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Enhancing glutamatergic transmission during adolescence reverses early-life stress-induced deficits in the rewarding effects of cocaine in rats

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ABSTRACT

Adolescence marks a critical time when the brain is highly susceptible to pathological insult yet also uniquely amenable to therapeutic intervention. It is during adolescence that the onset of the majority of psychiatric disorders, including substance use disorder (SUDs), occurs. It has been well established that stress, particularly during early development, can contribute to the pathological changes which contribute to the development of SUDs. Glutamate as the main excitatory neurotransmitter in the mammalian CNS plays a key role in various physiological processes, including reward function, and in mediating the effects of psychological stress. We hypothesised impairing glutamatergic signalling during the key adolescent period would attenuate early-life stress induced impaired reward function. To test this, we induced early-life stress in male rats using the maternal-separation procedure. During the critical adolescent period (PND25–46) animals were treated with the glutamate transporter activator, riluzole, or the NMDA receptor antagonist, memantine. Adult reward function was assessed using voluntary cocaine intake measured via intravenous self-administration. We found that early-life stress in the form of maternal-separation impaired reward function, reducing the number of successful cocaine-infusions achieved during the intravenous self-administration procedure as well impairing drug-induced reinstatement of cocaine-taking behaviour. Interestingly, riluzole and memantine treatment reversed this stress-induced impairment. These data suggest that reducing glutamatergic signalling may be a viable therapeutic strategy for treating vulnerable individuals at risk of developing SUDs including certain adolescent populations, particularly those which may have experienced trauma during early-life.

1. Introduction

Substance use disorder (SUD) describes the emergence of a pattern of drug use where an individual experiences a compulsion to seek and take drugs, loss of control over drug use, as well as the emergence of a negative emotional state (Koob, 2009). Long-term drug use induces alterations to neurochemical and molecular signalling cascades in reward pathways which precipitate further seeking and intake of the drug (Jonkman and Kenny, 2013; Koob, 2009; Lupien, 2014; Van Dam et al., 2014). This pattern of drug intake is pervasive, disabling, and greatly impairs the quality of life of an individual.

It is well established that adolescence and early adulthood are particularly vulnerable periods for the development of SUDs; over 11% of adolescents (13–18 years) in the United States fulfil the criteria for drug dependence (Merikangas et al., 2010). Risk factors for the development of SUDS present in adolescents include high levels of impulsivity (Shedler and Block, 1990) and alterations in reward and reinforcement regulation (Doremus-Fitzwater et al., 2010). Early-life and adolescence mark unique periods of brain

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development characterised by high levels of plasticity (Bateson, 2007) and the major restructuring of neuronal connections (Lenroot and Giedd, 2006) governed by environmental stimuli (Giedd, 2008; Paus et al., 2008). This environmentally-induced rewiring of the developing brain is crucial for the learning and development of skills essential to survival in adulthood. However, this highly-plastic neuronal environment makes the brain highly susceptible to pathological insult (Bondi et al., 2014; Enoch, 2011; Meyer-Lindenberg and Tost, 2012; O'Connor and Cryan, 2014) including psychological stress which has been well established as predisposing individuals to addictive disorders later in life (De Bellis, 2002; Enoch, 2011; Koob, 2008). Indeed, preclinical studies have demonstrated psychological stress induced early in life can affect reward-function in adulthood; both increasing reward-induced behavioural-reinforcement (Flagel et al., 2003; Kosten et al., 2000; Matthews et al., 1999) and decreasing reward intake, possibly through anhedonia (Martini and Valverde, 2012; Matthews et al., 1999; Silveira et al., 2010). Thus, a need to clarify the mechanisms by which exposure to a psychological stress can alter drug-intake in adulthood remains.

Glutamate is the main excitatory neurotransmitter in the mammalian central nervous system (CNS) and plays a key role in the induction of goal-directed behaviour as well as mediating drug-induced plasticity (Mameli et al., 2007; Sun et al., 2005; You et al., 2007). Glutamatergic and dopaminergic signalling converges at the level of the nucleus accumbens, coupling glutamate encoded environmental stimuli with dopaminergic reinforcement signals allowing drug-related cues to increase in salience increasing sensitivity to drug-related stimuli (Brown et al., 2011; Day et al., 2007; Stuber et al., 2008). Furthermore, the fronto-striatal circuits implicated in regulating compulsive and impulsive behaviours, key features of SUDS (Fineberg et al., 2010) are densely populated by glutamate receptors (Monaghan et al., 1985). Thus, the glutamatergic system is key to the regulation of reward systems and goal-directed behaviour.

Interestingly, early-life stress can disturb the glutamatergic signalling machinery (O'Connor et al., 2013a) and moreover can perturb normal glutamatergic function potentially inducing a hyperglutamatergic state (Musazzi et al., 2011; O'Connor et al., 2013a). As such, disruptions to the glutamatergic machinery may contribute to altered reward function induced by early-life psychological stress. We hypothesise that reducing glutamatergic signalling during the key adolescent development stage may serve to attenuate early-life stress-induced perturbations to brain reward systems.

