Adolescent Exposure to CB1 Receptor Agonist Elicits a Disinhibited PFC State in Adulthood

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Abstract

Adolescence is a developmental period associated with high rates of risk behavior, such as drug experimentation, that can alter neuronal development. The prefrontal cortex (PFC), an area of the brain functional in executive functions, can be affected by drug experimentation. Adolescent drug use has been associated with deficient PFC inhibition in adulthood, which is similar to PFC disinhibition in schizophrenics (Caballero & Tseng, 2012). Although PFC development can be interrupted through many pathways, little is known about effects of cannabinoids on PFC development. The effect of adolescent exposure to cannabinoid receptor 1 (CB1) agonist, WIN, on PFC inhibition in adulthood was examined using electrophysiology. WIN exposure elicited a disinhibited PFC in only the adolescent treatment group (PD35-40). Overall, data imply that a disinhibited prefrontal state in adulthood is due to disrupted neurotransmitter signaling responsible for PFC development during adolescence.

Introduction

Adolescence
Adolescence is defined as the period of physical, psychological and social transition between childhood and adulthood (Blakemore, 2008). This transition is a vulnerable period for brain development because of its association with risk-seeking behavior (Spear, 2000). For example, adolescents exhibit higher rates of experimental substance use than adults, such as beginning to smoke before the age of 18 (Giovino, 1999). Recently, there has been an increasing concern about cannabis use during adolescence since it has been associated with an increased risk of developing neuropsychiatric disorders later in life (Moore et al., 2007). Due to higher rates of experimental substance use during adolescence, there is a higher potential for interrupted psychological and social transitioning from childhood to adulthood.
During adolescence, the brain continues to undergo many structural and maturational changes in which adult cognitive functions develop (Giedd, Keshavan & Paus., 2008). These changes in synaptic density are characterized by increases and decreases in white and gray matter in the brain. Increases in white matter are interpreted as reflecting increased myelination (Blakemore & Choudhury, 2006). Decreases in cortical gray matter occur after the age of 12 (Giedd et al., 1999), while white matter can increase well after puberty (Sowell et al., 2003) and up until young adulthood (Jernigan et al., 1991). This remodeling of brain areas creates a window where environmental factors can affect the trajectories of cortical projections (Caballero & Tseng, 2012). Synapses must be pruned and myelinated for proper communication between brain regions and for further development of cognitive function.

The Prefrontal Cortex and Adolescence
The prefrontal cortex (PFC) is the crucial brain region involved in executive functions that undergoes late pruning in gray matter during adolescence (Rainer, Asaad, & Miller, 1998), making PFC vulnerable to adolescent drug experimentation. Altered PFC development could have detrimental consequences to adult cognitive ability. Executive functions include skills such as working memory, response inhibition, conflict processing, and problem solving, which are dysfunctional in schizophrenics (Minzenberg, Laird, Thelen, Carter & Glahn, 2009). Synaptic pruning occurs dramatically in the PFC after puberty (Rakic, Bourgeois, & Goldman Rackic, 1994) and contributes to fine-tuning of functional networks (Giedd et al., 1999). Without these post-pubescent synaptic pruning events, PFC related abilities would not be able to arise (McGivern, Andersen, Byrd, Mutter, & Reilly, 2002). The PFC undergoes synaptic pruning later than other brain structures because decreases in prefrontal gray matter density occur after posterior structures lose gray matter (Gogtay et al., 2004). Drug or alcohol exposure during adolescence can potentially change normal neurodevelopment and can serve as a precursor for other PFC related disorders later in life (see review by Spear, 2000). Because of its delay in synaptic pruning, the PFC is susceptible to neurodevelopmental insult during adolescence.

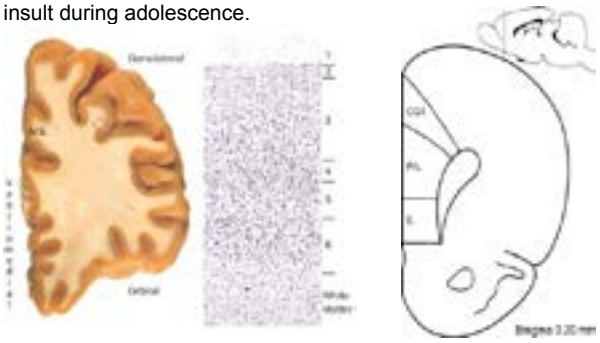

Figure 1. The PFC of human and rat. The PFC is a several millimeter thick layer of gray matter that consists of orbital, ventromedial, and dorsolateral regions as seen in the coronal block (left panel) that was cut anterior to the corpus callosum through the left hemisphere. A Nissl-stained section of the dorsolateral PFC (center panel) shows the six layers of the PFC in which pyramidal neurons and interneurons are distributed with white matter underneath (Adapted from Lewis, 2004). The PFC of a rat consists of the cingulate cortex (CG1), prelimbic (PrL), and infralimbic (IL) subregions (right panel), the number indicates the distance of the coronal section from Bregma.

