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Cognitive Impairments in Drug Addicts

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1. Introduction

Recent work exploring the effects of abusing alcohol, central stimulants, and opiates on the central nervous system (CNS) have demonstrated a variety of adverse effects related to mental health. In several laboratories and clinics substantial damages of brain function are seen to result from these drugs. Among the harmful effects of the abusing drugs on brain are those contributing to accelerated obsolescence. These putative aging effects including inhibition of neurogenesis and enhanced apoptosis underline the dark side of drug addiction and will doubtlessy be a challenge for future research (Carvalho, 2009). An observation that has received special attention during recent years is that chronic drug users display pronounced impairment in brain areas associated with executive and memory function (Ersche et al., 2006).

Addiction to drugs is characterized as a compulsive behavior, including drug seeking, drug use, and drug cravings but it is also considered as a disorder of altered cognition (Gould, 2010). Indeed, brain areas and processes involved in drug addiction substantially overlap with those known to be of relevance for cognitive functions. Studies have indicated that abusing drugs may alter the normal structure in these regions and influence functions that induce cognitive shifts and promote continued drug use. Processes during early stages of drug abuse is suggested to promote strong maladaptive connections between use of drugs and environmental input underlying future cravings and drug-seeking behaviors. Continued drug use causes cognitive deficits that aggravate the difficulty of establishing sustained abstinence (Gould, 2010). In fact, drug addiction has been characterized as a disease of "pathological learning" by several investigators (Hyman, 2005; Gould, 2010).

In earlier days abusing drugs were considered only to induce non-specific effects on the brain. Today, it is widely believed that they may produce selective adaptations in very specific brain regions. These neuroadaptations have been extensively examined in order to clarify mechanisms underlying the development and maintenance of addiction to find strategies for relevant treatment. The hippocampus is an area included in the limbic structures that is of particular interest, as it is found to be essential for several aspects related to the addictive process. A remarked neuroadaptation caused by addictive drugs, such as alcohol, central stimulants and opiates involves diminished neurogenesis in the subgranular zone (SGZ) of the hippocampus. Indeed, it has been proposed that decreased adult neurogenesis in the SGZ could modify the hippocampal function in such a way that it contributes to relapse and a maintained addictive behavior (Arguello et al., 2008). It also

raises the possibility that decreased neurogenesis may contribute to cognitive deficits elicited by these abusing drugs.

In addition to hippocampal structures the prefrontal cortex and its different subregions have also been hypothesized to represent this cognitive control system (George et al., 2010; Ridderinkhof et al., 2004). Neurons in the dorsolateral prefrontal cortex are suggested to be involved in activity that in delayed matching to sample tasks persists throughout the delay period (Weiss and Disterhoft, 2011). Moreover, age-related changes in the prefrontal cortex microcolumnar organization are shown to correlate with age-related declines in cognition. Activity that persists beyond the induction of a specific stimulus is believed to mediate working memory processes, and disruption of those processes is related to memory deficits that often accompany the aging process. The prefrontal cortex is known as an area with enhanced vulnerability to alcohol-induced damage. It is suggested that inhibition of adult neurogenesis may be a factor that underlie alcohol-mediated cognitive dysfunction, which in turn may be a cause to decreased behavioral control over consumption (Nixon and McClain, 2010). Also, an influence of opioids and stimulant drugs on hippocampal neurogenesis in adults has been confirmed (Eisch et al., 2000). Exposure to psychotropic drugs is suggested to regulate the rate of neurogenesis in the adult brain, suggesting a possible role for neurogenesis in the drug-induced impairments seen in cognitive functions (Duman et al., 2001).

This article is aimed to provide a comprehensive collocation of the impact of abusing drugs on cognitive functions. It describes adverse effects on learning and memory of selected drugs and how these compounds interact with neuronal circuits involved in these behaviors. Possible approaches to deal with these drug-induced damages from the pharmacological point of view will also be discussed.

2. Memory and learning

Memory is described as a multi-system phenomenon in the brain. Each system has been associated with a separate memory function targeting different neurological substrates. For example, declarative memory is attributed to a function of retaining conscious memories of facts and sights. The establishment of new declarative memories is related to structures in the diencephalon and the medial temporal lobe, and it has been proposed that these memory imprints are generated in specific areas of the cerebral cortex. For example, brain areas implicated in deficits in declarative memory include the prefrontal cortex and the hippocampus. The frontal cortex is recognized as an important substrate for features related to reasoning and memory content of the declarative memory (Samuelson, 2011; Weiss and Disterhoft, 2011). Classical conditioning, skill learning and repetition learning, i.e. nondeclarative forms of memory, are documented through changes in the way they are carried out and are not considered to involve conscious recollection. The functional anatomy of these nondeclarative forms of memory are believed to comprise the basal ganglia, cerebellum and cerebral cortex.

A concept of synaptic plasticity essential for the storage of long-term memory (LTM) at the cellular level is the long-term potentiation (LTP). LTP is shown to enhance the signal transmission between neighboring neurons over a long period of time and it can be induced by high-frequency stimulation of the synapse, and at this level it represents an important

target for studies of memory enhancement. LTP is an attractive candidate for explanation of cellular mechanisms underlying learning and memory as it shares many features with LTM. Both LTP and LTM are triggered rapidly, and each of them seems to be dependent on the biosynthetic process for protein formation and the proteins, which are formed, are belived to have a role in associative memory and have been suggested to last over a long period of time. Furthermore, LTP is found to be linked to a number of different types of learning, and these are shown to include the simple classical conditioning observed in experimental animals as well as the more complex, higher-level cognition that is experienced by humans (Cooke and Bliss, 2006).

