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Effects of Cannabinoids on Neurotransmission

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Abstract The CB_1 cannabinoid receptor is widely distributed in the central and peripheral nervous system. Within the neuron, the CB_1 receptor is often localised in axon terminals, and its activation leads to inhibition of transmitter release. The consequence is inhibition of neurotransmission via a presynaptic mechanism. Inhibition of glutamatergic, GABAergic, glycinergic, cholinergic, noradrenergic and serotonergic neurotransmission has been observed in many regions

of the central nervous system. In the peripheral nervous system, CB_1 receptor-mediated inhibition of adrenergic, cholinergic and sensory neuroeffector transmission has been frequently observed. It is characteristic for the ubiquitous operation of CB_1 receptor-mediated presynaptic inhibition that antagonistic components of functional systems (for example, the excitatory and inhibitory inputs of the same neuron) are simultaneously inhibited by cannabinoids. Inhibition of voltage-dependent calcium channels, activation of potassium channels and direct interference with the synaptic vesicle release mechanism are all implicated in the cannabinoid-evoked inhibition of transmitter release. Many presynaptic CB_1 receptors are subject to an endogenous tone, i.e. they are constitutively active and/or are continuously activated by endocannabinoids. Compared with the abundant data on presynaptic inhibition by cannabinoids, there are only a few examples for cannabinoid action on the somadendritic parts of neurons in situ.

Keywords Acetylcholine · Axon terminal · CB_1 cannabinoid receptor · GABA · Glutamate · Neurotransmission · Noradrenaline · Presynaptic inhibition · Transmitter release

1 Introduction

As described in the chapter by Mackie (this volume), the CB_1 cannabinoid receptor is widely distributed in the central and peripheral nervous system. One of the primary consequences of activation of CB_1 receptors is the inhibition or activation of ion channels. For example, voltage-dependent calcium channels are typically inhibited by cannabinoids, whereas several kinds of potassium channels are activated. Theoretically, due to their influence on ion channels, cannabinoids can change the function of neurons in several ways. By acting in the dendrites, they can interfere with the conduction of synaptic currents to the soma of the neuron. By acting in the soma, they can interfere with the generation of action potentials. By acting on ion channels in axon terminals, they can inhibit transmitter release from the terminals; the consequence is inhibition of neurotransmission with a presynaptic mechanism. Inhibition of neurotransmission appears to be, at present, the best-characterised electrophysiological effect of cannabinoids, and this review focuses on this effect. Before analysing the presynaptic effect, we describe cannabinoid effects on ion channels and the anatomical evidence for the presence of cannabinoid receptors in axon terminals. Presynaptic inhibition by endogenous cannabinoids released by postsynaptic neurons—retrograde signaling—is described in the chapter by Vaughan and Christie (this volume).

2 Effects of Cannabinoids on Ion Channels

The somadendritic region of most neurons is accessible for electrophysiological studies. In contrast, direct electrophysiological recording from axon terminals of

mammals is either impossible or extremely difficult. Accordingly, we know relatively well how cannabinoids change the function of ion channels in the somadendritic region. Our knowledge on electrophysiological changes in axon terminals is limited; we can only assume that ion channels are influenced similarly as in the somadendritic region. In this section, effects on the somadendritic region are dealt with.

2.1 Effects of Cannabinoids on Voltage-Gated Ion Channels

2.1.1 Calcium Channels

In the majority of studies, cannabinoids depressed voltage-dependent calcium channels. According to the first observations, activation of CB_1 receptors inhibits N-type voltage-dependent calcium channels in neuronal cell lines (Caulfield and Brown 1992; Mackie and Hille 1992; Mackie et al. 1993). No inhibition occurred in pertussis toxin-treated cells, indicating the involvement of G proteins containing $G\alpha_{i/o}$ subunits. Later, this observation was extended to isolated rat hippocampal neurons and cerebellar granule cells (Twitchell et al. 1997; Nogueron et al. 2001). In isolated rat sympathetic ganglion neurons that previously had been injected with CB_1 receptor cRNA, cannabinoids also inhibited N-type calcium channels (Pan et al. 1996). Q-type calcium channels were also inhibited in CB_1 receptor-transfected AtT20 cells (Mackie et al. 1995). The endogenous cannabinoid (endocannabinoid) anandamide inhibits T-type calcium channels; this effect is, however, not mediated by CB_1 receptors (Chemin et al. 2001).

There are at least two examples for stimulation of calcium channels by cannabinoids: L-type calcium currents in a neuronal cell line (Rubovitch et al. 2002) and in retinal rods of the tiger salamander (Straiker and Sullivan 2003) were enhanced by cannabinoids.

2.1.2 Potassium Channels

Activated CB_1 receptors can also change the function of several types of potassium channels. In oocytes and AtT20 cells artificially expressing the CB_1 receptor, stimulation of inwardly rectifying potassium channels was repeatedly observed (Henry and Chavkin 1995; Mackie et al. 1995; Garcia et al. 1998; McAllister et al. 1999). Potassium A currents in cultured hippocampal neurons are stimulated by cannabinoids (Deadwyler et al. 1995; Mu et al. 2000). The effects of cannabinoids on potassium M currents in hippocampal brain slices have also been studied; M currents were inhibited, which means an enhancement of neuronal excitability (Schweitzer 2000). The potassium K current is inhibited by cannabinoids in cultured hippocampal neurons (Hampson et al. 2000). As in the case of calcium channels, anandamide can elicit a CB_1 receptor-independent effect on potassium

channels, i.e. it inhibits the acid-sensitive background potassium channel TASK-1 (Maingret et al. 2001).

