CHAPTER SEVEN

The Neuropathology of Drug Abuse

Andreas Büttner
Institute of Forensic Medicine, University of Rostock, Rostock, Germany

1. INTRODUCTION

Drug abuse represents a substantial problem worldwide and is associated with significant morbidity and mortality. The predominant substances taken alone or in combination include cannabis, opiates, cocaine, amphetamines, methamphetamine and "designer drugs" (Karch, 2008; Quinn et al., 1997). In addition, alcohol and other central nervous system (CNS) depressants are frequently consumed by drug abusers (polysubstance abuse) (Bird, 2010; Coffin et al., 2003; Karch, 2008; Molina and Hargrove, 2011; Preti et al., 2002; Quinn et al., 1997). Besides cardiovascular complications, psychiatric and neurological disturbances are the most common manifestations of drug toxicity (Brust, 2004; Cardoso and Jankovic, 1993; Goforth et al., 2010; Gruber et al., 2007; Mackesy-Amiti et al., 2012; Neiman et al., 2000). Although most of our knowledge of the effects of drugs has been derived from animal models, a variety of CNS alterations is observed in human drug abusers (Büttner and Weis, 2004; Büttner, 2011; Karch, 2008).

However, since polysubstance abuse is observed in the majority of cases, it is difficult to relate the human CNS findings to a specific substance. Another difficulty is to differentiate between substance-specific and secondary effects by adulterants or the lifestyle of the drug abuser (Büttner and Weis, 2004; Büttner, 2011; Karch, 2008). In injecting drug abusers there is also a high risk for CNS infections leading to additional brain pathologies (Anthony et al., 2008; Backmund et al., 2005; Büttner and Weis, 2004; Büttner, 2011; Karch, 2008; Wang et al., 2011).

In the past, detailed postmortem studies of human drug abusers were scarce and the reports predominantly focused on the consequences of hypoxia-ischemia or cerebrovascular events. However, recent studies could demonstrate fundamental drug-induced effects on the cellular elements of the human CNS. In addition, various alterations of neurotransmitters, receptors and second messengers have been detected (Büttner and Weis, 2004; Büttner, 2011; Karch, 2008).

The present chapter gives an updated overview on the neuropathology of the most prevalent abused illicit drugs based on former articles (Büttner and Weis, 2004; Büttner, 2011) followed by a synthesis of the recent postmortem findings.

The Effects of Drug Abuse on the Human Nervous System
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2.1. NEUROBIOLOGICAL BASICS OF DRUG ABUSE

2.1.1. Overview

The reinforcing properties and the addictive potential of most drugs of abuse are predominantly mediated by the brain "reward-system" with the mesolimbic dopaminergic system, the orbitofrontal cortex, and the extended amygdala as its major anatomical basis (Feltenstein and See, 2008; Goldstein and Volkow, 2002; Guo et al., 2009; Hyman and Malenka, 2001; Koob and Volkow, 2010; Koob and Le Moal, 2006; Leshner and Koob, 1999; Lucantonio et al., 2012; Nestler, 2001; Rapaka and Sadée, 2008; Sell et al., 1999; Shalev et al., 2002; Stewart, 2000; Urban and Martinez, 2012; Volkow and Fowler, 2000; Weiss and Koob, 2000; Wise, 2009). Moreover, the locus coeruleus seems to be an important key nucleus for the mediation of drug abuse (Dyuizen and Lamash, 2009; Gold, 1993; Lane-Ladd et al., 1997; McClung et al., 2005; Van Bockstaele et al., 2010). Alterations of various intracellular messenger pathways, transcription factors, and immediate early genes in these circuits seem to be responsible for the development of chronic drug abuse and addiction (Bowers et al., 2004; Harlan and Garcia, 1998; Hyman and Malenka, 2001; Kelz and Nestler, 2000; Kirby et al., 2011; Nestler, 2001; Rapaka and Sadée, 2008; Traynor, 2010; Uzbay and Oglesby, 2001; Van Bockstaele et al., 2010).

Moreover, environmental and genetic factors are influencing variables (Kendler et al., 2012). However, possible genetic risk factors for drug addiction are still under investigation (Hemby, 2010; Kendler et al., 2012; Kuhar et al., 2001; Kumar et al., 2011; Levran et al., 2008; Lull et al., 2010; Nestler and Landsman, 2001; Pietrzykowski, 2010; Robison and Nestler, 2011; Stallings et al., 2003; Torres and Horowitz, 1999; Zill et al., 2011).

2.1.2. Neuroimaging Studies in Drug Abuse

Neuroimaging studies of human drug abusers have demonstrated brain atrophy, focal demyelinations and hyperintense lesions, focal perfusions deficits, metabolic disturbances, neurochemical abnormalities, and structural abnormalities in the white matter. Details of these alterations are described elsewhere (Büttner and Weis, 2004; Geibprasert et al., 2010; Kaufman, 2001; Netrakom et al., 1999; Tamrazi and Almast, 2012). Although most of these changes have been attributed to ischemic-hypoxic conditions, the underlying cause or possible neuropathological correlates of these findings are still unclear.

