CHAPTER THIRTEEN

Effects of Cannabis and Cannabinoids in the Human Nervous System

Harold Kalant[1,2]
[1]Department of Pharmacology & Toxicology, University of Toronto, ON, Canada
[2]Centre for Addiction and Mental Health, Toronto, ON, Canada

1. INTRODUCTION

1.1. Definitions and Concepts

The term *cannabis*, when used without any further qualifying term, is generally understood to mean a crude preparation of the dried upper leaves and flowering tops of the plant *Cannabis sativa* or *Cannabis indica*. Such preparations, known by a variety of names such as marijuana, bhang, maconha in different countries and languages, have been used virtually worldwide for centuries or possibly millennia, for medicinal, ceremonial, and recreational purposes (Kalant, 1972; Russo, 2007). All of these uses are based upon the pharmacological actions of a group of substances called *cannabinoids*, of which the most important is Δ^9-tetrahydrocannabinol (THC), that are also responsible for most of the undesired or adverse effects of cannabis, regardless of the intended purpose for which it is used.

The definition of a cannabinoid was originally a chemical designation applied to a group of constituents of the cannabis plant that shared a common molecular structure thought to be characteristic of the cannabis plant, or were derived from such a structure (Joyce and Curry, 1970; Mechoulam, 1970). More recent evidence suggests that similar chemical structures may also be found in other plants than cannabis (Gertsch et al., 2010). It was formerly thought that the biological activity of cannabinoids depended upon their lipophilicity, which would enable them to exert a nonspecific action in the lipid phase of cell membranes, comparable to that of general anesthetics (Thomas et al., 1990).

However, in the late 1980s, two membrane-bound receptors were identified in mammalian tissues, through which the pharmacologically active cannabinoids exerted their actions, and which were therefore named *CB1 and CB2 cannabinoid receptors* (Devane et al., 1988; Bidaut-Russell et al., 1990; Svizenska et al., 2008). Endogenous ligands for those receptors were found shortly afterward, that were named *endocannabinoids*, and that do not share the same ring structure as the *phytocannabinoids* isolated from the cannabis plant. The two best-studied endocannabinoids are arachidonoyl ethanolamine (AEA, anandamide) and 2-arachidonylglycerol (2-AG), although many analogous N-acylethanolamides, including the palmitoyl, oleoyl, and stearoyl analogs (PEA, OEA, and SEA respectively), and arachidonoyldopamine are present in even larger amounts in the brain (Hansen, 2010;

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De Petrocellis and Di Marzo, 2009). In addition, virodhamine, an O-acyl analog of AEA in which the ethanolamine hydroxyl group is joined to the arachidonic carbonyl group in an ester linkage, was identified in rat brain and a number of peripheral tissues (Porter et al., 2002; Ottria et al., 2012). These endocannabinoids are synthesized enzymatically by specific lipases from lipoproteins in the cell membranes, act locally upon the receptors, and are then degraded by other enzymes in the immediate cellular vicinity. The whole complex of synthesizing enzymes, endocannabinoids, endocannabinoid receptors, and degradative enzymes is referred to as the *endocannabinoid system*. Finally, many entirely synthetic molecules have now been produced that are capable of binding to the cannabinoid receptors, or to the enzymes that produce or degrade the endocannabinoids.

As a result of these discoveries, the term *cannabinoid* is now defined functionally rather than chemically. It is applied to any molecule—phytocannabinoid, endocannabinoid, or synthetic analog—that can interact with components of the endocannabinoid system, whether as a receptor agonist, partial agonist or antagonist, or as an enzyme substrate or inhibitor. The term will be used in the latter sense in this review.

Although the actions of phytocannabinoids are exerted through the endocannabinoid system, the pattern of effects of cannabis as usually used, though similar to that of the endocannabinoids, is not identical and in some particulars even appears to be opposite. The possible reasons for the differences will be discussed in the course of this review. The shared basic mechanisms of action, as well as the differences, also underlie the actual and proposed therapeutic uses of cannabis and cannabinoids (Pertwee, 2009, 2012a), and the adverse effects that are commonly encountered in both medical and nonmedical use.

1.2 Structure and Orientation of the Chapter

The chapter begins with a brief overview of the endocannabinoid system and its roles in different functions of the nervous system. In relation to each of these functions, differences between the effects of the endocannabinoids and of exogenous phytocannabinoids will be indicated where knowledge permits. A proposed explanation for the differences will then be offered. The principal part of the chapter will be devoted to a review of the therapeutic and adverse effects of cannabis and pure cannabinoids in the human nervous system that will not include therapeutic recommendations or advocacy of specific policies.

2.1. ACTIONS AND EFFECTS OF ENDOCANNABINOIDS AND CANNABIS

2.1.1. Location and Functions of the Endocannabinoid System

Some of the components of the endocannabinoid system appeared early in the course of evolution, being found in a number of unrelated invertebrates (McPartland, 2004), but the presence together of all the components of the functional system may be limited to vertebrates (Elphick and Egertova, 2001).

Within the mammalian nervous system, CB1 receptors are very widely distributed, including most prominently the cerebellar cortex, hippocampus, basal ganglia, hypothalamus, amygdala, cerebral cortex, and spinal cord pain pathways (Pertwee, 2001; Egerton et al., 2006; McPartland et al., 2007). CB2 receptors are found in peripheral sensory neurons and some brainstem neurons, as well as in microglia, which are derived from macrophages (Kaur et al., 2001) but can influence the activity of adjacent neurons (Malan et al., 2002).

By far, the greatest part of the research on the endocannabinoid system has been done in rodents, but the regional and cellular distribution of CB1 receptors and of fatty acid amide hydrolase (FAAH), the enzyme which degrades anandamide, in human brain is in good general agreement with those in rat and monkey brain (Romero et al., 2002; Ong and Mackie, 1999). Therefore, it is a reasonable assumption that the endocannabinoid system in the human brain functions in much the same way as in the brains of rodents and other mammals.

More recently, other receptors that also bind endocannabinoids and mediate some of their physiological effects have been identified in mammalian brain and other tissues. A G-protein-linked enzyme designated as GPR55, and previously considered an "orphan receptor" found in substantial amounts in various parts of the brain, adrenals, small intestine and spleen, has been identified as a cannabinoid receptor (Pertwee, 2007; Rydberg et al., 2007). AEA, PEA, OEA and virodhamine bind to it as agonists at nanomolar concentrations, and even some phytocannabinoid and synthetic cannabinoid CB1 agonists bind more strongly to the GPR55 as agonists than they do to the CB1 receptor (Pertwee, 2007; Rydberg et al., 2007; Kreitzer and Stella, 2009). Perhaps even more importantly, cannabidiol (CBD) was found to bind strongly as an inhibitor to GPR55 (Rydberg et al., 2007). Another G protein-linked "orphan" receptor, designated GPR18, also appears to function as a cannabinoid receptor for the CBD analog o-1602 (Ashton, 2012; Console-Bram et al., 2012; McHugh, 2012), although the evidence is not uniformly consistent with this view (Lu et al., 2013).

Anandamide and N-arachidonoyldopamine also act as agonists at a transient receptor potential vanilloid-type one channel known as TRPV1 or vanilloid receptor 1 (De Petrocellis and Di Marzo, 2009). This is a calcium channel that is distributed very widely throughout the body, including sensory neurons, brain, epithelium, muscle, liver, bone, blood vessels, lymphocytes, and other cell types. In many of these cell types, the TRPV1 channels and CB1 receptors are found together, and interact in the regulation of cytosolic Ca^2 concentration.

The constituents of the endocannabinoid system have been shown repeatedly to be localized in synapses, in which the CB receptors are located in the presynaptic terminal. Impulse activation of the presynaptic terminal, with release of its neurotransmitter, activates the postsynaptic neuron, and Ca^{2+} influx together with membrane depolarization stimulate the production of endocannabinoids by postsynaptic enzyme action on membrane phospholipoproteins (Wang and Ueda, 2009). Anandamide and 2-AG are released

into the synaptic cleft and diffuse back to the presynaptic CB receptors. Combination with the receptors produces an inhibitory effect on the further presynaptic release of neurotransmitter. This occurs only in presynaptic terminals that have been activated; application of endocannabinoid to a resting terminal does not affect its subsequent release of neurotransmitter (Heifets and Castillo, 2009). The remaining free endocannabinoid is carried into the presynaptic terminal by a specific transporter, where anandamide is degraded by an FAAH and 2-AG by a monoacylglycerol lipase (Bisogno et al., 2001; Kano et al., 2009; Saturnino et al., 2010). The wide distribution of FAAH in the human central nervous system is similar to that of the cannabinoid receptors (Romero et al., 2002).

