Neuropharmacology xxx (2014) 1–10

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Structural plasticity of the brain to psychostimulant use

Fred Nyberg*

Department of Pharmaceutical Biosciences, Uppsala University, P.O. Box 591, S-751 24 Uppsala, Sweden

Keywords:
Addiction
Amphetamine
Central stimulants
Cocaine
Cognition
MDMA
Neuroplasticity

A B S T R A C T

Over the past years it has become evident that repeated exposure to a variety of psychoactive stimulants, like amphetamine, cocaine, MDMA (3,4-methylenedioxy-N-methylamphetamine), methylphenidate and nicotine may produce profound behavioral changes as well as structural and neurochemical alterations in the brain that may persist long after drug administration has ceased. These stimulants have been shown to produce long-lasting enhanced embranchments of dendrites and increasing spine density in brain regions linked to behavioral sensitization and compulsive patterns characteristic of drug seeking and drug addiction. In this regard, addiction to stimulant drugs represents a compulsory behavior that includes drug seeking, drug use and drug craving, but is also characterized as a cognitive disorder. In this article, recent findings regarding the impact of central stimulants on plasticity in brain regions of relevance for addictive behavior will be highlighted. A particular focus will be given to changes in neuroplasticity that occur in areas related to memory and cognition. Possible routes for the reversal of altered brain plasticity will also be discussed.

This article is part of a Special Issue entitled 'CNS Stimulants'.

1. Introduction

Studies have shown that considerable alterations in brain organization may occur in response to various events and experiences. This may lead to changes that can alter substantially the pattern of neuronal activation. Thus, the physical structure and functional arrangement of the brain may be altered by environmental influences. This phenomenon is known as neuroplasticity, a concept that has introduced the view that the brain may change throughout life and replaces the previously held idea that it should be considered as a static, non-changeable organ.

Brain plasticity is recognized as an important aspect in the understanding of processes that occur in the brain during its whole life span. It occurs not only during early brain development and aging, but also as a response to various traumas or chemical substances. The brain appears to be modifiable following chronic intake of addictive drugs and addiction is now considered as a brain disease characterized by modifications or alterations in various signaling systems involved in brain reward, stress and compulsive behavior.

It is widely accepted that memories associated with drugs of abuse, such as amphetamine, cocaine and other central stimulants, increase relapse vulnerability to substance use. It has also been confirmed that chronic intake of drugs of abuse may induce a decline in cognitive function and thereby accelerate aging processes (see Nyberg, 2012).

The effects of central stimulants on cognitive and addictive behaviors include alterations in brain plasticity and various transmitter systems related to these behaviors. It is also clear that brain plasticity, or neuroplasticity, includes synaptic as well as non-synaptic changes.

Current data have suggested that neuroplasticity may occur at different levels. It may result from changes at the cellular level induced by for example, learning or stress, and by drugs of abuse affecting the activity of various transmitter pathways (Kolb et al., 2011; Pittenger, 2013). In response to injury, large-scale alterations in various brain structures may also affect neuroplasticity. Therefore, neuroplasticity is widely considered to represent an important phenomenon, not only in healthy development, learning and memory, but also in brain trauma and during recovery from brain damage. The role of illicit drugs and their capacity to affect brain plasticity has received much attention (e.g. Feltenstein and See, 2013). A special interest has been directed to neuronal adaptations induced by central stimulants (Dietz et al., 2009).

Recent studies have indicated a high prevalence of stimulant drug use in many Western countries and increasing use of these drugs over the past few decades (Gonzales et al., 2010; Ciccarone, 2011; Vardakou et al., 2011). The purpose of taking central

* Tel.: +46 18 471 4166; fax: +46 708 174166.
E-mail address: fred.nyberg@farmbio.uu.se.

http://dx.doi.org/10.1016/j.neuropharm.2014.07.004
0028-3908/

stimulants is a desire to evoke a sense of wellbeing and pleasure, and also to enhance cognitive and social performance. However, continuous and chronic use of these drugs is associated with harmful effects, including substantial deficits in many aspects of mental health. Long-term abuse of stimulants elicits neurodegenerative effects leading to disabilities in learning and memory processes (Ciccarone, 2011; McKetin and Mattick, 1997; Krasnova et al., 2005). These effects seem to result from alterations in brain plasticity.

It should be emphasized that epigenetic mechanisms have also been implicated in the modulation of neural plasticity. They may act as mediators of several functions in the CNS, including neuronal–glial differentiation and adult neurogenesis, but also in addictive behavior, memory and cognitive function (Ravi and Kannan, 2013).

This article aims to highlight current knowledge about the effects of central stimulants, including amphetamines, cocaine, 3,4-methylenedioxymethamphetamine (MDMA), and analogs thereof, on neuroplasticity related to cognitive function and addictive behavior. It will provide a focus on mechanisms underlying alterations in brain plasticity both at the structural and molecular levels.