2.2. CNS ALTERATIONS OF THE MAJOR DRUGS OF ABUSE

2.2.1. Cannabis

Cannabis is the most frequently drug in use today (Iversen, 2003; Karch, 2008). The primary psychoactive component of cannabis is Δ9-tetrahydrocannabinol (THC). THC is a lipophilic substance and is distributed heterogeneously within the brain, with

predominance in neocortical, limbic, sensory, and motor areas (Ashton, 2001). Since cannabis increases the activity of dopaminergic neurons in the mesolimbic dopaminergic system, the drug has reinforcing and abuse potential (Ameri, 1999; Diana et al., 1998; French et al., 1997; Hoffman and Lupica, 2001; Tanda et al., 1997) and may lead to psychological dependency (Abood and Martin, 1992; Ambrosio et al., 1999; Ashton, 2001; Johns, 2001; Nahas, 2001; Smith, 2002). THC and other cannabinoids exert their effects by the interaction with specific cannabinoid (CB) receptors that are members of the G protein-coupled receptor family (Ameri, 1999; Breivogel and Sim-Selley, 2009; Console-Bram et al., 2012; Howlett et al., 2002; Köfalvi, 2008; Pertwee, 1997). Two CB receptors, CB1 and CB2, have been well characterized (Breivogel and Sim-Selley, 2009; Console-Bram et al., 2012; Fride, 2002; Glass et al., 1997; Howlett et al., 2002; Köfalvi, 2008): CB1 receptors are present predominantly in the central and peripheral nervous system, whereby CB2 receptors are present predominantly on immune cells (Ameri, 1999; Childers and Breivogel, 1998; Fride, 2002; Köfalvi, 2008). Both receptors are involved in various signal transduction pathways (Ameri, 1999; Childers and Breivogel, 1998; Console-Bram et al., 2012; Howlett et al., 2002; Köfalvi, 2008; Fride, 2002; Wilson and Nicoll, 2002). After the identification of specific receptors, the discovery of endogenous cannabinoid agonists ("endocannabinoids") followed subsequently. These lipid mediators are involved in a variety of physiological functions and pathological conditions (Bari et al., 2010; Console-Bram et al., 2012; Di Marzo, 2011; Di Marzo et al., 1998; Fattore et al., 2007; Fride, 2002; Katona and Freund, 2012; Köfalvi, 2008; López-Moreno et al., 2008; Maccarrone, 2010; Maldonado et al., 2006; Orgado et al., 2009; Parolaro et al., 2010; Pazos et al., 2005; Pava and Woodward, 2012; Rodriguez de Fonseca et al., 2005; Sidhpura and Parsons, 2011; Solinas et al., 2008; Wilson and Nicoll, 2002).

The CB1 receptors are distributed heterogeneously within the brain with the highest density in the substantia nigra, basal ganglia, hippocampus and cerebellum (Devane et al., 1988; Glass et al., 1997; Herkenham, 1992; Herkenham et al., 1990; Mailleux et al., 1992). In the neocortex the highest density of CB1 receptors is found in the frontal cortex, dentate gyrus, mesolimbic dopaminergic system, and temporal lobe (Glass et al., 1997; Herkenham, 1992; Herkenham et al., 1990; Mailleux et al., 1992). This distribution correlates well with the effects of cannabis on memory, perception, and motor control. The very low density of CB1 receptors in the brainstem explains the low acute toxicity and the lack of lethality of cannabis (Abood and Martin, 1992; Ameri, 1999; Herkenham et al., 1990). However, recent findings revealed a THC-induced generation of free radicals with toxic effect on cultured hippocampal, cortical and neonatal neurons indicating a neurotoxic potential of cannabis (Scallet, 1991; Campbell, 2001; Chan et al., 1998; Guzmán et al., 2001; Hampson and Deadwyler, 1999). These findings might be responsible for the cognitive deficits seen in chronic cannabis abusers (Hampson and Deadwyler, 1999).

2.2.2. CNS Complications

Cardiovascular and CNS complications are the most frequently seen consequences of acute cannabis toxicity (Johns, 2001). The latter may manifest as panic attacks, anxiety, depression, or psychosis (Hollister, 1986; Johns, 2001; Maykut, 1985). In addition, THC may affect cognition and impair verbal and memory skills (Ashton, 2001; Bolla et al., 2002; Pope et al., 2001; Schwartz, 2002). These impairments seem to be reversible and neuropathological changes are not visible (Iversen, 2003). In the context of polysubstance abuse cannabis increases the depressive effect of alcohol, sedatives, and opiates (Nahas, 2001; Reid and Bornheim, 2001). The interaction of cannabis with psychostimulants can be either additive or antagonistic (Nahas, 2001; Reid and Bornheim, 2001).

Although cannabis is widespread abused, there are only very few reported cases of CNS complications. Cerebrovascular events, e.g. cerebral infarction or transitory ischemic attacks, have been related to a cannabis-induced vasospasm or a cannabis-induced hypotension (Barnes et al., 1991; Mouzak et al., 2000; Thanvi and Treadwell, 2009; Zachariah, 1991). However, whether these events are truly associated with cannabis abuse or purely coincidental remains to be established.

2.3. OPIOIDS AND DERIVATIVES

2.3.1. Overview

Opioids, particularly heroin, are the leading substances causing death in drug abusers. The main opioid derivatives include morphine, hydrocodone, oxycodone, hydromorphine, codeine, and other narcotics such as fentanyl, meperidene, methadone, and opium (Bird, 2010; Karch, 2008; Quinn et al., 1997). Heroin is manufactured from opium and usually taken intravenously (Karch, 2008). Intranasal and subcutaneous administration is also common. Heroin alkaloid may be inhaled by heating on metallic foil (“chasing the dragon”) (Karch, 2008; Krinsky and Reichard, 2012). Heroin crosses the blood–brain barrier (BBB) faster than morphine leading to an extreme euphoria lasting for several minutes (Brust, 1995; Karch, 2008).

In opioid overdose, coma, respiratory depression, and miosis represent the classical clinical triad (Brust, 1995). A nonfatal overdose has been reported by up to 70% of intravenous heroin abusers during their lives (Coffin et al., 2003). Risk factors for opioid-induced deaths include overdose, concomitant use of other CNS depressants, and loss of tolerance after a period of abstinence (Bird, 2010; Coffin et al., 2003; Preti et al., 2002; Darke et al., 2010; Darke, 2003; Darke and Zador, 1996; Gerostamoulos et al., 2001; Minett et al., 2010; Polettini et al., 1999; Püschel et al., 1993; Quaglio et al., 2001; Sporer, 1999; Warner-Smith et al., 2001).