The Prefrontal Cortex: Structure and Anatomy
The PFC is one of the last areas in the brain to undergo changes, making its projections more susceptible to external stimuli experienced during adolescence (Caballero & Tseng, 2012). It resides behind the forehead in the frontal lobe of the brain and is defined as the region rostral to motor and premotor areas (Uylings & van Eden, 1990). The PFC consists of the orbital, medial and lateral subregions, which influence emotional behavior, temporal organization of behavior, and reasoning (Fuster, 2001) (Fig. 1). This region connects to an array of other cerebral structures that include the brainstem, thalamus, basal ganglia and limbic system (Fuster, 2001). It is also an area of prominent cortical projection from the medial dorsal nucleus of

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the thalamus (Uylings & van Eden, 1990). All prefrontal regions receive neuron projections from the hippocampus, directly or indirectly (Rosene & Van Hoesen, 1977). The PFC is extensively involved in with many systems; therefore, any pathway interruption could have detrimental effects on PFC function.

The PFC also receives dopamine (Tseng & O'Donnell, 2007) which has a critical role in normal cognitive process (Seamans & Yang, 2004). Rat and primate PFCs receive inputs from the ventral tegmental area (Williams & Goldman-Rakic, 1998). These connections between cerebral structures facilitate executive function in the PFC because executive functions, such as working memory and response inhibitions (Goldman-Rakic, 1987), arise with the same underlying interaction between pyramidal neurons and interneurons. Deficits in higher cognitive functions often do not show until early adulthood due to the late development of the PFC (Tseng, Chambers, & Lipska, 2009). Diminished inhibition in adulthood within the PFC seems to be related to developmental disorders associated with inadequate control of inappropriate behaviors and thoughts (Casey, Giedd, & Thomas, 2000). Altering neurotransmitter inputs can cause poor inhibition within the PFC.

There are two main classes of neurons, interneurons and pyramidal neurons, which are involved in executive function within the PFC (Somogyi, Tamas, Lujan, & Buhl, 1998). As a main excitatory component of the cortex (Spruston, Larkman, Lubke, & Blakemore, 2008), pyramidal neurons compose about 70% of the cortex (Druga, 2009). Pyramidal neurons undergo extensive changes in dendritic morphology during postnatal development (Kasper et al., 1994). They have a pyramidal dendritic morphology (Fig. 2) that uses glutamate as a neurotransmitter (Druga, 2009). On the other hand, pyramidal neuron firing is inhibited by interneurons, which serve to balance cortical excitability (Ali, 2009). Interneurons consist of 20-30% of cortical neurons and are found in all neocortical layers (Druga, 2009). They secrete gamma-aminobutyric acid (GABA) as a neurotransmitter and the inhibitory effect of interneurons occurs when GABA is released, resulting in the hyperpolarization of the postsynaptic membrane.

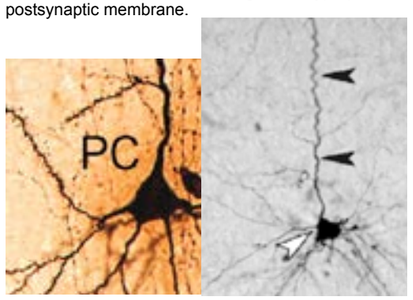


Figure 2. Pyramidal neurons. A pyramidal cell (PC) and a fast spiking interneuron (FS) of the primate dorsolateral prefrontal cortex, filled with 0.5% biocytin (left panel) (Gonzalez-Burgos et al., 2005). A pyramidal neuron from the medial PFC stained with neurobiotin shows the thick apical dendrite, indicated by the black arrows, and pyramidal cell body, indicated by the white arrow (Adapted from Tseng, Lewis, Lipska, & O'Donnell, 2007).

