Altering endocannabinoid neurotransmission at critical developmental ages: impact on rodent emotionality and cognitive performance

Viviana Trezza1*, Patrizia Campolongo2, Antonia Manduca1, Maria Morena2, Maura Palmery2, Louk J. M. J. Vanderschuren3,4 and Vincenzo Cuomo2

1 Department of Biology, University “Roma Tre”, Rome, Italy
2 Department of Physiology and Pharmacology, University of Rome Sapienza, Rome, Italy
3 Department of Neuroscience and Pharmacology, Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, Utrecht, Netherlands
4 Department of Animals in Science and Society, Division of Behavioural Neuroscience, Faculty of Veterinary Medicine, Utrecht University, Utrecht, Netherlands

INTRODUCTION

The endocannabinoid system consists of two types of G-protein-coupled receptors (CB1, highly expressed in the brain, and CB2, more abundant in immune cells), their endogenous lipid ligands, and the enzymatic machinery for their synthesis and degradation (Piomelli, 2003; Di Marzo et al., 2005; De Petrocelli and Di Marzo, 2009). Endogenous ligands for cannabinoid receptors, i.e., endocannabinoids [mainly anandamide and 2-arachidonoylglycerol (2-AG)], are synthesized on demand in an activity-dependent manner and released from postsynaptic neurons (Freund et al., 2003; Piomelli, 2003). Once released into the synaptic cleft, the newly synthesized endocannabinoids travel in retrograde direction and bind to cannabinoid receptors on presynaptic terminals (Freund et al., 2003; Piomelli et al., 2003). The primary consequences of activation of cannabinoid receptors are regulation of ion channel activity and neurotransmitter release (Szabo and Schlicker, 2005). Thus, by acting on cannabinoid receptors on both excitatory and inhibitory terminals, endocannabinoids play a major role in several forms of short- and long-term synaptic plasticity (Freund et al., 2003; Piomelli, 2003; Chevaleyre et al., 2006). Endocannabinoid modulation of synaptic activity affects several biological functions, including regulation of emotionality and cognitive performance (Wotjak, 2005; Moreira and Lutz, 2008; Campolongo et al., 2009a,b; Lutz, 2009; Akirav, 2011; Marco et al., 2011; Rubino and Parolaro, 2011; Ferzian et al., 2011; Zanettini et al., 2011). It has indeed repeatedly been shown that cannabis exposure produces a wide range of subjective emotional effects in humans (Tunving, 1985; Williamson and Evans, 2000; Degenhardt et al., 2000; Di Forti et al., 2007; Murray et al., 2007; Fattore and Fratta, 2011). Furthermore, many clinical studies have reported that acute challenges with or prolonged use of cannabis and its products may impair attentional processing and working memory in humans (Iversen, 2003; Ranganathan and D’Souza, 2006; Pattij et al., 2008; Solowij and Pesa, 2010; Fattore and Fratta, 2011). These observations have their counterpart in animal studies, showing that cannabinoid compounds elicit dose-dependent and environment-dependent anxiolytic and anxiogenic effects in rodent models of anxiety (O’reilly et al., 1990; Rodriguez de Fonseca et al., 1996, 1997; Haller et al., 2002, 2004a,b; Martin et al., 2002; Kathuria et al., 2003; Wotjak et al., 2003; Bortolato et al., 2004; Moreira et al., 2008; Marco et al., 2011), and affect learning and memory in rodents (Castellano et al., 2003; Riedel and Davies, 2005; Wotjak et al., 2005; Schneider et al., 2008; Suenaga and Ichitan, 2008; Biehl et al., 2009; Maresceno and Lefebvre, 2009; Akirav, 2011).

In both humans and rodents, the endocannabinoid system is present and active in the central nervous system (CNS)
from early developmental ages (Berrendero et al., 1998; Fernandez-Ruiz et al., 2000; Mato et al., 2003; Fried, 2004; Galvés-Roque et al., 2006; Harkany et al., 2007) and continues to develop throughout adolescence (Rodríguez de Fonseca et al., 1993; Belue et al., 1995; Romero et al., 1997; Berrendero et al., 1999). Therefore, developmental exposure to cannabinoid compounds can have profound effects on brain architecture, chemistry and neurobehavioral function, by changing for instance neurotransmitter levels, and by modulating expression of their receptors, transporters, and degrading enzymes.

