Neuropharmacology 76 (2014) 416–424

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Invited review

Trajectory of adolescent cannabis use on addiction vulnerability

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ARTICLE INFO

Article history:
Received 11 March 2013
Received in revised form
16 July 2013
Accepted 19 July 2013

Keywords:
Marijuana
Cannabinoid
Opioid neuropeptide
Nucleus accumbens
Prefrontal cortex

ABSTRACT

The adolescent brain is a period of dynamic development making it vulnerable to environmental factors such as drug exposure. Of the illicit drugs, cannabis is most used by teenagers since it is perceived by many to be of little harm. This perception has led to a growing number of states approving its legalization and increased accessibility. Most of the debates and ensuing policies regarding cannabis were done without consideration of its impact on one of the most vulnerable population, namely teens, or without consideration of scientific data. We provide an overview of the endocannabinoid system in relation to adolescent cannabis exposure and provide insights regarding factors such as genetics and behavioral traits that confer risk for subsequent addiction. While it is clear that more systematic scientific studies are needed to understand the long-term impact of adolescent cannabis exposure on brain and behavior, the current evidence suggests that it has a far-reaching influence on adult addictive behaviors particularly for certain subsets of vulnerable individuals.

This article is part of a Special Issue entitled 'NIDA 40th Anniversary Issue'.

1. Introduction

Adolescence is an important stage of behavioral maturation and brain development during which the high degree of neuroplasticity that occurs in this ontogenetic period places the adolescent brain at particular risk to environmental factors such as drug exposure. Marijuana (*Cannabis sativa*) continues to be the illicit drug most commonly used by teenagers in the United States as well as in other Western societies (Johnston et al., 2012; SAMHSA, 2011). Although cannabis is not as highly addictive as other substances, such as heroin and cocaine, cannabis-dependent individuals still greatly outnumber those reporting dependence on other illicit drugs and the number of people seeking treatment for cannabis dependence continues to increase yearly (SAMHSA, 2011).

Despite these facts, there is a growing perception, particularly in adolescents and young adults (Kilmer et al., 2007; Lopez-Quintero and Neumark, 2010), that cannabis is 'harmless' especially when compared to other abused substances like nicotine (tobacco) and alcohol that are legal. Reasons cited for this perception include the consideration that cannabis-associated mortality is lower than tobacco and alcohol, which are associated with cancer and overdose/vehicular accidents, respectively. In addition, cannabinoids provide medicinal benefits (Hermanson and Marnett, 2011; Hill et al., 2012) in contrast to tobacco and alcohol, which have no medical indications. These and other considerations have contributed to the decriminalization, or even legalization, of cannabis in a number of states within the USA. Economic factors have also been suggested as a rationalization for legalization as a potential source of tax revenue for state governments. Despite some cogent arguments in the current debates regarding legalization and increased availability of cannabis, most of the discussion and policies have been made without significant consideration of scientific data.

Growing evidence suggests a differential effect of cannabis exposure on the human brain based on the age of exposure, but the question remains as to the potential long-term mental health consequences of cannabis exposure in teens. Few scientific studies have systematically investigated the long-term impact of cannabis use in relation to the developing teenage brain, the population most crucial to the current debates. Nevertheless, the available data to date, as discussed in this review, suggest that adolescent cannabis exposure induces significant protracted effects suggestive of enhanced vulnerability to addiction and psychiatric disorders in later life, at least in certain subsets of individuals.