There is some evidence that cannabinoids such as CBD, which have biological activity but little or no affinity for either CB1 or CB2 receptors (though it is now known to act through the GPR55 and GPR18 receptors), as well as some of the newer synthetic analogs, may act on the enzymes that produce or degrade the endocannabinoids and thus alter the amounts available to act on the CB1 or CB2 receptors (Bisogno et al., 2001; Massi et al., 2008; Saturnino et al., 2010). However, Massi et al. reported that CBD stimulated FAAH activity and reduced anandamide content in glioma tumor tissue, whereas Watanabe et al. and Bisogno et al. reported that CBD inhibited FAAH activity in mouse brain microsomes and neuroblastoma cell membranes; the CBD concentrations used in these studies were fairly similar, but the tumor cell lines were different. THC and cannabinol, which do act on CB receptors, were also reported to inhibit FAAH (Watanabe et al., 1996), thus raising the possibility that the more active cannabinoids might act directly on their receptors as well as indirectly by altering the levels of free endocannabinoids.

The common functional effect of endocannabinoid action at most synapses is inhibition of release of neurotransmitter from the presynaptic terminal. This has been found in a variety of neurons that release different transmitters, some excitatory and others inhibitory. Among the transmitters found to be affected in the same manner are glutamate, gamma-aminobutyrate (GABA), glycine, acetylcholine, norepinephrine, dopamine, and serotonin (Pazos et al., 2005; Egerton et al., 2006; Katona et al., 2006; Moreira and Lutz, 2008; Kano et al., 2009). Therefore, the endocannabinoids function as modulators of other modulators, and the net effect upon any specific neuronal pathway may depend upon the balance of other modulatory inputs to that pathway that can be altered by the endocannabinoids. If 2-AG, for example, is acting primarily to inhibit release of glutamate, the result will be a depression of activity of the glutamate-stimulated neuron, whereas if it is acting primarily on GABA release, the net effect will be a disinhibition of the GABA-inhibited neuron (Freund et al., 2003; Moreira and Lutz, 2008). The process differs in various respects, however, in excitatory and inhibitory synapses (Heifets and Castillo, 2009). For example, anandamide is involved in synaptic plasticity of corticostriatal dopaminergic neurons, while 2-AG is involved in hippocampal glutaminergic neurons. The time requirement for co-occurrence of presynaptic activation and endocannabinoid

receptor occupation to produce LTD varies from milliseconds in somatosensory cortex to several minutes in hippocampus and dorsal striatum. Regardless of these and other mechanistic differences, the general role of endocannabinoids is essentially similar in synaptic plasticity changes in almost all parts of the brain.

These endocannabinoid effects on excitatory and inhibitory synaptic transmission constitute an important form of synaptic plasticity, defined as the ability of a synapse to exhibit adaptive modification of the postsynaptic response as a result of changes in presynaptic impulse frequency and in external stimuli (Alger, 2009). Synaptic plasticity is involved in such widely different functions as associative learning, control of motor function, tolerance, and sensory adaptation. Such adaptive changes can be of short or long duration. Depolarization-induced suppression of inhibitory transmission (DSI) and depolarization-induced suppression of excitatory transmission (DSE) are very rapid and short-lasting forms (Diana and Marty, 2004; Sheinin et al., 2008) that are induced by very brief presynaptic impulses, and appear to be mediated entirely by the retrograde endocannabinoid signaling within the synapse. Repeated or tetanic presynaptic neuronal excitation, on the other hand, gives rise to long-term potentiation (LTP) or long-term depression (LTD) that probably involves additional mechanisms such as altered expression or activation of the enzymes that produce or degrade the endocannabinoids, and altered responsiveness of the CB receptors (Zhu, 2006; Heifets and Castillo, 2009).

Another potential source of endocannabinoid response variation is the existence of extrasynaptic receptors. GABA activation of $GABA_A$ receptors located intrasynaptically gives rise to short-lasting phasic inhibition, whereas action on extrasynaptic receptors gives rise to tonic inhibition (Farrant and Nusser, 2005). Sigel et al. (2011) have reported a direct effect of 2-AG upon certain extrasynaptic GABA receptors that results in potentiation of the inhibitory response to GABA. However, the concentration of 2-AG required for this effect was in the low micromolar range, and a similar concentration of THC did not produce GABA potentiation. Mice lacking CB1 and CB2 receptors showed hypomotility when injected with 2-AG (10 mg/kg intra-venous), but mice lacking these extrasynaptic-type GABA receptors showed hypermotility. These 2-AG concentrations and doses are very high in comparison with concentrations and dosages of THC used by humans. It is therefore not yet clear whether direct action of endocannabinoids on GABA receptors plays a role in the effects experienced by humans.

An additional level of modulation of endocannabinoid action is provided by the presence of allosteric binding sites on the cannabinoid receptors (Console-Bram et al., 2012). These are sites at which molecules other than endocannabinoids may bind and, in so doing, may produce conformational changes in the receptor that alter the binding affinity and efficacy of the principal or orthosteric binding site for the endocannabinoids. Allosteric modulators may be purely synthetic (Price et al., 2005) or endogenous molecules (Bauer et al., 2012; Pamplona et al., 2012; Pertwee, 2012b). Conversely, classical endocannabinoids can act as allosteric modulators of receptors for other transmitters or

modulators. For example, 2-AG has been reported to be a negative allosteric modulator of the A3 adenosine receptor (Lane et al., 2010). The effects of allosteric modulators on the cannabinoid receptors are specific for both the receptor type and the intracellular signaling cascade through which the actions of the receptor are mediated (Anavi-Goffer et al., 2012). Therefore, they raise the possibility that this approach may yield highly selective agents for therapeutic modulation of very specific effects of cannabinoid therapy while minimizing the risk of unwanted side effects.

Three further points are important for any comparison of the endocannabinoid system with the effects of cannabis and phytocannabinoids in humans. The first is the fact that release of endocannabinoids is an "on-demand" process that occurs when the postsynaptic neuron is activated by the binding of the neurotransmitter with its postsynaptic receptor. The resulting depolarization, together with Ca^{2+} entry, mainly triggers the rapid synthesis and release of newly formed endocannabinoid, although there is also some evidence that "on-demand" release of preformed endocannabinoid from some unidentified pool may occur (Basavarajappa, 2007; Bisogno and Di Marzo, 2007; Min et al., 2010; Alger and Kim, 2011). In either case, this type of "on-demand" release is rapid, short-lasting, and optimally suited for immediate response to temporary environmental and physiological stimuli (Moreira and Lutz, 2008). Long-lasting changes in endocannabinoid tonic function that are involved in such processes as learning and memory appear to be mediated by changes in receptor response and in expression and activity of endocannabinoid synthesizing and degrading enzymes (Alger and Kim, 2011).

The second, and related, point is that rapid on-demand synthesis and release implies that the amounts of endocannabinoid involved in normal regulation of synaptic function are relatively small. If the CB receptors are exposed to much larger amounts over longer periods, a state that has been referred to as "overload" (Lichtman et al., 2010), it results in desensitization and downregulation of CB1 receptors. Acute inhibition of monoacylglycerol lipase greatly increased the brain levels of 2-AG and resulted in exaggerated CB1-induced behavioral and physiological effects, including analgesia, hypothermia, and hypomotility (Kinsey et al., 2009). In contrast, genetic knockout of the enzyme in mice produced chronically elevated levels of 2-AG but unchanged or decreased behavioral responses, because of CB1 desensitization (Chanda et al., 2010). Since cannabis and its contained THC produce longer-lasting effects than the very short effects of on-demand endocannabinoid release, it has been suggested that they are more likely to result in overload phenomena that may be related to some of their adverse effects. For example, Sarne et al. (2011) suggested that dose-related overload may convert neuroprotective effects of THC into neurotoxic effects. Similarly, the facilitation of extinction learning by the CB1 agonist WIN 55,212-22, involving LTP of synaptic transmission in the prefrontal cortex, hippocampus, and amygdala, changes to an impairment of extinction learning when the same agonist is given chronically (Kaplan and Moore, 2011). This point will be discussed further below.

The third point is that the vast bulk of research literature on cannabinoids and synaptic plasticity deals with the endocannabinoids. There is remarkably little literature on the effects of cannabis, phytocannabinoids and other exogenous CB ligands in relation to synaptic plasticity. Liu et al. (2010) examined LTP in glutamate synapses on dopaminergic neurons in the rat brain ventral tegmental area (VTA). A single exposure to THC or to HU210, a synthetic CB1 agonist, did not produce LTD in those synapses, but after five daily injections there was a transient depression of the excitatory neurotransmission. Robbe et al. (2003) similarly studied LTD in tetanically stimulated glutamate synapses of afferent fibers from the prefrontal cortex to the nucleus accumbens of the mouse, as well as in GABA synapses. Both the excitatory and the inhibitory synapses showed LTD development that was mediated by endocannabinoids. However, application of an exogenous CB1 agonist, WIN-51,221, markedly decreased excitatory transmission, but also blocked the development of endocannabinoid-mediated LTD.