Developmental studies on the effects of cannabinoid drugs are of special relevance for two main reasons. First, cannabis preparations are the illicit drugs most widely used by young people, peaking between 15 and 30 years of age (NIDA, 2005; Hall and Degenhardt, 2009; SAMHSA, 2009). Importantly, there is an emerging trend for continued cannabis use in people aged 30-40 (NIDA, 2005; SAMHSA, 2009). This pattern of use potentially exposes the developing brain to cannabis at two periods: first, in offspring of cannabis-using mothers during the perinatal and/or prenatal period; second, in adolescent cannabis users during neural maturation. Therefore, a better understanding of the mechanisms by which exposure to cannabinoid drugs during development leads to neurobehavioral alterations or induces neuropsychiatric disorders later in life is an important issue. Furthermore, in addition to the well-known therapeutic effects of drugs directly acting at cannabinoid receptors (e.g., as appetite stimulants, anti-emetics, analgesics in neuro-pathic pain; Pacher et al., 2006; Di Marzo, 2009; Bermúdez-Silva et al., 2010), the endocannabinoid system is now emerging as a novel therapeutic target for the treatment of the emotional and cognitive disturbances that characterize some neuropsychiatric disorders (Piomelli et al., 2006; Vinod and Hungund, 2006; Petrosino and Di Marzo, 2010; Marco et al., 2011), including neurodevelopmental disorders. However, the potential therapeutic application of cannabinoid drugs in young populations requires a profound investigation of possible adverse effects of such compounds, particularly on the CNS of immature individuals.

In order to provide a deeper understanding of the long-lasting, subtle neurobehavioral effects of developmental exposure to cannabinoid drugs, and to adopt effective public health strategies, it is critical to stimulate a dialog between human and animal studies. While studies in humans are, of course, most relevant for understanding the human situation, they can only provide limited information about the specific molecular and cellular consequences that underlie drug-induced behavioral and neural changes. The important advantage of animal studies is that they allow for exquisite control over the possible confounding factors that characterize human studies, and for examination of the independent contribution of a certain drug to adverse neurodevelopmental consequences.

Here, we examine and discuss preclinical evidence for how cannabinoid exposure during critical developmental ages, such as the perinatal, prenatal, and adolescent periods, affects emotionality and cognitive performance in rodents, thus providing a framework for understanding the impact of cannabinoid exposure on the developing brain.

**EFFECTS OF DEVELOPMENTAL EXPOSURE TO CANNABINOIDS ON COGNITIVE PERFORMANCE IN RODENTS**

**PRENATAL AND PERINATAL CANNABINOID EXPOSURE**

First, we will briefly summarize the results of human studies that investigated the consequences of developmental exposure to cannabinoids on cognitive performance, and then we will focus on rodent studies.

Since the late 1970s, two extended longitudinal cohort studies, the Ottawa Prenatal Prospective Study (OPPS) and the Maternal Health Practices and Child Development Study (MHPCD), have been measuring the cognitive functions of children born from mothers who consumed Cannabis sativa preparations during pregnancy (Day et al., 1992; Fried, 2002b; Trezza et al., 2008b; Campolongo et al., 2009c, 2010). These studies showed that the consequences of prenatal exposure to cannabis are rather subtle. Immediately after birth, there is little evidence for a prenatal cannabis effect either upon growth or behaviour (Fried and Watsaon, 1988). However, beyond the age of 3, there are findings suggesting an association between prenatal cannabis exposure and aspects of cognitive behavior that fall in the domain of executive functions (Fried and Watskin, 1990; Day et al., 1992, 1994; Fried et al., 1998; Fried and Smith, 2001; Fried, 2002b; Trezza et al., 2008b).

Executive functions refer to higher-order cognitive functions such as cognitive flexibility, sustained and focused attention, planning and working memory. These functions enable us to organize and manage the many tasks in our daily life, for instance, to account for short- and long-term consequences of our actions, to make real time evaluations of our actions, and make necessary adjustments if these actions are not achieving the desired results. Impairments in executive functions have a major impact on our ability to perform tasks as planning, prioritizing, organizing, paying attention to and remembering details, and controlling our emotional reactions. In particular, the facets of executive functions which appear to be affected by cannabis exposure are the domains of attention/impulsivity and problem solving situations requiring integration and manipulation of basic visuoperceptual skills (Fried and Watskin, 1990; Day et al., 1992, 1994; Fried et al., 1998; Fried and Smith, 2001; Fried, 2002b; Trezza et al., 2008b).