Although LTP is not demonstrated in all brain regions it has been clearly seen in many areas, including amygdala, hippocampus, nucleus accumbens and prefrontal cortex, i.e. regions involved in drug reward but also in memory and learning (Kenney and Gould, 2008). For instance, enhanced activity in amygdala and enhanced amygdala-hippocampus connectivity leading to long-lasting, non-temporary memory alterations has been described (Edelson et al., 2011). It was further indicated that the hippocampus is essential for the transfer of short-term memories to LTMs (Santini et al., 2001; Glannon, 2006). In addition, clinical investigations including neuropsychological patients as well as studies using experimental animals have suggested that, in addition to its critical role in the LTM formation, the hippocampal structure is essential for the integrating and processing of spatial and coherent information (Kim and Lee, 2011).

The molecular mechanism underlying memory potentiation is suggested to involve the excitatory amino acid glutamate (Abel and Lattal, 2001). Glutamate binding activates both the N-methyl-D-aspartyl (NMDA) and the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors located on the cell membrane of the nerve cells. These events lead to the opening of calcium and sodium channels into the nerve cells. The calcium influx activates the enzyme adenylate cyclase, which in turn converts ATP to cAMP. Subsequent to this event the cAMP actuates a sequential activation of protein kinase A, mitogen-activated protein kinase/extracellular signal-regulated protein kinase, as well as the cAMP response element-binding factor (CREB). The activated CREB attaches to DNA and induces transcription and subsequently an increased production of proteins essential for the construction of new synapses (Abel and Lattal, 2001).

Regarding the NMDA receptor it has been shown in experimental animal models that the organization of the receptor subunits NR1, NR2A, NR2B and NR2D is essential for the memory promoting effect of glutamate. For instance, transgenic mice overexpressing the NR2B subunit exhibit improved performance in memory tests (Tang et al., 1999). Also the ratio of the NR2B to NR2A ratio has been shown as a relevant marker on cognitive functioning in the rat. Increased ratio of NR2B/NR2A has been seen to increase LTP (Le Grevès et al., 2002; Le Grevés et al., 2006; Zhao et al., 2005).

A considerable amount of evidence supports an important role for glutamate and its ligand-gated ionotropic receptors (i.e. NMDA, AMPA, and kainic acid (KA) subtypes) in mediating addictive behaviors have been collected over the years (Wolf, 1998; Tzschentke and Schmidt, 2003; Kalivas, 2004; Gass and Olive, 2009). However, the role of metabotropic glutamate (mGlu) receptors in the neural mechanisms underlying drug addiction has become apparent only within the latest decades (Olive, 2010). Evidence for a role of Group I (mGlu$_1$ and

mGlu$_5$) receptors in regulating drug intake, reward, reinforcement, and reinstatement of drug-seeking behavior have emerged from recent pharmacological and genetic studies (Olive, 2009) . However, these kind of mGlu receptors is also suggested to mediate cognitive processes including learning and memory, behavioral flexibility, and extinction (Moghaddam, 2004; Simonyi et al., 2005; Gravius et al., 2006; Gass and Olive, 2009) and deficits in these expressions of cognition are frequently observed in drug addicts.

3. Drug effects on cognitive function

As mentioned above drug addiction is seen as a chronic relapsing disorder with persistent brain alterations associated with cognitive, motivational and emotional alterations and studies have indicated the presence of extensive cognitive alterations in many individuals diagnosed with substance use disorders (Goldstein and Volkow, 2002; Fernández-Serrano et al., 2010). Thus, over the past decades the influence of abusing drugs on cognitive capabilities in addicts has been the subject for many studies in various clinical and basic science laboratories. Although it has been known for long that alcoholism is connected with deficient memory and learning and seems to accelerate aging processes, negative effects of chronic use of narcotics on cognitive functions have become evident during more recent times. This section focuses on adverse effects induced by some frequently used drugs, including alcohol, central stimulants, and opioids. All these substances have been reported to affect many aspects of memory and learning.

3.1 Alcohol-induced effects on memory and cognition

Emerging data from past and current research provide evidence for cognitive impairments of alcohol-dependent patients, particularly regarding their ability to perform tasks sensitive to frontal lobe function. This fact has brought up the importance of a significant abstinence allowing individuals with these impairments to recover (Glass et al., 2009; Loeber et al., 2009).

The adverse effect of alcohol on cognitive function is typified by the well-known Wernicke-Korsakoff syndrome (WKS). This disorder is a neurological disturbance and it is caused by the lack of thiamine (vitamin B$_1$) in the brain. Its onset is linked to mal nutrition or to alcoholism. In Western countries WKS is perhaps the most common alcohol-induced memory disturbance. It is characterized by neuropathological changes in the diencephalon, including the anterior part of the thalamus, and the mammillary body caused by thiamine deficiency (Kopelman et al., 2009). The most characteristic neuropsychological feature of WKS is a marked decline in memory capabilities, whereas other intellectual abilities are relatively preserved. Alcohol-related dementia is generally defined as alcohol-induced dementia in the Diagnostic and Statistical Manual of Mental Disorders IV- Text Revision (DSM-IV- TR). It has been described as an organic brain syndrome induced by over-consumption of alcohol, which causes severe cognitive impairment, including executive dysfunction, lack of emotional control and disturbances in memory function (Asada et al., 2010).

Evidence that emerges from experimental studies has shown that early exposure to alcohol sensitizes the neurocircuitry of addiction and affects chromatin remodeling. These events could give rise to altered plasticity in reward-related cognitive processes that contribute to

vulnerability to drug addiction in adolescents (Guerri and Pascual, 2010). There are potential mechanisms by which alcohol affects brain development and causes brain impairments including cognitive and behavioral dysfunctions but also neurochemical processes underlying the adolescent-specific vulnerability to drug addiction (Guerri and Pascual, 2010).

Moreover, in heavy episodic drinkers reduced psychomotor speed and a decline in accuracy when performing tasks of attention, working memory, implicit memory as well as associate learning and memory have been reported (Cairney et al., 2007). For instance, among the population of Aboriginal Australians, who were heavy episodic alcoholic users, specific cognitive abnormalities that suggest frontostriatal abnormalities have been observed in association with chronic alcoholism (Cairney et al., 2007).