Koch et al. (2009) studied the effect of Sativex®, a standardized cannabis extract containing equal concentrations of THC and CBD, on LTP and LTD as represented by sustained increase or decrease, respectively, in motor cortex evoked potentials in human subjects. Transcranial theta burst stimulation (TBS) was used to produce the LTP and LTD: continuous TBS produced LTD, whereas intermittent TBS produced LTP, in the absence of any cannabinoid treatment. After four weeks of daily Sativex treatment, the LTP phenomenon was unaltered, but the LTD was replaced by increase in the amplitude of the evoked potentials, i.e. by an apparent LTP. The authors referred to this as a "shift in the polarity of synaptic plasticity", but correctly pointed out that it was not certain that the change was caused by the drug treatment, or that the changes in evoked potential amplitude produced by TBS really are the same phenomenon as endocannabinoid-dependent synaptic plasticity. It should be noted that once again the effect of exogenous cannabinoids was seen only after chronic treatment.

2.1.2. Neuronal Proliferation and Maturation

Synaptic plasticity, though an important mechanism of adaptation in the nervous system, is not the only one. Important long-term adaptations may involve the production of new neurons from neural stem cells that are found in the ventricular ependyma and subependyma and in the hippocampus of the adult brain (Morshead and Van der Kooy, 2001; Wolf and Ullrich, 2008; Oudin et al., 2011). Proliferation, differentiation, and migration of these cells to their ultimate locations in other sites in the brain are believed to play an important role in the formation of new memory circuits and in repair of neuronal damage. Endocannabinoids have been shown to initiate and stimulate proliferation and migration of neural stem cells (Molina-Holgado et al., 2007; Rubio-Araiz et al., 2008; Wolf and Ullrich, 2008; Galve-Roperh et al., 2009; Oudin et al., 2011). In contrast, anandamide was found to inhibit the differentiation of the stem cells into mature neuronal phenotypes (Rueda et al., 2002), but differentiation did occur when the diacylglycerol lipases that synthesize

2-AG were sharply downregulated (Walker et al., 2010). Thus, endocannabinoids stimulate proliferation of neural stem cells and their migration to end locations, but differentiation does not occur until a different controlling factor, possibly glutamatergic, takes over.

No comparable studies of the effects of exogenous cannabinoids on neural stem cell proliferation, migration, or differentiation could be found. However, there are numerous publications concerning the effects of cannabis or cannabinoids on other aspects of neural maturation in the fetus and the adolescent, both human and nonhuman. The effects of intrauterine exposure to cannabis or single cannabinoids on morphological and functional development of the rat brain from infancy to adulthood have been described in several comprehensive reviews (Dalterio, 1986; Campolongo et al., 2009a,b). Prenatal exposure gave rise to impairments in cognitive and locomotor functions and emotionality that were evident when the offspring reached adulthood.

For obvious reasons, it is not possible to study the effects of in utero exposure on brain morphology in humans in the same detail as is possible in laboratory animals, and alterations of brain development in the humans must to a considerable extent be inferred from functional alterations. Developmental studies in humans exposed to cannabis in utero have been in continuous progress for many years (Fried et al., 2003; Goldschmidt et al., 2000; Richardson et al., 2002; Smith et al., 2010). These studies have shown mild but persistent changes in memory, problem solving, attention, and impulsivity that are suggestive of maturational defects in the brain.

It has been known for many years that adolescent rats are more sensitive to brain developmental disturbances by exposure to cannabis than adult rats are. Prepubertal rats exposed to a limited period of cannabis administration, and then studied after prolonged abstinence, showed long-lasting deficits in learning and memory, as well as increased anxiety behaviors, that persisted into adulthood (Fehr et al., 1976; Stiglick and Kalant, 1982), whereas rats receiving the same exposure as young adults did not develop these alterations (Stiglick and Kalant, 1985; O'Shea et al., 2004). These findings raise the possibility that during brain maturation in adolescence, heavy exposure to cannabis might prevent the growth of axons and the establishment of large numbers of synaptic connections that normally accompany experience and learning. It is necessary to avoid untested generalizations, however. After the same drug exposure and testing schedule as in the circular maze experiments, rats that were exposed to cannabis as adults showed faster shuttle-box avoidance learning than placebo-treated controls (Stiglick and Kalant, 1985), but it is not possible to say whether this represented improved learning or hypersensitivity to footshock.

Possible support for this interpretation is provided by the results of MRI studies of the brains of late teen-aged males who had used cannabis heavily throughout adolescence. Wilson et al. (2000) reported smaller overall brain size and thinner cortex in early heavy users than in age-matched users who did not begin until after age 17. Lopez-Larson et al. (2011) similarly found significant cortical thinness in frontal cortex and insula, compared to matched nonusers, and the degree of thinning appeared to be greater, the earlier

the age of onset of heavy use. In similarly matched groups of late teenagers, Ashtari et al. (2009) found altered frontal–temporal connections (arcuate tract) in early-onset users compared to nonusers; this tract was among areas that they had previously found to undergo substantial maturational change during adolescence. Hermann et al. (2007) compared a group of young adult cannabis users (mean age 20 ± 2 years) who had begun cannabis use at about 16 years of age with a matched group of nonusers, with the respective status confirmed by hair analysis for THC and CBD. Tests of attention, memory and short-term auditory memory were significantly impaired in the user group, and spectroscopic magnet resonance imaging of the brain revealed evidence of a reduced neuronal and axonal integrity (reduced ratio of N-acetylaspartate to total creatinine) in the prefrontal cortex of the users. Unfortunately, the age of first use of cannabis is low enough that it is not possible to be sure whether the observed effects were due to impaired maturation or to chronic toxicity that might occur at any age. A similar relation between age of onset of cannabis use and alteration of cerebral circulation has been observed.

It has been suggested by various authors (e.g. Galve-Roperh et al., 2009; Bossong and Niesink, 2010; Caballero and Tseng, 2012) that impaired brain maturation caused by cannabis use during early adolescence may constitute the neurological basis for later onset of schizophrenia. This point will be pursued below in relation to specific disturbances of neuronal function.

2.1.3. Neuroprotection

One of the widely studied effects of cannabinoids is their neuroprotective effect, i.e. the ability to prevent or decrease the severity of brain damage caused by a variety of circulatory, mechanical, metabolic, or toxic injuries. Both CB1 and CB2 receptors contribute to this protective effect. For example, CB1 receptor knock-out mice show increased severity, both anatomical and functional, of ischemic stroke than wild type littermates (Parmentier-Batteur et al., 2002). There is a very large body of recent literature, including numerous excellent reviews, concerning the nature and mechanisms of the neuroprotective actions of the endocannabinoid system in both human brain diseases and experimental animal models. Some reviews have concentrated on specific groups of brain diseases in which endocannabinoids have been reported to be potentially useful, including cerebrovascular occlusion and reperfusion (Zhang et al., 2009; Alonso-Alconada et al., 2010, 2011), traumatic brain damage (Shohami et al., 2011), neuroinflammatory diseases (Eljaschewitsch et al., 2006; Zhang et al., 2009; Kubajewska and Constantinescu, 2010) and neurodegenerative conditions such as Parkinson, Huntington and Alzheimer diseases (Palazuelos et al., 2009; Scotter et al., 2010; Fernandez-Ruiz et al., 2011). Other reviews have concentrated principally on the molecular mechanisms by which endocannabinoids can exert neuroprotective action, such as prevention of excitotoxicity (Marsicano et al., 2003), immunomodulation, (Bisogno and Di Marzo, 2010) and combinations of multiple mechanisms (Eljaschewitsch et al., 2006).

Despite their somewhat different orientations, these reviews give a very consistent picture of the neuroprotective action of endocannabinoids, and of the numerous elements of which it consists. These include, among others:

- inhibition of glutamatergic afferents, with resulting prevention of excitotoxicity
- inhibition of MAP kinase-induced and tumor necrosis factor α-induced inflammatory responses by microglia and macrophages to brain tissue injury that result in aggravation of the damage
- antioxidant action of phenolic groups against reactive oxygen species (ROS), and decreased formation of ROS by monoamine oxidase, cyclooxygenase, etc., under influence of nitric oxide, $Ca^{2+}$and other factors in injured brain tissue
- decreased neuronal activity, produced in part by hypothermia (Leker et al., 2003), resulting in decreased metabolic requirements, with consequent reduction of damage during hypoxia and glucose deficiency.

