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Drugs of abuse and addiction: A slippery slope toward liver injury

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ABSTRACT

Substances of abuse induce alteration in neurobehavioral symptoms, which can lead to simultaneous exacerbation of liver injury. The biochemical changes of liver are significantly observed in the abused group of people using illicit drugs or drugs that are abused. A huge amount of work has been carried out by scientists for validation experiments using animal models to assess hepatotoxicity in cases of drugs of abuse. The risk of hepatotoxicity from these psychostimulants has been determined by different research groups. Hepatotoxicity of these drugs has been recently highlighted and isolated case reports always have been documented in relation to misuse of the drugs. These drugs induce liver toxicity on acute or chronic dose dependent process, which ultimately lead to liver damage, acute fatty infiltration, cholestatic jaundice, liver granulomas, hepatitis, liver cirrhosis etc. Considering the importance of drug-induced hepatotoxicity as a major cause of liver damage, this review emphasizes on various drugs of abuse and addiction which induce hepatotoxicity along with their mechanism of liver damage in clinical aspect as well as *in vitro* and *in vivo* approach. However, the mechanisms of drug-induced hepatotoxicity is dependent on reactive metabolite formation via metabolism, modification of covalent bonding between cellular components with drug and its metabolites, reactive oxygen species generation inside and outside of hepatocytes, activation of signal transduction pathways that alter cell death or survival mechanism, and cellular mitochondrial damage, which leads to alteration in ATP generation have been notified here. Moreover, how the cytokines are modulated by these drugs has been mentioned here.

1. Introduction

This review is aimed to discuss the toxic effect of drugs of abuse and addiction in liver by providing a global overview and analysis of developments of hepatotoxicity, based on the best available data in 'pubmed'. This article also provides the global information of latest advancement in hepatotoxicity developed in users of illicit drugs including cannabis, cocaine, amphetamine, opioids, methadone, nicotine, oxycodone etc. termed as substancesof addiction. The article considers the research findings published by different groups using *in vivo*, *in vitro* models and human studies understanding the effect of exposure to substance of abuse within laboratory scope.

Usage of Illicit drugs can have a profoundly negative effect on a person's health. It can lead to premature death as evident in cases of overdose, but can also severely curtail the quality of life through disability (any short-term or long-term health loss), such as liver disease, or infection with HIV and hepatitis B and C as a result of sharing contaminated needles or syringes [1]. A study published in 2010reveal that drug dependence on illicit drugs was responsible for a staggering 3.6 million years of life lost through premature death and 16.4 million years of life lived with disability globally. The increase in the global burden of disease from cannabis, amphetamine and cocaine dependence between 1990 and 2010 is essentially attributable to population growth; but this is not the case for opioid dependence, which contributed most to the burden of disease. It has been observed that the demand for illicit drugs varied depending upon the geographic region with cannabis use being more prevalent in Africa, North America, and Latin America while opioids are preferred in Asia and Europe and cocaine in Latin America and in the Caribbean islands.

The adverse health is a major issue of those people using the illicit substances for the purpose of addiction [2,3]. The impact of drug abuse and dependence can affect almost every organ in the human body. The illicit drugs usually weaken the immune system, increasing susceptibility to infections. It can cause abnormal

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cardiovascular conditions ranging from abnormal heart rate to heart attacks. Injected illicit drugs without doctors' advice can also lead to collapsed heart valves and infections of the blood vessels of abusers. Moreover, the use of these substances causes the liver to have to work harder, possibly causing significant damage or liver failure as liver is responsible for detoxification. A report stated that nearly 4% of pregnant women in the United States use illicit drugs such as marijuana, cocaine, ecstasy, derivatives of amphetamine, and heroin. These illicit drugs may pose various risks for pregnant women and their unborn babies. Some of these drugs can cause a baby to be born too small or premature, or to have withdrawal symptoms, birth defects or learning and behavioural problems [4].

Hepatotoxicity usually arises hours to a few days after an acute overdose, generally following or accompanying with involvement of other major organs. The clinical phenotype of illicit drugs induced hepatotoxicity is usually acute hepatic necrosis. Initially, serum aminotransferase and LDH levels are markedly elevated with increase in alkaline phosphatase. Liver histology usually shows necrosis and fatty change that resemble ischemic hepatitis or liver injury due to hyperthermia and some related factors that may partially mediate the hepatotoxic effects of illicit drugs. In this article, we will be highlighting the mechanisms involved in liver injury induced by eleven important drugs of abuse and addiction including Cocaine, Amphetamine, Oxycodone, Heroin, Nicotine, Methadone, Cannabis/Marijuana, Fentanyl, Meperidine, Hydromorphone and chemotherapeutic drugs.

