Drug addiction and behavioural sensitization biology essay

Science, Biology

Entrance into addicted state clearly results from the interplay between inherited predisposition (e. g. via genetic variants mediating the personality traits associated with drug-seeking behaviour and dependence) and the environment (e. g. actual exposure to drugs of abuse) (Nestler, 2001; Goldman et al., 2005; Wong et al., 2011). There is evidence that stressful and traumatic experiences in early life have also a long-lasting impact on individual's behaviour. However, the mechanisms which mediate the effects of the early environment on behaviour are not yet fully understood. Recent findings suggest that epigenome, which consists of the machinery for programming long-term gene expression profiles and thus defines gene function and phenotype, can be modulated by a variety of environmental factors, including nutrients, chemicals and early-life environment (Weaver et al., 2004; Waterland et al., 2006; Roth et al., 2009; Szyf, 2009). Therefore, the epigenome provides an important interface between genes and environment and may be viewed as a potential mechanism underlying the rapid form of environmentally driven adaptation (Franklin and Mansuy, 2010). It is hypothesized that epigenetic processes (such as DNA methylation and histone modifications) may be the underlying mechanisms via the environmental factor alter gene expression and therefore changes the risk of a wide range psychopathology, including drug addiction. Thus, a better understanding of the mechanisms that predispose individuals to the environmental factors associated with drug-taking behaviour and the systems that translate the response to environmental stimuli (e. g. drug exposure) into long-lasting cellular memories in the brain are fundamental to unlocking the neurobiological changes that are implicated in drug addiction

(Wong et al., 2010). Based on these data, the general aim of the current thesis was to investigate the role of DNA methylation and environmental factors (such as S-adenosylmethionine and early life stress) in molecular mechanism associated with cocaine-induced behavioural sensitization in mice and rats. Therefore, we first assessed a potential role of DNA methylation in cocaine-induced behavioural sensitization in mice. Further, our aim was to investigate whether the environmental factors such as S-adenosylmethionine (SAM) via affecting epigenome could alter cocaine-induced gene expression and locomotor sensitization in mice. Finally, using maternal separation as an early life stress model, we evaluated whether the early life stress on rats could alter cocaine sensitivity in adulthood via DNA methylation.

REVIEW OF LITERATURE

1. Drug addiction and behavioural sensitization

Drug addiction is simply defined as an abnormal behavioural outcome involving a cascade of neurochemical changes mainly in the brain’s rewarding circuitry. The main features of drug addiction are compulsive drug use despite adverse consequences and high rates of relapse during periods of abstinence (Mendelson and Mello, 1996; Thomas et al., 2008). Once a person becomes addicted to drugs of abuse, only few effective therapies exist. Therefore, understanding of the neural mechanisms that underlie the transition from recreational drug use to a chronically addicted state and the mechanisms which are responsible for the persistence of addictive behaviours even after prolonged drug abstinence, would provide clues into

how block or reverse the addicted state and thereby diminish the rate of relapse (for a review see Renthal and Nestler, 2008). Psychostimulants, such as cocaine and amphetamine, change a neuronal structure and function in the specific brain regions, resulting in persistent changes at the molecular, cellular systems and behavioural levels (Paulson et al., 1991; Koob and LeMoal, 2001; Nestler, 2001; McQuown and Wood, 2010). Repeated administration of psychostimulants induces an enhanced behavioural response to subsequent drug exposure, a phenomenon known as psychomotor or behavioural sensitization that can persist for months (Robinson and Berridge, 1993; Pierce and Kalivas, 1997). Behavioural sensitization can be separated into two components - induction and expression of sensitization. Induction of sensitization refers to the progressive increase in locomotor activity during the repeated drug treatment. Expression of sensitization is demonstrated following challenge with a low dose of psychostimulant after a drug-free period (McQuown and Wood, 2010). Psychostimulant-induced behavioural sensitization in rodents provides a model for addictive behaviours such as those associated with craving and relapse, as well as for psychotic complications of psychostimulant abuse (Koob and Bloom, 1988; Robinson and Berridge, 1993; Chen et al., 2003). Results from many neuropharmacological studies in animal models indicate that drugs of abuse activate the brain reward circuitry, which centres on dopaminergic neurons in the ventral tegmental area (VTA) of the midbrain and their projections to the limbic system, in particular, the nucleus accumbens (NAc), dorsal striatum, amygdala, hippocampus and regions of prefrontal cortex (Figure 1) (Koob and Moal,

2005; Kalivas and Volkow, 2005; Hyman et al., 2006; Robinson and Nestler, 2011). Described reward circuitry is activated by stimuli that promote evolutionary fitness of the organism, such as food, play, sex, and social stimulation. Compared to the natural rewards, drugs of abuse activate this reward circuitry far more strongly and persistently, and without association with productive behavioural outcomes. Chronic exposure to drugs modulates described brain reward regions in part through a homeostatic desensitization that renders the individual unable to attain sufficient feelings of reward in the absence of drug (for a review see Robinson and Nestler, 2011). Figure 1. The brain on the left describes dopaminergic afferents that originate in the ventral tegmental area (VTA) and release dopamine in the NAc and other limbic targets. The brain on the right describes glutamatergic regions - medial prefrontal cortex (mPFC), orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), thalamus (Thal), hippocampus and amygdale that are important for reward and send excitatory projections to the NAc (modified from Robinson and Nestler, 2011). The addictive phenotype can persist for the length of an individual’s life with drug craving and relapse occurring after weeks, months or even years of abstinence. This persistence suggests that drugs of abuse induce long-lasting changes in the brain that underlie addiction behaviours. Moreover, it has been hypothesized that persistent alterations in gene expression could be responsible for the long-term behavioural and structural changes. The classic mechanism for regulation of gene expression is through the actions of transcription factors. Transcription factors are proteins, which in response to cell signalling pathways are able to bind to specific DNA sequences in the promoter regions of target genes, and