The changes have been described in brain tissue of humans dying of the various diseases mentioned, as well as of animals with experimental models of these diseases (Scotter et al., 2010). Endocannabinoid levels are increased in injured brain tissue, as well as in animals subjected to intense excitatory brain stimulation by kainic acid (Marsicano et al., 2003), possibly as a defensive reaction to the injury. Both CB1 and CB2 receptors affect residual damage in different ways. There is less information about the role of CB2 receptors in neuroprotection, and the existing information is somewhat confusing. The protective action of CB2 agonists appears to consist mainly of anti-inflammatory activity, whereas that of CB1 agonists is to a considerable extent due to hypothermia. In keeping with that interpretation, maximum protection against ischemia/reperfusion damage was reported to occur with a combination of CB2 agonist and CB1 antagonist (Zhang et al., 2008). A further problem with CB1 agonists is that at doses giving maximum neuroprotection they produce psychoactive effects that would be undesirable side effects in the presence of brain injury. Inhibition of FAAH has been proposed as a more selective manner of achieving the same protective action without the undesired psychoactivity (Hwang et al., 2010).

THC, CBD, HU-210, dexanabinol (HU-211), ajulemic acid (HU-239) and numerous other synthetic cannabinoids also exert neuroprotective activity similar to that of the endocannabinoids in experimental models. The protective effect of CBD is not exerted through either CB1 or CB2 receptors, but a 5-HT_{1A} receptor blocker prevented the protective effect of CBD on infract size and cerebral blood flow (Mishima et al., 2005). This raises the possibility, but does not prove, that CBD acts as a 5-HT receptor agonist. A further point of interest about the neuroprotective effect of CBD is that the intensity of effect at first increased with increasing dose, reached a maximum, and then decreased and finally disappeared with further increases of dose. This is reminiscent of the endocannabinoid "overload" described in Section 2.1 above.

The duration of neuroprotective activity with repeated administration of cannabinoids is a matter of potential importance with respect to the possibility of clinical use. In the mouse model of ischemic stroke produced by middle cerebral artery occlusion, daily administration of THC for 14 days resulted in desensitization and downregulation of CB1 receptors, and the beneficial effects of THC on body temperature, cerebral blood flow, and infarct size were markedly reduced; this did not happen with CBD (Hayakawa et al., 2007).

Crude cannabis preparations do not appear to have been tested for their neuroprotective effect. Moreover, despite the promising results with individual cannabinoids in preclinical studies, there is virtually no literature on clinical trials. One study with dexanabinol (Knoller et al., 2002), consisting of a Phase II trial in patients with severe closed head injury, showed promising results in that intracranial pressure was promptly reduced in the dexanabinol group but not the placebo group, the cerebral perfusion pressure was significantly better, and the 3- and 6-month total outcome was superior to that in the placebo group. However, no Phase III trial has so far been reported.

In contrast, there is also evidence of neurotoxic effects of exogenous cannabinoids such as THC and WIN55,212-2 when added to neuronal cultures or injected into the cerebral ventricles, or when administered together with ethanol (Fowler et al., 2010). The toxic effects were produced at higher cannabinoid concentrations than those required to activate CB receptors in their physiological functions. The question of possible neurotoxic effects of cannabis in heavy users will be taken up further below.

2.1.4. Sensory Pathways

2.1.4.1. Olfactory

Sensory detection of odors occurs via G-protein-linked receptors found in the nasal mucosa, as well as in other parts of the olfactory tract. CB1 receptors and TRPV1 receptors, as well as other components of the endocannabinoid system, are also found in a variety of locations in peripheral and central sensory pathways, including the olfactory pathway. Therefore, it seems likely that cannabinoids affect olfactory sensation (Lötsch et al, 2012). Indeed, Walter et al. (2011) did report that THC increased odor threshold for vanillin and decreased odor discrimination in healthy normosmic humans. However, effects on sensory impulse transmission are varied. In the olfactory pathway, for example, 2-AG has been found to influence odor detection differently in hungry vs sated *Xenopus* larvae. In the hungry larvae, the activity of 2-AG synthesizing enzymes is increased, and 2-AG levels in the sensory epithelium are increased. The result is a reduced threshold for olfactory stimulus detection, which is thought to help the larvae detect and locate food (Breunig et al., 2010). In contrast, 1 μM THC inhibited excitatory evoked potentials in the rat olfactory cortex, whereas cannabis extract with the THC removed had a stimulatory effect (Whalley et al., 2004). However, neither THC (doses up to 10 mg/kg) nor the FAAH inhibitor URB-597 affected the acquisition or the performance of an olfactory discrimination task in intact rats (Sokolic et al., 2011). Both drugs did impair

performance after reversal of the cues; this is interpreted as an impairment of learning rather than of the sensory modality itself.

2.1.4.2. Auditory

The endocannabinoid 2-AG appears to play a similar role in the avian and murine auditory systems as in the other neuronal pathways already discussed. Released postsynaptically, it acts on presynaptic CB1 receptors located primarily on activated glutamatergic terminals to reduce the release of glutamate (Penzo and Pena, 2009; Zhao et al., 2009; Sedlacek et al., 2011). Since the postsynaptic cells involved are inhibitory, the result of the endocannabinoid effect on them is disinhibition of the principal cells of the cochlear nucleus; the end result is not related to auditory acuity, but to perceptual localization of the source of a sound.

Auditory gating is the process by which irrelevant stimuli are filtered out, permitting attention to be focused on the relevant ones in a given situation. This can be studied in humans and in rodents by electroencephalographic recording of the evoked responses to a conditioned tone paired with a confounding tone. The ratio of the two responses is a measure of the efficacy of gating. The synthetic cannabinoid agonist WIN55,212-2 disrupted gating, and its effect was prevented by prior administration of the CB1 antagonist SR141716A (Dissanayake et al., 2008). Impairment of sensory gating has been found repeatedly in schizophrenic patients, and it has been suggested that this action of cannabinoids might be a mechanism contributing to the precipitation of schizophrenia (Hajós et al., 2008).

A possibly related phenomenon is the auditory evoked mismatch negativity, which is a negative wave in the EEG evoked by the unexpected introduction of a discordant auditory stimulus into a train of repeated stimuli. Impairment of mismatch negativity is interpreted as a deficit in attention to one's environmental stimulus input, and is also seen in schizophrenic subjects. In healthy human subjects, the mismatch negativity was impaired by rimonabant, a CB1 antagonist (Roser et al., 2011), which suggests that the endocannabinoid system normally contributes to the production of the negativity. In chronic heavy cannabis users, in contrast, the mismatch negativity recorded from frontal electrodes was significantly reduced in comparison to occasional light users and nonusers (Roser et al., 2010; Rentzsch et al., 2011). In contrast, among schizophrenic patients, those who used cannabis regularly had greater mismatch negativity than those who did not use (Rentzsch et al., 2011); this might be indicative of cannabis use as self-medication by some schizophrenic patients.

In contrast to the olfactory studies mentioned in Section 2.4.1, a similarly designed auditory discrimination task, once learned, was clearly impaired by THC and by URB-597, but unaffected by the CB1 antagonist rimonabant (Sokolic et al., 2011). THC and URB-597 also impaired performance of the auditory task after cue reversal. It is not clear whether the adverse effect of THC and of endocannabinoid on performance of the learned discrimination represents an effect on auditory perception or on choice of the appropriate response. The absence of an effect of rimonabant alone also

suggests that the endocannabinoid system is not essential for maintenance of normal test performance, and therefore raises the possibility that the adverse effect of THC and URB-597 is again an "overload" phenomenon.

2.1.4.3. Pain

As noted earlier, the constituents of the endocannabinoid system are found in abundance along the pain pathways in the dorsal horns of the spinal cord, as well as in the thalamus, dorsal raphe nucleus, and the periaqueductal grey matter (Pertwee, 2001; Bushlin et al., 2010). In experimental models of neuropathic pain, osteoarthritis, endometriosis, and other causes of chronic pain, the concentrations of CB1 receptors as well as of endocannabinoids and their synthesizing enzymes in the spinal and supraspinal pain pathways are increased (Petrosino et al., 2007; Dmitrieva et al., 2010; Sagar et al., 2010). Administration of CB1 agonists, or inhibition of FAAH, reduced pain responses more in animals with chronic pain than in healthy controls (Sagar et al., 2010). CB2 receptors, which were formerly thought to exist essentially in peripheral nonneural tissues, are now known to be present also in peripheral sensory nerves and in parts of the central pain pathways (Anand et al., 2009). CB2-selective agonists have produced analgesia or reduction of hyperalgesia in models of neuropathic and inflammatory pain. There is extensive anatomical overlap of the opioid and cannabinoid receptor systems, and it appears probable that functional interactions between them occur in the production of analgesia.