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http://dx.doi.org/10.1016/j.neuropharm.2013.07.028

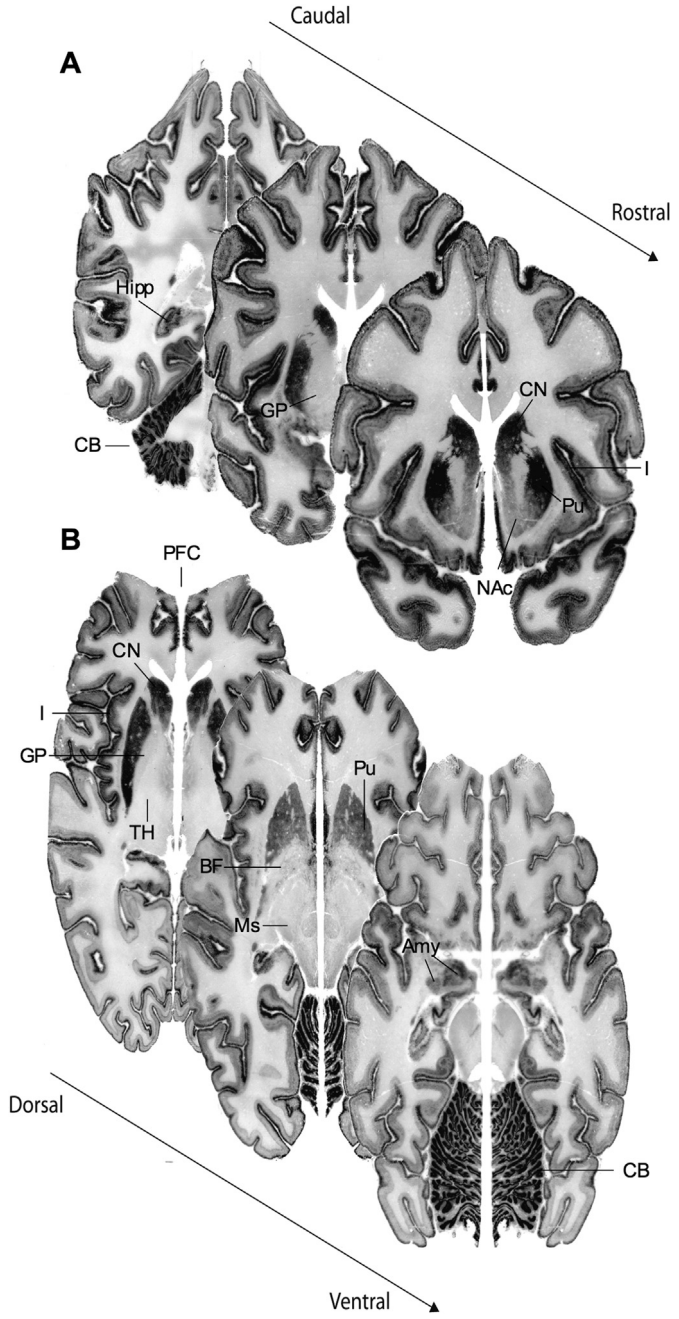

Fig. 1. Cannabinoid receptor mRNA (*CNR1*) expression in the human brain emphasizes this gene's abundant expression in cerebral cortex – such as insular cortex (I) and prefrontal cortex (PFC) – as well as the caudate nucleus (CN), putamen (Pu), nucleus accumbens (NAc), hippocampus (Hipp), amygdala (Amy), and cerebellum (CB). Absent-to-low mRNA expression is notable in the thalamus (T), basal forebrain (BF), globus pallidus (GP), and midbrain (Ms).