2.3.2. Neuropathological Findings

Rapid death after lethal heroin ingestion usually does not lead to any morphological evidence of cell injury. In cases of delayed death, ischemic-hypoxic neuronal damage

will be apparent. In up to 90% of all deaths due to opioids, brain edema and vascular congestion are seen at autopsy (Adelman and Aronson, 1969; Büttner and Weis, 2006; Gosztonyi et al., 1993; Metter, 1978; Oehmichen et al., 1996; Pearson et al., 1972a; Richter et al., 1973). After a survival period of 5 h or longer, ischemic-hypoxic neuronal damage with cytoplasmic eosinophilia, loss of Nissl substance, and nuclear shrinkage are seen on histological examination (Oehmichen et al., 1996; Pearson et al., 1972a).

Bilateral ischemic-hypoxic lesions of the globus pallidus, as seen in Figure 1, have been observed in 5–10% of heroin abusers (Andersen and Skullerud, 1999; Daras et al., 2001; Ginsberg et al., 1976; Pearson et al., 1975; Richter et al., 1973; Rißе and Weiler, 1984; Yee et al., 1994; Zuckerman et al., 1996).

Cerebral infarction in heroin abusers has rarely been described (Quaglio et al., 2001; Adle-Biassette et al., 1996; Bartolomei et al., 1992; Brust and Richter, 1976; Caplan et al., 1982; Herskowitz and Gross, 1973; Jensen et al., 1990; Kelly et al., 1992; Niehaus and Meyer, 1998; Sloan et al., 1991; Vila and Chamorro, 1997). As the main pathogenetic mechanism a global cerebral hypoxia (Adle-Biassette et al., 1996; Brust and Richter, 1976; Jensen et al., 1990; Kelly et al., 1992; Niehaus and Meyer, 1998; Vila and Chamorro, 1997), a focal decrease of the perfusion pressure (Niehaus and Meyer, 1998), a cerebral arteritis, necrotizing angiitis (Kelly et al., 1992; Halpern and Citron, 1971; King et al., 1978; Woods and Strewler, 1972), or vasculitis (Brust, 1997; Brust and Richter, 1976; Niehaus and Meyer, 1998; Rumbaugh et al., 1971), and an embolism from adulterants (Adle-Biassette et al., 1996; Bartolomei et al., 1992; Kelly et al., 1992; Sloan et al., 1991; Vila and Chamorro, 1997) has been proposed. Other concepts implied a hypersensitivity reaction of the blood vessels to heroin in persons who were re-exposed to heroin after a period of abstinence (Caplan et al., 1982; Kelly et al., 1992; Rumbaugh et al., 1971; Woods and Strewler, 1972), or a positional vascular compression (Karch, 2008).

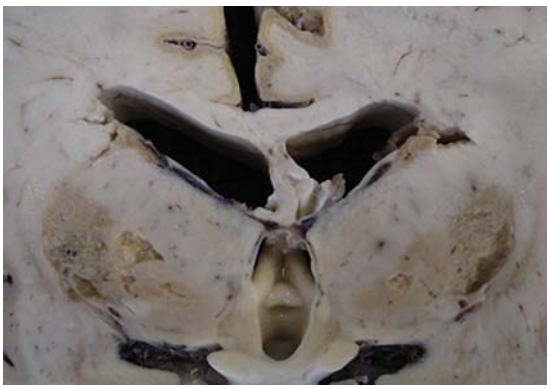

Figure 1 Gross Section of Bilateral Ischemic-Hypoxic Lesions of the Basal Ganglia with Concomitant Laminar Necrosis after 3 Months of Persistent Vegetative State.

Hypoxic-ischemic leukoencephalopathy results from hypoxia secondary to respiratory depression (Ginsberg et al., 1976; Zuckerman et al., 1996; O'Brien and Todd, 2009; Protass, 1971; Shprecher and Mehta, 2010). It is characterized by different degrees of myelin damage (Ginsberg et al., 1976; Pearson and Richter, 1979; Protass, 1971). In addition, loss of neurons in the hippocampal formation, Purkinje cell layer and/or olivary nucleus is frequently seen (Oehmichen et al., 1996). In surviving persons suffering from persistent vegetative state, laminar and subcortical necroses, with extensive nerve cell loss and reactive astrogliosis are observed (O'Brien and Todd, 2009; Protass, 1971; Shprecher and Mehta, 2010).

CNS infections predominantly result from high-risk injection techniques and from the immunosuppression caused by chronic opiate abuse (Adelman and Aronson, 1969; Büttner and Weis, 2004; Karch, 2008; Pearson and Richter, 1979; Roy et al., 2006; Wang et al., 2011). Besides HIV-1 or hepatitis virus, bacterial abscess, meningitis, or ventriculitis (Büttner and Weis, 2004; Karch, 2008; Richter et al., 1973) as well as fungal infections (Büttner and Weis, 2004; Karch, 2008) have been reported. Endocarditis might lead to septic foci in the brain (Büttner and Weis, 2004; Karch, 2008; Louria et al., 1967; Richter et al., 1973; Pearson and Richter, 1979) or to intracranial mycotic aneurysms (Adelman and Aronson, 1969; Brust, 1995; Pearson and Richter, 1979; Richter et al., 1973).

In single instances, transverse myelitis/myelopathy has been reported in heroin abusers (Bernasconi et al., 1996; Brust, 2004; Büttner and Weis, 2004; Ell et al., 1981; Goodhart et al., 1982; Karch, 2008; McCreary et al., 2000; Nyffeler et al., 2003; Pearson et al., 1972b; Richter and Rosenberg, 1968; Riva et al., 2007; Sahni et al., 2008).

