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# Marijuana: Neurotoxic or Neuroprotective?

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## I. Introduction

Marijuana is the dried leaves, flowers, stems, and seeds from the plant *Cannabis sativa*. It has a several psychoactive chemicals along with a relatively well-characterized delta-9-tetrahydro-cannabional ($\Delta^9$-THC). Marijuana can also be concentrated in a resin called hashish or a black sticky liquid called hash oil.It is the most common illicit drug in the United States. Even though federal government considers marijuana as a Schedule I substance, several states have legalized it for medicinal and recreational use (www.drugabuse.gov).

Numerous compounds are produced when marijuana is smoked, which may have acute or chronic effect. G protein-coupledcannabinoid (CB) receptors are involved to respond acute effects of cannabinoids and the development of tolerance. CB1 receptors are predominantly available in the hippocampus, striatum, and cerebellum in the brain (Ameri 1999).Another cannabinoid receptor, CB2, is mostly found in spleen, which has only about 44% nucleotide sequence similarity with CB1 receptor(Ameri 1999).

Even though marijuana is the most common street drug, it has been employed as a therapeutic drug. There are well-proofed potential medicinal actions of marijuana, such as antiemetic, analgesia, anticonvulsant, and lower intraocular pressure (Hollister 1986).However, psychological effects, development of tolerance, and the abuse potential of marijuana have discouraged their medicinal use. In addition, the public debate exists whether or not marijuana should be legalized. Thus, it is the aim of this review to present the effect of marijuana and its psychoactive components on brain and evaluate if it is neuroprotective or neurotoxic.

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## II. Neurological Effects

Although marijuana have shown direct cellular effects on a number of organ systems such as immune system, liver, reproductive system, and digestive system, major behavioral and pharmacological effects involve the central nervous system (CNS)(Ameri 1999). The behavioral effects of marijuana may vary depending on dose and route of administration, expectations of subjects, and individual vulnerability to certain effect. Marijuana at low doses generally produces euphoric, relaxation, and stimulatory effects, and at higher doses they exert predominantly depression(Lukas et al. 1995). Acute marijuana is associated with impaired functioning in cognitive and performance tasks such as reaction time, learning perception, motor coordination and attention (Court 1998; Heishman et al. 1997). Multiple studies have implicated that marijuana deficits short-term memory, whichmeditate CB1 receptors(Heyser et al. 1993; Lichtman and Martin 1996).

One biological effects of $\Delta^9$-THC is their ability of inhibiting pain transmission(Martin et al. 1996), potentially involving neuronal pathway of $\kappa$ opioid receptors with distal or converging pathway of cannabinoid receptors(Ameri 1999; Calignano et al. 1998).

Multiple studies suggest that marijuana possess antiepileptic properties in animal seizure models and human patients (Carlini and Cunha 1981; Karler and Turkanis 1981). Available evidences predictedthe antiepileptic property of marijuana is due to its interaction with the glutamatergic transmission in the central nervous system (Feigenbaum et al. 1989).

## III. Marijuana-Induced CNS Modification: Neurotoxic or Neuroprotective?

Multiple studies revealed neuroprotective and neurotoxic effects of marijuana in animal models or human systems. It was shown to induce beneficial or detrimental effects at cellular level(Bash et al. 2003; Sarne and Keren 2004).

Many epidemiological studies have demonstrated that chronic use of marijuana deteriorates cognitive functions, specific impairment of attention, memory, and executive function (Pope and Yurgelun-Todd 1996; Schweinsburg et al. 2008; Solowij et al. 1995). Interestingly, unlike ethanol, cognitive impairment caused by marijuana is not clearly dose-dependent.

However, chronic (at least several months) marijuana exposure may cause long-term impairment (Pope and Yurgelun-Todd 1996).A major psychoactive ingredient of marijuana, $\Delta^9$-THC, persistently reduced maze learning ability in rats(Fehr et al. 1976; Stiglick and Kalant 1982; Stiglick et al. 1984). Similar results were detected in rats with hippocampal lesions, suggesting the possibility of neurotoxic effects of marijuana in the hippocampus (Morris et al. 1982). In addition, neuronal death and reduced synaptic density and dendritic length of pyramidal neurons were measured in the hippocampus of chronic marijuana administered rats(Landfield et al. 1988; Lawston et al. 2000). Furthermore, THC induced neuronal death in the neuronal cell lines, cultured hippocampal neurons or hippocampal slices(Chan et al. 1998). Chan et al. presented evidences of $\Delta^9$-THC inducing apoptosis of hippocampal neurons by shrinking neuronal bodies and nuclei as well as DNA fragmentation (Chan et al. 1998). Furthermore, the neuronal cell loss is assumed to be responsible for impairment in memory after long-lasting consumption of marijuana. 10 and 1 μM THC are found to induce 50% hippocampal neuronal death in 2 hr and 5 days, respectively (Chan et al. 1998). In a separate report, marijuana was considered to produce toxic encephalopathy in young humans (Court 1998).