To test this hypothesis we employed the well validated maternal-separation procedure to induce early-life stress (O'Mahony et al., 2011; O'Mahony et al., 2009). Following this, glutamatergic signalling was reduced during adolescence using the EAAT2 activator riluzole or the NMDA receptor antagonist memantine. Both of these glutamatergic agents are clinically approved for use in humans and can reverse stress-induced deficits in preclinical behavioural models (Gosselin et al., 2010; Reus et al., 2012). Cocaine reinforcement and intake was assessed using the intravenous self-administration procedure.

2. Methods

2.1. Experimental design

Three separate experiments were conducted. Each experiment consisted of an early-life stress phase (maternal-separation), a chronic adolescent drug or vehicle treatment phase and cocaine-self- administration portion in adulthood (Figs. 2a, 5a and 6a). Firstly, we investigated the effects of early-life maternal-separation stress on cocaine intake in adulthood (Figs. 2 and 3). When a strong difference was seen, it was important to assess whether chronic injection delivery and handling during the critical adolescent development phase may have any effects on cocaine intake in adulthood (Fig. 4). Thus, a study was conducted which consisted of 4 groups; 1) Non-separated with no injection stress (NS – No Injection Stress), 2) Maternally-Separated with no injection stress (MS – No Injection Stress), 3) Non-separated with injection stress (NS – Injection Stress) and 4) Maternally-Separated with injection stress (MS – Injection Stress). Next the ability of riluzole, delivered during the critical adolescent development period, to reverse the observed early-life stress-induced change to cocaine-reinforcement in adulthood was investigated. This experiment had 5 groups; 1) Non-separated with vehicle treatment (NS –Vehicle), 2) Maternally-separated with vehicle treatment (MS – Vehicle), 3) Maternally-separated with 1 mg/kg riluzole treatment (MS – Riluzole 1 mg/kg), 4) Maternally-separated with 3 mg/kg riluzole treatment (MS – Riluzole 3 mg/kg) and 5) Maternally-separated with 10 mg/kg riluzole treatment (MS – Riluzole 10 mg/kg). Finally, like riluzole, we assessed memantine's potential, when administered in adolescence, to reverse the observed early-life stress-induced change to cocaine-reinforcement in adulthood. This experiment had 5 groups; 1) Non-separated with vehicle treatment (NS – Vehicle), 2) Maternally-separated with vehicle treatment (MS – Vehicle), 3) Maternally-separated with 3 mg/kg memantine treatment (MS – Memantine 3 mg/kg), 4) Maternally-separated with 10 mg/kg memantine treatment (MS – Memantine 10 mg/kg) and 5) Maternally-separated with 30 mg/kg memantine treatment (MS – Memantine 30 mg/kg). All drug doses are based on previously published data (Gosselin et al., 2010; Reus et al., 2012) as well as data collected in pilot experiments.

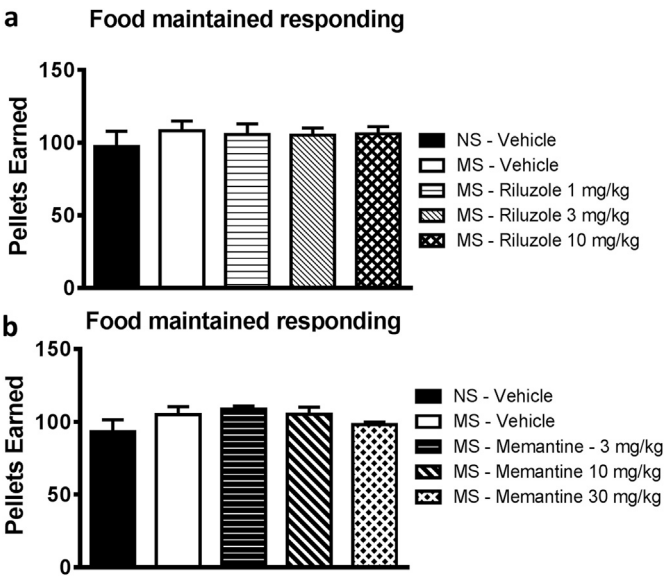

Fig. 1. Early-life maternal-separation stress alone, or combined with adolescent riluzole or memantine treatment, did not affect food-training performance. (a) Average number of food pellets earned during a 1 h testing session under the FR5TO20 schedule in MS and riluzole treated animals. (b) Average number of food pellets earned during a 1 h testing session under the FR5TO20 schedule in MS and memantine treated animals.

2.2. Animals

Male and female rats (270–300 g) were obtained (Harlan, UK) for the purposes of breeding animals to be used as experimental