The deficits in executive functions induced by prenatal cannabis exposure seem to be long-lasting, since 18- to 22-year-old young adults exposed to cannabis during pregnancy showed altered neurocognitive functioning during visuospatial working memory processing (Smith et al., 2006). Although there is a convergence of evidence in human studies, the very limited number of studies which have followed children beyond the age of 3 emphasizes the need for further, well-controlled investigations in this area. Furthermore, it cannot be excluded from human studies that genetic and environmental variables also contribute to the relationship between maternal cannabis use and long-term cognitive deficits in the offspring. Therefore, the long-term effects of prenatal exposure to cannabinoid drugs on cognitive functions in rodents have received a great deal of attention. Prenatal exposure to a moderate dose of the synthetic CB1 cannabinoid receptor agonist WIN55,212-2 (0.5 mg/kg from GD 5 to GD 20) has been shown to induce...
a disruption of memory retention in 40- and 80-day-old rats offspring tested in the inhibitory avoidance task (Mereu et al., 2003). This cognitive impairment was not due to alterations of non-associative nature, since the approach latency during the acquisition trials of the task was unaffected. The memory impairment in WIN55,212-2-exposed offspring was associated with alterations in hippocampal long-term potentiation (Mereu et al., 2003). In vivo microdialysis experiments also showed a significant decrease in basal and K+ evoked extracellular glutamate levels in the hippocampus of juvenile and adult rats born from WIN55,212-2-treated dams (Mereu et al., 2003). The decrease in hippocampal glutamate overflow was suggested to be the cause of disrupted long-term potentiation, which could, in turn, underlie the long-lasting memory impairment caused by gestational exposure to the cannabinoid receptor agonist (Mereu et al., 2003). To further support the hypothesis that changes in glutamatergic neurotransmission might be responsible of the cognitive impairment observed in WIN55,212-2-exposed offspring, in vivo microdialysis experiments showed that basal and K+ evoked glutamate levels were significantly lower in the cerebral cortex of both adult (90-day-old) and adolescent (40-day-old) rats exposed to WIN55,212-2 during gestation than in those born from vehicle-treated mothers (Antonelli et al., 2004; Castaldo et al., 2007; Ferraro et al., 2009). Interestingly, the cognitive deficits induced by prenatal exposure to WIN55,212-2 appeared already at early developmental ages. Thus, 10- to 12-day-old WIN55,212-2-exposed pups showed a poorer performance in homing behavior, a simple form of learning occurring during the early phases of postnatal life (Antonelli et al., 2005). At the neurochemical level, basal and K+ evoked glutamate levels were significantly lower in primary cell cultures of hippocampus (Mereu et al., 2003) and cerebral cortex (Antonelli et al., 2005, 2006) obtained from pups exposed to WIN55,212-2 compared to pups from the control group. The alteration of cortical glutamate transmission induced by prenatal WIN55,212-2 exposure was also associated with a significant reduction of NMDA receptor-mediated regulation of glutamate levels (Ferraro et al., 2009). In fact, the NMDA-induced concentration-dependent increase of glutamate levels observed in cortical cell cultures obtained from neonates born from vehicle-treated dams was completely lost in cell cultures obtained from pups prenatally exposed to WIN55,212-2 (Antonelli et al., 2005). These results suggest that chronic prenatal treatment with WIN55,212-2 induces a loss of NMDA receptor activity in the exposed offspring (Antonelli et al., 2005; Ferraro et al., 2009).

Morphological experiments have shown that prenatal exposure to WIN55,212-2 also affects neuronal proliferation: a different neurite growth pattern was observed in cortical cell cultures obtained from pups born from mothers exposed to WIN55,212-2 during pregnancy (Antonelli et al., 2005; Ferraro et al., 2009). Cortical cell cultures from vehicle-exposed pups showed a high number of healthy neurons, which developed in a monolayer and form a complex network of neurites. On the contrary, cortical cultures obtained from pups exposed to WIN55,212-2 during pregnancy showed a minor population of neurons and abnormal neurite outgrowth, characterized by impairments of neurite branching (Antonelli et al., 2005; Ferraro et al., 2009).

Exposure to cannabinoid agonists during critical periods of brain development is known to cause long-term changes in the functionality of several neurotransmitter systems in adulthood, such as alterations in dopaminergic (Rodríguez de Fonseca et al., 1991; Bonnin et al., 1994, 1995), opioidergic (Vela et al., 1995, 1998), noradrenergic (Molina-Holgado et al., 1996), and GABAergic (Garcia-Gil et al., 1999a) systems. In addition, prenatal exposure to WIN55,212-2 has been found to induce long-term changes in the activity of the endocannabinoid system: in particular, the functionality of CB1 receptors in the hippocampus differed between adult WIN55,212-2- and vehicle-exposed offspring (Castelli et al., 2007). Thus, it can be speculated on basis of the in vivo and in vitro results that gestational WIN55,212-2-exposure produces enduring alterations of the endocannabinoid system in the developing brain, which may lead to a long-lasting and irreversible disruption of glutamate cortical and hippocampal function (Castelli et al., 2007; Ferraro et al., 2009).