The analgesic effect of THC and other exogenous cannabinoids, as well as of standardized cannabis extract containing both THC and CBD, has been well demonstrated in humans suffering from chronic neuropathic pain, cancer pain, and chronic musculoskeletal pain. A very thorough review of all clinical trials involving smoked cannabis, oral cannabinoids of CB1 and CB2 specificity, and modulators of endocannabinoid metabolism in the treatment of neuropathic pain concluded that all forms of cannabinoid therapy appear to provide some degree of relief of pain, though CB1 agonists produce significant side effects due to their psychoactivity (Rahn and Hohmann, 2009). Ware et al. (2010a,b) have also reported modest relief of chronic neuropathic pain by low-dose smoked cannabis, which also provided improved sleep and only minor side effects.

Cannabinoids have not shown satisfactory analgesic effect against acute pain such as postsurgical pain, and in this respect they are less versatile as analgesics than morphine and other strong opioids. However, there is some clinical support for the utility of combined therapy with cannabinoids and opioids in the treatment of chronic pain (Narang et al., 2008; Elikottil et al., 2009) as a way of obtaining superior analgesia with reduced side effects of each drug. The comparability of analgesic effects of cannabinoids in animal models of chronic pain and human patients gives no evidence for endocannabinoid overload in this action.

2.1.5. Nausea

Nausea and vomiting are initiated by the coordinated interaction of a number of subnuclei of the nucleus of the tractus solitarius in the medulla oblongata, where afferent information from brainstem chemoreceptors, vagal afferent fibers from the stomach and intestine, gustatory and vestibular inputs, and descending fibers from the cerebral cortex is integrated (Hornby, 2001). The dorsal vagal complex contains neurons with CB1 receptors, which are inhibitory and 5-HT_3 receptors, which are excitatory to the vagal afferent fibers that activate the integrated emetic process. Thus, it is a site at which CB1 agonists and 5-HT_3 antagonists can exert antiemetic and antinauseant effects.

An animal model of chemically induced nausea in the rat, which lacks the neural organization for vomiting, is a mouth-gaping response and posture that is produced by stimuli that evoke nausea in humans. This response, produced by cisplatin or lithium in the rat, is alleviated both by 5-HT_3 antagonists such as ondansetron and granisetron, and by CB1 agonists such as THC, anadamide and WIN55,212-2 (Parker and Limebeer, 2006). GPR55 receptors are also found in this region, but there is not yet sufficient evidence to permit a conclusion as to whether they also participate in control of the nausea response (Schicho and Storr, 2012). Both in this rat model and in humans, however, nausea and vomiting due to cancer chemotherapy or to HIV drugs is controlled by lower doses of ondansetron and related drugs than of THC, which in turn is better than the older phenothiazine antinauseants (Söderpalm et al., 2001; Machado Rocha et al., 2008). The effect of THC cannot be improved by raising the dose because the psychoactive side effects are too troubling to many patients, especially older patients who have not previously used cannabis for nonmedical purposes. However, the combination of lower doses of ondansetron and a CB1 agonist might give a superior effect with fewer side effects (Parker and Limebeer, 2006).

2.1.6. Appetite and Food Intake

Perhaps not surprisingly, regulation of appetite and food intake involves many of the same nervous system structures that regulate nausea and vomiting. Excellent reviews are available (Fride et al., 2005; Capasso and Izzo, 2008). As in the case of nausea, endocannabinoids participate in all the peripheral and central components that converge on the dorsal vagal nucleus. Vagal afferents from the gastrointestinal tract carry information indicating the presence of food, which tends to inhibit further food intake. Endocannabinoids inhibit these vagal fibers and thus tend to promote further eating. Centers in the hypothalamus similarly convey information to the hindbrain about the chemical composition of the blood as affected by the ingested food. The limbic system provides information about the sensory qualities of the food ("pleasing" or "displeasing"), and cerebral cortical inputs convey information about environmental context that may affect the act of consuming food. All of these separate inputs are integrated in the hindbrain dorsal vagal nucleus and the hypothalamus. The net effect of CB1 agonists is typically to promote food intake, and of CB1 antagonists to decrease or inhibit food intake.

There is a selective interaction with different dietary constituents. In sham-feeding experiments, in which the ingested food exits via a gastric cannula so that only its orosensory effects are in play, administration of a fatty diet stimulated endocannabinoid production in the rat small intestine, whereas carbohydrate or protein meals did not (DiPatrizio et al., 2011). Conversely, infusion of the CB1 antagonist rimonabant into the jejunum reduced the sham-ingestion of a fatty meal but not of normal chow. These effects were shown to involve only the local CB1 receptors on neurons of the enteric plexus. In both rats and humans, administration of THC, anandamide, or 2-AG causes hyperphagia and weight gain, which is blocked by rimonabant, and fasting increases the levels of anandamide and 2-AG in the Nucleus accumbens and hypothalamus as well as in the small intestine (Capasso and Izzo, 2008). Obese humans have presumably chronically increased activity of the intestinal endocannabinoid system, and administration of CB1 antagonists reduces food consumption and body weight (Bermudez-Silva et al., 2010). The availability of selective agents that act only in the periphery may make future therapeutic use possible in the treatment of obesity, without the dangerous depression and suicide risk that resulted in the termination of such use of rimonabant.

Fride et al. (2005) make a fascinating connection between the endocannabinoid actions in the newborn and in the adult. In the newborn, the binding of endocannabinoids to CB1 receptors promotes an early postnatal commencement of suckling. This is inhibited by CB1 antagonists such as rimonabant, if given within the first 24 h after birth. The only food the suckling response provides is maternal milk, which has a complete balance of the necessary nutritional factors for infant survival and growth. Thus, the "pleasing" gustatory quality of the food works in harmony with the intestinal appetite stimulus and the motor response of suckling to maximize the protective effect on the infant. In contrast, in the adult, the pleasing sensory qualities of experiencing the effects of the food cause the ingestion-stimulating effect of cannabis and CB1-linked cannabinoids to be directed toward high-sugar and high-fat snack foods. Thus, the weight gain produced by cannabis or THC in cachectic patients leads to weight gain associated with fat deposition in adipose tissue, rather than to protein synthesis and tissue regeneration, and superior effect has been reported with megestrol acetate than with dronabinol (Bruera, 1992; Tchekmedyian et al., 1992; Jatoi et al., 2002). However, these comparisons were carried out before the advent of newer more selective cannabinoid agents that might permit the use of higher dosage without the adverse psychoactive effects of CB1 agonists.

2.1.7. Sleep

Cannabis has a long history of use as a sedative and hypnotic medication. The earlier literature concerning the effects of cannabis, THC, and other exogenous cannabinoids on sleep patterns in the rat and human has been reviewed recently by Arias-Carrión et al. (2011). The major effects observed were increased slow-wave sleep and REM sleep and reduced waking time. These were later shown to be essentially the same as the effects of anandamide (Mechoulam et al., 1997; Murillo-Rodríguez et al., 1998) and opposite

to those of the CB1 antagonist SR141716A (Santucci et al., 1996). Later research has shown the effects of activation and inhibition of the synthesizing and degrading enzymes and the membrane transporter of anandamide, as well as its downstream intracellular signaling mechanisms, to be fully consistent with the cannabinoid effects mentioned above.

There appears to be a reciprocal interaction between the endocannabinoid system and sleep (Chen and Bazan, 2005). Anandamide and 2-AG undergo reciprocal cyclic changes in concentration in rat brain during the light and dark phases of the diurnal cycle (Valenti et al., 2004). This pattern was disrupted by prolonged sleep deprivation, especially of REM sleep, which resulted in increased levels of 2-AG in the hippocampus but no change in anandamide. These changes were accompanied by disruptions of synaptic plasticity and hippocampal memory processes. Such changes in function as a result of sleep deprivation serve to confirm the role of the endocannabinoid system as a regulator of these functions in the normal state.

Other cannabinoids such as nabilone and Sativex® also improve the subjective qualities of sleep in patients with painful or other sleep-disturbing illnesses (Russo et al., 2007; Ware et al., 2010a,b). Tolerance to these effects on sleep is said not to occur with prolonged use of cannabis preparations; this is somewhat surprising, given the "overload" phenomena, receptor desensitization and response alterations seen with other effects of cannabinoids noted above, and deserves further study.

2.1.8. Affective Responses

Cannabinoid effects on affective responses have been studied most extensively in relation to depression and to anxiety and stress (Ashton and Moore, 2011). Numerous studies have indicated a mood-elevating and antidepressant activity of the endocannabinoid system. FAAH knockout mice, which have elevated brain levels of endocannabinoids, also had higher baseline serotonergic activity in the frontal cortex and showed less anxiety in the open-field test and greater social interaction than the normal controls (Cassano et al., 2011). The CB1 antagonist rimonabant abolished the difference in behavioral patterns, and also abolished the serotonin response to stimulation of the cortex and hippocampus, which appears to be an important locus of endocannabinoid modulation in affective responses (Haj-Dahmane and Shen, 2011). Inhibition of endocannabinoid synthesis in rats produces immobility in the forced swim test, which is regarded as depression-like behavior. In contrast, the CB1 agonist WIN55,212-2 exerts antidepressant-like behavior, which is abolished both by rimonabant and by serotonin depletion before the test (Bambico et al., 2007; Mangieri and Piomelli, 2007; Gorzalka and Hill, 2011). These changes are to some extent paralleled in humans by low circulating levels of endocannabinoids and reduced CB1 receptor activity in depressed patients, and the production of depression and risk of suicide in human patients receiving rimonabant for the treatment of obesity (Lazary et al., 2011).