In contrast to the above reports, marijuana induces the expression of endocannabinoid 2-arachidonoyl glycerol (2-AG), which reduced brain edema and infarct volume following severe closed head injury(Sarne et al. 2011). In addition, CB1 and CB2 receptors agonist Bay 38-7271 demonstrated neuroprotective properties in traumatic brain injury and focal ischemic rat models (Sarne et al. 2011; Sarne and Keren 2004). Additionally, the role of endogenous cannabinoid system is suggested to be neuroprotective (Guzman et al. 2001; Mechoulam et al. 2002). Multiple *in vitro* studies have reported protection of neurons in culture by cannabinoid agonists acting through CB1 receptors(Shen and Thayer 1998). Also, CB1 receptor acting cannabinoid agonists protected hippocampal neurons from synaptically- mediated excitotoxicity (Abood et al. 2001). Furthermore, the cannabinoid agonist CP-55, 940 protected cortical neurons from glutamatergic excitotoxicity by CB1 receptor-mediated voltage-dependent calcium channels inhibition (Hampson and Grimaldi 2001). Other synthetic cannabinoid WIN55 and 2122 administered daily (twice, 2 mg/kg) to rats increased hippocampal granule cell density and dendritic length in the CA3 pyramidal cell layer (Chan et al. 1996).

Some studies did not show any effect of marijuana in central nervous system. An MRI study found no evidence of cerebral atrophy or regional changes in tissue volumes among 18 current, frequent, adult marijuana users compared to 13 adult non-users (Block et al. 2000). A study claimed ultrastructural changes in septum and hippocampal in rhesus monkeys by marijuana smoking(Harper et al. 1977; Heath et al. 1980), however, subsequent larger study failed to show effect of marijuana in the histopathology of monkey brain (Scallet 1991). The neuroprotective or neurotoxic effect of marijuana is potentially determined by the amount inhaled or ingested as shown in Fig. 1.

## IV. Summary

The increasing legalization of marijuana for medical and recreational use renewed the interest in its potential effect on health and therapeutic applications. Marijuana, THC, and other cannabinoid agonists all have a common problem of a narrow therapeutic window between clinical benefits and the unwanted psychic side-effects. Further elaborated studies at multiple doses for short- and long- term consumption is essential prior to conclude beneficial or detrimental effect of marijuana in the central nervous system.

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## Figure Legend

**Figure 1. Marijuana dose determines beneficial or detrimental effect of marijuana consumption.** Research so far indicated that low dose of marijuana has beneficial and neuroprotective response. However, higher marijuana dose stimulate psychoactive impairment as well asmemory and attention deficits, potentially due to its neurotoxic effect.

## Figure

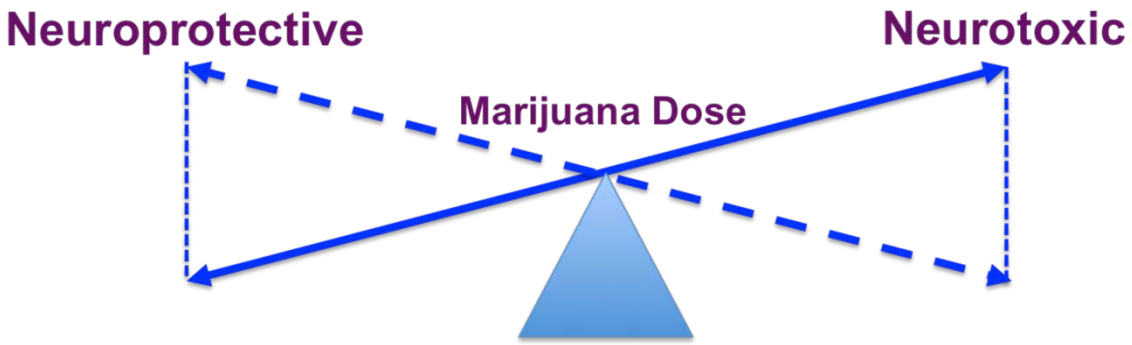


*Fig. 1*