In the brains of alcoholics the frontal lobes, with significant neuronal losses in the superior frontal cortex, are shown to be the most insulted areas (Kubota et al., 2001; Sullivan and Pfefferbaum, 2005). These lobes are known to regulate complex cognitive skills including working memory, attention, temporal ordering, mood, motivation, risk taking and wanting as well as discrimination and reversal learning that underlie judgment. Studies have revealed that a complicated mechanism may underlie alcohol-induced damage to the brain. Also, the mechanism underlying the abstinence-induced regeneration seems to be complex. The magnitude of neurodegeneration and the potential for recovery and regeneration vary between different regions of the brain and seem to be dependent on several factors, such as pattern of intake, age and genetics (Crews and Nixon, 2009). Moreover, binge ethanol exposure of rats is seen to reduce hippocampal neurogenesis (Nixon and Crews, 2002) and brain degeneration in the binge ethanol treatment model is generally widely circulated and diffused, in similarity to what is observed in human alcoholics.

A recent study performed in order to investigate the harmful effects of binge alcohol on the hippocampal neurogenesis in adolescent non-human primates suggested that the liquid drug may interfere with the migration and distribution of hippocampal preneuronal progenitors (Taffe et al., 2010). Furthermore, the decreased neurogenesis induced by alcohol in the hippocampus was seen to be paralleled by an increase in neural degeneration thought to be mediated by non-apoptotic pathways. This effect remained for quite a long time following alcohol discontinuation and it was suggested to cause the deterioration in hippocampus-associated cognitive tasks that are frequently seen in alcoholics (Taffe et al., 2010).

Regarding the mechanism underlying alcohol-induced neurodegeneration and cognitive impairment the involvement of glutamatergic neurotransmission seems well documented, however, many details of the underlying mechanism remains unknown. Studies have been focused both on the NMDA receptor system and the group II metabotropic glutamate receptor. A recent study examined the effect of the agonist LY379268 on its ability to prevent neuronal death and learning deficits in a rat model of binge-like exposure to alcohol (Cippitelli et al., 2010). It was found that neurodegeneration was most extensive in the ventral hippocampus and the entorhinal cortex (EC) and the glutamate receptor agonist was potently neuroprotective in the EC but not in the dentate gyrus of the hippocampus. In additional experiments, binge alcohol exposure suppressed the expression of transforming growth factor beta (TGF-beta) expression in both the EC and dentate gyrus, while the

glutamate agonist increased TGF-beta in the EC only. It was further reported that the neuroprotective effects of the glutamate agonist were paralleled with prevention of deficits in spatial reversal learning. These data was considered to give support for a protective role of TGF-beta and group II metabotropic glutamate receptor agonists in alcohol-induced neurodegeneration (Cippitelli et al., 2010).

However, studies have confirmed that alcohol may damage specific regions both in the adult and the adolescent brain (Alfonso-Loeches and Guerri, 2011). The mechanisms behind this damage is suggested to involve excitotoxicity, free radical formation and neuroinflammatory destructions caused by activation of the immune system and mediated through Toll-like receptor 4 (TLR4 receptor). Alcohol is also shown to act on specific cell surface receptors, e.g. the NMDA, GABA-A receptors and on certain ion channels, like L-type Ca^{2+} channels and GIRKs but the drug is also found to interact with various signaling pathways, e.g. PKA and PKC signaling. All these multi-targets are belived to underlie the wide variety of behavioral effects seen to result from chronic intake of ethanol (Alfonso-Loeches and Guerri, 2011).

Several effects of alcohol seems to involve the endogenous opioid systems (EOS). Opioid peptides, including beta-endorphin, have a role in mediating the reward effect of the drug. However, also some adverse effects are mediated through the EOS. A recent study on human alcohol-dependent subjects investigated whether the EOS is altered in brain areas involved in cognitive control of addiction. Human post-mortem brain specimens, including the dorsolateral prefrontal cortex (dl-PFC), orbitofrontal cortex (OFC) and hippocampus, from alcoholic and control subjects were examined. The expression of the prodynorphin gene transcript and dynorphin peptides in dl-PFC, the κ-opioid peptide (KOP) receptor message in OFC and dynorphins in hippocampus were all up-regulated in alcoholics. No significant changes in expression of other EOS gene transcripts were reported. Activation of the KOP receptor by the up-regulated dynorphin peptides in alcoholic brains was suggested to at least partly underlie neurocognitive dysfunctions relevant for addiction and disrupted inhibitory control (Bazov et al., 2011). In a subsequent study focused on genetic, epigenetic and environmental factors and their influence on the risk for alcoholism the result was indicative of a causal link between alcoholism-associated prodynorphin 3'-UTR CpG-SNP methylation, activation of prodynorphin transcription and vulnerability of individuals with the C, non-risk allele(s) to develop alcohol dependence (Taqi et al., 2011).

A study highlighting the specific attentional processes impaired in alcoholics concluded that a representative sample of alcoholics show specific deficits of attention as opposed to a general decline of attention at treatment intake. It was thus reported that sober alcoholics appear to be as efficient as controls at selecting on the basis of location, however, when they are required to select on the basis of semantic information or required to respond to two independent sources of information they are at a deficit (Tedstone and Coyle, 2004).

Taking together it appears that chronic alcohol intake under a variety of condiditions impairs cognitive factors including various aspects of memory and learning, attention, risk taking, motivation, mood and wanting. Specific brain areas targeted by the drug in this context includes hippocampus and frontal cortex. The mechanisms underlying the effects of

ethanol involve inhibition of neurogenesis and interaction with a number of signal pathways, including glutamate, monoamines and endogenous opioids.