2. Aspects on memory and learning

Memory has been described as a multi-system composite of the brain. Each system is connected to a separate memory function that targets different neurological substrates. The *declarative memory*, for instance, is believed to play a role in the process of retaining conscious memories of facts and sights. The formation and establishment of new declarative memories is linked to structures in the medial temporal lobe and diencephalon. Memory imprints in these structures are associated with specific areas located in the cerebral cortex. Impaired declarative memories are linked to the prefrontal cortex and the hippocampus. The frontal cortex is essential for functions associated with reasoning and retention of declarative memory (Samuelson, 2011; Weiss and Disterhoft, 2011). Brain areas of *non-declarative* forms of memory are thought to include the cerebral cortex, cerebellum and the basal ganglia (Nyberg, 2012).

At the cellular level, an important concept of synaptic plasticity relevant for the storage of long-term memory (LTM) is long-term potentiation (LTP). LTP potentiates signal transmission between adjacent neurons and can be induced by high-frequency stimulation of the synapse. Furthermore, LTP represents an important variable for defining the cellular mechanisms underlying learning and memory, as it is associated with many features of LTM. Both LTP and LTM are triggered rapidly and may last over a long period of time. Studies have demonstrated that each of them is dependent on biosynthetic processes for protein formation. The proteins formed are believed to have a role in associative memory, and LTP is shown to be involved in many different types of learning. These include simple classical conditioning observed in experimental animals, but also in more complex, higher-level cognition that is experienced by humans (Cooke and Bliss, 2005).

Neuroplasticity linked to LTP has been found in many brain regions, including the amygdala, hippocampus, nucleus accumbens and prefrontal cortex, i.e. regions involved in drug reward, and also in memory and learning (Kenney and Gould, 2008). For example, increased activity in the amygdala and enhanced amygdala-hippocampus connectivity leading to long-lasting, non-temporary memory alterations have been described (Edelson et al., 2011). Further, it has been indicated that the hippocampal formation is essential for the transfer of short-term memories to LTMs (Santini et al., 2001; Glannon, 2006). Moreover, both clinical studies and investigations performed in animals have shown that, besides its critical role in the generation of LTM, the hippocampus performs an important role in the processing and the integration of spatial and coherent information (Kim and Lee, 2011).

Regarding the molecular mechanism underlying memory potentiation, previous research has underlined a critical importance of the excitatory amino acid glutamate (Abel and Lattal, 2001). Glutamate may bind to and activate both N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, which are located on the cell surface membrane of neurons. The activation of these sites results in the opening of calcium and sodium channels into the nerve cells. Increased influx of calcium leads to the activation of adenylate cyclase, a membrane enzyme, which in turn converts ATP to cAMP. Subsequently, the formed cAMP contributes 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, induces transcription and increases production of several proteins essential for the construction of new synapses (Abel and Lattal, 2001).

Using animal models, it was possible to demonstrate that organization of the NMDA receptor subunits, NR1, NR2A, NR2B and NR2D, is essential for glutamate to induce its promoting effects on the memory. For instance, in experiments with transgenic mice it was found that overexpressing the NR2B subunit significantly improved performance in memory tests (Tang et al., 1999). Also, the ratio of the NR2B/NR2A was shown to be a relevant marker of cognitive functioning in the rat. Increasing the NR2B/NR2A ratio has been shown to affect the process that promotes LTP and memory (Le Greves et al., 2002; Le Greves et al., 2006; Zhao et al., 2005; Nyberg and Hallberg, 2013). Moreover, a considerable body of evidence has found an important role for glutamate and its ligand-gated NMDA, AMPA, and kainic acid (KA) receptor subtypes in mediating addictive behaviors (Wolf, 1998; Tzschentke and Schmidt, 2003; Kalivas, 2004; Gass and Olive, 2009). However, the role of metabotropic glutamate (mGlu) receptors in neural mechanisms underlying drug addiction has become apparent only within the last decade (Olive, 2010). Data supporting a role of Group I (mGlu1 and $mGlu_5$) receptors in regulating drug intake, reward, reinforcement and reinstatement of drug-seeking behavior have emerged from comparatively recent pharmacological and genetic studies (Olive, 2009). The metabotropic mGlu receptors are also thought 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 seen in drug addicts.

3. Neuroplasticity and memory formation at the structural level

Over recent years, accumulating data has suggested that memory and cognitive function are constructed and maintained by support from structural and functional plasticity in post-synaptic dendritic spines at excitatory synapses. It is believed that these events are driven by filamentous actin (F-actin) polymerization and that maintenance of memories depends upon the preservation of polymerized actin (Young et al., 2014).

The formation of LTM is thus believed to involve alterations of synaptic efficacy that is induced by modifications in both neural transmission and morphology. The actin cytoskeleton has been shown to promote presynaptic vesicle movement, postsynaptic glutamate receptor trafficking and also morphogenesis of dendritic spines (Lamprecht, 2014). The structure and dynamic of the actin cytoskeleton that gives rise to these events are regulated by extracellular signals induced by its regulatory proteins, i.e. these

Please cite this article in press as: Nyberg, F., Structural plasticity of the brain to psychostimulant use, Neuropharmacology (2014), http://dx.doi.org/10.1016/j.neuropharm.2014.07.004