Spongiform leukoencephalopathy has been described almost exclusively after inhalation of preheated heroin (Büttner and Weis, 2004; Karch, 2008; Kriegstein et al., 1997; Krinsky and Reichard, 2012; Nuytten et al., 1998; Rizzuto et al., 1997; Wolters et al., 1982). Lipophilic toxic contaminants in conjunction with ischemia-hypoxia are assumed to be the cause, but a definite toxin has not yet been identified (Nuytten et al., 1998; Krinsky and Reichard, 2012; Wolters et al., 1982). The affected brain shows a diffuse white matter spongiform and vacuolar degeneration with loss of oligodendrocytes, axonal reduction, astrogliosis, and subcortical U fiber sparing (Krinsky and Reichard, 2012; Rizzuto et al., 1997; Wolters et al., 1982). The gray matter, brainstem, spinal cord and peripheral nerves are usually unremarkable (Kriegstein et al., 1997; Krinsky and Reichard, 2012; Nuytten et al., 1998; Rizzuto et al., 1997; Wolters et al., 1982). Spongiform leukoencephalopathy distinguishes from delayed leukoencephalopathy following severe hypoxia by the presence of spongiosis with astrogliosis and the absence of typical ischemic-hypoxic lesions (Rizzuto et al., 1997).

2.3.3. Alterations of Neurotransmitters, Receptors, and Second Messengers

The effects of opioids are mediated by specific CNS receptors (Akil et al., 1998; Gold, 1993; Miotto et al., 1996; Mayer and Höllt, 2006; Nestler, 2001; Van Bockstaele et al.,

2010; Waldhoer et al., 2004). Whether chronic opioid abuse leads to a reduced density of these receptors is not yet fully resolved. Some authors reported a similar density of μ- and δ-opioid in the brain of heroin abusers as compared to controls (Gabilondo et al., 1994; García-Sevilla et al., 1997a; Meana et al., 2000; Nestler, 1997; Schmidt et al., 2000, 2001). Others found an increased density of μ-opioid receptor-immunoreactive neurons (Schmidt et al., 2003).

In the development of opioid addiction, the second messenger-signaling system, involving guanosine triphosphate binding (G-) proteins, seems to play a crucial role (Escriba et al., 1994; Hashimoto et al., 1996; Law et al., 2000; Maher et al., 2005; Nestler, 2001; Shichinohe et al., 1998, 2001; Yao et al., 2005). After acute administration to laboratory animals, opioids inhibit adenylyl cyclase activity that converts ATP to cAMP, resulting in decreased cellular cAMP levels (Nestler, 2001). Chronically, opioid exposure induces an upregulation in this adenylyl cyclase-cAMP system mediated via the transcription factor CREB (cAMP response element-binding protein, which is interpreted to be a compensatory mechanism in order to maintain homeostasis (Nestler, 2001; Shichinohe et al., 1998, 2001; Lane-Ladd et al., 1997)). Postmortem studies could demonstrate that chronic heroin abuse causes an increase in certain G-proteins in different regions of the brain (Escriba et al., 1994; Hashimoto et al., 1996). Based on these studies, opioid addiction seems to be associated with abnormalities in second messenger and signal transduction systems involving G-proteins (Escriba et al., 1994; Meana et al., 2000; Hashimoto et al., 1996).

Further findings in the brain of heroin abusers include a decreased level of Ca2+-dependent protein kinase C (PKC)-α (García-Sevilla et al., 1997a), an increased level of a membrane-associated G-protein-coupled receptor kinase (Ozaita et al., 1998), a downregulation of the adenylyl-cyclase subtype I (Shichinohe et al., 1998), a decrease in the density of alpha 2-adrenoreceptors (Gabilondo et al., 1994), a decrease in the immunoreactivity of PKC-αβ (Busquets et al., 1995), decreased levels of immunoreactive neurofilament proteins (García-Sevilla et al., 1997b), and alterations of striatal dopaminergic and serotonergic markers (Kish et al., 2001).

Furthermore, a postmortem study could demonstrate that chronic opioid abuse induces a downregulation of I2-imidazoline receptors in astrocytes and, thereby, presumably downregulates the functions associated with these receptors (Sastre et al., 1996).

2.3.4. Substances for Maintenance Therapy

Codeine, dihydrocodeine, methadone, fentanyl, buprenorphine, and other opioids, sometimes clinically prescribed for maintenance therapy, are often detected in deaths associated for heroin addiction. Monointoxication with one of these substances is the exception and additional CNS depressants, mainly alcohol and benzodiazepines, can be detected frequently (Auriacombe et al., 2001; Barrett et al., 1996; Bell et al., 2009; Bryant et al., 2004; Cooper et al., 1999; Corkery et al., 2004; Darke et al., 2011; Drummer et al.,

1992; Gaulier et al., 2000; Gerostamoulos et al., 1996; Graß et al., 2003; Harding-Pink, 1993; Heinemann et al., 2000; Hickman et al., 2003; Hull et al., 2007; Jumbelic, 2010; Karch and Stephens, 2000; Kintz, 2001; Kreek, 1997; Krinsky et al., 2011; Milroy and Forrest, 2000; Pelissier-Alicot et al., 2010; Pirnay et al., 2004; Seldén et al., 2012; Seymour et al., 2003; Stoops et al., 2010; Worm et al., 1993; Wong et al., 2010; Zamparutti et al., 2011). The neuropathological findings in these cases are similar to those seen in heroin-associated deaths.

2.4. COCAINE

2.4.1. Overview

Cocaine is a potent CNS stimulant and crosses the BBB very rapidly due to its high lipophilic properties (Büttner and Weis, 2004; Karch, 2008; Oyesiku et al., 1993; Prakash and Das, 1993; Quinn et al., 1997; Spiehler and Reed, 1985; White and Lambe, 2003). In the presence of alcohol, cocaine is metabolized to cocaethylene, which also crosses the BBB rapidly. With a longer half-life time, cocaethylene accumulates to a 4-times higher concentration and has a similar pharmacologic profile to cocaine (Andrews, 1997; Hearn et al., 1991; Horowitz and Torres, 1999; Quinn et al., 1997). Within the brain, receptors with varying affinities are present for cocaine and its major metabolites (Biegon et al., 1992; Calligaro and Eldefrawi, 1987; Kalasinsky et al., 2000; Volkow et al., 1995).

