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Ontogeny of sensorimotor gating and short-term memory processing throughout the adolescent period in rats

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ABSTRACT

Adolescence and puberty are highly susceptible developmental periods during which the neuronal organization and maturation of the brain is completed. The endocannabinoid (eCB) system, which is well known to modulate cognitive processing, undergoes profound and transient developmental changes during adolescence. With the present study we were aiming to examine the ontogeny of cognitive skills throughout adolescence in male rats and clarify the potential modulatory role of CB1 receptor signalling. Cognitive skills were assessed repeatedly every 10th day in rats throughout adolescence. All animals were tested for object recognition memory and prepulse inhibition of the acoustic startle reflex. Although cognitive performance in short-term memory as well as sensorimotor gating abilities were decreased during puberty compared to adulthood, both tasks were found to show different developmental trajectories throughout adolescence. A low dose of the CB1 receptor antagonist/inverse agonist SR141716 was found to improve recognition memory specifically in pubertal animals while not affecting behavioral performance at other ages tested. The present findings demonstrate that the developmental trajectory of cognitive abilities does not occur linearly for all cognitive processes and is strongly influenced by pubertal maturation. Developmental alterations within the eCB system at puberty onset may be involved in these changes in cognitive processing.

1. Introduction

Adolescence, the transitional stage between childhood and adulthood, is characterized by highly dynamic processes of neuronal and behavioral adjustment. These developmental alterations are essential across species to allow for the maturation of adult social and cognitive skills, required to increase independence (Spear, 2000; Casey et al., 2008; Schneider, 2013). At the same time, adolescent neurodevelopment also comprises a critical period of vulnerability for unintentional injuries, suboptimal choices, and the emergence of various neuropsychiatric disorders (Merikangas et al., 2009; Paus et al., 2008; Kessler et al., 2007). Understanding the basis of psychiatric disorders therefore requires a comprehensive knowledge of how neurodevelopmental processes affect and modulate behavioral characteristics during adolescence. The onset of schizophrenia for example, a disorder which typically manifests during late adolescence or early adulthood, coincides with cognitive maturation of cortical areas and concomitant refinement of cognitive executive processes. A failure in these maturational events may thus play a critical role in the pathophysiology of schizophrenia (Catts et al., 2013).

In humans, the development of cognitive abilities displays heterogeneous trajectories. Some cognitive skills are already established in early childhood while other more complex functions continue to develop well into adolescence (Catts et al., 2013). Moreover, certain learning and cognitive processes seem to decline with the onset of puberty (Chung and Thomson, 1995; McGivern et al., 2002). Puberty refers to the restricted time period around mid-adolescence when sexual maturation is completed (Schneider, 2013). But notably, gonadal alterations in puberty and adolescent behavioral maturation are intimately linked in timing through multiple and complex interactions between neuronal developmental processes and gonadal steroid hormones (Sisk and Foster, 2004; Schneider, 2013).

Most ontogenetic investigations of cognitive processes in laboratory rodents have focused on the pre-weanling and weanling period. However, in recent years adolescence has also gained increasing attention, although longitudinal studies covering the

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complete adolescent period are still scarce. When testing adolescent animals for cognitive skills, one needs to consider that adolescent individuals differ notably from adults in their brain reward neuro-circuitry and in the way they process and respond to rewarding and aversive stimuli (Doremus-Fitzwater et al., 2010; Friemel et al., 2010). For the present study we therefore decided to focus on cognitive skills that can be assessed independently from negative/positive reinforcement in rodents and can be measured repeatedly in the same test animal, such as recognition memory and sensorimotor gating.

The spontaneous object recognition test was chosen for assessing the developmental trajectory of short-term memory processing. Recognition memory is generally regarded as the ability to discriminate the familiarity of items previously encountered. The test is based on the natural tendency of rodents to investigate and prefer novel objects, odors or social partners over familiar ones (Ennaceur and Delacour, 1988; Goepfrich et al., 2013; Schneider et al., 2008). Short-term recognition memory for objects has been shown to emerge quite early during postnatal development and appears to be completely functional in rats from postnatal day (pd) 17 on (Westbrook et al., 2014; Anderson et al., 2004). However, the development of recognition memory from pre-weaning ages through puberty until late adolescence has only been examined in part and still requires more detailed clarification.

Prepulse inhibition (PPI) is the natural reduction in the magnitude of the acoustic startle reflex (ASR) if a weaker, non-startling pre-stimulus is presented shortly before the startling stimulus. Since the ASR can be assessed equally well in humans as in laboratory rodents, modulations of the ASR show a high degree of face validity and translational value (Koch, 1999; Fendt and Koch, 2013). PPI has been suggested to provide a measure of sensorimotor gating, since it reflects the degree to which a motor reflex is gated by a preceding sensory stimulus (prepulse) (for review see Fendt and Koch, 2013). Sensorimotor gating is a fundamental protective mechanism that momentarily prevents or attenuates an overload of higher cortical areas with irrelevant information and hence protects ongoing cognitive processes against external interferences (Cromwell et al., 2008). Similar to recognition memory, comprehensive studies investigating the ontogeny of PPI throughout the complete adolescent period are still missing, since most studies investigated only selective time points during postnatal development and report partially contradictory findings. However, there is some evidence from studies in mice and rats that the ASR, as well as PPI increase with age (Pietropaolo and Crusio, 2009; Rybalko et al., 2015; Schwabe et al., 2007; Fendt et al., 2008).