2.1.3 Sodium Channels

In an early study, Turkanis et al. (1991) showed that Δ^9-tetrahydrocannabinol inhibits voltage-dependent sodium channels; the involved primary receptor was not identified in this study. More recently, it was observed that anandamide and the synthetic CB_1/CB_2 receptor agonist WIN55212-2 inhibited voltage-dependent sodium channels in synaptosomes prepared from mouse brain (Nicholson et al. 2003). Since the effects were not attenuated by the CB_1 receptor antagonist AM251, the involvement of CB_1 receptors can be excluded.

2.2 Effects of Cannabinoids on Ligand-Gated Ion Channels

The function of several types of ligand-gated ion channels is changed by cannabinoids—as a rule, these effects are not mediated by CB_1 receptors. In isolated rat nodose ganglion neurons, cannabinoids inhibited serotonin-3 ($5\text{-}HT_3$) receptor-mediated currents (Fan 1995). This observation was verified and extended in a recent study. In HEK293 cells expressing the human $5\text{-}HT_{3A}$ receptor, several cannabinoids inhibited the 5-HT-evoked current (Barann et al. 2002). CB_1 receptors could not be involved in this effect, since HEK293 cells do not express CB_1 receptors.

The function of AMPA-type glutamate receptors (Akinshola et al. 1999) and nicotinic acetylcholine receptors (Oz et al. 2003), expressed in oocytes, was inhibited by anandamide. These effects are, again, CB_1 and CB_2 receptor-independent.

2.3 What Is the Functional Consequence of the Inhibition of Somadendritic Ion Channels?

The majority of the experiments in which the effect of cannabinoids on somadendritic ion channels was studied were carried out on cell lines, on cells artificially expressing the CB_1 receptor or on isolated neurons. It is not known whether the effects also occur under natural conditions. For example, cannabinoid receptor agonists did not influence voltage-dependent calcium channels in caudate-putamen medium spiny neurons (Szabo et al. 1998), although these neurons are known to synthesise CB_1 receptors. It is conceivable that in neurons under physiological conditions, the density of somadendritic CB_1 receptors is too low for modulation of certain ion channels. Alternatively, the coupling mechanism between receptor and ion channel may not be functional.

Another important question also remains unanswered. We basically do not know how modulation of somadendritic ion channels by cannabinoids affects the excitability or integrative capacity of neurons. There are only a few experiments in which neurons were studied in situ (in brain slices), and cannabinoid effects were restricted to the somadendritic region of the neurons (by blockade of the synaptic input of the neurons), and cannabinoids elicited an effect. One such experiment was carried out by Kreitzer et al. (2002): cannabinoids lowered the firing rate of cerebellar interneurons and this was attributed to the activation of barium-sensitive potassium channels. In the experiments of Himmi et al. (1998), cannabinoids changed the firing rate of nucleus tractus solitarii neurons in brain slices; since the synaptic input was not blocked, it is not known whether the change in firing rate was due to an effect on the neurons themselves, or to an effect on their synaptic input.

3
Anatomical Evidence for the Presence of CB_1 Cannabinoid Receptors in Axon Terminals

The wide distribution of the CB_1 receptor in the nervous system is described in the chapter by Mackie (this volume). The prerequisite for presynaptic inhibition of neurotransmission is that the receptor is localised in axon terminals. The following paragraph lists known examples for localisation of CB_1 receptors in axon terminals.

In the cerebellum, CB_1 receptors in terminals of basket cells can be seen at the light microscopic level (Tsou et al. 1998; Diana et al. 2002). Electron microscopical studies have indicated that a great portion of CB_1 receptors in the caudate-putamen (Rodriguez et al. 2001), hippocampus (Katona et al. 1999, 2000; Hájos et al. 2000) and amygdala (Katona et al. 2001) is in axon terminals. Comparison of the site of CB_1 receptor synthesis (which was determined by in situ hybridisation) with the distribution of receptor protein (which was determined with receptor autoradiography and immunohistochemistry) indicates localisation of CB_1 receptors in terminals of parallel fibres in the cerebellum and in terminals of striatonigral neurons in the substantia nigra pars reticulata (compare, for example, Mailleux and Vanderhaeghen 1992; Matsuda et al. 1993; Tsou et al. 1998). The changes in the CB_1 receptor distribution pattern during neurodegeneration accompanying Huntington's disease and experimentally elicited neurodegeneration also suggest that CB_1 receptors in the substantia nigra pars reticulata are localised in striatonigral axon terminals (Herkenham et al. 1991; Glass et al. 2000).

In a few instances, it was shown that CB_1 receptors are not uniformly distributed in a neuron, but are preferentially localised in the axon terminal. For example, CB_1 receptors were well visible in cerebellar basket cell terminals, but not in the somata of these neurons (Diana et al. 2002). Preferential localisation of CB_1 receptors in axon terminals was also observed in hippocampal neurons (Twitchell et al. 1997; Irving et al. 2000).

4
Effects of Cannabinoids on Neurotransmission in the Central Nervous System

Two methods were used to study the effect of cannabinoids on presynaptic axon terminals. The more frequently used electrophysiological approach measures neurotransmission. In brain slices or neuronal cultures, electrical currents in postsynaptic neurons are recorded with patch-clamp or microelectrode techniques. Presynaptic axon terminals are electrically stimulated and the postsynaptic current resulting from stimulation of ligand-gated ion channels of postsynaptic neurons by the released transmitter is determined. The change in the postsynaptic current amplitude is a measure of the change in synaptic transmission.

In the other method, the release of endogenous or radiolabelled neurotransmitters from presynaptic axon terminals is determined chemically. Although this latter method shows directly what happens at the level of axon terminals, it does not measure "neurotransmission".

In electrophysiological experiments, cannabinoids inhibited neurotransmission. The inhibition was always due to inhibition of transmitter release from axon terminals and never to interference of cannabinoids with the postsynaptic effects of the neurotransmitters. The experiments in which transmitter release was determined neurochemically also indicated that cannabinoids inhibit transmitter release from axon terminals. In most instances the presynaptic cannabinoid receptors can be classified as CB_1 receptors (but some exceptions are given in Tables 1 and 2). Effects of cannabinoids on the release of individual transmitters are discussed below. Effects of cannabinoids on neurotransmission have also been reviewed by Schlicker and Kathmann (2001).