The CNS effects of cocaine are mainly mediated through interactions and alterations of the neurotransmitters dopamine, norepinephrine, serotonin, acetylcholine, and gamma aminobutyric acid (Karch, 2008; Quinn et al., 1997; Prakash and Das, 1993; Strang et al., 1993; White and Lambe, 2003). After binding to specific receptors at presynaptic sites, cocaine prevents neurotransmitter reuptake (Büttner and Weis, 2004; Karch, 2008; Quinn et al., 1997; White and Lambe, 2003). The predominant synaptic effect of cocaine is the release of dopamine from the synaptic vesicles and the blocking of dopamine reuptake resulting in an enhanced dopaminergic neurotransmission (Büttner and Weis, 2004; Karch, 2008; Quinn et al., 1997; White and Lambe, 2003).

The abuse potential of cocaine is based on its reinforcing properties and the rapid development of tolerance to the euphoric effects (Bowers et al., 2004; Hemby, 2010; Kalivas and McFarland, 2003; Lucantonio et al., 2012; Nestler, 2001; Quinn et al., 1997; Shalev et al., 2002; Stewart, 2000; Strang et al., 1993; Weiss and Koob, 2000).

2.4.2. Cerebrovascular Complications

Cocaine is the most common drug of abuse associated with cerebrovascular events (Kaku and Lowenstein, 1990; Kelly et al., 1992; Levine et al., 1991). Intracerebral and subarachnoidal hemorrhages as well as hemorrhagic or ischemic stroke have been reported frequently (Aggarwal et al., 1996; Bhattacharya et al., 2011; Brown et al., 1992; Brust, 1993; Cregler and Mark, 1986; Daras et al., 1994; Davis and Swalwell, 1996; Fessler et al.,

1997; Herning et al., 1999; Jacobs et al., 1989; Klonoff et al., 1989; Konzen et al., 1995; Levine and Welch, 1988; Lundberg et al., 1977; Mangiardi et al., 1988; Martin-Schild et al., 2010; Merkel et al., 1995; Mittleman and Wetli, 1987; Mody et al., 1988; Nanda et al., 2000, 2006; Nolte et al., 1996; Oyesiku et al., 1993; Peterson et al., 1991; Petty et al., 1990; Qureshi et al., 1997, 2001; Sen et al., 1999; Sloan et al., 1991; Tardiff et al., 1989; Toossi et al., 2010; Treadwell and Robinson, 2007; Vannemreddy et al., 2008; Wojak and Flamm, 1987). Cocaine-associated cerebrovascular complications occur primarily in young adults with a peak in the early thirties (Brown et al., 1992; Klonoff et al., 1989; Karch, 2008; Levine et al., 1991; McEvoy et al., 2000; Petitti et al., 1998).

Cocaine-associated ischemic infarctions are attributed to cerebral vasospasm as a result of the vasoconstrictive effects of cocaine and its metabolites (Albuquerque and Kurth, 1993; Andrews, 1997; Covert et al., 1994; Cregler and Mark, 1986; Daras et al., 1994; Fessler et al., 1997; Gottschalk and Kosten, 2002; He et al., 1994; Karch, 2008; Kaufman et al., 1998; Kelly et al., 1992; Konzen et al., 1995; Levine et al., 1991; Madden et al., 1995; Schreiber et al., 1994; Spiehler and Reed, 1985; Strickland et al., 1993). Other mechanisms include cocaine-induced cardiac arrhythmia with secondary embolic or hemodynamic cerebral ischemia basis (Brust, 1993; Cregler and Mark, 1986; Konzen et al., 1995; Levine et al., 1991; Petty et al., 1990), or the effects of cocaine on hemostasis with increased platelet aggregation (Jennings et al., 1993; Konzen et al., 1995; Kugelmass et al., 1993; Rinder et al., 1994; Treadwell and Robinson, 2007; Yao et al., 2011).

Cocaine-associated intracerebral and subarachnoidal hemorrhages as seen in Figures 2 and 3 are associated with underlying arteriovenous malformations or aneurysms in about half of the affected persons (Cregler and Mark, 1986; Davis and Swalwell, 1996; Fessler et al., 1997; Klonoff et al., 1989; Levine and Welch, 1988; Levine et al., 1991; Mangiardi et al., 1988; McEvoy et al., 2000; Mittleman and Wetli, 1987; Nolte et al., 1996; Oyesiku et al., 1993; Peterson et al., 1991; Sloan et al., 1991; Tardiff et al., 1989; Vannemreddy et al., 2008). A sudden elevation of blood pressure is believed to be the cause (Brown et al., 1992; Daras et al., 1994; Davis and Swalwell, 1996; Fessler et al., 1997; Jacobs et al., 1989; Kelly et al., 1992; Klonoff et al., 1989; Levine et al., 1991; Mangiardi et al., 1988; Nolte et al., 1996; Oyesiku et al., 1993; Tardiff et al., 1989). Compared to the nondrug-using population, cocaine abuse has been shown to predispose to aneurysm rupture at an earlier age and in much smaller aneurysms (McEvoy et al., 2000; Nanda et al., 2000; Oyesiku et al., 1993; Vannemreddy et al., 2008).

As another pathogenetic mechanism for the occurrence of cerebrovascular events, a cocaine-induced vasculitis has been proposed but could only be demonstrated in rare instances (Brown et al., 1992; Brust, 1997; Diez-Tejedor et al., 1998; Fredericks et al., 1991; Kaye and Fainstat, 1987; Klonoff et al., 1989; Krendel et al., 1990; Levine and Welch, 1988; Martin et al., 1995; Merkel et al., 1995; Morrow and McQuillen, 1993; Peterson et al., 1991).