3.2 Effects of central stimulants on cognition

Epidemiological studies have confirmed a high prevalence of stimulant drugs and that these drugs are being used increasingly over the past decades (Gonzales et al., 2010; Ciccarone, 2011; Vardakou et al., 2011). They have been taken in order to enhance social or cognitive performance but also to induce euphoria and wellbeing. However, chronic use of these drugs has been associated with substantial deficits in learning and verbal memory. Thus the harmful consequences of long-term stimulant abuse also seem to include neurodegenerative effects leading to cognitive disabilities (Ciccarone, 2011; McKetin and Mattik, 1997; Krasnova et al., 2005).

3.2.1 Amphetamine

The psychostimulant amphetamine is shown to improve cognition in healthy subjects but also in attention-deficit hyperactivity disorder as well as in other neuropsychiatric disorders. However, at higher doses the stimulant may induce impaired cognitive function (Reske et al., 2010), particularly those mediated by the prefrontal cortex (Xu et al., 2010). Also, chronic use of amphetamine induces significantly impaired performance in cognitive tests (Ornstein et al., 2000). Data has indicated that amphetamine as well as other psychostimulants affects the capacity of the brain to stimulate neurogenesis, and that their effects also include disruption of the blood-brain barrier (BBB) (Silva et al., 2010). Thus, in chronic use the psychostimulatory effect of amphetamine is not only connected with reward and euphoria but also with impairments in attention and memory. These cognitive deficits have been suggested to be related to neurotoxic effects of the drug (Krasnova et al., 2005). Amphetamine injection is shown to affect dopaminergic terminals in striatal cells and to increase levels of cleaved caspase-3, a marker of apoptosis. Furthermore, the stimunlant is also demonstrated to increase the expression of p53 and Bax at both transcriptional and protein levels, whereas it decreased the levels of the Bcl-2 protein, all these events in agreement with increased apopotosis (Krasonova et al., 2005). Amphetamine is also shown to affect dopamine circuits in the prefrontal cortex (Dunn and Killcross, 2007; Fletcher et al., 2007) and thereby inducing impaired cognitive function.

3.2.2 Cocaine

Long-lasting memory deficits have been seen in individuals chronically abused to cocaine (Beatty et al., 1995; Bolla et al., 1999), although some ambiguities in respect to the specificity of this impairment remain to be fully clarified. Also, in studies using preclinical models of addiction it was demonstrated that stress and mechanisms related to the HPA-axis may contribute to impaired learning (Ehninger and Kempermann, 2006). In a more recent study it was shown that the deficiences in learning and memory seen in individuals addicted to cocaine are associated with increased levels of cortisol but also with the outcomes of cocaine use after inpatient treatment (Fox et al., 2009). Learning-related deficits was found to include poor immediate and retardent verbal recall and recognition as well as a selective reduction in working memory. These findings were seen to be in congruence with studies implicating

that neuroadaptations in cocaine addicts affects learning and memory function, which in turn, appeared to affect the outcomes of drug use (Fox et al., 2009).

Sudai and collaborators investigated the effects of cocaine on cell proliferation and neurogenesis in the hippocampal dentate gyrus of adult rats (Sudai et al., 2011). The influence of the stimulant drug on working memory during abstinence was examined using the water T-maze test. Results suggested that cocaine, in addition to its effects on the reward system, also may inhibit the generation and development of new cells in the hippocampus, and thereby reduce the capacity of the working memory (Sudai et al., 2011).

In studies on mechanisms underlying the effects of cocaine on memory function several laboratories have focused on brain circuits and transmitter substances known to be involved in stress and memory formation. Muriach and collaborators described a study on nuclear factor kappa B (NFKappaB). NFKappaB is known as a sensor of oxidative stress and it is demonstrated to have a role in memory formation that could be involved in addiction mechanisms. They reported a mechanistic role of NFKappaB in alterations induced by cocaine and observed memory disabilities that was impaired and correlated negatively with the NFkappaB activity in the frontal cortex (Muriach et al., 2010). Cocaine has also been shown to induce neuroadaptive effects in hippocampal regions by enhancing LTP through interaction with the dopamine transporter and a subsequent enhancement of dopamine (Thomson et al., 2005). Subsequent studies have confirmed that endogenous dopamine in the presence of cocaine facilitates the elevation of basal hippopcampal LTP (Stramiello and Wagner, 2010). Cocaine may also induce impairments in working memory by action on dopaminergic circuits in the prefrontal cortex (George et al., 2008).

3.2.3 Methamphetamine, ecstasy and mephedrone

In addition to amphetamine, during the past years chronic use of several stimulant drugs with similar structure have been shown to impair cognitive functions. Among these compounds are methamphetamine, ecstasy and perhaps also cathinones (Gouzoulis-Mayfrank and Daumann, 2009; Rogers et al., 2009; Hoffman and Al'Absi, 2010). All these substances are not in clinical use and are classified as illegal drugs. They are easily accessible at internet and are misused in many countries. Regarding their mechanism of action ecstasy was shown to cause selective and persistent damages on central serotonergic nerve terminals, while methamphetamine produces lesions in both the serotonergic and dopaminergic systems. Also mephedrone seems to affect both transmitter systems (Kehr et al., 2011).

Chronic methamphetamine is shown to cause persisting cognitive deficits in human addicts as well as in animals exposed to this central stimulant (Reichel et al., 2011). Recent findings suggest that methamphetamine may induce a hypofunction in cortical areas that are important for executive function that in turn underlies the cognitive control deficits seen in individuals dependent on this drug (Nestor et al., 2011).

Methamphetamine-induced changes in the serotonin transporter SERT function in areas associated with cognition may underlie memory deficits independently of overt neurotoxic effects (Reichel et al., 2011). Moreover, data has indicated that also the σ receptors may be implicated in various acute and subchronic effects of methamphetamine. These include locomotor stimulation, development of sensitization and neurotoxicity, effects that may be

attenuated by σ receptor antagonists. The σ receptors are also suggested to be involved in methamphetamine-induced deficits in cognitive and motor function (Kaushal and Masumoto, 2011).