4.1
Fast Excitatory Neurotransmission

Activation of CB_1 receptors inhibits the release of the excitatory neurotransmitter glutamate in many brain regions and in the spinal cord (Table 1).

Inhibition was seen in nuclei belonging to the extrapyramidal motor control system: caudate-putamen, globus pallidus and substantia nigra pars reticulata (Fig. 1 shows an example of presynaptic inhibition of glutamatergic neurotransmission in the substantia nigra pars reticulata; see Fig. 6 for an overview of cannabinoid effects on neurotransmission in the extrapyramidal motor control system). Inhibition of neurotransmission was also observed in the ventral tegmental area, hippocampus and the nucleus accumbens—these regions are parts of the limbic system. Inhibition of the excitatory synaptic transmission in the hippocampus could contribute to the anticonvulsive effect of cannabinoids. Purkinje cells in the cerebellar cortex receive excitatory inputs from parallel fibres and climbing fibres; both kinds of excitatory inputs are inhibited by activated CB_1 receptors (see Fig. 7 for an overview of cannabinoid effects on neurotransmission in the cerebellar cortex). Moreover, cannabinoids depress the glutamatergic neurotransmission

Table 1. Inhibition of glutamatergic neurotransmission (*continued on next page*)

Neurotransmitter	Species	Region	Method	Mechanism of presynaptic inhibition	Reference(s)
Glutamate	Rat	Cortex (brain slice)	Electrophysiology (patch clamp)	Vesicle release machinery inhibited	Auclair et al. 2000
Glutamate[a]	Rat	Cortex (cell culture)	Endogenous glutamate chemically determined	IP_3 is involved	Ferraro et al. 2001
Glutamate	Rat	Caudate-putamen (brain slice)	Electrophysiology (patch clamp)	Vesicle release machinery inhibited	Gerdeman and Lovinger 2001
Glutamate	Rat	Caudate-putamen (brain slice)	Electrophysiology (patch clamp, extracell. recording)	The inhibition is pertussis toxin sensitive Vesicle release machinery not inhibited Ca^{2+} channels involved	Huang et al. 2001, 2002
Glutamate	Rat	Caudate-putamen (brain slice)	Electrophysiology (extracell. recording), [^{3}H]glutamate release	Glutamate uptake is inhibited, glutamate causes presynaptic inhibition via mGluR	Brown et al. 2003b
Glutamate	Mouse	Nucleus accumbens (brain slice)	Electrophysiology (patch clamp, extracell. recording)	Vesicle release machinery inhibited Ca^{2+} channels not involved K^+ channels involved cAMP and PKA not involved	Robbe et al. 2001
Glutamate	Mouse	Globus pallidus (brain slice)	Electrophysiology (patch clamp)	No details given	Wallmichrath and Szabo 2003
Glutamate	Rat	Ventral tegmental area	Electrophysiology (patch clamp)	Vesicle release machinery inhibited	Melis et al. 2004
Glutamate	Rat	Substantia nigra pars reticulata (brain slice)	Electrophysiology (patch clamp)	No details given	Szabo et al. 2000
Glutamate	Rat	Hippocampus (brain slice)	Electrophysiology (extracell. recording)	No details given	Ameri et al. 1999; Ameri and Simmet 2000
Glutamate	Rat	Hippocampus (brain slice)	Electrophysiology (extracell. recording)	No details given	Al-Hayani and Davies 2000

Table 1. (*continued*)

Neurotransmitter	Species	Region	Method	Mechanism of presynaptic inhibition	Reference(s)
Glutamate	Rat	Hippocampus (cell culture)	Electrophysiology (patch clamp)	Vesicle release machinery inhibited Ca^{2+} channels involved	Sullivan 1999
Glutamate	Rat	Hippocampus (cell culture)	Electrophysiology (patch clamp), microfluorometry (Ca^{2+} spikes determined)	The inhibition is pertussis toxin sensitive	Shen et al. 1996, Shen and Thayer 1999, Kouznetsova et al. 2002
Glutamate? GABA?	Rat	Hippocampus (cell culture)	Release of the vesicle marker FM1–43	No details given	Kim and Thayer 2000
Glutamate	Rat	Hippocampus (synaptosomes)	Endogenous glutamate chemically determined (4-AP evoked release)	The inhibition is pertussis toxin sensitive Ca^{2+} channels involved Vesicle release machinery not inhibited PKA not involved	Wang 2003
Glutamate	Mouse, rat	Hippocampus (brain slice)	Electrophysiology (patch clamp)	No CB_1 receptors are involved	Hájos et al. 2001; Hájos and Freund 2002
Glutamate	Rat, mouse	Hippocampus (synaptosomes)	[^{3}H]Glutamate release	No CB_1 receptors are involved	Köfalvi et al. 2003
Glutamate	Mouse	Hippocampus (brain slice)	Electrophysiology (patch clamp)	The inhibition is pertussis toxin sensitive Vesicle release machinery inhibited	Misner and Sullivan 1999
Glutamate	Mouse	Amygdala	Electrophysiology (patch clamp, extracell. recording)	The inhibition is pertussis toxin sensitive Vesicle release machinery inhibited K^+ channels involved Ca^{2+} channels not involved	Azad et al. 2003
Glutamate	Rat	Cerebellum (brain slice)	Electrophysiology (patch clamp)	Vesicle release machinery inhibited K^+ channels involved Ca^{2+} channels only indirectly involved	Levenes et al. 1998, Daniel and Crepel 2001
Glutamate	Rat	Cerebellum (brain slice)	Electrophysiology (patch clamp)	Vesicle release machinery not inhibited	Takahashi and Linden 2000