As for the clinical relevance of these preclinical studies, it is important to estimate, by extrapolation, whether the dose of the synthetic cannabinoid agonist WIN55,212-2 is comparable to that of the main active ingredient of cannabis, Δ9-tetrahydrocannabinol (THC), absorbed by cannabis users. It has been estimated that a dose of 5 mg/kg of THC in rats corresponds to a moderate, or even to a low, exposure to cannabis in humans (Mereu et al., 2003). Furthermore, in line with studies that used a protocol of prenatal WIN55,212-2 exposure, it has been demonstrated that the active ingredient of cannabis, THC, administered perinatally induces cognitive impairments in the adult offspring (Campolongo et al., 2007). Importantly, perinatal exposure to THC not only induced a long-term memory impairment in the adult offspring, as revealed by the inhibitory avoidance test, but also a disruption in short-term olfactory memory, as assessed in the social discrimination test (Campolongo et al., 2007). This form of memory, that plays a crucial role in the processing of social information, requires integral glutamatergic projections from the hippocampal formation to prefrontal areas (Steckley et al., 1998; McGaugh, 2002), and then back from the prefrontal cortex to the hippocampus. Interestingly, the cognitive impairments observed in THC-exposed adult offspring were associated with long-lasting alterations in the cortical expression of genes related to glutamatergic neurotransmission, together with a decrease in the cortical extracellular levels of this neurotransmitter (Campolongo et al., 2007). Furthermore, in line with studies that used a protocol of prenatal WIN55,212-2 exposure, the neurochemical changes induced by prenatal THC exposure appeared early in development, as altered regulation of glutamate release and...
decreased functional activity and expression of GLUT1 and GLAST glutamate transporters in the hippocampus of adolescent rats perinatally exposed to THC have been reported (Castaldo et al., 2010). Again, these studies strongly suggest that changes in glutamatergic neurotransmission might be responsible for the cognitive deficits induced by prenatal cannabinoid exposure.

**ADOLESCENT CANNABINOID EXPOSURE**

In most Western Countries, the first episodes of cannabis use often occur during adolescence (NIDA, 2003; Hall and Degenhardt, 2009; SAMHSA, 2009). Adolescence is a critical phase for CNS development during the transition from childhood to adulthood (Spear, 2000; Andersen, 2003). It is a period characterized by widespread neuronal plasticity and maturation at the neural and network level, when the brain undergoes both progressive and regressive changes including extensive synaptic remodeling and pruning and alterations in neurotransmitter levels and their receptors in cortical and limbic brain regions across different species (Spear, 2000; Andersen, 2003), processes in which the endocannabinoid system plays a major role (Spear, 2000; Andersen, 2003; Freund et al., 2001; Bossong and Niesink, 2011; Rubino et al., 2011).

Both neuropsychological and functional imaging studies indicate that the detrimental effects of cannabis on cognitive performance may be more pronounced when cannabis is used during adolescence (Ehrenreich et al., 1999; Iager and Ramsey, 2008; Schweinsburg et al., 2008; Bossong and Niesink, 2011). Most imaging studies in adolescent subjects reported cannabinoid-induced alterations in working memory (Jacobsen et al., 2004, 2007; Schweinsburg et al., 2008). Studies making a distinction between the initiation of cannabis use in adolescence and in adulthood showed attention deficits and poor cognitive performance in early-onset cannabis users (onset before age 17), but not in late-onset users or control subjects (Ehrenreich et al., 1999; Pope Jr. et al., 2003).

Despite the increasing use of cannabis among adolescents and the sometimes conflicting results provided by clinical studies, it is only in recent years that the short- and long-term behavioral effects of acute and chronic adolescent exposure to cannabinoid compounds in rodents have been investigated in more detail (Rubino and Parisotto, 2008; Trezza et al., 2008b; Realmoli et al., 2009; Rubino et al., 2011).

Quinn et al. (2008) showed that adolescent but not adult rats displayed significantly impaired object recognition memory and altered protein expression profiles in the hippocampus following repeated THC exposure. Similarly, Schneider and Koch (2003) showed that chronic perinatal treatment with WIN55,212-2 resulted in impaired object recognition memory in adulthood, associated with disrupted prepulse inhibition of the acoustic startle response and lower break points in a progressive-ratio operant behavioral task (Schneider and Koch, 2003). Again, it is worth noting that if the chronic cannabinoid treatment was administered during adulthood, none of the tested behaviors was affected (Schneider and Koch, 2003). Gender-specific effects of chronic adolescent cannabinoid exposure have also been reported (O'Shea et al., 2004, 2006). In these studies, the cannabinoid receptor agonist CP-55,940 was administered daily for 21 consecutive days to either adolescent or adult male and female rats. Following a long drug-free period, working memory was assessed in the object recognition task (O'Shea et al., 2004, 2006). In females, cannabinoid-treated adolescent, but not adult rats demonstrated impaired working memory compared to vehicle-treated controls (O'Shea et al., 2004, 2006). Interestingly, in males, cannabinoid treatment during adolescence and adulthood produced similar working memory deficits (O'Shea et al., 2004). Thus, in females, adolescent males may be more susceptible and adults more resilient to long-lasting cannabinoid-induced cognitive deficits, whereas in males, both adolescents and adults are equally vulnerable. Deficits in object recognition memory have also been reported in adult female rats treated chronically with THC during adolescence (Realmoli et al., 2011).

