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Different Effects of Cannabis Abuse on Adolescent and Adult Brain

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Abstract
Cannabis abuse is a common phenomenon among adolescents. The dominant psychoactive substance in *Cannabis sativa* is tetrahydrocannabinol (THC). However, in the past 40 years the content of the psychoactive ingredient THC in most of the preparations is not constant but has increased due to other breeding and culturing conditions. THC acts as the endocannabinoids at CB1 and CB2 receptors but pharmacologically can be described as a partial (not a pure) agonist. Recent evidence shows that activation of the CB1 receptor by THC can diminish the production of neuronal growth factor in neurons and affect other signalling cascades involved in synapsis formation. Since these factors play an important role in the brain development and in the neuronal conversion processes during puberty, it seems reasonable that THC can affect the adolescent brain in another manner than the adult brain. Accordingly, in adolescent cannabis users structural changes were observed with loss of grey matter in certain brain areas. Moreover, recent studies show different effects of THC on adolescent and adult brains and on behaviour. These studies indicate that early THC abuse can result in neuropsychological deficits. This review gives an overview over the present knowledge in this field.

Introduction

A typical case in the counselling situation in the German public health care system is a young adult who has been sent by the job centre and who needs support after he stopped his first education because he felt that this does not fit to him, and who failed during the second education because he was overwhelmed with the conditions and requirements asked for by the trainer. The young adult seems unfocused, his memory is sketchy, in particular the short-term memory, and the affect is indifferent and a bit sappy. The intelligence is in the normal range. It is reported that he has a lack in daily structure. A deeper exploration shows that he started to use cannabis, first as marijuana joints, later as dabs, with 15 years at school. With 17, he stopped school and started the education.

This is a very typical example seen today often in various counselling situations. Cannabis with its various preparations is frequently used by adolescents. In a cross-sec-

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tional study comprising all pupils in the 10th classes of an eastern German county, it was found that 25% of the pupils with a mean age of 16 years used cannabis [1]. Similar prevalence was reported by others: in Frankfurt, Germany, 35% of the pupils had experience with cannabis consumption [2], and in whole of Germany the 2016 report of the Bundesregierung shows 3.1% illegal drugs in the group of persons aged 18–20 years, and 23% cannabis [3].

In France 24% of the ninth grade pupils [4], 40.5% of the 15- to 16-year-old boys and girls in United Kingdom [5], 36% of boys and 38% of girls of the adolescents in Czech Republic, 28% of boys and 25% of girls of the adolescents in Slovakia, and 28% of boys and 20% of girls of the adolescents in Poland [6] consumed cannabis. The most common way of administration is smoking. In this case, the maximum effect occurs after about 15 min and lasts for about 1 h. If administered orally, the absorption is slower and the effect starts with delay. Besides this, there is a growing field for use and evaluation of indications of cannabinoids in medicine (see [7]). This should be clearly separated from "abuse," which is the topic of the present review on effects of cannabis abuse in adolescents and adults.

According to the current data, in mid-European countries about 1/4 or 1/3 of the adolescents consume cannabis. The consume frequency is not exactly known. However, according to the data of the Drogenbeauftragte der Bundesregierung 2019, 1.2% of the adolescents (12–17 years) consume regularly, 3.1% consumed at least once in the last 30 days, and 8.0% consumed at least once in the last 12 months [8]. In 18- to 25-year-old young adults, 5.9% consume regularly, 9.2% in the last 30 days, and 22.0% in the last 12 months. The data for 18- to 59-year-old adults were 1.2, 3.4, and 8.3%, respectively [8]. An important issue in this context is whether exposure to cannabis in adolescence may differ from the effects of exposure in adulthood.

In the German young adult population (18–25 years), the life prevalence of cannabis consume is about 33% [3]. In the 18- to 59-year population of adults, this prevalence is 30.2% [3]. However, there is increasing evidence that cannabinoids affect the adult and adolescent brain in different ways: in younger people, cannabinoid use elicits long-lasting neuropsychological deficits [9] which is not or less pronounced in adults [10, 11]. In another investigation, authors concluded that duration of use (rather than frequency) may be the primary factor contributing to cognitive deficits [12], while others showed that early onset of cannabis use is associated with neuropsychological deficits [13]. The focus of the present review is to discuss mechanisms which may underlie these effects and differences.