Table 1. (*continued*)

Neurotransmitter	Species	Region	Method	Mechanism of presynaptic inhibition	Reference(s)
Glutamate	Rat	Cerebellum (brain slice)	Electrophysiology (patch clamp)	No details given	Kreitzer and Regehr 2001
Glutamate	Mouse	Cerebellum (brain slice)	Electrophysiology (patch clamp)	No details given	Maejima et al. 2001
Glutamate	Mouse	Synaptosomes from whole brain	Endogenous glutamate chemically determined (veratridine-evoked release)	No CB_1 receptors are involved Na^+ channels inhibited	Nicholson et al. 2003
Glutamate	Rat	Spinal cord (cord slice)	Electrophysiology (patch clamp)	Vesicle release machinery inhibited	Morisset and Urban 2001

4-AP, 4-aminopyridine; cAMP, cyclic adenosine monophosphate; extracell., extracellular; GABA, γ-aminobutyric acid; PKA, protein kinase A.
[a] In this exceptional study, cannabinoids did not decrease glutamate release, but increased it.

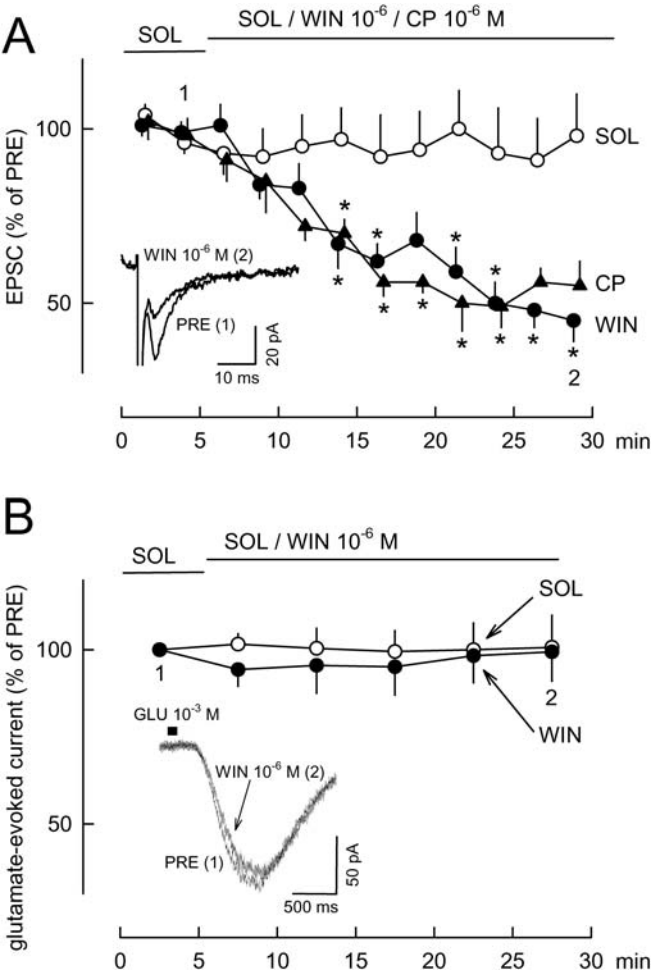

Fig. 1A, B. Cannabinoids inhibit glutamatergic synaptic transmission in the substantia nigra pars reticulata (SNR) of the rat via a presynaptic mechanism. The major glutamatergic afferent input of SNR neurons originates in the subthalamic nucleus. **A** SNR neurons were patch-clamped and their glutamatergic afferent axons electrically stimulated. The stimulation elicited excitatory postsynaptic currents (*EPSC*s) in SNR neurons. EPSCs remained stable in solvent (*SOL*)-superfused slices. The synthetic cannabinoid agonists WIN55212-2 (*WIN*) and CP55940 (*CP*) inhibited the EPSCs. **B** SNR neurons were patched-clamped and glutamate (*GLU*) was pressure-ejected from a pipette in their vicinity. Glutamate-evoked currents remained stable in SOL-superfused slices. Superfusion of WIN also did not change the glutamate-evoked currents. This observation indicates that cannabinoids do not interfere with the postsynaptic effect of glutamate; thus, the inhibition of neurotransmission seen in panel **A** is due to presynaptic inhibition of glutamate release from axon terminals. In both panels, a typical original recording obtained in a WIN experiment (*inset*) and the statistical analysis are shown. *PRE*, initial reference period. See Szabo et al. (2000) for details of the experiments. *, Significant difference from SOL ($p<0.05$)

between primary sensory fibres and neurons in the dorsal horn of the spinal cord: this effect could be the basis of the spinal analgesia produced by cannabinoids.

According to recent observations, some effects of cannabinoids on glutamatergic transmission in the hippocampus are not mediated by CB_1 receptors (and also not by CB_2 receptors). Synthetic cannabinoids depressed excitatory neurotransmission also in brain slices from CB_1 receptor-knockout mice and in the presence of some CB_1 antagonists (Hájos et al. 2001; Hájos and Freund 2002). Similarly, cannabinoid-evoked glutamate release from hippocampal synaptosomes was resistant to CB_1 antagonists and persisted in CB_1 receptor-knockout mice (Köfalvi et al. 2003; but in a similar preparation, effects were sensitive to a CB_1 antagonist; Wang 2003). Based on such observations, the existence of a new cannabinoid receptor was postulated. It must be noted that the involvement of known non-cannabinoid receptors or ion channels—for which cannabinoids might possess a hitherto unrecognised affinity—was not excluded in these studies.