Developmental and gender sensitivity to cannabinoid compounds has been further investigated by Cha et al. (2006, 2007), who assessed spatial memory in the Morris water maze task following acute and chronic THC exposure in male and female adolescent and adult rats. Acute THC exposure led to greater learning impairments in adolescent than in adult male and female rats tested in both the spatial and non-spatial versions of the water maze tasks (Cha et al., 2006, 2007). Conversely, chronic THC administration during either adolescence or adulthood had no effect on spatial learning in animals of both sexes tested after a long drug-free period (Cha et al., 2006, 2007). Thus, while adolescents may be more sensitive to the acute effects of cannabinoids, both adolescents and adults demonstrated similar recovery of cognitive performance following discontinuation of chronic treatment (Cha et al., 2006, 2007). In line with these findings, it has been reported that adolescent exposure to the cannabinoid receptor agonist CP-55,940 did not affect adult performance of animals of both sexes in the water maze task (Higuera-Matas et al., 2009). However, following adolescent exposure to THC, spatial working memory in the radial maze task was impaired in both male and female adult rats, while aversive memory in the inhibitory avoidance task was unaffected (Rubino et al., 2009a,b). The neural underpinnings of the spatial working memory impairments observed in the latter studies may differ between males and females (Rubino and Parisotto, 2011). Indeed, adult female rats showed reduced levels of proteins involved in synaptic plasticity and altered pattern of protein expression in synaptosomes from prefrontal cortex, with no alterations in the hippocampus (Rubino et al., 2009a,b). Conversely, in adult male rats pre-exposed to THC during adolescence, the spatial working memory deficit was related to reduced levels of markers of neuroplasticity and morphological alterations in the hippocampus (Rubino et al., 2009b). These results suggest that the same protocol of adolescent THC exposure, although resulting in similar behavioral endpoints, may have different neuronal consequences in the brain of male or female rats.

Long-term sexually dimorphic effects induced by adolescent THC exposure on cognitive performance have also been described by Harte and Dow-Edwards (2010), who examined the effects of adolescent THC exposure on visual spatial learning in adulthood using the active place avoidance test. This cognitive task allows to simultaneously assess the ability to learn and retrieve spatial information, as well as flexibility of learning, by training animals to actively move over a slowly rotating arena and avoid an unmarked...
sector, entering which is punished by a mild footshock. The shock sector is defined in a stable position with respect to the experimental room. Animals must thus localize the shock sector exclusively by its spatial relations to distal orienting cues located in the room and walk into the safe part of the arena in a direction opposite to arena rotation (Cimadevilla et al., 2000). By using this task, Harte and Dow-Edwards (2010) showed that THC administration during early adolescence had no effect on the acquisition of the task. However, male and female animals treated with THC during early adolescence made more errors on the reversal trial requiring flexibility in learning. Conversely, THC administration during late adolescence had no effect in both sexes. Therefore, early adolescence appeared to be more sensitive to the cognitive effects of THC than late adolescence (Harte and Dow-Edwards, 2010). These findings indicate that the time window during adolescence in which THC is administered can have a profound influence on its long-lasting cognitive outcomes.

**SUMMARY**

Taken together, the preclinical studies outlined here show that maternal and adolescent exposure to either natural or synthetic cannabinoid agonists alters cognitive performance in the offspring. The cognitive alterations displayed by cannabinoid-treated rats are long-lasting, since they persist into adulthood. Furthermore, in line with clinical observations, it appears from preclinical studies that adolescent rats may be more susceptible than adults to the cognitive effects induced by chronic exposure to cannabinoid compounds.