For that purpose, the literature from 1960 to 2019 (PubMed database) was investigated for the keywords "cannabis," "marijuana," "hashish," "tetrahydrocannabinol," "cannabidiol," "endocannabinoids," "adolescent," and "adult." In addition, drug reports from Germany and the Netherlands were included. Moreover, the IUPHAR database was checked for "cannabinoid receptor," "CB1," "CB2," and "endocannabinoids."

Cannabis Receptors

Cannabinoids act typically at cannabis receptors (CB). The main cannabis receptors CB1 and CB2 belong to the group of G-protein-coupled receptors (GPCR) and can be activated by endogenous endocannabinoids, phytocannabinoids, or synthetic cannabinoids [14]. CB1, encoded by the *CNR1* gene, is typically coupled to Gi/o-suppressing AC activity and cAMP formation but can switch to Gs or Gq [15]. The CB1 subtype is expressed in the brain (highest expression in the olfactory bulb, hippocampus, basal ganglia, and cerebellum), peripheral nervous system (mostly expressed in sympathetic nerve terminals), and peripheral tissues such as the gut, heart, liver, reproductive system, immune system, and airways in a region-specific manner [15–18]. Unselective agonists at the CB1 are HU-210, CP55940, and WIN55212-2 [19], CB1-selective agonists are arachidonyl-2-chloroethyamide, arachidonylcyclopropylamide, O-1812, and R-(+)-ethanandamide [20–23], while tetrahydrocannabinol (THC) acts as a partial agonist [19, 20]. Rimonabant and AM6545 are used as antagonists at the CB1 [19, 24].

The second type of cannabis receptor, the CB2, encoded by the*CNR2* gene, is also a GPCR and is typically coupled to Gi/o. Agonists at this receptor are HU-210, CP55940, and WIN55212-2 [19] and antagonists are SR144528 and AM-630 [25, 26]. As at CB1, THC acts as a partial agonist at the CB2 [19].

The CB2 subtype is expressed in peripheral organs with immune function, such as the spleen, tonsils, thymus, as well as cells like macrophages and leukocytes. CB2 also is present in microglia and vascular structures. Moreover, CB2 is expressed in the lungs, testes, and central nervous system [27]. Besides the CB receptors CB1 and CB2, other receptor proteins have been identified as possible targets for the endocannabinoid system such as CPR55, GPR119, and transient receptor potential vanilloid 1 (TRPV1) [14].

While the receptors, their coupling, and possible agonists and antagonists have been characterized, the physi-