In contrast to these antidepressant effects of the finely adjusted actions of the endocannabinoid system, high doses of cannabis in humans appear to increase the risk of depression, especially in the young (Ashton and Moore, 2011). Daily administration of WIN55,212-2 to adolescent rats for 20 days produced depression-like effects in behavioral tests and electrphysiological evidence of decreased serotonergic activity, whereas the same treatment did not produce such results in adult rats (Bambico et al., 2010). Population studies in several countries have yielded similar observations of increased risk of later onset of depression in adolescents who began regular use of cannabis before the age of 14–15 (Kalant, 2004), though the nature of the link is still not wholly clear (Degenhardt et al., 2003, 2007; Hall and Degenhardt, 2009). Despite this uncertainty, the fact that cannabis use did not exert an *anti*depressant action in these heavy users implies some difference from the endocannabinoid actions described above, such as receptor desensitization, for example.

The effects of cannabinoids on anxiety, fear, and stress-related affective reactions have also received much attention in the clinical and research literature. As is well known, the acute application of a stressor to a normal organism elicits sequential release of hypothalamic corticotrophin-releasing factor (CRF), pituitary adrenocorticotropic hormone (ACTH), adrenal corticosteroid that produces metabolic adaptations throughout the body, assisting in the response to stress. This sequential response is in part initiated by the endocannabinoid system, through a rapid increase in FAAH activity, thus reducing the amount of anandamide acting on glutamatergic terminals. The resulting disinhibition of glutamatergic stimulus greatly increases the tonic activity of the hypothalamic–pituitary axis (Hill et al., 2010) The released corticosteroid completes a feedback circuit by activating corticosteroid receptors both in the hypothalamus and in the medial prefrontal cortex (mPFC) that sharply reduce ACTH secretion when the stressor has been removed. The response to activation of these glucocorticoid receptors also involves the endocannabinoid system. Local application of a CB1 receptor antagonist to the rat mPFC delays the termination of ACTH secretion after the end of the stress, and mice lacking CB1 receptors also show a prolonged secretory response (Hill et al., 2011).

Activation of the endocannabinoid system also influences the affective components of the stress response, and stress-associated memory and conditioning, as well as initiating stress-associated analgesia (Finn, 2010). Stress-induced analgesia is mediated by activation of a descending inhibitory pathway that modulates transmission in the ascending pain pathway (Vaughan, 2006; Butler and Finn, 2009). This process involves endocannabinoid receptors on both glutamatergic and GABAergic synapses, at various levels in the brain and spinal cord, as well as interactions between the endocannabinoid and the endogenous opioid systems. It seems probable that stress-induced analgesia is generated at the same points as the cannabinoid-induced analgesia described in Section 2.4.3, and that stress is simply one of a number of factors that can activate the same pathways.

Other parts of the stress response include fear as an acute reaction (Marsicano et al., 2002), and anxiety and depression as components of chronic or repeated stress reactions. CB1 receptors are present in high concentration in the amygdala, hippocampus, and cortex, and many studies have observed altered emotionality as a result of activation or blockade of these receptors. Mutant mice lacking them, and rats subject to pharmacological blockade of them, show anxiety-like and depression-like patterns of behavior on a variety of tests, together with reduced basal secretion and reduced responsiveness of the adrenal cortex (Viveros et al., 2005). CBD, though not a CB1 agonist, can affect anxiety through other sites of action on the endocannabinoid system. Crippa et al. (2004, 2011) attempted to localize the site of the anxiolytic action of CBD in the human brain by studying changes in regional cerebral blood flow in normal subjects and in patients with generalized social anxiety disorder. In a double-blind placebo-controlled crossover study, CBD produced a reduction in anticipatory anxiety in the healthy subjects and in subjective anxiety ratings in the patients (relative to placebo), and also reduced blood flow in the hippocampus, left parahippocampal gyrus and inferior temporal gyrus. However, there was no correlation between the anxiety ratings and the magnitude of changes in blood flow.

Localization at such a macrostructural level is difficult to interpret when one considers the functional differences of endocannabinoid activity in substructures only millimeters apart. For example, the acquisition of conditioned fear responses in rats and mice depends on the level of endocannabinoid signaling in different parts of the amygdala: acute blockade of CB1 receptors in the central amygdala greatly increased conditioned fear responses (Kamprath et al., 2011), while CB1 blockade in the basolateral amygdala prevented the formation of conditioned fear responses (Tan et al., 2011). These findings suggest that the effects of cannabinoids on fear-conditioned responses in the intact organism are highly variable, depending on the relative degrees of cannabinoid modulation in different parts of the brain under the influence of various external factors.

That such is indeed the case in both experimental animals and humans is amply documented in several excellent reviews (Viveros et al., 2005; Moreira and Lutz, 2008; Akirav, 2011). There is a clear and strong pattern of biphasic dose–response relations, with anxiolytic effects predominating at low doses of exogenous cannabinoid agonists or low levels of endocannabinoid activation, and anxiogenic effects predominating at high doses. Moreover, the effects at a given dose can vary greatly as a function of altered external circumstances or concurrent physiologic influences, combined action with other drugs, and of individual experience with cannabis or cannabinoids. An additional source of variability that has received very little attention until recently is sex difference in the responses of the endocannabinoid system, especially at times of sexual maturation (Krebs-Kraft et al., 2010;Viveros et al., 2011). This is an important topic that merits much more research than it has had in the past.

2.1.9. Seizure Susceptibility

In keeping with its inhibitory effect on excitatory impulse transmission, the endogenous cannabinoid system also exerts an inhibitory influence on seizure susceptibility. It has been known for many years that cannabis has antiseizure activity in humans (Kalant, 1972; Russo, 2007). In rat models of epilepsy, both THC and CBD exert antiseizure activity similar to that of phenytoin (Sofia et al., 1976; Corcoran et al., 1978; Consroe et al., 1982).

More recent research demonstrates the role of the endocannabinoid system in this action by various types of evidence. For example, the CB1 agonist WIN55,252-2 delayed the development of kindled seizures in rats, whereas the FAAH inhibitor URB597 failed to do so because it also inhibited neuronal proliferation (Wendt et al., 2011). Conversely, the CB1 receptor blocker SR141716 facilitated the reacquisition of audiogenic epilepsy in rats that had lost their seizures through repeated testing (Vinogradova et al., 2011). In rats subjected to a single period of pilocarpine-induced status epilepticus, the subsequent development of epilepsy took place over a period of about a month, but was preceded by a marked loss of hippocampal CB1 receptors (Falenski et al., 2009). The FAAH inhibitor URB597 protected mice against electroshock-induced seizures, and the effect was synergistic or additive with the effect of diazepam, depending on the dose ratios of the two drugs (Naderi et al., 2008). Another FAAH inhibitor, AM374, also increased anandamide levels in the rat hippocampus and protected against kainite-induced seizures as well as excitotoxic neuronal damage (Karanian et al., 2007). In the fetus and the newborn rat brain, glutamatergic excitatory activity is not yet highly developed and GABAergic synapses are excitatory rather than inhibitory (Bernard et al., 2005). In this situation, blockade of CB1 receptors also led to epileptic discharges, but through a different locus of action than in the mature brain.

One study provides apparently conflicting findings, in that the ketogenic diet prevented induction of pentylenetetrazole-induced seizures in mice without affecting either CB1 receptor expression or brain levels of endocannabinoids (Hansen et al., 2009). The levels of a number of other acylethanolamines, especially oleoylethanolamide, were actually reduced in the animals on ketogenic diet. However, these animals grew much more slowly than their normal diet controls, and their plasma contained more than twice as much betahydroxybutyrate, so that the mechanism of the antiepileptic effect of the ketogenic diet may be quite different from, and independent of, that of the endocannabinoid effect. This should not be surprising, since the endocannabinoid system is obviously not the only factor affecting neuronal excitability.

Unlike normal mice, mice totally lacking FAAH had greatly increased levels of endogenous anandamide in the hippocampus, and reacted to exogenous anandamide administration with a greatly increased susceptibility to kainate- or bicuculline-induced seizures (Clement et al., 2003). Perhaps analogously, prolonged exposure to WIN55,212-2 in a hippocampal culture model led to downregulation of CB1 receptors in both glutamatergic and GABAergic synapses, and the progressive appearance of low-Mg^{2+}-induced

seizure discharges despite the continued presence of the WIN55,212-2 (Blair et al., 2009). Both of these examples appear to represent "overload" effects comparable to those noted above with other actions of the endocannabinoids.