Prolonged exposure of G protein-coupled receptors to their agonists leads to desensitisation due to diminished coupling of the receptors with G proteins and receptor internalisation. This phenomenon was observed also in the case of CB_1 receptor-mediated inhibition of neurotransmission. Cannabinoid-evoked inhibition of glutamatergic and γ-aminobutyric acid (GABA)ergic neurotransmission in the nucleus accumbens was diminished by treatment of animals for 1 week with natural and synthetic cannabinoids (Hoffman et al. 2003a). Cannabinoid-evoked inhibition of excitatory neurotransmission between cultured hippocampal neurons was also strongly desensitised by a 24-h treatment of the neurons with a cannabinoid (Kouznetsova et al. 2002).

4.2 Fast Inhibitory Neurotransmission

CB_1 receptor-mediated inhibition of GABAergic neurotransmission has been observed in many brain regions, belonging to different functional systems (Table 2).

Thus, cannabinoids depress cerebral cortical GABAergic neurotransmission. Neurotransmission is also depressed in nuclei belonging to the extrapyramidal motor control system: caudate-putamen, globus pallidus and substantia nigra pars reticulata (Fig. 6 also shows cannabinoid effects on inhibitory neurotransmission in the extrapyramidal motor control system). GABAergic synaptic transmission in the cerebellum, a major brain region involved in motor control, is inhibited as well (Fig. 7 also shows cannabinoid effects on inhibitory neurotransmission in the cerebellar cortex). Figure 2 shows inhibition of GABAergic neurotransmission in the cerebellar cortex, and Fig. 3 shows that the inhibition is due to the inhibition of GABA release from presynaptic axon terminals. In several nuclei belonging to the limbic system (e.g. hippocampus and amygdala), activation of CB_1 receptors leads to depression of inhibitory neurotransmission. Inhibition of GABA release in the ventral tegmental area—where the mesolimbic reward pathway originates—could explain the euphoria produced by cannabinoids. The rostral ventromedial medulla oblongata and the periaqueductal grey in the midbrain are involved in nocicep-

Table 2. Inhibition of GABAergic neurotransmission (*continued on next page*)

Neurotransmitter	Species	Region	Method	Mechanism of presynaptic inhibition	Reference(s)
GABA	Mouse	Cortex (brain slice)	Electrophysiology (patch clamp)	Vesicle release machinery not inhibited	Trettel and Levine 2002, 2003
GABA	Rat	Caudate-putamen (brain slice)	Electrophysiology (patch clamp)	No details given	Szabo et al. 1998
GABA	Mouse	Nucleus accumbens (brain slice)	Electrophysiology (patch clamp)	Vesicle release machinery inhibited	Manzoni and Bockaert 2001
GABA	Rat	Nucleus accumbens (brain slice)	Electrophysiology (patch clamp)	Vesicle release machinery weakly inhibited	Hoffman and Lupica 2001; Hoffman et al. 2003a
GABA	Mouse	Globus pallidus (brain slice)	Electrophysiology (patch clamp)	Vesicle release machinery not inhibited	Engler and Szabo 2003, 2004
GABA	Rat	Substantia nigra pars reticulata (brain slice)	Electrophysiology (patch clamp)	No details given	Chan et al. 1998, Chan and Yung 1998
GABA	Rat	Substantia nigra pars reticulata (brain slice)	Electrophysiology (patch clamp)	No details given	Wallmichrath and Szabo 2002a
GABA	Mouse	Substantia nigra pars reticulata (brain slice)	Electrophysiology (patch clamp)	Vesicle release machinery not inhibited	Wallmichrath and Szabo 2002b
GABA	Rat	Ventral tegmental area (brain slice)	Electrophysiology (patch clamp)	Vesicle release machinery not inhibited	Szabo et al. 2002
GABA ($GABA_B$-mediated transmission)	Rat	Ventral tegmental area (brain slice)	Electrophysiology (patch clamp)	No details given	Riegel et al. 2003
GABA	Rat	Hippocampus (brain slice)	Electrophysiology (patch clamp)	Vesicle release machinery not inhibited	Hájos et al. 2000
GABA	Rat	Hippocampus (brain slice)	Electrophysiology (patch clamp)	Vesicle release machinery not inhibited K^+ channels not involved	Hoffman and Lupica 2000

Table 2. (*continued*)

Neurotransmitter	Species	Region	Method	Mechanism of presynaptic inhibition	Reference(s)
GABA	Rat	Hippocampus (brain slice)	Electrophysiology (patch clamp)	No details given	Hoffman et al. 2003b
GABA	Rat	Hippocampus (brain slice)	Electrophysiology (patch clamp)	Vesicle release machinery inhibited	Wilson and Nicoll 2001
GABA	Rat	Hippocampus (cell culture)	Electrophysiology (patch clamp)	Vesicle release machinery inhibited	Irving et al. 2000
GABA	Rat	Hippocampus (cell culture)	Electrophysiology (patch clamp)	No details given	Ohno-Shosaku et al. 2001
GABA	Rat	Hippocampus (brain slice)	[^{3}H]GABA release	No details given	Katona et al. 1999
GABA	Mouse	Hippocampus (brain slice)	Electrophysiology (patch clamp)	No details given	Hájos et al. 2001
GABA	Man	Hippocampus (brain slice)	[^{3}H]GABA release	No details given	Katona et al. 2000
GABA	Man	Hippocampus (brain slice)	Electrophysiology (patch clamp)	Vesicle release machinery not inhibited	Nakatsuka et al. 2003
GABA	Rat, mouse	Amygdala (brain slice)	Electrophysiology (patch clamp)	Vesicle release machinery not inhibited	Katona et al. 2001
GABA	Mouse	Amygdala (brain slice)	Electrophysiology (patch clamp)	Vesicle release machinery inhibited	Azad et al. 2003
GABA	Rat	Periaqueductal grey (brain slice)	Electrophysiology (patch clamp)	Vesicle release machinery inhibited	Vaughan et al. 2000
GABA	Rat	Rostral ventro-medial medulla oblongata (brain slice)	Electrophysiology (patch clamp)	Vesicle release machinery inhibited	Vaughan et al. 1999
GABA	Rat	Cerebellum (brain slice)	Electrophysiology (patch clamp)	Intracellular Ca^{2+} concentration decreased	Kreitzer and Regehr 2001