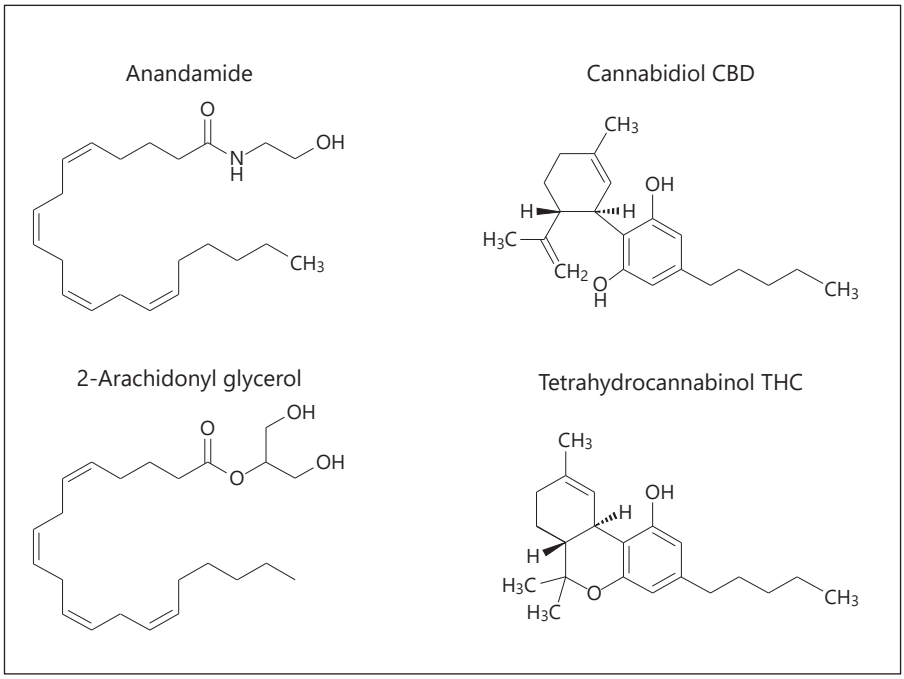

Fig. 1. Chemical structure of endocannabinoids (2-arachidonyl glycerol and anandamide) and phytocannabinoids (tetrahydrocannabinol and cannabidiol).

ological or even pathophysiological function of the cannabinoid receptors is still a matter of debate. Pharmacologically, cannabinoids are used because of their antinociception, anti-inflammation, anticonvulsant, and antiemetic (e.g., in cancer medicine) properties [15]. The physiological mediators at CB1 and CB2 comprise *N*-arachidonoyl-ethanolamine (AEA, anandamide) and 2-arachidonoylgylcerol (2-AG), which are derivatives of arachidonic acid (see Fig. 1).

Physiologically, the endocannabinoid system plays a role in the brain in short- and long- term depression at both excitatory and inhibitory synapses by negative feedback mechanisms on neurotransmitter release [28, 29]. CB1-mediated self-inhibition has been described in neurons of the CA1 area in hippocampus and in neocortical interneurons and some pyramidal neurons (for review, see [15]). In the brain, endocannabinoid signalling has been considered to be involved in sleep regulation, reward reaction, anxiety control, appetite control, neuroprotection, and neural development. In the cardiovascular system, negative inotropy and vasodilation have been associated with cannabinoids. In the gastrointestinal tract, motility and enteroendocrine functions seem to be influenced [15]. Moreover, endocannabinoids can act as immunomodulatory effectors [30]. Thus, CB2 is the cannabinoid receptor which is predominantly expressed by immune cells and which upon stimulation seems to inhibit migratory activities of immune cells [31].

Pathophysiologically, it has been suggested that an overactive endocannabinoid system may contribute to the development of diabetes mellitus [32]. An involvement of the endocannabinoid system in the pathogenesis of schizophrenia has also been suggested [33]. Moreover, dysfunction of the endocannabinoid system has been discussed to be involved in kidney disease [34] and liver fibrosis [35]. CB1 activation by endocannabinoids has been suggested to be involved in proinflammatory cardiovascular processes and in atherosclerosis, while CB2 stimulation appeared to be protective [31]. In addition, it has been shown that CB1 antagonists and CB2 agonists may protect against diabetic nephropathy [31].

Exogenous cannabinoids mainly origin from plant products made from *Cannabis sativa* like hashish and marijuana. *Cannabis sativa* contains several phytocannabinoids with THC and cannabidiol (CBD) being the most prominent (see Fig. 1).

Finally, it is pharmacologically important to discriminate endogenous and exogenous cannabinoids, since THC acts as a partial agonist [19, 20], which means that in presence of endogenous endocannabinoids (agonists) it may antagonize or attenuate the effects of the endocannabinoids, while in absence of endocannabinoid stimulation it rather works in an agonistic manner. Furthermore, this is affected by the receptor density. Thus, the resulting effect of THC may also depend on the context of endogenous stimulation of the cannabinoid system.