However, another possible explanation of enhanced seizure susceptibility caused by either endocannabinoid overactivity or exogenous cannabinoid administration is based on the balance of glutamatergic and GABAergic activity in the animal model employed. If the model is one that involves primarily GABA-dependent control of neuronal excitability, and sufficiently high doses of cannabinoid are used that strongly inhibit GABAergic synaptic transmission, the result could be increased seizure susceptibility (Lutz, 2004).

Despite the abundance of experimental literature on the subject, there is almost nothing on clinical evaluation of cannabis or cannabinoids in the treatment of epilepsy in humans. There are a number of survey reports, such as that by concerning 136 patients seen in an epilepsy clinic, of whom 48% reported use of cannabis at some time and 21% were current users. Approximately two-thirds of the current users reported beneficial effects on seizure severity and half reported lower seizure frequency; the others reported no effect on their epilepsy. There are also very rare case reports (e.g. Mortati et al., 2007) of marked improvement after initiation of therapy with cannabis extract. However, there is only one double-blind placebo-controlled study of epileptic patients who received supplementary treatment with CBD after conventional medications failed to provide adequate control. Each patient remained on the previous medication but received in addition oral capsules of CBD or placebo in a cross-over design. The addition of CBD resulted in significant reduction of seizure frequency (Cunha et al., 1980). The lack of further studies is surprising, but the availability of a variety of endocannabinoid agents without unwanted psychoactive effects may encourage well-designed clinical trials.

2.1.10. Motor Control

The extensive and complex role of the endocannabinoid system in the functional control of the motor pathways has been thoroughly described in detail in several comprehensive reviews (van der Stelt and Di Marzo, 2003; Fernández-Ruiz, 2009; El Manira and Kyriakatos, 2010). The topic has interested many investigators because of the hope that knowledge of the mechanisms of endocannabinoid modulation of motor control might yield cannabinoid-derived medications capable of providing symptomatic relief, and possibly correction of the underlying pathology, in motor control disorders such as Parkinson's disease (PD), Huntington's disease (HD), Tourette's syndrome and others. Several points in these recent reviews suggest a basis for that hope: (1) There is a very heavy concentration of CB1 receptors, and of the enzymes for synthesis and degradation of the endocannabinoids, in the basal ganglia, cerebellum, and other brain structures involved in motor coordination and control. Indeed, the acquisition of a conditioned delayed eyeblink response, which involves LTD of synapses on cerebellar Purkinje cells, has been proposed as a quantitative measure of endocannabinoid function (Edwards

and Skosnik, 2007). (2) The receptors are located on the presynaptic terminals of all the main fiber types involved in motor control, including glutamatergic, GABAergic, and dopaminergic axons (Morera-Herreras et al., 2012). (3) Alterations of the receptors have been found in tissue from the brains of patients with PD and HD, and the alterations have regressed in those who have responded well to treatment.

In the presymptomatic stages of both PD and HD, the CB1 receptors in the basal ganglia are downregulated and desensitized both in human patients and in animal models of PD and HD, and anandamide levels in the cerebrospinal fluid are elevated, possibly as a compensatory response (Pisani et al., 2010). This would lead to increased excitotoxicity, oxidative stress, and inflammatory reaction, as described in Section 2.3, and thus add to the toll of neuronal loss until the symptomatic stage is reached. In the latter stage the patterns of alteration in the two diseases differ. In PD, the CB1 receptors become upregulated and the resulting block of excitatory transmission gives rise to the characteristic motor inhibition and bradykinesia. In HD, in contrast, the receptor downregulation is increased, leading to hyperkinesia. These receptor changes have been found both in tissue from patients and in animal models (Fernández-Ruiz, 2009).

Theoretically, a CB1 receptor blocker should be helpful in late stage PD to alleviate bradykinesia. Trials in animal models have yielded some suggestive results, but the only controlled, double-blind cross-over study in 19 human PD patients showed neither benefit nor harm from the oral administration of an alcoholic extract of cannabis with a THC:CBD ratio of 2:1 (Carroll et al., 2004; Health Canada, 2010). Similarly, in theory the hyperkinesia of advanced HD might benefit from the inhibitory action of CB1 agonists, but this possibility has not yet been tested in a well-designed clinical trial. Such a trial of CBD in patients with symptomatic HD showed no significant response to treatment with even a fairly high dose (Consroe et al., 1991; Health Canada, 2010), but this is not really relevant because CBD is neither a CB1 nor a CB2 ligand, and it is an inhibitor of the GPR55. A small number of uncontrolled case reports yielded conflicting findings. However, a later trial of nabilone, an agonist at both CB1 and CB2 receptors, in 44 patients with advanced HD found no improvement in overall motor score, but there was a small but significant improvement of chorea (Curtis et al., 2009b). The latter study provides justification for further study with a wider dose range, and possibly more selectively acting drugs. Overall, however, it seems likely that the changes in endocannabinoid activity in both Huntington's and Parkinson's diseases affect too many different control mechanisms to make single-drug therapy likely to be very successful.

Tourette's syndrome offers a different problem from that seen in PD and HD, in that it does not involve malfunction of the regulation of motor pathways, but rather, the sudden initiation of contextually irrelevant movements. It is therefore considered a neuropsychiatric disorder rather than a purely neurological problem. Claims have been made for the success of THC treatment of this disorder. However, a fairly recent

Cochrane review found only two methodologically sound published trials (Curtis et al., 2009a) and concluded that THC treatment had yielded only minimal improvement in tic frequency and severity, insufficient to warrant the use of cannabinoid therapy.

Perhaps the greatest current interest in relation to cannabinoids and motor control attaches to its effects on spasticity in patients with multiple sclerosis. An antispasticity action was described in the Indian Hemp Drugs Commission Report (Kalant, 1972), and many modern publications have dealt with the effects of cannabis or individual cannabinoids. However, the reported results have been rather contradictory (Kalant and Porath-Waller, 2012). A review by Zajicek and Apostu (2011) concluded that in the best-designed trials, cannabinoids relieved the pain and the subjective sensation of spasm, but that objective measurements of spasm failed to demonstrate a clear effect. However, in a recent randomized, double-blind, placebo-controlled clinical trial, 30 patients with poorly controlled spasticity, and who were not using cannabis or other illicit drugs, were tested with smoked cannabis in a carefully controlled dosage. This resulted in significant reduction of both subjective and objective measures of spasticity after cannabis treatment, versus no change after placebo. However, the dose of cannabis that reduced the score on the modified Ashworth scale of spasticity also resulted in a significant increase in unwanted psychoactive effects (Corey-Bloom et al., 2012). These results suggest that the earlier contradictory results may have been due to insufficiently high dosage of cannabinoid, but that effective doses may exceed the tolerable limit in many or most patients.

2.1.11. Cognitive Functions

2.1.11.1. Cognition-Related Brain Functions in Animals

Given the important roles of synaptic plasticity and of axonal sprouting and new synapse formation in learning, laying down of new memory traces, extinction or active unlearning, tolerance and physiological adaptations of various kinds, it can readily be anticipated that the endocannabinoid system must be involved as part of the neuronal mechanisms of many cognitive functions. Surprisingly, however, there is very little published work on a facilitatory role of endocannabinoid signaling in learning and memory. Most of the support for such a role is inferred from the finding of negative effects in knockout mice lacking CB1 receptors, which show inability to extinguish a conditioned fear response, or to develop sensitization of the rewarding effects of cocaine (Marsicano et al., 2002; Heifets and Castillo, 2009). Conversely, the endocannabinoid transporter AM404, which facilitates endocannabinoid binding to the receptors, and the CB1 agonist WIN55,212-2, both enhanced extinction of conditioned fear and water maze spatial learned responses (Chhatwal et al., 2005; Pamplona et al., 2006). More recently, Campolongo et al. (2009) reported that infusion of WIN55,212-2 directly into the basolateral amygdala of rats immediately after inhibitory avoidance training facilitated the consolidation of the learned response, and a CB1 receptor blocker inhibite consolidation.

Davies et al. (2002) suggested that a possible reason for failure to find more examples of facilitation of learning by endocannabinoid or cannabinoid action might be that almost all experimenters have used systemic administration of the cannabinoid, which would affect allcannabinoid binding sites in the brain. Since the actions of endocannabinoids, in particular, are highly variable at different brain sites, different neuron types, and different behavioral tests, the resulting medley of actions would make it very difficult to recognize facilitatory actions; the results cited above are consistent with this concept of variability of endocannabinoid function. Biphasic dose–response curves can also be seen with CB1 receptor blockers. AM251, a CB1 blocker, given at low doses to rats improved recognition memory, but at high doses it had no effect (Bialuk and Winnicka, 2011). This adds to the complexity of the picture but at present no comprehensive explanation is apparent.