Table 2. (*continued*)

Neurotransmitter	Species	Region	Method	Mechanism of presynaptic inhibition	Reference(s)
GABA	Rat	Cerebellum (brain slice)	Electrophysiology (patch clamp)	Vesicle release machinery inhibited Intracellular Ca^{2+} concentration decreased	Diana et al. 2002
GABA	Rat	Cerebellum (brain slice)	Electrophysiology (patch clamp)	Vesicle release machinery inhibited	Szabo et al. 2004
GABA	Mouse	Cerebellum (brain slice)	Electrophysiology (patch clamp)	No details given	Yoshida et al. 2002
GABA	Mouse	Synaptosomes from whole brain	Endogenous GABA chemically determined, Veratridine-induced release	No CB_1 receptors are involved Na^+ channels inhibited	Nicholson et al. 2003
GABA, glycine	Rat	Superficial medullary dorsal horn	Electrophysiology (patch clamp)	Vesicle release machinery inhibited	Jennings et al. 2001

GABA, γ-aminobutyric acid.

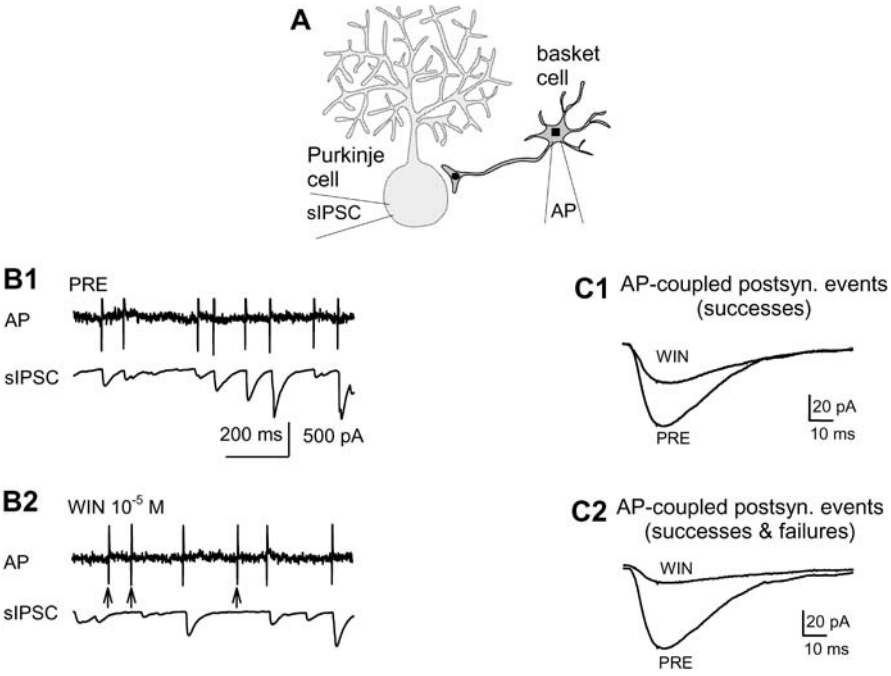

Fig. 2A–C. Cannabinoids inhibit GABAergic synaptic transmission between basket and Purkinje cells in the cerebellar cortex of the rat. **A** The basket cell synthesises CB_1 receptor mRNA (■) and the CB_1 receptor protein (●) is localised in the axon terminal. Action potentials (*APs*) of a basket cell and spontaneous inhibitory postsynaptic currents (*sIPSCs*) in a synaptically coupled Purkinje cell were recorded simultaneously. **B1, B2** APs and sIPSCs were recorded during the initial reference period (*PRE*) and during superfusion with WIN55212-2 (*WIN*). During PRE (**B1**), every presynaptic AP was accompanied by a postsynaptic IPSC: synaptic transmission was always successful. During WIN superfusion (**B2**), synaptic failures appear (marked by *arrows*). Enhancement of synaptic failure is typical for drugs that decrease probability of transmitter release from the presynaptic axon terminal. **C1** AP-coupled postsynaptic currents were averaged only if transmission was successful. The decrease in amplitude indicates inhibition of neurotransmission by WIN. **C2** All AP-coupled postsynaptic currents were averaged (successes and failures). The WIN-evoked inhibition is greater (than in **C1**), because WIN also increased the number of failures. The figure represents five experiments with a similar outcome. See Szabo et al. (2004) for details of the experiments

tive information processing; in both regions, GABAergic synaptic transmission is inhibited by cannabinoids.

In the above-mentioned experiments, cannabinoids inhibited fast GABAergic transmission by inhibiting GABA release from axon terminals. It is expected that if GABA release is inhibited, then $GABA_B$ receptor-mediated slow inhibitory transmission will be inhibited as well. This was indeed observed in the ventral tegmental area (Riegel et al. 2003).

In addition to GABA, glycine is also involved in fast inhibitory neurotransmission. Activation of CB_1 receptors inhibits both GABAergic and glycinergic synaptic transmission in the medulla oblongata (Jennings et al. 2001; see Table 2).