Abuse of methamphetamine has also been seen to result in impaired adult hippocampal neurogenesis, and effects of this stimulant drug on neural progenitor cells is suggested to be mediated by protein nitration (Venkatesan et al., 2011). This observation was considered to open for new strategies regarding design and development of therapeutic approaches for methamphetamine-abusing individuals with neurologic dysfunction or even for other disorders with impaired hippocampal neurogenesis.

Use of ecstasy is shown to reduce cognitive functioning by reducing levels of dopamine and serotonin in CNS areas of importance for memory and learning (Gouzoulis-Mayfrank and Daumann, 2009; Chummun et al., 2011). Ecstasy is an abusing drug related to amphetamine and can act as a stimulant producing euphoria by enhancing dopamine levels in the nucleus accumbens in conformity to but to a lesser extent than amphetamine and cocaine. However, ecstasy may also interact with serotonergic payhways and long term exposure to this drug results in decreased activity in both serotonin and dopamine neurons (Kehr et al., 2011). The reduction in these transmitter systems is seen as dose-related impairments in cognitive function, in particular regarding complex cognitive skills. The decreased serotonergic and dopaminergic activity is also believed to cause changes in mood, hallucinations, altered perception and memory loss. Previous and current research demonstrate that abusing ecstasy is strongly associated with deteriorated working memory, and that this worsening correlates to the total lifetime of ecstasy consumption. These findings stresses the long-term, cumulative behavioral manifestations linked to ecstasy use in humans (Nulsen et al., 2010). Ecstasy users often show decreased levels of serotonin, its metabolite 5-HIAA, tryptophan hydroxylase and SERT density during abstinence. They also display functional impairments in learning and memory but also in higher cognitive processing, as well as sleep disturbance and deficits related appetite and reduced psychiatric wellbeing (Canales, 2010). These psychobiological impairments appeared most pronounced in heavy ecstasy users and may reflect losses in serotonergic axones in certain brain regions, in particular the frontal lobes, temporal lobes and hippocampus. These complications seem to last long after cessation of ecstasy use, suggesting that these drug-induced neurological impairments may be permanent. It is believed that at least some of the harmful effects on memory of ecstasy abuse could result from its neurotoxic actions on adult hippocampal neurogenesis. Evidence suggests that stimulant abuse negatively affects cognitive functions that are regulated and influenced by adult hippocampal neurogenesis, including contextual memory, spatial memory, working memory and cognitive flexibility (Canales, 2010).

4-methylmethcathinone (mephedrone) represents a designer stimulant that is among the most popular of the naturally occurring psychostimulant cathinone derivatives. A web-based survey has shown that mephedrone users consider the effects of this drug to compare best with those of ecstasy (Carhart-Harris et al., 2011), which agrees with research studies comparing the effects of mephedrone and ecstasy on brain 5HT and dopamine (Kehr et al., 2011). This cathinone has been readily available for purchase both online and in the streets and has been promoted by aggressive web-based marketing. Its abuse in many western countries has been described as a serious public health concern (Hadlock et al., 2011). In conformity with ecstasy, metamphetamine and methcathinone, repeated mephedrone

injections causes a rapid decrease in the striatal dopamine and in the hippocampal 5HT transporter function. Mephedrone is also shown to inhibit both synaptosomal dopamine and 5HT reuptake. Similar to ecstasy but unlike methamphetamine or methcathinone, repeated mephedrone also causes persistent serotonergic, but not dopaminergic, deficits (Hadlock et al., 2011, Kehr et al., 2011). No studies on learning and memory impairments in mephedrone abusers has yet been published, however, due to similarieties with ecstasy and methamphetamine research investigating the actual domains of cognition in chronic and abstinent mephedrone users seems to be warranted in the future.

4. Opioid-induced adverse effects on cognitive functions

A variety of neuropathologic adaptations have been detected in the brains of heroin addicts. These include pathology caused by bacterial infections, viral infections, such as HIV-1 infection, but also complications such as hypoxic–ischemic *encephalopathy* with cerebral edema, ischemic neuronal damage and neuronal loss (Büttner et al., 2000). However, chronic exposure to opiates, such as heroin, morphine and to some extent also methadone are shown to impair cognitive function (Mintzer and Stiltzer, 2002; Gruber et al., 2007; Soyka et al., 2011). Heroin is characterized as one of the most frequently abused illegal drugs, and addiction to this drug is linked to significant attention deficits and inadequate performance on memory tasks (Guerra et al., 1987). Furthermore, chronic exposure to morphine is also shown to cause vigilance and attention impairments in chronic pain patients (Mao et al., 2002) and impairs acquisition of reference memory in rats (Spain and Newsom, 1991; Lu et al., 2010). Also addicts in methadone maintenance programs or chronic pain patients treated with methadone are shown to display cognitive impairmats (Mitzler and Stitzer, 2002; Soyka et al., 2010). These findings suggest an effect of chronic opiates on brain regions related to learning and memory, such as the frontal cortex (Ornstein et al., 2000; Yang et al., 2009) and the hippocampus (Lu et al., 2010)

Regarding the mechanisms by which opioids induce cognitive impairments through action on hippocampal and prefrontal cortex structures it is shown that these drugs may enhance apoptosis and inhibted neurogenesis. An opioid-induced attenuation of neurogenesis in hippocampus was earlier seen in male rats exposed to morphine (Eisch et al., 2000). Thus, opiates, such as morphine, is seen to reduce neurogenesis in the adult hippocampal subgranular zone (SGZ), suggesting that a waning neurogenesis contributes to opioid-induced deficits in cognitive function (Arguello et al., 2008). Enhanced apoptosis following exposure to opioids was reported to involve an upregulation of the proapoptotic caspase-3 and Bax proteins following NMDA receptor activation (Mao et al., 2002). Also, chronic methadone have been shown to up-regulate several pro-apoptotic proteins in the cortex and hippocampus, indicating activation of both the NMDA-receptor and mitochondrial apoptotic pathways (Tramullas et al., 2007). In addition, morphine-induced expression of the Toll-like receptor 9 (TLR9) and microglia apoptosis was suggested to involve the μ-opioid peptide receptor, MOP (He et al., 2011). It was further suggested that inhibition of the TLR9 and/or blockage of the MOP receptor may be a possible route for preventing opioid-induced brain damage.