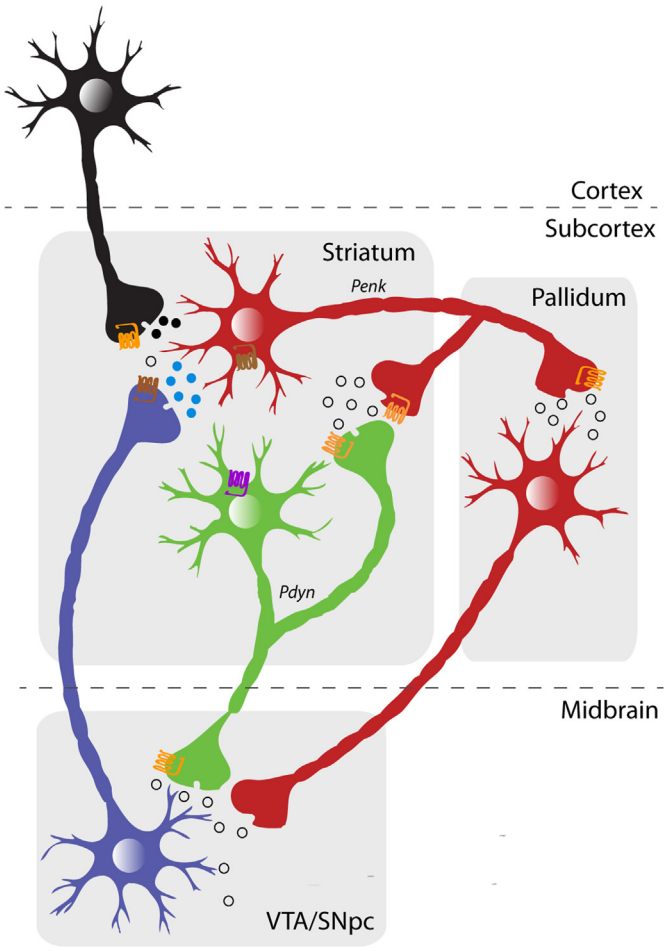

Fig. 2. Schematic illustration of the striatonigral 'Go' andstriatopallidal 'NoGo' pathways. These medium spiny output neurons are distinguishable based on their targets and subcellular markers, namely the expression of D_1R (purple) and D_2R (brown), respectively. Both cell-types, however, express CB_1R (orange). This dissociation is based mainly on the dorsal striatal circuit, but a similar organization, particularly with respect to the 'NoGo' pathway, exists for the ventral striatal circuit.

2. Neurobiology of the endocannabinoid system

The main psychoactive component of cannabis, Δ^9-tetrahydrocannabinol (THC), acts primarily via cannabinoid receptors (CBRs) — CB_1R and CB_2R (Gerard et al., 1991; Griffin et al., 2000; Matsuda et al., 1990; Munro et al., 1993). The CB_1R is one of the most abundant G-protein-coupled receptor in the brain (Herkenham et al., 1990, 1991a) and is $G_{i/o}$-coupled, suppressing neurotransmitter release (Howlett et al., 2002). The expression of CB_1R is most pronounced within the basal ganglia, cerebellum, cerebral cortex, hippocampus and amygdala (Biegon and Kerman, 2001; Glass et al., 1997; Herkenham et al., 1990, 1991b; Mailleux et al., 1992; Pettit et al., 1998; Wang et al., 2003) (Fig. 1), consistent with cannabis exerting significant effects on motor function, cognition, and emotional regulation. Recent evidence, though initially controversial, suggests that CB_2R is also expressed within the central nervous system in immune cells as well as glia and potentially neurons (Gong et al., 2006; Lanciego et al., 2011; Onaivi et al., 2006; Van Sickle et al., 2005). Nevertheless, the broad and abundant expression of CB_1R in neuronal circuits relevant to addiction and psychiatric disorders still place a prominent emphasis on cannabis' modulation of this CBR subtype in relation to psychiatric vulnerability.

Imaging studies of rodents (Verdurand et al., 2011) and human subjects (Mato et al., 2003) suggest global increases in CB_1R throughout early life into adolescence, at which period adult levels are generally maintained (Belue et al., 1995; McLaughlin et al., 1994; Rodriguez de Fonseca et al., 1993), but there are also reports of reduced CB_1R expression from juvenile to adulthood that mirrors developmental changes in CB_1R-mediated signaling (Heng et al., 2011). Some of the inconsistencies regarding the ontogenic pattern of the CB_1R may be due to regional, as opposed to global, developmental differences in the receptor development in addition to differences in mRNA, receptor protein or receptor binding being