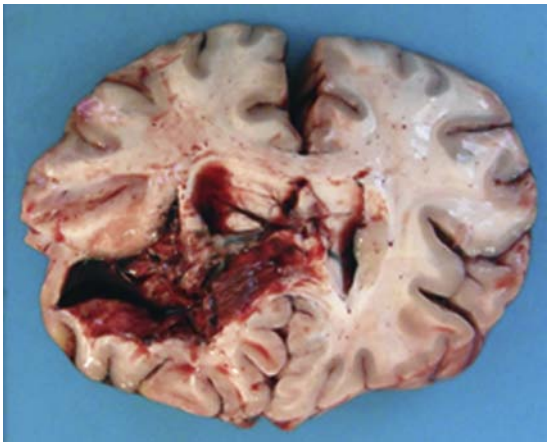

Figure 2 Gross Section of an Intracerebral Hemorrhage with Rupture into the Ventricular System.

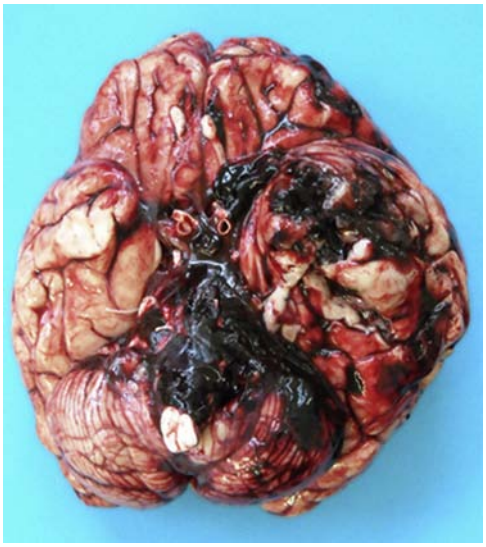

Figure 3 Gross Section of a Subarachnoid Hemorrhage at the Base of the Brain.

2.4.3. Alterations of Neurotransmitters, Receptors, and Gene Expression

In cocaine-related deaths marked reductions in the levels of dopamine, enkephalin mRNA, μ opioid receptor binding, and dopamine uptake site binding as well as elevation in levels of dynorphin mRNA and κ opioid receptor and receptor binding have been described in various brain regions (Hurd and Herkenham, 1993; Little et al., 1993, 1996, 1998, 2003; Staley et al., 1997; Wilson et al., 1996a). The decrease in the levels of dopamine was not paralleled by an increase of a dopamine D1 and D2 gene

expression (Meador-Woodruff et al., 1993). There was also an increase of cocaine binding sites on the dopamine transporter with a decrease of dopamine D1 and D3 receptor density in specific regions of the brain reward system (Little et al., 1993, 1996, 1998; Mash et al., 2002; Segal et al., 1997; Staley et al., 1994). A cocaine-induced damage to the dopaminergic system has also been suggested by a marked reduction in vesicular monoamine transporter-2 immunoreactivity (Little et al., 2003), and of the transcription factor NURR1 (Bannon et al., 2002). An increase of the serotonin transporter has been detected in the striatum, substantia nigra, and the limbic system (Mash et al., 2000). Moreover, a disturbed phospholipid metabolism could be demonstrated in cocaine abusers (Ross et al., 1996, 2002).

2.5. AMPHETAMINES, METHAMPHETAMINE, AND DESIGNER DRUGS

2.5.1. Overview

Over the past years, the abuse of amphetamines, methamphetamine, and designer drugs has significantly increased worldwide (Albertson et al., 1999; Carroll et al., 2012; Freese et al., 2002; Karch, 2008; Koesters et al., 2002; Rome, 2001; Smith et al., 2002). Amphetamines and methamphetamine are psychostimulants and include a broad spectrum of substances (Büttner and Weis, 2004; Karch, 2008; Kish, 2008; Quinn et al., 1997). Their potent sympathomimetic effects include an elevation of pulse rate and blood pressure, an increased level of alertness, and decreased fatigue (Cruickshank and Dyer, 2009; Quinn et al., 1997; Sulzer et al., 2005). Adverse effects include seizures, agitation and psychosis, often accompanied by aggressive behavior and suicide (Baskin-Sommers and Sommers, 2006; Derlet et al., 1989; Hart and Wallace, 1975; Logan et al., 1998; Martin et al., 2009; Zhu et al., 2000). Deaths after amphetamines and methamphetamine abuse have also been reported in several autopsy series (Darke et al., 2008; Gould et al., 2009; Karch et al., 1999; Kaye et al., 2008; Logan et al., 1998; Lora-Tamayo et al., 1997; Raikos et al., 2002; Shaw, 1999; Zhu et al., 2000).

2.5.2. Cerebrovascular Complications

After cocaine, amphetamines and methamphetamine are the second-most-common causes of ischemic or hemorrhagic stroke occurring in persons younger than 45 years (Heye and Hankey, 1996; Kaku and Lowenstein, 1990; Karch, 2008; Perez et al., 1999; Rothrock et al., 1988; Yen et al., 1994). In addition, subarachnoidal and intracerebral hemorrhages have been described (Caplan et al., 1982; Davis and Swalwell, 1996; Delaney and Estes, 1980; D'Souza and Shraberg, 1981; Harrington et al., 1983; Imanse and Vanneste, 1990; Karch et al., 1999; Kelly et al., 1992; Klys et al., 2005; Lessing and Hyman, 1989; Lukes, 1983; McEvoy et al., 2000; Moriya and Hashimoto, 2002; Petitti et al., 1998; Sloan et al., 1991; Selmi et al., 1995; Shibata et al., 1991; Zhu et al., 2000).

A sudden elevation in blood pressure (Heye and Hankey, 1996; Kelly et al., 1992; Logan et al., 1998) or the vasoconstrictive effects of both substances (Perez et al., 1999) are the principal cause. In single cases, a cerebral vasculitis has also been reported (Bostwick, 1981; Brust, 1997; Kelly et al., 1992; Margolis and Newton, 1971; Matick et al., 1983; Zhu et al., 2000). The neuropathological findings in these cases are similar to those seen in cocaine-associated cerebrovascular events as seen in Figures 2 and 3.