Composition and Composition Changes of Cannabis/Marijuana Preparations

Over the last 20–30 years, the composition of cannabis products has changed due to the fact that cannabis is grown in doors and that strains are cultivated with different THC and CBD contents and THC:CBD ratios [36, 37] (Table 1). Thus, it was found in a large European study in samples from 28 EU countries and Norway and Turkey that from 2006 until 2016 the THC content in resin and in herbal cannabis increased from 8.14 to 17.22% and from 5.0 to 10.22%, respectively [38]. A similar development was found in samples from France over a 25-year period ranging from 1992 to 2015 [39]. Comparable increases in THC content in the resin were found in Denmark from 2000 (mean: 8.3%) to 2017 (mean: 25.3%) with an increase in THC:CBD ratio from 1.4 in 2008 to 4.4 in 2017 [40].

Interestingly, in the Netherlands the THC content remained nearly unaltered (resin THC content: between 16 and 17% during the timespan from 2005 until 2015) [41]. However, that means that in the Netherlands the THC resin content in 2005 was with 16% in the range, which was achieved in other European countries at 2016.

Depending on genetic selection, breeding conditions, outdoor or in door cultivation, etc., the content in certain cannabinoids in the herbs varies [42]. This data shows that it is important to define the terms "cannabis," "marijuana," "hashish," etc. in terms of THC content and CBD:THC ratio and to take the changes in this composition over the last decades into account [36–44] (see Table 1). Data from earlier studies may not be directly comparable to more recent studies due to the altered composition of the preparations.

Table 1. Changes in the composition of marijuana and hashish (see [36–44])

Year	Substance, %	Hashish	Marijuana
1975	THC	1.0–6.0 (mean: 3–4)	0.3–4.0 (mean: 1–2)
	CBD	0.1–2.0	0.28
2017	THC	4.0–30.0 (mean: 14)	4.0–25.0 (mean: 15)
	CBD	4.0	0.15

Neuronal Effects of Cannabis Abuse and Special Effects in Adolescents

The brain is continually developing until the age of about 25 [45]. New MRI technologies revealed that from birth to early adulthood, there are transformation processes regarding grey and white matter. In principle, the process in adolescence can be described as a reduction of redundant grey matter and increase in white matter [46–48]. With birth and infancy, there is a huge formation of new synapses, in particular in the cortex. Later on, a pruning process is observed with eliminating unused or redundant connections and improving those synapses that are used. This is from a histological point of view a part of the process of learning, aiming at improving the efficacy of the brain. During this process, many neurons are lost, so that the adult has about 41% fewer neurons than the newborn [49]. Increased loss of grey matter in the medial prefrontal cortex was found in drug users, in particular in those who used multiple drugs [50].

The brain, however, does not mature in all regions at the same time: more rudimentary regions, such as those enabling movement and somatosensory functions and general information processing, mature first (in childhood), while others being involved in impulse control, strategic planning, or social behaviour mature later in adolescence together with the maturation of the prefrontal cortex [47]. The total process may be considered as a highly complex "genetically patterned process of consolidating anatomical network hubs" [51]. Finally, the process of increasing white matter connections and eliminating redundant grey matter leads to increased cognitive functioning [46, 48, 52].

Taken together, this means that the adolescent brain is a structure "under reconstruction" with complex neurophysiological processes of network formation. This may make the adolescent brain more prone to damages by substance abuse as compared to the adult brain and may lead to different impairment.

It has been shown that cannabis leads to lower circulating levels of brain-derived neurotrophic factor (BDNF) in physically active cannabis users [53]. In another study, chronic cannabis use resulted in lower serum levels of nerve growth factor (NGF) [54], while BDNF was not altered in this group. The connection between neurotrophic factors such as BDNF and NGF seems even more complex, if patients suffering from a psychosis such as schizophrenia are taken into account: in schizophrenic patients, chronic cannabis intake results in elevated NGF levels [55]. Cannabis-using schizophrenic patients also exhibited elevated BDNF levels [56].

Interestingly, the same authors observed normalization of NGF levels after effective antipsychotic treatment [57]. NGF has been found to be elevated in response to inflammatory brain diseases such as multiple sclerosis or systemic lupus erythematosus [58–60] and thus may be indicative for neuronal impairment.