Interneurons and the PFC

Interneurons are a very diverse population of cells (Petilla Interneuron Nomenclature Group et al., 2008). They are classified by whether they target pyramidal cells, glial cells, other interneurons, or vascular system cells (Petilla Interneuron Nomenclature Group et al., 2008). Interneurons can be oval, spindle, or multipolar in morphology, and dendrites can be smooth, aspiny, or sparsely spiny (Druga, 2009). Interneurons can be basket, chandelier, double-bouquet, bi-tufted, and more (Markram et al., 2004). In the neocortex, interneurons can be further classified by their expression of calcium binding proteins such as parvalbumin (PV), calretinin and cholecystokinin (Petilla Interneuron Nomenclature Group et al., 2008), and the largest group of GABAergic interneurons express PV and calretinin (Druga, 2009). Calcium binding proteins function to buffer intracellular calcium and regulate calcium pools important for synaptic plasticity (Druga, 2009).

They also have a wide variety of firing properties that vary from bursting, stuttering, fast spiking, and irregular spiking cells (Petilla Interneuron Nomenclature Group et al., 2008). Fast spiking units are important because they play an important role in working memory function (Rao, Williams, & Goldman-Rakic, 1999), by sharpening and tuning pyramidal cell signaling in working memory tasks (Wang, Tegner, Constantinidis, & Goldman-Rakic 2004). A majority of basket cells are fast spiking (Kubota, Hattori, & Yui, 1994). In the PFC, these fast spiking cells, express PV (Caballero, Flores-Barrera, Cass, & Tseng , in press) (Fig. 3). Most PV positive interneurons are basket cells but another type of interneuron termed chandelier is also fast spiking and sometimes PV positive, but both innervate pyramidal neurons (Conde, Lund, Jacobowitz, Bainbridge, & Lewis, 1994).

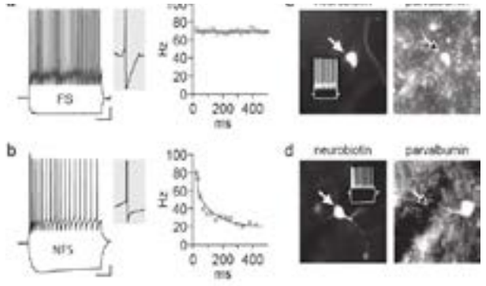


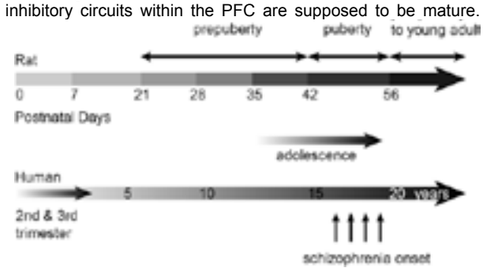
Figure 3. Fast spiking PV positive interneurons. (a,b) Traces of electrophysiological recordings showing characteristics of prefrontal fast spiking (FS) and non-fast spiking (NFS) interneurons in response to somatic current depolarization. Fast spiking interneurons have a fast after hyperpolarization potential (middle inset), whereas non-fast spiking interneurons have an un-adapted firing response characterized by a constant firing rate. (c,d) Neurobiotin labeled and rabbit anti-PV probed fast spiking and non-fast spiking interneurons are shown as indicated by the arrow. Fast spiking interneurons were PV positive, and non-fast spiking interneurons were not (Adapted from Caballero et al., in press).

PV positive interneurons are of interest because it has been indicated that only glutamatergic inputs, specifically those contacting the GABAergic PV positive interneurons, are developmentally regulated during adolescence (Caballero et al., in press). There is specific attention paid to the development of PV positive interneurons because reduction in PV was seen in the PFCs of schizophrenic individuals (Druga, 2009). These fast spiking interneurons control much of pyramidal neuron firing activity in the PFC, allowing for regulated activity (Rao et al., 1999). During adolescence, there is an increase in the glutamatergic drive onto these PV positive interneurons (Caballero et al., in press). Suppressing or inhibiting the drive could lead to underdeveloped PFC circuitry (O'Donnell,

2011). Overall, it may be more harmful to interrupt PV positive interneuron development because they are primarily responsible for fast spiking inhibition.

PFC Development and Schizophrenia

During adolescence, prefrontal interneurons require an increase of glutamatergic drive in order to properly develop (Tseng et al., 2009). Drugs that interfere with glutamatergic drive onto interneurons may have the potential to alter the course of PFC interneuron development, which may underlie PFC dysfunction in schizophrenia (Caballero & Tseng, 2012). Interruptions in maturational events can potentially lead to long term illnesses of the brain given that most anxiety disorders, bipolar disorder, substance abuse and psychoses arise during adolescence (Giedd et al., 2008). Schizophrenia is a debilitating disorder characterized by illogical thinking, lack of reasoning and disconnection with reality affecting 1% of people worldwide (Lewis & Lieberman, 2000). Schizophrenia arises during late adolescence or early adulthood (Fig. 3) with an average onset around the age of 22 years for men and 25 years for women (Hafner et al., 2003). It is interesting to see that schizophrenia can begin at a time where inhibitory circuits within the PFC are supposed to be mature.