2.5.3. Neurotoxicity

The neurotoxic consequences of amphetamines and methamphetamine on the dopaminergic system have been described in various animal species and in humans by numerous neuroimaging and postmortem studies (Bennett et al., 1997; Broening et al., 1997; Brown et al., 2000; Cadet and Krasnova, 2009; Davidson et al., 2001; Ernst et al., 2000; Friedman et al., 1998; Frost and Cadet, 2000; Hanson et al., 1998; Iacovelli et al., 2006; Kuperman et al., 1997; McCann et al., 1998; Melega et al., 2000; Metzger et al., 2000; O'Dell et al., 1991; Ricaurte and McCann, 1992; Robinson and Becker, 1986; Seiden and Sabol, 1996; Sekine et al., 2001; Tong et al., 2003; Trulson et al., 1985; Villemagne et al., 1998; Volkow et al., 2001a,b; Wagner et al., 1980a,b; Wilson et al., 1996b). Similar alterations have been detected in the serotonergic system (Axt and Molliver, 1991; Cadet and Krasnova, 2009; Frost and Cadet, 2000; Fukui et al., 1989; Haughey et al., 2000). However, whether these neurochemical alterations are irreversible and reflect neuroadaptation or neurotoxicity is still unclear (Harvey et al., 2000).

2.6. AMPHETAMINE AND METHAMPHETAMINE DERIVATIVES

2.6.1. Overview

Common amphetamine and methamphetamine derivatives 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), mephedrone, 4-MTA (4-methylthioamphetamine), and PMA (4-para-methoxyamphetamine) (Christophersen, 2000; Felgate et al., 1998; Freese et al., 2002; James and Dinan, 1998; Karch, 2008; Koesters et al., 2002; Winstock et al., 2002, 2011). The street name "ecstasy" subsumes different hallucinogenic amphetamine derivatives with MDMA and MDE being the main components (Cole et al., 2002; Morefield et al., 2011; Wolff et al., 1995).

2.6.2. MDMA

MDMA is the most commonly abused substance of the above mentioned derivatives. MDMA acts predominantly on the serotonergic system with sympathomimetic properties and modulates psychomotor and neuroendocrine functions (Battaglia et al., 1988; Christophersen, 2000; De la Torre et al., 2004; Downing, 1986; Freese et al.,

2002; Green et al., 1995; Kalant, 2001; Liester et al., 1992; Liechti and Vollenweider, 2001; McCann et al., 2000; Rochester and Kirchner, 1999; White et al., 1996). The unique effect of MDMA is the feeling of intimacy and closeness, designated as "entactogenic" (Nichols, 1986).

Fatalities after "ecstasy" consumption have been reported, which were frequently associated with coagulopathy and hyperthermia (Arimany et al., 1998; Byard et al., 1998; Chadwick et al., 1991; Dowling et al., 1987; Fineschi et al., 1999; Forrest et al., 1994; Gill et al., 2002; Henry et al., 1992; Libiseller et al., 2005; Milroy, 2011; Milroy et al., 1996; Schifano, 2004; Turillazzi et al., 2010; Walubo and Seger, 1999).

Moreover, ischemic and hemorrhagic stroke (Hanyu et al., 1995; Harries and De Silva, 1992; Hughes et al., 1993; Manchanda and Connolly, 1993; Muntan and Tuckler, 2006; Schlaeppi et al., 1999) as well as subarachnoidal hemorrhage (Gledhill et al., 1993), and leukoencephalopathy (Bertram et al., 1999) have been described in single cases after "ecstasy" abuse.

In one postmortem study, necrosis of the globus pallidus, diffuse astrogliosis, and spongiform changes of the white matter have been noted (Squier et al., 1995). Further findings in deaths after "ecstasy" consumption consisted of the complications of hyperthermia with disseminated intravascular coagulopathy and included cerebral edema, focal hemorrhages, and nerve cell loss (Milroy et al., 1996).

2.6.3. Neurotoxicity

After acute and long-term MDMA exposure, neurotoxic effects have been demonstrated in animals and nonhuman primates (Battaglia et al., 1988; Hatzidimitriou et al., 1999; Huether et al., 1997; Insel et al., 1989; McKenna and Peroutka, 1990; Ricaurte et al., 2000a; Ricaurte et al., 2000b; Schmidt, 1987; Scallet et al., 1988). The serotonergic system seems to be predominantly affected (Hatzidimitriou et al., 1999; Ricaurte et al., 2000b; Scallet et al., 1988). However, the underlying pathogenetic mechanisms are not fully resolved (Cadet, 1998; Curran, 2000; Lyles and Cadet, 2003; Seiden and Sabol, 1996; Sprague et al., 1998; Turner and Parrott, 2000). In humans, there is also evidence that MDMA might be neurotoxic (Bolla et al., 1998; Buchert et al., 2003; Chang et al., 1999; Gerra et al., 2000; Green and Goodwin, 1996; Hegadoren et al., 1999; McCann et al., 2000; Obrocki et al., 2002; Parrott, 2001, 2002; Reneman et al., 2001; Ricaurte et al., 2000a; Soar et al., 2001), since impaired cognitive performance and an increased incidence of neuropsychiatric disorders have been reported in MDMA abusers (Reneman et al., 2001; Soar et al., 2001). Nevertheless, it is still not fully resolved how to extrapolate animal and nonhuman primate data to the human condition and whether persistent neurotoxicity occurs in humans (Cadet, 1998; Curran, 2000; Gouzoulis-Mayfrank and Daumann, 2006; Kish, 2002; Lyles and Cadet, 2003; McCann et al., 2001; McGuire, 2000; Turner and Parrott, 2000).