Davies et al. argued that the proper type of experiment would involve local injection of the cannabinoid or endocannabinoid directly into specific sites in the hippocampus. Nevertheless, a number of such experiments have been carried out (Akirav, 2011) and the consistent pattern has been that cannabinoid agonists inhibit learning both when given systemically and when injected intracerebrally (Akirav, 2011). Working memory appears to be the most sensitive to disruption by very low doses of THC (Varvel et al., 2001; Egerton et al., 2006). These findings suggest that if there is a more general facilitatory role of endocannabinoids on a greater variety of cognitive tests, the reversal point at which inhibitory effects predominate must be very low relative to those observed with anxiety, neuroprotection, and other functions described above.

2.1.11.2. Cerebral Blood Flow Studies

In contrast to these studies of the cellular anatomy of cannabinoid actions, others have approached the subject by studies in the intact organism. One such approach has been functional imaging of the brain, both in rodents and in humans. Acute intravenous administration of THC or its active metabolite 11-hydroxy-THC produced a variable pattern of changes in regional blood flow in the rat brain, with increases in about half of the areas measured, and decreases in the others (Bloom et al., 1997). After administration of anandamide, the picture was more prominently one of decreased regional flow, with more regions being affected for longer after higher doses (Stein et al., 1998). The assumption underlying these studies is that regional blood flow is a reflection of neuronal activity, but in the light of the extreme diversity of different neuron types within the same small region, and the complex interactions among them as illustrated by the mechanism of postsynaptically formed endocannabinoid acting at inhibitory presynaptic receptors, it is difficult to see what functional interpretation can be placed on the changes observed. The difference in cannabinoid effects within areas in the amygdala that are only millimeters apart serves to illustrate this point.

Essentially, the same problem is seen in the blood flow studies in humans. Acute administration resulted in global increases in cerebral blood flow, and regional increases

in the frontal lobes, that were accompanied by subjective changes ("high", anxiety, anger, confusion) and increases in heart rate, that were correlated in magnitude with the peak plasma THC level (Mathew and Wilson, 1993). However, neither the blood flow measures nor the physiological and emotional measures are sufficiently fine-grained to permit any mechanistic interpretation. The same limitation of interpretability applies to another acute study in which a cognitive performance task was also included (O'Leary et al., 2002). In addition, the trials were not truly acute because, for ethical reasons, only experienced marijuana users were allowed to take part, so that the effects may well have been modified by varying degrees of tolerance or abstinence. In another study in which the participants had to perform two versions of a decision-making task, one version that allowed for reasonable calculation and the other that was more probabilistic in nature (Vaidya et al., 2012). Somewhat more selective changes in regional cerebral blood flow were seen according to the nature of the task, but in both tasks the chronic users had greater increases in blood flow than the nonuser controls. This again illustrates the difficulties of interpretation: did the greater increase in blood flow signify an adaptive response to the drug, or a need for greater cerebral energy expenditure because of poorer task efficiency? Two other studies (Tunving et al., 1986; Lundqvist et al., 2001) in chronic users who were withdrawn for only 1–2 days before blood flow measurement, and who were not required to perform any mental task during the study, found either reduced hemispheric blood flow or no difference from controls. Those who had initially low blood flow showed significant improvement when reexamined after 9–60 days of detoxication.

In view of the many individual and intergroup differences in these studies, and the multiple differences in the results of the studies, it is not surprising that a systematic review of 41 human brain imaging studies found such heterogeneity that no meta-analysis was possible (Martin-Santos et al., 2010).

2.1.11.3. Human Cognitive Functions

There have been many studies of the effects of cannabis on a variety of cognitive functions in human users of cannabis, both acute and chronic. Two extensive literature reviews give very representative pictures of the most consistent findings. Ranganathan and D'Souza (2006) dealt primarily with effects on memory, and found dose-related impairments of immediate and delayed recall of information presented while the subjects were under the influence of the drug. Encoding, consolidation and retrieval of memory were all affected, despite many sources of variation in different subject selection methods, function tests used, sample sizes and other aspects of design.

More recent evidence continues to yield similar findings. For example, Solowij et al. (2011), in a study of 181 subjects aged 16–20 years, found that cannabis users (mean duration of use 2.4 years) found significantly worse measures of verbal learning and memory than in alcohol users and in nonusers of any drug. The impairment was worse, the earlier the age of onset of regular use of cannabis and the greater the extent of use. Essentially, similar results have been obtained by others as well (Wagner et al., 2010; Takagi et al., 2011).

Dose-dependent acute inhibitory effects of THC on attention and information processing in human subjects have been studied by measurement of P300 EEG responses during performance of a monitoring task (D'Souza et al., 2012). This is clearly a cannabinoid effect, because a triplet repeat polymorphism in the gene encoding the CB1 receptor caused a marked change in sensitivity to the effect of THC on the P300 response (Stadelmann et al., 2011). However, fMRI studies have shown different effects on auditory and visual information processing (Winton-Brown et al., 2011). A 10 mg dose of THC that produced anxiety, intoxication and psychotic symptoms in healthy volunteers decreased activation in both temporal cortices during auditory processing, but variably increased or decreased activation in different areas of the visual cortex during visual processing. CBD, which did not produce cannabis-like subjective symptoms, had effects opposite to those of THC in the temporal cortex.

Crean et al. (2011) reviewed a broader spectrum of cognitive functions designated as executive functions. These included attention, concentration, decision-making, impulsivity, inhibition (self-control of responses), reaction time, risk taking, verbal fluency, and working memory. All these functions have been found to be impaired acutely in a dose-dependent manner, but there is no unanimity because on each of the functions described there are some studies that found no difference between users and nonusers. Once again, variations in experimental design and execution, differences in definition of *acute* versus *chronic* and *withdrawal*, and length of time elapsed since last use undoubtedly account for much of the differences in conclusions.

In long-term users seen after periods of withdrawal of at least 21 days, which the authors presumably consider sufficient for essentially complete detoxication, so that persistent intoxication effects do not confuse the assessment of residual brain changes, there is again a considerable measure of disagreement among the various studies, due to the same sources of variation mentioned above. Crean et al. conclude that while some components of executive function usually recover completely with the passage of time after cessation of cannabis use, those in which deficits are most likely to persist for very long periods of time are decision making, concept formation, and planning. Just as with effects on maturation, residual long-term effect on executive functions are most likely to occur in those who began regular cannabis use early in adolescence (or during intrauterine development), used cannabis most heavily and for the longest time. There is generally good agreement between the conclusions based on these studies and the clinical impressions based on population studies (e.g. Kalant, 2004; Hall and Degenhardt, 2009).

A growing body of evidence attests to the ability of cannabis to impair psychomotor functions involved in complex tasks such as operation of motor vehicles or aircraft (Kalant, 2004; Ramaekers et al., 2004; Kelly et al., 2004; Sewell et al., 2009; Calabria et al., 2010). It is beyond the scope of the present review to examine this evidence in greater detail, but it represents a significant health and social problem resulting from the actions of cannabis on complex mental functions.

3. CONCLUSIONS

- There has been enormous progress made in recent years, in analyzing the structure and functions of the endocannabinoid system in the nervous system, and it is clear that it is involved in modulating a very broad range of nervous system activities, including synaptic transmission, neuronal growth and maturation, integration of incoming information from many different sources within the body and outside, and linkage between information and responses. However, there are still large gaps in knowledge at the cellular level, and knowledge of the basic workings of the endocannabinoid system still do not offer comprehensive understanding of the effects at the level of the whole organism, including the subjective effects underlying nonmedical use, and the functional effects that may be therapeutically useful or harmful.
- In theory, such a broad range of functions offers the possibility of many therapeutic applications, and it seems probable that in the future many clinically useful developments will become available. They will be useful to the degree that they offer highly selective and controllable degrees of intervention in the workings of the endocannabinoid system, which crude cannabis (marijuana) does not offer, and to the extent that they are therefore free of the undesirable psychoactive effects of currently available cannabinoids.
- There are major differences between the low-dose effects of endogenous cannabinoids and the higher-dose and more prolonged effects of phytocannabinoids. As a result, most of the potentially therapeutically useful effects of cannabinoids are likely to come from the development of endocannabinoid derivatives and analogs, while the higher-dose effects are mainly related to the adverse effects of crude cannabis preparations. The major adverse effects in the nervous system are related to alterations in neuronal growth and maturation, and to impairments of cognitive function including memory and executive functions.
- As with most drugs, the adverse effects are closely related to the age at which use begins, the amount and duration of use, and the length of time after cessation of use.

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