The opiate elicited apoptosis in human fetal microglia and neurons (Hu et al., 2002), was also associated with morphine tolerance (Mao et al., 2002). The apoptotic effect of morphine is blocked by the opioid receptor antagonist naloxone (Hu et al., 2002), indicating an opioid

receptor mechanism involved in this effect. The effect of morphine is known to be mediated mainly through the MOP receptor although, at high concentrations, this opiate is known also to interact with both the delta-opioid peptide (DOP) and the KOP receptors. Furthermore, it appears that the opioid receptor subtypes (MOP, DOP, and KOP) may regulate different aspects of neuronal development (Hauser et al., 2000). Evidence suggesting that the MOP receptor could play an important role in regulating progenitor cell survival has recently been described (Harburg et al., 2007). In addition, morphine was earlier shown to promote anomal programmed cell death by increasing the expression of the proapoptotic Fas receptor protein and decreasing the expression of the antiapoptotic Bcl-2 oncoprotein by maintaining the activation of opioid receptors (Boronat et al., 2001). Studies also indicated that opiate-induced alteration of hippocampal function most likely results from inhibited neurogenesis (Eisch and Harburg, 2006).

5. Reversal of drug-induced impairments of abusing drugs

It is obvious from the above that chronic use of many addictive drugs may elicit pronounced effects on brain structures associated with cognitive functions leading to impaired learning and memory capabilities. It is not yet clarified whether the effects are reversible or persist over the life time. However, it seems that for many individual addicts these drug-induced damages may contribute to accelerated senescence. Many attempts to develop therapeutic strategies to deal with this complication have been reported. Indeed, attempts to design molecules that may counteract these deficits and enhance cognitive capabilities have been reported over the past decade. Several approaches to reverse cognitive impairmnts induced by central stimulanta have been reported. In the following this article will describe attempts to reverse morphine-induced damage in the hippocampus with the far aim to reconstitute cognitive abilities in experimental animals exposed to opioids.

5.1 Attempts to reverse of opioid-induced impairments on cognition

In a previous study we demonstrated that a single dose of morphine may affect the expression of the growth hormone (GH) receptor as well as the GH binding protein (GHBP) in the rat hippocampus. The gene transcripts were significantly attenuated 4 h following drug injection but was restored after 24 h (Thörnwall-LeGreves et al., 2001). In rats chronically treated with morphine, a decrease in GH binding was observed during the acute phase but this alteration was restored when animals were tolerant to the drug (Zhai et al., 1995).

As mentioned above, chronic morphine may reduce neurogenesis in the granule cell layer of hippocampus in the adult rat and a similar effect was seen in male rats after chronic self-administration of heroin (Eisch et al., 2000). Furthermore, studies have shown that opioid effects on nerve cell regeneration is not mediated through interactions with the HPA-axis, as similar effects were found also in rats subjected to adrenalectomy and subsequent corticosterone replacement. These observations suggest that the opioid regulation of neurogenesis in the adult rat hippocampus may be mediated by direct effects of the opioid drugs on the hippocampal function. The recent study by Arguello and co-workers, as mentioned above, demonstrated that chronic morphine attenuates neurogenesis in the SGZ by impeding cell-dividing, primarily in the S-phase, and inhibiting progenitor cell progression to a more mature stage (Arguello et al., 2008). In order to find strategies to reverse the opioid-induced damage to the hippocampal function it is essential to look for

agents that may stimulate hippocampal progenitors and thereby increase neurogenesis and regeneration of nerve cells. The above mentioned opioid effects on GH and its receptor suggest that the somatotrophic axis may be of importance in this regard. Indeed, both GH and its mediator insulin-like growth factor-I (IGF-I) have been reported to induce neuroprotective effects and also stimulate neurogenesis (Isgaard et al., 2007; Nyberg, 2009).

5.1.1 The impact of the somatotrophic axis on neuroprotection

Data indicating a substantial impact of the somatotrophic axis on nerve cell regeneration has been reported (Isgaard et al., 2007). IGF-I treatment was found to promote cell genesis in the brains of adult GH- and IGF-1-deficient rodents (Anderson et al., 2002; Aberg et al, 2009). In the hippocampus, treatment with bovine GH (bGH) induced an increase in the number of BrdU/NeuN-positive cells proportionally to the recorded increase in the number of BrdU-positive cells. In vitro incorporation of ^{3}[H]-labeled thymidine demonstrated that short-time exposure to bGH enhanced the cell proliferation in adult hippocampal progenitor cells. This observation demonstrated that peripherally administrated GH may increase the number of new cells in the brain of adult rats and that the hormone may exert a direct proliferative effect on neuronal progenitor cells (Aberg et al., 2006; Aberg et al., 2009).

Positive effects of GH on neurogenesis have been observed in several laboratories. A study by Harvey and co-workers showed that the hormone is produced in the retinal ganglion cells of embryonic chicks, in which GH stimulates cell survival during neurogenesis. The mechanism underlying this action was investigated in neural retina explants collected from 6-8 days-old embryos. These explants were allowed to incubate with GH for some days and the hormone was seen to reduce the number of spontaneous apoptotic cells. This anti-apoptotic action of the hormone was accompanied by a reduction in the expression of the apoptotic marker caspase-3 but also by a reduced expression of the caspase independent apoptosis inducing factor-1. These actions were considered specific, since other constituents known to be involved in apoptotic signaling, such as bcl-2, bcl-x and bid, remained unaffected. The result from this study was suggested to indicate that GH-induced retinal cell survival involved pathways dependent and independent on caspase activity (Harvey et al., 2006).