2.7. NEUROPATHOLOGICAL INVESTIGATIONS OF (POLY-) DRUG ABUSERS

In the past, there were only few reports of pathological findings in the brains of human drug abusers. The authors described predominantly brain edema, vascular congestion, ischemic nerve cell damage, and neuronal loss (Adelman and Aronson, 1969; Gosztonyi et al., 1993; Makrigeorgi-Butera et al., 1996; Metter, 1978; Oehmichen et al., 1996; Pearson et al., 1972a; Richter et al., 1973). These changes have been ascribed as secondary findings due to drug-induced respiratory depression (Makrigeorgi-Butera et al., 1996; Oehmichen et al., 1996). However, in recent studies, widespread morphological alterations within the cellular network of the brain have been detected in (poly) substance abusers with heroin as the leading cause of death (Büttner and Weis, 2006). The findings consisted of a marked neuronal loss (Büttner and Weis, 2006), as shown in Figure 4. There is also a reduced density of GFAP-positive astrocytes (Büttner and Weis, 2006), and an axonal damage (Büttner and Weis, 2006; Büttner et al., 2006) that was accompanied by a microglia activation (Anthony et al., 2005; Büttner and Weis, 2006; Büttner et al., 2006; Gosztonyi et al., 1993; Makrigeorgi-Butera et al., 1996; Tomlinson et al., 1999). Cerebrovascular changes consisted of reactive endothelial cell proliferation, endothelial swelling and endothelial cell hyperplasia, degenerative hyaline vessel wall thickening, and a decrease of the collagen type IV content of the basal lamina (Büttner

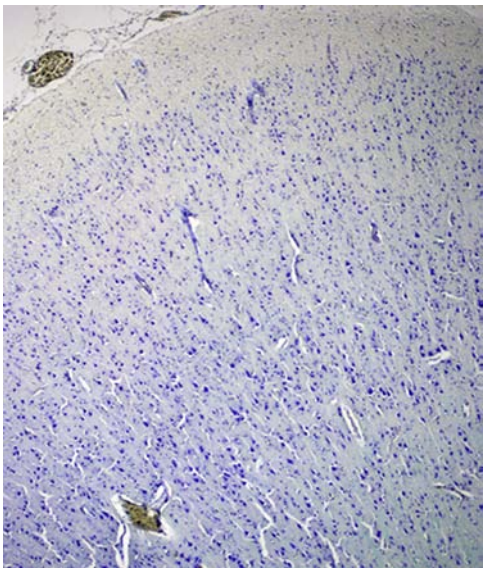

Figure 4 Microscopic Section of the Parietal Lobe Showing Nerve Cell Loss (Luxol-Fast-Blue Stain, Original Magnification x40).

and Weis, 2006; Büttner et al., 2005). In addition, there is a disruption of the tight junctions at the BBB (Bell et al., 2006).

Besides agonal ischemic-hypoxic conditions, the neuronal loss seems to be induced directly by drugs of abuse and, indirectly, by a drug-induced damage of astrocytes, axons, and the cerebral microvessels (Büttner and Weis, 2006).

The widespread axonal damage as demonstrated with β-APP immunohistochemistry and the activation of microglia predominantly in the white matter indicates a chronic progressive process (Anthony et al., 2005; Büttner and Weis, 2006; Büttner et al., 2006; Gosztonyi et al., 1993; Makrigeorgi-Butera et al., 1996; Tomlinson et al., 1999) and is suggestive for a toxic-metabolic drug effect. These findings might represent the morphological correlate of the demyelinations and hyperintense areas observed on neuroimaging.

The numerical reduction of GFAP-positive astrocytes (Büttner and Weis, 2006) might be caused by the interference of drugs with the GFAP-gene transcription, or the generation of free radicals (Anderson et al., 2003; Miguel-Hidalgo, 2009; Sastre et al., 1996; Stadlin et al., 1988).

The observation of concentric small-vessel wall thickening, perivascular space dilatation, perivascular pigment deposition, vessel wall mineralization, and occasional perivascular inflammatory cell infiltrates (Bell et al., 2002, 2006; Büttner and Weis, 2006) in the brains of drug abusers were similar to those observed in AIDS-patients (Connor et al., 2000). Besides, the above mentioned cerebrovascular changes represent a noninflammatory vasculopathy that is indicative for a disturbed BBB and might be another morphological substrate of the alterations seen on neuroimaging.

2.8. NEURODEGENERATION AND DRUGS OF ABUSE

Recent neuroimaging and postmortem studies indicate that drug abusers might develop neurodegeneration or Parkinsonism as they age (Callaghan et al., 2012; Davidson et al., 2001; Guilarte, 2001; Iacovelli et al., 2006; Kish, 2002, 2003; Kuniyoshi and Jankovic, 2003; Little et al., 2009; Mash et al., 2003; Tang et al., 2003; Thrash et al., 2009). In younger opiate abusers, an increase in hyperphosphorylated tau-positive neurofibrillary pretangles, fully formed tangles, and neuritic threads was found (Anthony et al., 2010; Ramage et al., 2005). In these cases, ubiquitin-positive neuronal inclusions were also present. Within the substantia nigra of drug abusers, the numerical density of the pigmented neurons was decreased (Büttner and Weis, 2006) and ubiquitinated cytoplasmic neuronal inclusions have been detected (Bell et al., 2002). The accumulation of α-synuclein protein in long-term cocaine abusers is suggestive for an increased risk for the development of Parkinsonism (Mash et al., 2003). In "ecstasy" and methamphetamine abusers, there is evidence for axonal damage and subsequent reduction (Davidson et al., 2001; Guilarte, 2001; Iacovelli et al., 2006; Thrash et al., 2009).

These studies strongly suggest a drug-related neurodegeneration. However, whether or to what extent neurodegeneration occurs in human drug abusers remains to be established.

3. CONCLUSIONS

There is a broad spectrum of neuropathological alterations in the brains of drug abusers involving nearly all types of CNS cells. However, a clear demarcation between the primary neuropathological effects of a specific drug and the nonspecific changes occurring secondarily is rarely possible. Nevertheless, recent studies have demonstrated morphological correlates of the neuroimaging findings seen in the brains of drug abusers and provided evidence for a drug-related neurodegeneration. Based on these findings future studies may further elucidate the profound disturbances of drugs of abuse on the complex network of CNS cell-interactions.

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