2. Clinical and pathological symptoms

One of the most challenging disorders encountered by gastroenterologists is drug-induced liver injury (DILI). There are two main forms of DILI: intrinsic and idiosyncratic. The former refers to liver toxicity affecting all individuals albeit with different degree while the later hepatotoxicity affects rare individuals. In addition, chronic DILI refers to the inability of liver enzymes to return back to the baseline level. The risk factors along with clinical symptoms are very much critical for a clinician to evaluate of liver damage mediated by drug of abuse and addiction. The major risk factors, clinical symptoms, pathophysiological appearance of the liver injury caused by the following drugs are given below in Table 1.

3. Mechanisms of hepatotoxicity

The research findings of each of the following drugs have been segregated into *in vitro*, *in vivo* and human or patient studies. However, chemotherapeutic drugs have been segregated based on the types of drugs used.

3.1. Cocaine

Cocaine is a strong central nervous system stimulant that increases levels of the neurotransmitter dopamine in brain circuits regulating pleasure and movement. Normally, dopamine is released by neurons in these circuits in response to potential rewards (like the smell of good food) and then recycled back into the cell that released it, thereby shutting off the signal between neurons. Cocaine prevents the dopamine from being recycled, causing excessive amounts to build up in the synapse or junction between neurons. This amplifies the dopamine signal and ultimately disrupts normal brain communication. It is this flood of dopamine that causes cocaine's characteristic 'high'. Some users will increase their dose in an attempt to intensify and prolong their high level of pleasure, but this can also increase the risk of adverse psychological or physiological effects.

Cocaine affects the body in a variety of ways. It constricts blood vessels, dilates pupils, and increases body temperature, heart rate, and blood pressure. It can also cause headaches and gastrointestinal complications such as abdominal pain and nausea. Because cocaine tends to decrease appetite, chronic users can become malnourished as well. Besides its toxicity for the cardiovascular system, central nervous systems, cocaine causes liver injury in human and animal models [23,24].

3.1.1. Research findings

3.1.1.1. In vitro studies. Most of the studies performed to understand the hepatic toxicity of cocaine involve *in vivo* experiments. Nonetheless there are some studies which used *in vitro* experiments. In 1990, a group of scientists reported that cocaine and lidocaine interfere with epinephrine-induced changes in intracellular calcium concentration and glucose efflux from rat hepatocytes. Their results highlighted that cocaine and lidocaine decrease the ability of epinephrine to stimulate glucose efflux by interfering with the calcium-mediated, and not the cAMP-mediated intracellular pathway. It is therefore speculated that alterations in metabolic endocrine regulation may contribute to cocaine induced hepatotoxicity [25]. To check cocaine-induced changes in perfusion pressure and bile flow in perfused rat livers, perfusion pressure was measured in a constant flow system. A 15-min infusion of cocaine (1.47 mM) increased perfusion pressure (136 ± 15%), decreased bile flow (61 ± 5%), and decreased oxygen uptake (82 ± 5%). These acute effects of cocaine in the perfused liver were vascular (vasoconstriction) and functional (alteration in bile formation) [26]. Morphological and biochemical changes in mitochondriawas reported early in the course of cocaine-induced hepatotoxicity. This study was designed to evaluate the functional abnormalities of hepatic mitochondria accompanied with lipid peroxidation caused by cocaine, supporting the hypothesis that mitochondria is one of the major intracellular targets of cocaine hepatotoxicity [27]. Short term-cultured rat hepatocytes exposed to cocaine showed that cytochrome P450 modulated the rate of oxidative biotransformation of cocaine to norcocaine and to other metabolites *in vitro*. Glutathione depletion with buthioninesulfoximine both increased the covalent binding of cocaine to hepatic macromolecules and augmented the inhibitory effect on protein biosynthesis. The results indicate that in rat hepatocytes a high proportion of intracellular cocaine is converted to a reactive metabolite which irreversibly binds to protein, and irreversible binding of cocaine to hepatic protein is associated with impairment of hepatocellular function that could play a role in cocaine-mediated hepatotoxicity [28]. Cocaine is first N-demethylated to norcocaine, followed by oxidation to N-hydroxynorcocaineand norcocainenitroxide radicals. On the basis of ESR studies, the reaction is reported to be accompanied by formation of superoxide and lipid peroxyl radicals [29]. Cocaine hydrochloride was added to primary cultures of hepatocytes isolated from Sprague–Dawley rats to show the *in vitro* effect of the drug [26]. Cocaine showed its cytotoxicity as measured by lactate dehydrogenase release, to cells from 1 mM or it is greater concentration [26].

3.1.1.2. In vivo studies. Cocaine-induced hepatotoxicity in mice was first reported in 1978, which paved the way to understand how cocaine-induced toxicity studies were important to the society [30]. That ethanol administration enhances cocaine-induced hepatotoxicity was reported in 1981 [31]. Involvement of FAD-containing monooxygenase was found in cocaine-induced hepatotoxicity [32]. Norcocainenitroxide, a potential toxic metabolite of cocaine for liver was found to be produced via the one-electron oxidation of N-hydroxynorcocaine by hepatic microsomal enzymes in cocaine-induced rats in the presence of an NADPH-generating system [33]. The hepatotoxicity of cocaine in the