Studies over the past decades have clearly demonstrated that GH targets many areas of the CNS (for reviews, see Nyberg, 2000; 2007), and that GH deficits has been associated with cognitive impairments, memory loss, as well as diminished well being (Bengtsson et al., 1993: Burman and Deijen, 1998). GH replacement therapy in GH-deficient patients was demonstrated to ameliorate several adverse symptoms seen in these patients (Bengtsson et al., 1993: Burman and Deijen, 1998; McMillan et al., 2003). The hormone was also found to prevent neuronal loss in the aged rat hippocampus, confirming a neuroprotective effect of GH in old animals (Azcoitia et al, 2005). Decreased levels of circulating GH with age (van Dam et al., 2002) declining density of GH-binding sites with aging was found in several areas of the human brain, including the hippocampus (Lai et al., 1993). GH was also seen to enhance the expression of the rat hippocampal gene transcript of the NMDA receptor subunit NR2B (Le Greves et al., 2002). This receptor subunit is known to enhance memory and cognitive capabilities in an age-dependent manner while overexpressed (Tang et al., 1999). In addition, studies showed that GH replacement in hypophysectomized male rats may improve spatial performance and increase the hippocampal gene transcript levels of

some of the NMDA receptor subunits as well as the postsynaptic density protein 95 (Le Greves et al., 2006; 2011). All together, these observations were considered to indicate a link between decreased GH levels in elderly and deterioration of cognitive functions, with a clear indication that the hormone may improve memory and cognitive capabilities and this may be compatible with increased neurogenesis as a result of GH administration.

The mechanism by which GH induces its beneficial effects on memory and cognition is still not clarified in all its details. However, GH is shown to promote nerve cell regeneration as well as gliogenesis during the development of the fetal rat brain (Ajo et al., 2003), presumably through local production of IGF-1. Peripheral administrated GH reaching the CNS may induce a release of IGF-1 in the brain and this factor may in turn account for the mediation of brain effects of GH. However, local production of both GH and IGF-1 in certain areas of the brain has been suggested, as mice with decreased levels of circulating GH and IGF-1 exhibit normal levels of the corresponding gene transcripts in the hippocampus (Sun et al., 2005). Also, GH is shown to be produced in the hippocampal formation, where it is suggested to be involved in functions associated with his region, such as learning and response to stress (Donahue et al., 2006). Effects on these behaviors may be caused by the action of GH-induced release of IGF-1 as this mediator is also shown to affect hippocampal related behaviors. In fact, intracerebroventricular administration of IGF-1 was found to attenuate the age-related decline in hippocampal neurogenesis in rats (Lichtenwalner et al., 2001). Moreover, peripheral infusions of IGF-1 were seen to induce neurogenesis in the hippocampus of the adult rat (Aberg et al., 2000) and overexpression of IGF-1 promotes neurogenesis during the postnatal development (O'Kusky et al., 2000).

5.1.2 Reversal of opioid-induced impairments by growth hormone

In addition, a recent study showed that chronic morphine significantly and dose-dependently attenuates neuronal cell density in cultured hippocampal cells from murine fetus (Svensson et al., 2008). The ability of morphine as well as other opioids to inhibit cell growth and induce apoptosis is already known from previous work as described earlier in this section (see section 4). Therefore, the decline observed in neurite outgrowth in the mouse hippocampal primary cell cultures (Nyberg, 2009; Svensson et al., 2008) was expected, and a consequence of this decline should be that markers of apoptosis, such as lactate dehydrogenase (LDH) and caspase-3, will be affected. In fact, the activity and level of these enzymes were found to be significantly enhanced (Svensson et al., 2008). The enhanced activity of LDH in morphine-treated hippocampal cells strongly indicates that morphine may induce apoptosis in cells of this brain area. LDH, a mitochondrial dehydrogenase, is known to represent a critical component of the astrocyte–neuron lactate shuttle. It regulates the formation of lactate and influences its turnover within the cells. Caspase-3 is another enzyme that serves as a marker of apoptosis and cleaved caspase-3 represents an activated form of this enzyme that acts as a lethal protease at the most distal stage of the apoptotic pathway (Kuribayashi et al., 2006). This enzyme was also investigated in order to clarify whether the reduction seen in the hippocampal cell density involves elements related to apoptosis. It was noted that the level of cleaved caspase-3, measured by Western blot analysis, was significantly enhanced by chronic morphine (Svensson et al., 2008).

As noted above, the hippocampus represents a brain area localized within the limbic system and is well known as an important brain substrate required for the acquisition of declarative or explicit memory (Benfenati, 2007). From the literature cited above, it is evident that chronic administration of opiates may counteract cell growth and stimulate apoptosis, but it is also demonstrated that opiate-induced toxicity may include impaired neurogensis (Hauser et al., 2000; He et al., 2002; Mao et al., 2002; Eisch and Harburg, 2006). An impact of adult-generated neurons on learning and memory was earlier suggested as training on associative learning tasks was found to double these neurons in the rat brain dentate gyrus (Kenney and Gould, 2008; Gould, 2010). Consequently, memory dysfunctions induced by chronic exposure to opiates could result from decreased adult neurogensis as these drugs may inhibit neurogenesis in the adult hippocampus (Eisch and Harburg, 2006; Eisch et al., 2000). This inhibition might well reflect a decreased number of neural precursors caused by increased apoptosis of the newborn neurons. However, in recent years, several factors that may promote and enhance neurogenesis from preexisting neuronal precursors have been reported. Among them are GH and its mediator IGF-1 in addition to several other growth factors. IGF-1 is shown to be essential for hippocampal neurogenesis (Aberg et al., 2000, 2006). As mentioned above, this factor is regulated through the somatotrophic axis, where GH has an important role as an activator and releaser of IGF-1 as well as its binding proteins.