increase or decrease gene expression by promoting or blocking the recruitment of the RNA polymerase-II transcriptional complex. It has been proposed that drugs of abuse activate certain transcription factors and thereby cause adaptive changes in neuronal structure and function (Kalivas et al., 2003). Despite the fact that several different transcription factors exist, two, the most and best characterized transcription factors (related with drug addiction) are cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB) and ΔFosB (Nestler, 2001; McClung and Nestler, 2003). CREB forms homodimers that can bind to genes at cAMP response elements (CREs), but primarily activates transcription after it has been phosphorylated by protein kinase A (PKA) at serine133 (Ser133). Phosphorylation of CREB at Ser133 allows recruitment of CREB-binding protein (CBP) that then promotes transcription (Carlezon et al., 2005; Briand and Blendy, 2010; Robinson and Nestler, 2011). Psychostimulants and opiates upregulates the cAMP pathway and thereby increase CREB activity in multiple brain regions, including the NAc and dorsal striatum (Carlezon et al., 2005; Edwards et al., 2007; Briand and Blendy, 2010). Studies involving the inducible overexpression of CREB or a dominant negative mutant in bitransgenic mice or with viral vectors have demonstrated that CREB induction in the NAc decreases the rewarding effects of cocaine and opiates (Carlezon et al., 1998; Barrot et al., 2002; Robinson and Nestler, 2011). Data by Walters and Blendy (2001) demonstrated that mice who had partially deficient in CREB (CREBα, Δ mutant mice lack the α and Δ isoforms of CREB) showed an enhanced response to the reinforcing properties of cocaine compared with their wild-type controls in both conditioned place preference

(CPP) and sensitization behaviours (Walters and Blendy, 2001). These results suggest that drug-induced CREB activation/phosphorylation in the NAc comprises a negative feedback mechanism which dampens behavioural sensitivity to subsequent drug exposure (Carlezon et al., 2005; Chen et al., 2009). However, temporally CREB is induced rapidly following each drug treatment (effects are relatively short-lived) and returns to baseline after a few hours. Transcription factor ΔFosB (encoded by the fosB gene) a member of the Fos family, which consists of c-fos, fosb, fra-1 and fra-2 genes, is far more stable than all other transcription factors linked to addiction to date (Nestler et al., 2001; Nestler, 2008). ΔFosB heterodimerizes with Jun family proteins (c-Jun, JunB, JunD) to form activator protein-1 (AP-1; known as transcription factor AP-1) complexes which bind to AP-1 sites in responsive genes to regulate transcription (Curran and Franza 1988; Jorissen et al., 2007; Nestler, 2008). It has been found that acute exposure to drug of abuse causes transient increase in members of the transcription factor Fos family (including c-fos, fosB) in the NAc and dorsal striatum (Nestler, 2001). During repeated drug of abuse exposure the expression of transcription factor ΔFosB is increased several fold and often persists long after drug exposure ceases. Thus, ΔFosB extraordinary stability in neurons has led to the theory that it plays an important role in the onset of drug addiction (Bowers et al., 2004; McClung et al., 2004; Kalivas and O’Brien, 2008). Indeed, several previous studies have demonstrated that ΔFosB is linked directly to addiction-related behaviours. It has been found that prolonged ΔFosB expression in the NAc increases the rewarding effects of cocaine. For example, mice overexpressing ΔFosB demonstrated increased CPP, self-

administration and incentive motivation for cocaine (Kelz et al., 1999; Nestler et al., 2001; Colby et al., 2003; Peakman et al., 2003). However, mice that express a dominant-negative form of cJun (ΔcJun), which disrupts normal AP-1 function, demonstrated less preference for cocaine (Nestler, 2008). Thus, to summarize, it seems that gene expression induced by short-term ΔFosB and by CREB reduce the rewarding effects of cocaine, while prolonged ΔFosB expression increase drug reward. Furthermore, it has been demonstrated that gene expression after a short cocaine exposure was dependent on CREB, while gene expression after a longer cocaine treatment was ΔFosB dependent (McClung and Nestler, 2003; Nestler, 2008). Moreover, altered expression of AGS3 (activator of G protein signaling 3) (Bowers et al., 2004) and BDNF (brain-derived neurotrophic factor) (Grimm et al., 2003) has been reported weeks after the last drug experience (Renthal and Nestler, 2008). Manipulation of these genes in rodents regulates drug relapse behaviour (Bowers et al., 2004; Lu et al., 2004; Graham et al., 2007; Renthal and Nestler, 2008). A multitude of microarray studies under different experimental conditions have identified several potential target genes for drugs of abuse in distinct brain reward regions that may promote to their long-lasting behavioural effects (Freeman et al., 2001; McClung and Nestler, 2003; Yuferov et al., 2003; Yao et al., 2004; McClung et al., 2005; Winstanley et al., 2007; LaPlant and Nestler, 2011). Thus, several recent data suggest that epigenetic mechanisms (key cellular processes that interpret diverse environmental stimuli into long-lasting changes in gene expression via the regulation of chromatin structure) contributes to drug-induced transcriptional

and behavioural changes (Kumar et al., 2005; Levine et al., 2005; Renthal et al., 2007; Renthal and Nestler, 2008; Wang et al., 2010)..