**EFFECTS OF DEVELOPMENTAL EXPOSURE TO CANNABINOIDS ON EMOTIONALITY IN RODENTS**

Although C. sativa preparations have long been known to produce a wide range of subjective emotional effects, it is only in recent years that the crucial role of the endocannabinoid system in the modulation of emotional states has been underscored (Haller et al., 2002; Millan, 2003; Witschi et al., 2005; Mangieri and Piomelli, 2007; Trezza et al., 2008a; Bambico et al., 2009; Marco and Viveros, 2009; Marco et al., 2011; Zanettini et al., 2011). It has, indeed, been shown that CB1 cannabinoid receptors are highly expressed in brain areas involved in the modulation of emotions (Tou et al., 1998; Ameri, 1999; Davies et al., 2002). In these regions, endocannabinoids modulate the release of neurotransmitters and neuropeptides that play a key role in the control of emotionality, such as serotonin, dopamine (Tou et al., 1998; Katona et al., 2002; Schlöcker and Kathmann, 2001; Hermann et al., 2002) and the anxiogenic neuropeptides, CCK and CRF (Rodríguez de Fonseca et al., 1997; Ameri, 1999). Therefore, it is well conceivable that in utero cannabis exposure might produce changes in the emotional reactivity of the exposed offspring. Human studies support this hypothesis, by showing that prenatal exposure to cannabis in the first and third trimesters of pregnancy predicts levels of self-reported anxiety and depressive symptoms in children (Goldsmith et al., 2004; Gray et al., 2005; Leech et al., 2006). Again, however, only few clinical studies followed the exposed children past the age of 10 (Fried, 2002a,b; Fried et al., 2003; Goldsmith et al., 2004; Gray et al., 2005; Leech et al., 2006), so that most of the available information about the long-term consequences of in utero cannabis exposure on the emotional reactivity of the offspring comes from preclinical studies.

Concerning the neonatal age, we found that 12-day-old pups exposed to THC during the perinatal period displayed an increased rate of ultrasonic vocalizations (USVs) when separated from the mother and siblings compared to the control group (Trezza et al., 2008a). The USV test has been extensively validated and widely used to investigate the ontogeny of emotionality (Insel et al., 1986; Cuomo et al., 1987; Branchi et al., 2001, 2004). USVs are emitted by rodent pups in response to separation from the mother and the nest and play an important communicative role in mother–offspring interaction. They are, indeed, a potent stimulus for maternal retrieval and eliciting caregiving behaviors in the dam (Farrell and Albers, 2002; Trezza et al., 2011). As high rates of USVs are generally indicative of an anxiety-like state, the present results show that perinatal exposure to THC induces an increased emotional reactivity of the offspring (Trezza et al., 2008a). Conversely, a reduction of separation-induced USVs in rat pups either prenatally exposed to the synthetic cannabinoid agonist WIN55,212-2 (Antonelli et al., 2003) or acutely treated with the synthetic cannabinoid agonist CP-55,940 (McGregor et al., 1996) has also been reported, highlighting how different time windows of exposure to cannabinoids can induce opposite neurofunctional effects (Costa et al., 2008). However, differences in the cannabinoid agonist used, tested dose, and treatment schedule (acute vs. chronic treatment) could also account for the apparent discrepancies between these preclinical findings. Interestingly, the alterations we observed in the emotional reactivity of THC-exposed pups were long-lasting (Trezza et al., 2008a). Indeed, at adolescence, THC-exposed rats displayed lower social activity than controls in the social interaction test (Trezza et al., 2008a). These results are in agreement with findings showing that the synthetic cannabinoid agonist CP-55,940, repeatedly administered from PND 4 to PND 25, reduced social interaction in 60-day-old rats (O’Shea et al., 2006). In adulthood, THC-exposed rats showed increased anxiety in the elevated plus-maze: they spent more time in the closed arms of the maze, exhibited a significantly lower number of head dippings and a higher number of stretched-attend postures than vehicle-exposed rats (Trezza et al., 2008a). The number of total entries, however, was unaffected, indicating that perinatal THC treatment did not alter locomotor activity in the offspring. To further support an altered emotional reactivity induced by perinatal THC exposure, Newsom and Kelly reported that adult rats perinatally exposed to THC spent less time in the central part of an open field arena compared to vehicle-exposed animals, with no changes in general locomotor activity (Newsom and Kelly, 2008).

