Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Behavioral Sciences

The neuropathology of drug abuse

Andreas Büttner

The predominantly abused illicit substances include cannabis, opiates, cocaine, amphetamine, methamphetamine and their derivatives. Recently, the abuse of new psychoactive substances has become an increasing problem. In human drug abusers a broad spectrum of changes affecting the central nervous system are seen. The main alterations have been assumed to result from the consequences of ischemia and cerebrovascular diseases. However, detailed post-mortem investigations have shown widespread morphological alterations in the brains drug abusers. Further studies related drug abuse with the risk of accelerated brain aging and the development of neurodegenerative conditions.

Address
Institute of Legal Medicine, Rostock University Medical Center, St.-Georg-Strasse 108, 18055 Rostock, Germany

Corresponding author: Büttner, Andreas (andreas.buettner@med.uni-rostock.de)

Current Opinion in Behavioral Sciences 2017, **13**:8–12

This review comes from a themed issue on **Addiction**

Edited by **Scott Edwards** and **Karen D Ersche**

For a complete overview see the Issue and the Editorial

Available online 19th July 2016

http://dx.doi.org/10.1016/j.cobeha.2016.07.002

Introduction

Despite a large body of literature on animal models little is known about the morphological consequences of drugs of abuse on the human central nervous system. The predominant drugs of abuse consumed worldwide are cannabis, opiates, cocaine, amphetamine, methamphetamine, and 'designer drugs' with new psychoactive substances as a recent alarming development [1,2••]. Since the majority of drug abusers perform polydrug abuse including alcohol and nicotine [1–3] it is difficult to relate neuropathological alterations to a single substance. Furthermore, many drugs contain potentially neurotoxic adulterants and diluents [1,2••,4]. In injecting drug abusers or in drug abusers with risky sexual behavior there is also a high incidence of HIV-1, hepatitis B, or hepatitis C virus infection which may also compromise the brain [1,2••,5].

Neuroimaging findings

Neuroimaging studies revealed brain alterations in several, but drug-dependent different regions [6•,7–12] consisting of gray matter volume reduction, white matter impairment, focal perfusion deficits, as well as neurochemical abnormalities. Particularly involved are limbic and reward regions [6•]. The nucleus accumbens is a crucial region of the mesocorticolimbic system and plays an important role in mediating the rewarding effects of drugs of abuse. A recent structural MRI study of heroin-dependent patients showed an association between a decreased volume of the left nucleus accumbens and an increased depression score [13]. As the authors pointed out their findings could constitute a clinical marker to distinguish subgroups of patients by the volume of the nucleus accumbens with respect to depressive symptoms. The assumed underlying pathomechanisms of the observed structural abnormalities include direct toxic drug effects, ischemia-hypoxia, cerebrovascular conditions including vasoconstriction, vasculitis or hypertension, inflammation, and abnormal brain development [6•,7–9]. However, clinical correlations have rarely been provided and the exact morphological correlates of most of these findings are still unclear.

Cannabis

The main psychoactive component of cannabis, Δ9-tetrahydrocannabinol (THC), and other cannabinoids interact with specific receptors. Within the brain these cannabinoid-receptors are distributed heterogeneously with the highest density in regions associated with memory, perception and motor control [1,2••]. Their very low density in the brain stem explains the lack of lethality of cannabis. Despite the widespread consumption of cannabis there are only very few reports of brain alterations. Cannabis-related cerebrovascular events comprise ischemic stroke and an increased likelihood of aneurysmal subarachnoid hemorrhage [14–17]. However, these complications have rarely been reported and due to the frequent abuse of cannabis it is difficult and often impossible to establish whether these observations are really associated with cannabis, other ingested drugs, or purely coincidental.

The important question whether cannabis can cause irreversible brain damage, or lead to an increased risk for psychosis or schizophrenia is still a matter of debate [18].

Opioids and derivatives

Opioids, particularly heroin, are the predominant substances that cause death in drug abusers, often in the context of polydrug abuse [1,2••]. Opioid abusers are at high risk for fatal and non-fatal overdoses with ischemic–hypoxic brain damage [1,2••,19]. Upon autopsy rapid opiod deaths only reveal prominent brain swelling with

edema and vascular congestion. After a longer survival period of some hours symmetric ischemic lesions within the globus pallidus or hypoxic–ischemic leukoencephalopathy become obvious [1,2••,14,19]. In single instances stroke, transverse myelitis/myelopathy or spongiform leukoencephalopathy [1,2••,14,20] has been observed in heroin abusers. The latter condition has sporadically been described worldwide after the inhalation of pre-heated heroin ('chasing the dragon', 'Chinese blowing'). A lipophilic toxin related to contaminants with impairment of oligodendrocyte mitochondria in conjunction with cerebral hypoxia is considered to be the cause, but a definite toxin has not yet been identified [1].

