, noradrenaline and adrenaline secretion from the adrenal medulla, leading to several outcomes that vary according to the amount and duration. Once the threat is resolved a negative-feedback inhibition of the HPA axis occurs and the body returns to homeostasis. If the stressor does not resolve, the negative feedback of the hypothalamic–pituitary–adrenal axis is impaired, the body fails to return to homeostasis and stress becomes chronic [2].

In some cases, when the stress is acute yet severe, it causes trauma and may cause permanent effects on the body, especially during early years of childhood. The post-traumatic effects have been studied largely from a psychological angle, yet far too less from a metabolic view point [15].

Cortisol, referred to as the "stress hormone", is detectable via saliva, blood, urine and hair. Since the cortisol levels change throughout the day, saliva, blood and urine can indicate short-term cortisol levels whereas hair sample is enabled to detect long-term cortisol levels, which can indicate chronic stress [16].

There is still much unknown about the metabolic effects of the long term or traumatic stress on the human body. Stressors are present in our daily life, they can be caused by demographic, social or occupational sources, excessive smoking or alcohol consumption, endurance sports and vigorous physical activity, 3rd trimester of pregnancy (until 2 to 3 months postpartum), chronic pain and more. Every stress factor affects individuals differently, depending on their personal interpretation. Studies have shown that these stress factors are often interpreted more intensely by children [16-18].

When stress is mild, it can improve memory, cognitive function, weight lost and activate the acute phase of immune response. Cortisol inhibits the production of interleukin-2, T lymphocytes, prostaglandin, leukotrienes and inhibits the release of histamine and serotonin, also, it stimulates gluconeogenesis, increases protein catabolism, decreases insulin sensitivity of adipose tissue and increases the sensitivity to noradrenaline vasoconstrictor effects on the arterioles. [19] Hence, when the cortisol levels are abnormally high, the outcomes can be neurons atrophy, cognitive, emotional and behavioral dysfunctions, depression, it may increase vulnerability to psychiatric disorders, immunosuppression, diabetes, obesity, cancer and more. [20, 21]

Regarding traumatic stress, according to a study in 2009 [17], adults who have experienced (self reported) childhood trauma had a 6-fold increase risk of developing chronic fatigue syndrome (CFS). CFS is a serious, long-term illness that affects many systems of the body. The main symptom is severe fatigue, problems with thinking and concentrating; these symptoms aren't improved by rest [22].

A more recent study in 2014 [18] showed that childhood trauma can result in metabolic problems associated with elevated C-reactive proteins (CRP), which play a key role in the inflammatory response of the body. Elevated levels of CRP are otherwise associated with infections in the lung or burns. In this case, it is associated with a higher body mass index (BMI). As the body is stressed when there is an inflammation, these constant too high levels of CPR result in 'emotional eating' and therefore showed that people with childhood trauma were more likely to have an above average BMI.

It is important to be able to resolve our stress and return to homeostasis, it can be through lifestyle changes, for example, daily exercise, healthy nutrition, and stress reduction programs or nutraceuticals if needed [20].

2. Conclusion

In conclusion, all previously discussed drugs must be metabolized by the body following diverse pathways. These pathways are the result of catabolism of induced chemicals.

Ethanol, the most commonly used drug discussed affects the serotonin, dopamine, GABA and glutamate pathways in the brain and has a negative effect, both in moderate and heavy consumption. THC and CBD produce mainly neuro-cognitive effects on the human body, with no long-term adverse effects unless there is an overuse by individuals. MDMA, the strongest psychoactive drug analyzed in our review, acts similar to Oxytocin and enhances pro-social behavior, especially by increasing serotonin and norepinephrine levels. Depending on its origin, the impacts' strength varies greatly, which furthermore depends also on the sex of the person that is using it.

Considering all aspects of stress we are exposed to in our everyday life, in relative amounts is beneficial and protective for the body. In abnormally high amounts of stress response, whether arises from acute or chronic duration of elevated stress

response the outcomes are harmful and can be lethal.

Although the factors mentioned come from the body itself or induced from the surroundings, the conditions discussed can alter the body metabolism resulting in a specific altered coping mechanisms.

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