**ADOLESCENT CANNABINOID EXPOSURE**

The possible causal relation between cannabis use during adolescence and psychotic and affective neuropsychiatric diseases later in life is widely debated. While some clinical studies indicate that exposure to cannabis preparations during adolescence may be a risk factor for neuropsychiatric disorders such as schizophrenia, depression, and other mood pathologies (Arseneault et al., 2002; Fergusson et al., 2002, 2003; Patton et al., 2002; Degenhardt et al., 2008a). Conversely, a reduction of separation-induced USVs in rat pups either prenatally exposed to the synthetic cannabinoid agonist WIN55,212-2 (Antonelli et al., 2003) or acutely treated with the synthetic cannabinoid agonist CP-55,940 (McGregor et al., 1996) has also been reported, highlighting how different time windows of exposure to cannabinoids can induce opposite neurofunctional effects (Costa et al., 2008). However, differences in the cannabinoid agonist used, tested dose, and treatment schedule (acute vs. chronic treatment) could also account for the apparent discrepancies between these preclinical findings. Interestingly, the alterations we observed in the emotional reactivity of THC-exposed pups were long-lasting (Trezza et al., 2008a). Indeed, at adolescence, THC-exposed rats displayed lower social activity than controls in the social interaction test (Trezza et al., 2008a). These results are in agreement with findings showing that the synthetic cannabinoid agonist CP-55,940, repeatedly administered from PND 4 to PND 25, reduced social interaction in 60-day-old rats (O’Shea et al., 2006). In adulthood, THC-exposed rats showed increased anxiety in the elevated plus-maze: they spent more time in the closed arms of the maze, exhibited a significantly lower number of head dippings and a higher number of stretched-attend postures than vehicle-exposed rats (Trezza et al., 2008a). The number of total entries, however, was unaffected, indicating that perinatal THC treatment did not alter locomotor activity in the offspring. To further support an altered emotional reactivity induced by perinatal THC exposure, Newsom and Kelly reported that adult rats perinatally exposed to THC spent less time in the central part of an open field arena compared to vehicle-exposed animals, with no changes in general locomotor activity (Newsom and Kelly, 2008).
Despite the fact that the majority of preclinical studies supports the hypothesis that adolescent exposure to cannabinoid drugs alters emotional reactivity in adulthood, inconsistent and sometimes sex-dependent effects have also been reported (Rubino et al., 2011). For instance, some authors reported no changes in emotional reactivity in animals pretreated with cannabinoid drugs during adolescence and tested in the elevated plus-maze test after a washout period (Rubino et al., 2008; Hugues-Matas et al., 2009; Bambico et al., 2010), while others described cannabinoid-induced anxiolytic-like effects in the same behavioral test (Biscaia et al., 2003; Wegener and Koch, 2009). Contrasting results also emerged from other behavioral tests commonly used to assess emotional reactivity in rodents. For instance, cannabinoid exposure during adolescence induced anxiety-like behaviors in the novelty-suppressed feeding test (Bambico et al., 2010), which assesses anxiety-induced hypoactivity by measuring the inhibition of ingestion and approach to food when animals are exposed to an anxiety-provoking novel environment. Conversely, no evidence of increased anxiety induced by adolescent cannabinoid exposure was found in adult rats tested in the emergence test (O'Shea et al., 2006), that measures the animal's conflict between exploring a novel environment, and avoiding an open area. When emotionality was assessed by measuring exploratory behavior and the time spent in the central and peripheral parts of an open field arena, some authors reported no effects of adolescent cannabinoid exposure (Rubino et al., 2008; Bambico et al., 2010), while others reported anxiolytic-like responses (Biscaia et al., 2003; Wegener and Koch, 2009).

More consistent results have been obtained when the social interaction test was used to assess the emotional reactivity of adult rats exposed to cannabinoid drugs during adolescence. The synthetic cannabinoid agonist CP-55,940, administered for 21 days to adolescent rats, reduced social interaction at adulthood, both in male (O'Shea et al., 2006) and female (O'Shea et al., 2004) subjects. Similar results have been reported following chronic adolescent treatment with THC (Realini et al., 2011) or the synthetic cannabinoid receptor agonist WIN55,212-2 (Levyke and Schneider, 2011). There are many internal and external factors that influence an animal's sociability, and anxiety has been identified as one of them (File and Seth, 2003). Therefore, reduced social interaction is widely interpreted as reflecting increased anxiety. However, it can not be excluded from social interaction experiments that changes in sociability reflect other aspects of social behavior, such as social reward, or the subjective interpretation of social signals, that might also be affected by adolescent cannabinoid exposure. For instance, we have recently shown that the endocannabinoid system modulates the most abundant and rewarding form of social interaction displayed by adolescent mammals, that is social play behavior (Trezza et al., 2010). In particular, we found that systemic administration of indirect cannabinoid receptor agonists, i.e., drugs that increase endocannabinoid signaling by interfering with endocannabinoid deactivation, enhances social play through interaction with opioid and dopaminergic neurotransmission (Trezza and Vanderwal, 2008b, 2009). This suggests that during social play, endocannabinoids are released in brain areas mediating this behavior. Increased endocannabinoid activity might facilitate social play, so that drugs that prevent endocannabinoid deactivation likely enhance social play by magnifying the ongoing endocannabinoid tone. In contrast, we have also previously shown that stimulation of CB1 cannabinoid receptors throughout the brain using the cannabinoid receptor agonist WIN55,212-2 or the stable analog of anandamide, (R)-methanandamide reduced social play (Trezza and Vanderwal, 2008a, 2009). Therefore, it appears from these studies that the effects of cannabinoid drugs on social behavior differ according to the way the endocannabinoid system is targeted: drugs that prevent endocannabinoid deactivation enhance rewarding aspects of social interactions by magnifying ongoing endocannabinoid tone; conversely, drugs that directly activate cannabinoid receptors in multiple brain areas reduce sociability, perhaps by disrupting cognitive functions necessary to perform adequate social interactions (Egerton et al., 2006).
proposed that the endocannabinoid system regulates affective homeostasis by interacting with monoaminergic neurotransmission (for review, see Bambico et al., 2009). Thus, activation of cannabinoid receptors by cannabinoid receptor agonists modulates serotonin (Gobbi et al., 2005; Palazzo et al., 2006; Bambico et al., 2007) and noradrenaline (Gobbi et al., 2005; Oropeza et al., 2007) activity. CB1 receptors are expressed on serotonergic neurons in the dorsal raphe nucleus (Elphick and Egetova, 2000; Haring et al., 2007) as well as on noradrenergic neurons in the locus coeruleus (Oropeza et al., 2007). Furthermore, they are highly expressed in limbic mood-regulatory brain areas innervated by these nuclei, such as the amygdala (for review, see Bambico and Gobbi, 2008; Bambico et al., 2009). During adolescence, serotonergic, noradrenergic, and cannabinoid neurotransmission undergo critical changes (Spear, 2000; Schneider, 2008). Thus, chronic cannabinoid exposure during adolescence may interfere with the cross-talk between these neural systems, eventually leading to persistent affective dysfunctions.