On the other hand, NGF is not only a target of cannabinoid signalling, but also NGF can regulate the molecular machinery for the endocannabinoid 2-arachidonoyl glycerol signalling via tropomyosine kinase A receptors (NGF receptor) [61]. NGF has been demonstrated to sensitize transient receptor potential vanilloid 1 (TRPV1). CB1 receptor activation by the CB1 agonist arachidonyl-2′-chloroethyamide inhibited NGF-induced AKT phosphorylation and TRPV1 sensitization at least partially by attenuating NGF-induced PI2 signalling [62]. It remains unclear at present how a partial agonist such as THC [20] would act in presence of endogenous agonistic endocannabinoids. This might be an interesting area of future research.

Thus, the endocannabinoid system is important for short-term and long-term synaptic plasticity in several brain regions including those involved in appetite control, learning, and action selection [63]. One might speculate that a partial agonist may affect the endocannabinoid-regulated synapse plasticity. Taken together, there is a complex interplay between endogenous (agonistic) endocannabinoids, NGF, BDNF, and exogenous (partial agonistic) THC [19, 20] and cannabidiol [20].

Long-Term Effects of Cannabis Abuse in Adults and Adolescents

From the above considerations, one could imagine that early regular cannabis use in adolescence may have an impact on cerebral or cognitive functions. Indeed, it was found in 21 adolescent-onset cannabis users that verbal learning was slower in this group within 12 h after use of cannabis [64]. In addition, a deregulation of the BDNF pathway was found to be the consequence of marijuana use in adolescence [65].

However, other researchers did not find an effect of adolescent cannabis use on structural brain characteristics in adulthood [66]. On the other hand, the risk for the development of psychosis increases with the frequency of THC use [67]. Cannabis use in adolescence, in particular in the case of heavy users, is known to be related to impaired cognitive functioning [68], low educational attainment [69, 70], and educational problems [71] leading to socio-economic consequences. Moreover, early cannabis use is associated with lower income and lower work commitment in early adulthood [72–74]. In a Swedish study on 42,240 young men, of which 8.8% (3,734) reported to have used cannabis at the age of 18, an increased relative risk was found for cannabis users to be unemployed later on or to receive social welfare assistance [75]. Although this was overshadowed by confounders such as parental separation, the association between early cannabis use and negative social outcome remained significant after adjustment for confounders. However, a possible explanation is also that both cannabis use and adverse life-course are caused by underlying social or genetic factors unknown yet. Thus, Daniel et al. [76] found weak evidence that childhood disadvantage is associated with later cannabis use.

The risk of becoming addicted to cannabis also is dependent on first use age. Thus, 9–10% of persons who start to use cannabis will develop addiction. If use is initiated in adolescence, this percentage is increased to 16–17%. Daily users exhibit addiction in 25–50% [77].

THC can act in certain systems as a CB1 antagonist [19, 20] and – paradoxically – in others as an agonist. This is attributable to its pharmacological characteristics as a partial agonist and, therefore, depends on the concomitant activation of the system by other endogenous cannabinoids, the receptor density, and possible limitations of the post-receptor signal pathway [33]. Thus, THC is not simply mimicking or modulating the effects of endocannabinoids [19, 20] but rather evokes a complex interplay.

In long-term cannabis user, structural changes with reduced volumes have been detected by neuroimaging techniques in CB1-rich brain areas such as hippocampus, parahippocampus, and thalamus [78]. In adolescent chronic cannabis users also, structural changes were observed with loss of gray matter in the medial temporal cortex, parahippocampus, insula, and orbitofrontal cortex [79] and alterations in the amygdala and hippocampus [77, 80]. In particular, the functional connectivity among the neurons is predominantly impaired when users start in adolescence [81, 82].

Regarding abstinence, it was found that cessation of cannabis abuse did not lead to full recovery of cognitive deficits in adolescent-onset users. This indicates that early cannabis use (in adolescence) may result in greater loss of cognitive performance [83, 84]. However, this must be discussed with care because of possible confounding from socio-economic status [85].