Cocaine

Cocaine is a potent stimulant and the drug of abuse most frequently associated with fatal and non-fatal cerebrovascular complications [1,2••,14,19,21••]. Both hemorrhagic and ischemic stroke may be observed [1,2••,14,19,22–26] primarily in young adults. Ischemic stroke results from cocaine-induced vasospasm, whereas intracerebral and subarachnoid hemorrhages result from a sudden elevation of blood pressure and heart rate from the sympathomimetic effects of cocaine. In cocaine-related intracerebral and subarachnoid hemorrhage, underlying arteriovenous malformations or aneurysms are often observed [26]. Cocaine abuse has been shown to predispose aneurysm rupture at an earlier age and in much smaller aneurysms compared to non-drug using persons [26]. Besides cocaine-associated seizures, movement disorders ('crack dancing') and excited delirium are frequently observed in cocaine abusers [2••].

Amphetamines and methamphetamine and derivatives

Amphetamines, methamphetamine and their derivatives are psychostimulants that predominantly act on monoamine transporters [1,2••,19,21••]. They are the second-most-common cause (after cocaine) for fatal and non-fatal cerebrovascular complications. Furthermore, SAH and ICH have often been described [1,2••,19]. The pathophysiological mechanisms are analog to cocaine with a sudden elevation in blood pressure and vasospasm due to their potent sympathomimetic effects. Common substances of amphetamine and methamphetamine derivatives with similar effects on the dopaminergic and serotonergic system include DOM (4-methyl-2,5-dimethoxyamphetamine), DOB (4-bromo-2,5-dimethoxyamphetamine), MDA (3,4-methylenedioxyamphetamine), MDE (3,4-methylenedioxyethylamphetamine), MDMA (3,4-methylenedioxymethamphetamine, 'ecstasy') 4-MTA (4-methylthioamphetamine) and PMA (4-para-methoxyamphetamine).

The neurotoxic potential of these substances on the dopaminergic and serotonergic system have been described in various animal species and in humans. However, whether the animal and nonhuman primate data are applicable to humans or if these alterations are irreversible is still discussed controversial [27–30].

New psychoactive substances (NPS)

The abuse of new (novel) psychoactive substances (NPS) is an emerging trend over the past years. NPS constitute a heterogeneous group of substances, which can be categorized in different ways according to their pharmacological and chemical properties or their psychoactive effects [2••,31,32,33•,34–38,39•,40,41]. Some of them have been detected as adulterants in other drugs [4]. Nearly all of these substance are legal until specifically scheduled by legislation, therefore they are widely distributed.

Synthetic cannabinoids ('Spice', 'K2', 'Jamaica') are a heterogeneous group of compounds which share a similar chemical structure to Δ9-tetrahydrocannabinol (Δ9-THC), the main psychoactive component in cannabis [2••,31,32,34,35,37,38,39•]. Many of them are synthetic cannabinoid receptor agonists that were developed as research tools or potential medicines. The substance abbreviations typically start with the initials of the inventing chemists or laboratory (e.g. JWH, AM, CP, HU) followed by numbers. The most popular compound in this class is named JWH-018. These substances are more potent than Δ9-THC because they have greater binding affinity for the cannabinoid CB1 receptor, as opposed to the partial CB1/CB2 receptor agonism of Δ9-THC. Because of these properties they have a higher frequency and severity of negative effects than cannabis. Although there are several reports on acute intoxication, long-term or residual effects on the central nervous system are unknown. Fatal intoxications have also been reported for several of these substances [31,34,37,39•]. The predominant cause of death has been cardiac arrhythmias [37]. Detailed neuropathological examinations are lacking so far. In one voxel-based morphometry of structural magnetic resonance imaging a gray matter density reduction in the right and left thalamus and lower gray matter density in the left cerebellum has been observed in synthetic cannabinoid abusers [40].

Synthetic cathinones are chemically and pharmacologically related to cathinone, the psychoactive ingredient in the leaves of the khat plant. They are usually sold as 'bath salts' and abused for their psychostimulant and hallucinogenic effects [31–36,38]. The most common substances include the β-keto-amphetamines mephedrone, methylone, butylone and methylendioxypyrovalerone [31,35].

Tryptamines are a group of monoamine alkaloids, derived from the amino acid tryptophan and similar to serotonin (5-hydroxytryptamine, 5-HT). They act as 5HT2A receptor agonists and serotonin reuptake inhibitor inducing visual hallucinations, alterations in sensory perception, and depersonalization. The most common and potent