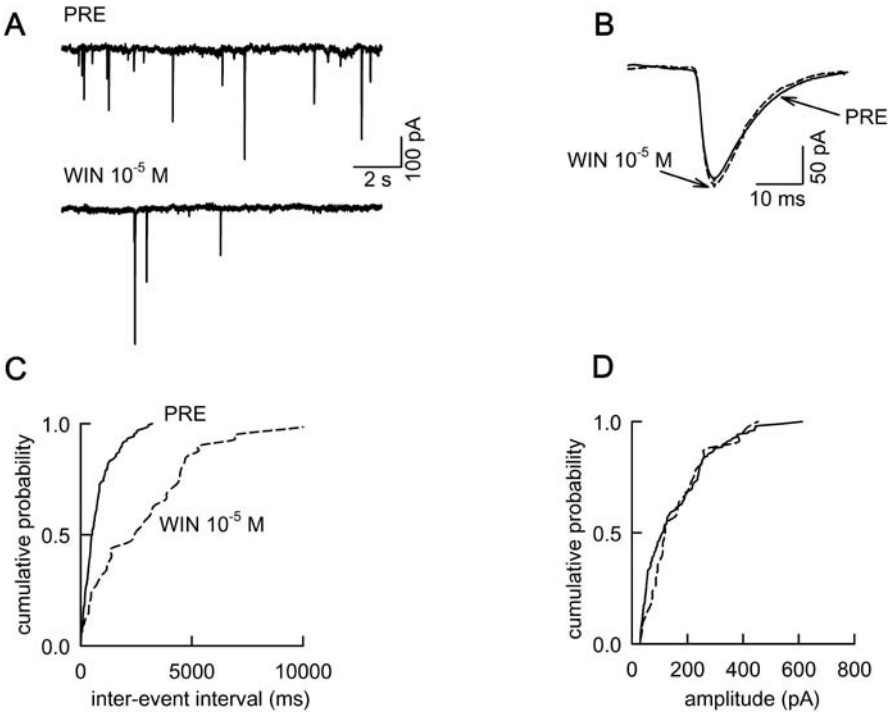

Fig. 3A–D. Cannabinoids inhibit GABAergic synaptic transmission between basket and Purkinje cells in the cerebellar cortex of the rat via a presynaptic mechanism. Miniature inhibitory postsynaptic currents (mIPSCs) were recorded in Purkinje cells in the presence of tetrodotoxin (3×10^{-7} M) during an initial reference period (*PRE*) and during superfusion with WIN55212-2 (*WIN*). **A** Original tracings from an experiment with WIN: WIN obviously lowers the frequency of mIPSCs. **B** Averaged mIPSCs from the experiment shown in **A**: WIN does not change the amplitude of mIPSCs. **C, D** Cumulative probability distribution plots of inter-event intervals and amplitudes of mIPSCs (same experiment as in **A**): the inhibitory effect of WIN on the frequency of mIPSCs and its lack of effect on the amplitude of mIPSCs is evident. Lack of effect of WIN on the amplitude of mIPSCs indicates that the cannabinoid does not interfere with the effect of GABA on the postsynaptic neuron—this is an indication that WIN inhibited neurotransmission between basket and Purkinje cells (see Fig. 2) via a presynaptic mechanism. Lowering the frequency of mIPSCs by WIN suggests that WIN directly interferes with the vesicle release machinery. The figure represents six experiments with a similar outcome. See Szabo et al. (2004) for details of the experiments

4.3 Neurotransmission via Monoamines and Acetylcholine

A synopsis of the inhibitory effects of cannabinoids on the release of the monoamines noradrenaline, dopamine and serotonin and of acetylcholine in the brain and the retina is given in Table 3. Noradrenaline release is inhibited via CB_1 receptors in the hippocampus of guinea-pig and man but not in the hippocampus of rat and mouse (Table 3, Fig. 4; Van Vliet et al. 2000). Although CB_1 receptors inhibit the release of dopamine from amacrine cells of the retina, contradictory results were obtained with respect to the modulation of dopamine release from

Table 3. Inhibition of the release of monoamines and acetylcholine in the brain and the retina

Neurotransmitter	Species	Region	Method	References
Noradrenaline	Guinea-pig	Cortex, hippocampus, hypothalamus, cerebellum (brain slice)	[^{3}H]Noradrenaline release	Schlicker et al. 1997
	Man	Hippocampus (brain slice)		
Dopamine	Rat	Caudate-putamen	[^{3}H]Dopamine release	Cadogan et al. 1997
Dopamine	Rat	Caudate-putamen	NMDA-stimulated [^{3}H]dopamine release	Kathmann et al. 1999
Dopamine	Guinea-pig	Retina	[^{3}H]Noradrenaline release	Schlicker et al. 1996
Serotonin	Mouse	Cortex (brain slice)	[^{3}H]Serotonin release	Nakazi et al. 2000
Acetylcholine	Rat	Hippocampus (brain slice)	[^{3}H]Acetylcholine release	Gifford and Ashby 1996
		Cortex, hippocampus (synaptosomes)		Gifford et al. 2000
Acetylcholine	Mouse	Cortex, hippocampus (brain slice)	[^{3}H]Acetylcholine release	Kathmann et al. 2001a
Acetylcholine	Mouse Man	Cortex (brain slice) Cortex (brain slice)	[^{3}H]Acetylcholine release	Steffens et al. 2003

NMDA, *N*-methyl-D-aspartate

the terminals of the striatonigral axons in the caudate-putamen. Dopamine release was depressed in some studies (Table 3), but not, however, in a study using voltammetry to measure dopamine release (Szabo et al. 1999). Serotonin release was slightly inhibited in the cortex of mice but not affected at all in the cortex of rats (Table 3; Van Vliet et al. 2000). Moreover, cannabinoids inhibit acetylcholine release in the hippocampus and cortex; inhibition also occurs in human cortex (Table 3). However, not all cholinergic neurons are affected by cannabinoids: e.g. acetylcholine release from the cholinergic interneurons of the caudate-putamen is not changed by cannabinoids (Gifford et al. 1997a; Kathmann et al. 2001a).