Nevertheless, the study by Meier et al. [83] showed for a 1,037 person birth cohort study from birth (1972/1973)

until the age of 38 years that persons who persistently used cannabis showed neuropsychological decline which was more prominent in those individuals who started cannabis use during adolescence. Importantly, these authors also showed that cessation of cannabis use did not fully restore the deficits [83]. Early use was associated in other studies with deficits in episodic memory, verbal fluency, and executive functioning [86–88].

Psychological problems such as sleep disorders, (hypo) manic symptoms, compulsive behaviour, depression, anxiety, hostility, or psychoticism have been observed to be more common if synthetic cannabinoids are used as compared to natural cannabinoids [89].

Moreover, Crane and co-workers [90, 91] reported on the background of earlier maturation of the female brain and gender-related differences in regional CB1 densities that the deficits in memory in rat studies were more pronounced in male rats. They assume that additionally ovarian hormones may enhance the association between cannabis use and cannabis-related stimuli. In humans, these authors found gender-related differences in the associations between age of onset of cannabis use and neuropsychological deficits [91].

Besides human studies, there are also animal experiments which support a negative effect of cannabis in adolescence on long-term development: in female rats, blockade of CB1 receptors from early to late adolescence seems to prevent the occurrence of pruning at glutamatergic synapses [92]. Other investigators found that adolescent exposure to THC in female rats resulted in impaired novel object recognition and reduced active social behaviour together with changes of selective histone modifications (H3K9me3) in the prefrontal cortex affecting the expression of genes involved in synaptic plasticity [93]. Interestingly, certain brain areas seem to react in a different manner to adolescent THC exposure: thus, in hippocampal postsynaptic fractions THC increased the expression of the NMDA receptor subunit GluN2B and of the AMPA subunits GluA1 and GluA2 and induced a persistent neuroinflammatory state with enhanced TNFa, iNOS, and COX2, while these alterations were not detectable in the prefrontal cortex [94]. In further support of these studies, chronic exposure to various cannabinoid agonists such as THC during adolescence, but not during adulthood, in rats of either gender was shown to induce long-term impairments in working memory [95–97]. THC exposure also impaired adolescent learning in male rats [98].

Other animal studies showed that THC exposure in adolescent rats altered in the prefrontal cortex those gene networks, which are related to cytoskeletal organization, cell morphogenesis, and dendritic development [99]. In addition, THC caused premature pruning of dendritic spines in early adulthood [99].

In another rat study, however, THC during adolescence did not produce robust alterations in adult behaviour after a period of abstinence, so that the authors concluded that the adverse effects, which are associated with adolescent cannabis use, might be due to non-cannabinoid concomitants of cannabis use [100]. On the other hand, it was also shown in rats that adolescent exposure to THC reverses the normal correlations between the endocannabinoids anandamide and 2-arachidonoglycerol in the nucleus accumbens (negative) and in the prefrontal cortex (positive) [101]. Taken together, most animal and clinical studies give evidence that adolescent exposure to THC leads to long-term changes with impairment of learning and social behaviour based on changes in the neurobiology of the prefrontal cortex, hippocampus, and nucleus accumbens.

Conclusion

It seems to make a difference whether an adult or an adolescent takes cannabis [102]. This difference appears to be based on the NGF-suppressing effect of THC due to the circumstance that NGF is involved in the complex adaption processes of the brain during puberty, and on changes in the BDNF pathway. Clinical and animal studies indicate that chronic cannabis use in adolescence may result in psycho-emotional deficits and may arrest the personality in a puberty-like state. However, not all individuals are affected in the same way, and there are large differences in the literature so that additional studies are needed to clarify which risk factors may contribute to a negative effect of cannabis use in adolescence.

Another important aspect in the discussions around cannabis is the fact that in today's cannabis and marijuana preparations the THC/CBD ratio is shifted to significantly higher THC content. Thus, studies from the seventies or eighties of the last century cannot be uncritically transferred to the actual situation, since at that time the THC content was much lower.

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