In order to investigate whether GH may reverse opiate-induced apoptosis or inhibition of neurogenesis, we examined the effect of human GH on murine primary hippocampal neuronal cell cultures exposed to morphine (Svensson et al., 2008). We observed that GH could significantly reverse the morphine-induced inhibition of neurite outgrowth and that cell density was restored after treatment with the hormone. The effect of GH was evident both when the hormone was added with morphine and when it was added after the opiate had induced its damaging effect. We also noted that GH reversed the morphine-induced effects on the apoptopic markers LDH and caspase-3 activity (Svensson et al., 2008). Thus, combining these observations with the effects of GH seen on memory and spatial performance in rats (Le Greves et al., 2006,; 2011) it appears that the hormone may be useful for the reversal of the adverse effects of morphine or other opiates on brain cells.

These data opens for future attemps also to use IGF-1 in order to reverse opioid-induced damage on the brain to improve cognitive capabilities. It also opens for the possibility to stimulate the somatotrophic axis to reverse cognitive impairments induced by other drugs of abuse. Actually, as can be seen below, growth factors have been used in attempt to counteract brain damages induced by alcohol.

5.2 Attempts to reverse alcohol-induced impairments in cognition

Studies on the reversal of the adverse effects induced by various drugs have shown that certain growth factors may be useful in attempts to counteract drug-induced cell damage and apoptosis. For instance, it was demonstrated (Gibson et al. 2002) that stimulation of human embryonic kidney cells HEK 293 and the breast cancer cell line MDA MB 231 with epidermal growth factor (EGF) effectively and dose-dependently protected these cells from tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis. This stimulatory effect was shown to reduce apoptosis by blocking both TRAIL-mediated

mitochondrial release of cytochrome c and activation of caspase-3. It was further shown that the survival response of EGF involved the activation of the protein kinase Akt. Activation of Akt was found to be sufficient for inibition of the TRAIL-induced apoptosis, and the expression of kinase-inactive Akt abolished the protective effect of EGF. In contrast, inhibition of the stimulatory effect of EGF on the extracellular-regulated kinase (ERK) activity did not affect EGF protection. From these findings it was concluded that activation of the EGF receptor generates a survival response against TRAIL-induced apoptosis by blocking the release of cytochrome c from the mitochondria, which, in turn, is mediated by the activation of Akt in epithelial-derived cells.

The effects of estrogens and certain growth factors subsequent to ethanol treatment were recently examined in order to assess the potential of these hormones to reverse the effects of ethanol-induced damage (Barclay et al., 2005). The result of these studies indicated that both IGF-I and bovine basic fibroblast growth factor (bFGF) reduced toxic effect of the drug on neuronal survival, whereas estrogen, bFGF, and nerve growth factor (NGF) seemed to increase the total neurite length after ethanol treatment (Barclay et al., 2005). In addition, heparin-binding epidermal growth factor (HB-EGF), also a member of the EGF family of growth factors, has been reported to prevent apoptosis and differentiation and, in a very recent study, it was shown that stimulation with HB-EGF could reverse alcohol-induced apoptosis in human embryonic stem cells (Nash et al., 2009). Another possibility for reversing alcohol-induced cell damage involves brain-derived neurotrophic factor (BDNF). BDNF signaling plays an important role in neural survival and differentiation and studies have shown that alcohol significantly reduces BDNF signaling in neuronal cells (Climent et al., 2002). Also, the antiproliferative action of ethanol can be modulated by changing the sensitivity of the autophosphorylation of the IGF-1 receptor to ethanol (Seiler et al., 2000). This raised the question of whether IGF-1 could counteract the antiproliferative effects induced by alcohol. In fact, studies have shown that alcohol inhibits differentiation of the neural stem and that this effect is reduced by both IGF-1 and BDNF (Tateno et al., 2004). These results suggest the possibility that stimulation of neurotrophic factor signaling can reverse apoptosis induced by alcohol exposure.

6. Conclusions

It is evident from studies reviewed in this article that most drugs of abuse may induce adverse effects on brain structures associated with cognitive functions. In most cases these effects seem to impact brain circuits linked to important aspects of cognition, such as memory and learning, attention, risk taking, motivation, mood and wanting. The deficits induced on these behaviors by alcohol and opioids are well documented, whereas those of central stimulants and other abusing drugs are less well characterized. As mentioned in this article an important issue is the approach to find strategies to reverse the drug-induced deficits and in the case of damages induced by alcohol and opioid abuse it seems that certain growth factors may be useful and open for new methods for successful therapy.

7. Acknowledgment

8. References

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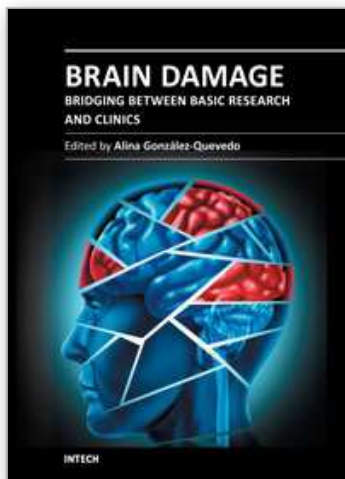
Brain Damage - Bridging Between Basic Research and Clinics

Edited by Dr. Alina Gonzalez-Quevedo

"Brain Damage - Bridging Between Basic Research and Clinics" represents a collection of papers in an attempt to provide an up-to-date approach to the fascinating topic of brain damage in different pathological situations, combining the authors' personal experiences with current knowledge in this field. In general, the necessary link between basic and clinical neurosciences is highlighted, as it is through this interaction that the theoretical understanding of the pathophysiological mechanisms can be successfully translated into better ways to diagnose, treat and prevent the catastrophic events that occur when the brain suffers from external or internal noxious events. The book spans different aspects of brain injury, starting from damage occurring in the fetal and child brain, followed by different neurodegenerative processes. Attention is also focused on the negative effects of drug addictions and sleep deprivation on the brain, as well as on the early assessment of brain injury for preventive strategies employing sensitive biomarkers.

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