Interestingly, it has been shown that the depression-like phenotype displayed by adult rats treated with cannabinoid drugs during adolescence was paralleled by changes in other biochemical parameters linked to depression, such as decreased CREB activation in the prefrontal cortex and hippocampus, increased CREB activation and dynorphin levels in the nucleus accumbens, decreased neurogenesis in the dentate gyrus of the hippocampus, likely triggered by a long-lasting impairment of CB1 receptor signaling in the ventral tegmental area, amygdala, and nucleus accumbens (Rubino et al., 2008; Realini et al., 2011; Rabino and Parolaro, 2011). Since endocannabinoid neurotransmission in these brain areas is fundamental for normal emotional behavior and stress responses (Viveros et al., 2005; Lavolette and Grace, 2006; Zanettini et al., 2011), then changes in cannabinoid receptor function induced by adolescent cannabinoid exposure might underlie the altered emotional responses in adulthood.

SUMMARY

Altogether, the preclinical studies currently available show that prenatal and adolescent cannabinoid exposure affects different aspects of emotional reactivity, from early developmental ages till adulthood. In particular, it appears from preclinical studies that the outcome of developmental cannabinoid exposure on emotional reactivity later in life might depend on the specific component of emotionality taxed in the different behavioral tests. For instance, anxiety-related behaviors in tests that depend on spontaneous, exploratory behavior, such as the elevated plus-maze and open field tests, appear to be more resistant to the long-term consequences of cannabinoid exposure. On the other hand, the anxiety-related measures in the novelty-suppressed feeding test, that depends on appetitive drive, and the reduction in social behavior observed in the social interaction test appear to be particularly sensitive to developmental cannabinoid exposure. The differences observed at the behavioral level might also be the result of the different neuroanatomical and molecular correlates involved in each behavioral test. The changes in anxiety- and depressive-like behaviors and the altered sociability induced by developmental cannabinoid exposure might, in turn, affect the ability of the subject to cope with every day challenges and with fellow group members. This hypothesis, however, needs to be further investigated.

CONCLUSIONS

The endocannabinoid system plays a relevant role in brain organization during pre- and post-natal life. In Western countries, C. sativa preparations are among the illicit drugs most commonly used by young people, including pregnant women. Therefore, understanding the long-lasting consequences of cannabis exposure on the developing brain is an important issue. The clinical findings currently available suggest an association between developmental cannabis exposure and executive dysfunctions. Furthermore, cannabis exposure during the prenatal/perinatal and adolescent periods has been shown to induce subtle changes in emotionality that may persist into adulthood. Although there is some consistency in the clinical literature, the very limited number of findings emphasizes the need for further, well-controlled follow-up studies in this area. Relevant information is available from preclinical studies, demonstrating that even low to moderate doses of cannabinoids, when administered during particular periods of brain development, can have profound consequences for brain maturation, leading to long-lasting alterations of cognitive functions and emotional behaviors. Although there is still scarce information about the neurobiological substrates of the observed behavioral alterations, it appears that developmental cannabis exposure induces changes in the endocannabinoid system and in other neurotransmitter systems that are already functional at early developmental ages. These alterations may disrupt the integrity of mood- and cognition-regulating brain circuits, thus inducing long-lasting emotional and cognitive disturbances.

Multiple experimental approaches, including genetics, molecular biology, pharmacology, neuropsychology, and neurophysiology, in both preclinical and clinical settings should be encouraged in the near future to further clarify the potential relationship between developmental cannabis exposure and long-lasting neurofunctional outcomes.

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