The endocannabinoid (eCB) system is considered to be an ubiquitous regulator of synaptic transmission in the brain that mediates various central and peripheral processes (Kano et al., 2009; Castillo et al., 2012). The eCB signalling system comprises the G-protein coupled cannabinoid receptors (CB1 and CB2 receptor), the two main endogenous ligands N-arachidonoylethanolamide and 2-arachidonoylglycerol, as well as their synthetic and metabolic enzymes. This evolutionarily ancient and widely distributed neuromodulatory system is crucial for sustaining and restoring neuronal homeostasis (Kano et al., 2009) and in particular CB1 receptor signalling has emerged as a critical mechanisms for mediating cognitive behavior and neuroplasticity (Wotjak, 2005; Castillo et al., 2012). Moreover, a transient increase in CB1 receptor signalling has been reported to occur during adolescent brain development, which may provide increased plasticity and behavioral flexibility required specifically during this developmental stage (Schneider et al., 2015). In line with these observations, pharmacological interference with the eCB system during puberty induces pronounced and persistent deficits in cognitive skills (e.g. Schneider and Koch, 2003; Schneider and Koch, 2007; Schneider et al., 2008). Given the modulatory role of CB1 receptor signaling on adolescent behavior, neuroplasticity, and cognition, the eCB system represents an interesting target system for mediating potential developmental changes in cognitive abilities such as object recognition and prepulse inhibition.

With the present study we aim to clarify the trajectory of short-term recognition memory and sensorimotor gating throughout the complete period of adolescence, including pubertal time points, in male rats. In male rats a peripubertal period can be defined from ~pd 38, shortly before the physiological onset of puberty (around pd 40), until pd 60 (Schneider, 2013). In contrast to puberty, the exact timing of adolescence is rather difficult to define. Per definition, adolescence covers the complete time span from childhood (shortly before puberty) to adulthood, including the pubertal period and hence, pubertal timing represents so far the only clear reference point. The adolescent period should start before the onset of puberty, shortly after weaning, and should extend well into young adulthood, after completion of sexual maturity (Schneider, 2013; Schneider, 2008). Therefore, behavioral performance in male rats was assessed repeatedly every 10th day from pd 30 until late adolescence on pd 70, and again in adult animals on pd 130. Additionally, we examined if pharmacological inhibition of CB1 receptor signaling by the antagonist/inverse agonist SR141716 at different developmental stages would affect behavioral performance differentially. Since CB1 receptor signaling and availability appears to be enhanced during adolescence, we here selected a sub-threshold dose of SR141716 (0.3 mg/kg) which has been previously shown not to affect behavior in adult animals (Schneider et al., 2015).

2. Material and methods

2.1. Animals

120 male Wistar Han (Wistar) rats with known birth dates (date of birth considered as pd 0) were purchased from Harlan Laboratories (Netherlands). They were delivered shortly after weaning and then housed in groups of four to six in MakrolonTM cages (Eurostandardtype IV) under a 12/12 h light-dark cycle. Animals had ad libitum access to food and tap water. All experiments were conducted in accordance with the ethical guidelines of the National Institutes of for the care and use of laboratory animals and were approved by the local animal care committee (Regierungspräsidium Karlsruhe, Germany).

2.2. Experimental design

To investigate the developmental trajectory of cognitive abilities during adolescence, one cohort of animals (n = 16) was tested repeatedly for object recognition memory and prepulse inhibition (PPI) of the acoustic startle reflex (ASR) every ten days throughout the entire period of adolescence from pd 30 to pd 70 as well as in adulthood (pd 130) (Schneider, 2013). 24 h prior to the first test session on pd 30 all animals were habituated once for 15 min to the open field arena. On the test day, animals were first tested for object recognition memory, followed 10 min later by PPI assessment. Preliminary findings in our lab indicated no confounding effects of this testing sequence. After a break following pd 70, animals were then re-tested again in the same test sequence after reaching adulthood at pd 130. A second cohort of adult animals (n = 16; >pd 100) was used as a control group to test for a potential impact of repeated testing on behavioral performance. This group was tested for object recognition memory and PPI of the ASR three times every ten days at the same intervals as the adolescent cohort.

In a second experiment we examined developmental effects of pharmacological CB1 receptor inhibition on cognitive performance on three selected time points: pd 30, 40, and 130. These

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