Adolescent exposure to cannabis can potentially increase the risk of having schizophrenia in adulthood. Cannabinoid receptor 1 (CB1) is responsible for most of the effects of Cannabis sativa derived ligand ∆9-Tetrahydrocannabinol (Kano, Ohno-Shosaku, Hashimotodani, Uchigashima, & Watanabe, 2009). The CB1 receptor is only present in the central nervous system, while the other known cannabinoid receptor, cannabinoid receptor 2, is in the periphery (Howlett et al., 2002). As a receptor part of the G protein-coupled receptor family (Matsuda, Lolait, Brownstein, Young, & Bonner, 1990), CB1 expression has been found to be highest in the PFC, limbic areas and the anterior cingulate cortex (Heng, Beverley, Steiner, & Tseng, 2011). High concentrations of CB1 receptors increase the risk for diminished neurotransmitter signaling.

Over-activating CB1 receptors on neurons driving interneuron development may cause lasting consequences in terms of inhibitory circuits within the PFC (Caballero & Tseng, 2012). Endogenous cannabinoids have been found to bind to the CB1 receptor in a retrograde fashion to inhibit neurotransmitter release (Howlett et al., 2002). The CB1 receptor is reported to control glutamate, GABA, acetylcholine, dopamine, and serotonin (see review by Lovinger, 2008). Although there are other pathways that influence glutamatergic drive toward interneurons, such as the dopamine system, the manipulation of the endocannabinoid system could reveal the role of the CB1 receptor on glutamatergic drive in interneuron development (Fig. 5).

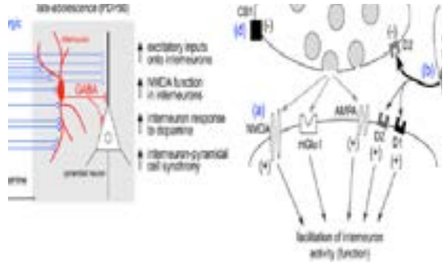


Figure 5. GABAergic interneuron development and the pathways involved.

It is thought that during adolescence, interneurons receive glutamatergic inputs that drive their development. The end result would be proper GABAergic transmission in the PFC during adulthood (left panel) (Caballero & Tseng, 2012). There are other elements of signaling that may affect the glutamatergic transmission to facilitate interneuron development. Any signaling alterations in a, b, c, or d may result in insufficient interneuron function (Tseng, 2013).

Overall, the entire endocannabinoid system influences many brain functions such as learning and memory, anxiety, depression, addiction, appetite and pain (see review by Kano et al., 2009). Current efforts show that cannabis use alters cortical network dynamics similar to those seen in schizophrenia, indicating that exogenous cannabinoids can alter the physiology of brain circuits involved with higher cognitive functions (Caballero & Tseng, 2012). Underlying mechanisms of PFC development in terms of the cannabinoid system are still to be explored, but further research is needed to assess the effect of cannabinoids on cortical development.

Gaps in Knowledge

While cannabis use has been recognized to influence neurodevelopmental disorders, little is known about these cannabinoid-mediated mechanisms. Although it has been demonstrated that exogenous cannabinoids yield detrimental long-term effects in adolescence, it is still unclear which mechanisms are affected during adolescence. Exposure to exogenous cannabinoids during adolescence could offset the natural role of the endocannabinoid system in the drive for development. In this study, the effects of either adult or adolescent exposure to synthetic cannabinoid WIN on adult PFC activity were examined in rats. Male Sprague-Dawley rats were used because they are a commonly used strain in brain function research. Therefore, data from this study can be compared with previously reported findings.

Hypothesis and Aims

The current study aims to investigate the effect of CB1 receptor agonist WIN on the state of the PFC, and whether the postnatal day (PD) at which the drug was administered plays a role. The hypothesis is that disinhibited PFC activity would arise in adolescent WIN treated rats compared to vehicle treated and adult treated rats. To test this hypothesis, the following aims were studied:

Aim 1: To determine whether WIN would affect the state of PFC inhibition at different frequencies.

Aim 2: To determine whether the age of WIN administration has long term effects on prefrontal inhibitory states.

Electrophysiology recordings will be used to determine

the level of inhibition in the PFC. Prefrontal activity will be elicited and recorded through hippocampal train stimulation. Statistics will be used to analyze recordings of prefrontal activity for differences in inhibition between WIN or vehicle treated groups for both adolescent and adult rats.

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