The papers listed in Table 3 and discussed in the preceding paragraph represent in vitro studies, and the question arises whether similar results are also obtained in vivo. This was examined in a series of studies on rats subjected to in vivo microdialysis; the ligands under study were administered intraperitoneally or intravenously. Cannabinoids indeed decrease acetylcholine release in the dorsal hippocampus (Mishima et al. 2002). In the studies by Tzavara et al. (2001, 2003a), in which cannabinoid agonists were not studied themselves, the CB_1 receptor inverse agonist SR 141716, which elicits effects opposite in direction to those of cannabi-

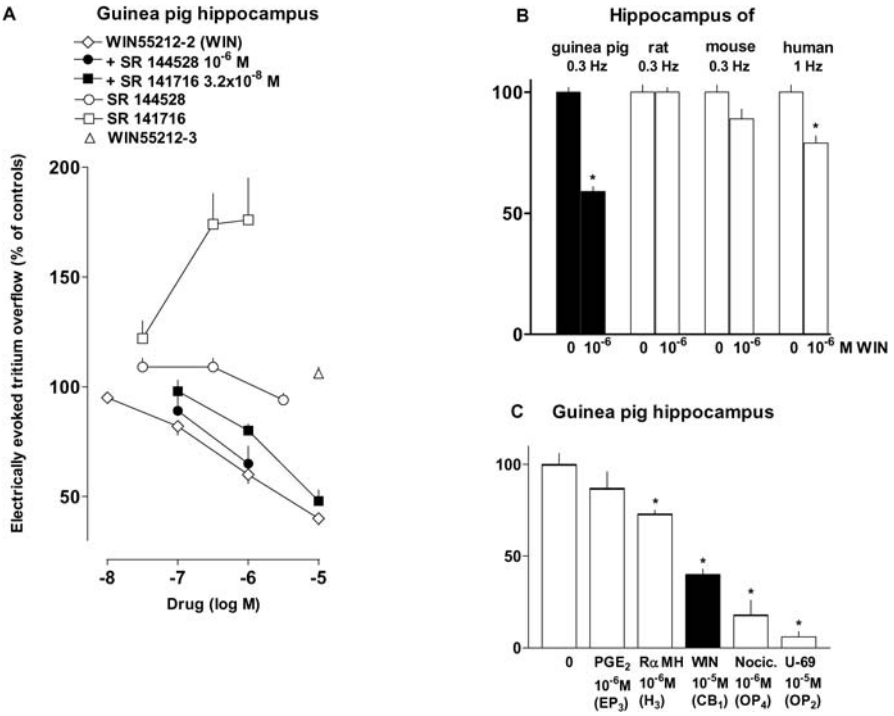

Fig. 4A–C. Cannabinoids inhibit noradrenaline release in the brain. **A** Guinea-pig hippocampal slices were preincubated with [^{3}H]noradrenaline and superfused. The electrically (0.3 Hz) evoked tritium overflow (which represents quasi-physiological noradrenaline release) was inhibited by WIN55212-2 but not affected by its enantiomer WIN55212-3. The concentration–response curve of WIN55212-2 (WIN) was shifted to the right by a low concentration of the CB_1 receptor antagonist SR 141716 (pA_2 8.2) but hardly affected by a high concentration of the CB_2 receptor antagonist SR 144528. Given alone, SR 141716 facilitated, whereas SR 144528 did not affect, noradrenaline release. In another series of experiments, not shown here, slices were superfused with K^+-rich (2.5×10^{-2} M) Ca^{2+}-free medium containing tetrodotoxin 10^{-6} M; under this experimental condition WIN inhibited tritium overflow evoked by re-introduction of Ca^{2+} 1.3×10^{-3} M (in a manner sensitive to SR 141716 3.2×10^{-7}), suggesting that the CB_1 receptors are located presynaptically on the noradrenergic axon terminals. **B** WIN inhibited noradrenaline release also in human hippocampus but failed to do so in rat and mouse hippocampus. Although SR 141716 3.2×10^{-7} M counteracted the effect of WIN in human hippocampus, it did not affect noradrenaline release by itself (not shown). (Since noradrenaline release is relatively low in human hippocampus we used a higher stimulation frequency than in hippocampal slices from the three animal species.) **C** In guinea-pig hippocampus, the inhibitory effect of WIN is higher than that of prostaglandin E_2 (*PGE_2*; acting via prostaglandin EP_3 receptors) and R-α-methylhistamine (*RαMH*; acting via histamine H_3 receptors), but lower than that of nociceptin (*Nocic.*; acting via opioid OP_4 receptors) and U-69,593 (*U-69*; acting via OP_2 receptors). Note that the concentrations of the five agonists cause maximum or near maximum effects at the respective presynaptic inhibitory receptors. *, Significant difference from control ($p<0.001$). See Schlicker et al. (1997) and Timm et al. (1998) for details of the experiments (some of the data shown here are unpublished)

noid agonists under a variety of conditions (for a more detailed discussion, see Sect. 7), increases noradrenaline release in the prefrontal cortex and anterior hypothalamus, dopamine release in the prefrontal cortex and serotonin release in

the prefrontal cortex and nucleus accumbens. On the other hand, cannabinoids increase rather than decrease striatal dopamine release (Malone and Taylor 1999) and acetylcholine release in the frontal cortex (Verrico et al. 2003). The situation is even more complicated with respect to the effects of cannabinoids on acetylcholine release in the medial prefrontal cortex and hippocampus. Low doses of cannabinoids increase (Acquas et al. 2000, 2001), whereas high doses decrease (Gessa et al. 1998; Carta et al. 1998), the release of this transmitter.

The fact that cannabinoids when given systemically increase rather than decrease transmitter release in various paradigms in vivo is in all likelihood not related to the fact that there are also facilitatory cannabinoid receptors. Inhibitory CB_1 receptors occur both on facilitatory and inhibitory neurons of complex neuronal networks and cannabinoids may therefore elicit inhibitory or facilitatory effects on transmitter release, depending on the exact site(s) where they act. Two typical networks in which presynaptic inhibitory CB_1 receptors occur on various sites are depicted in Figs. 6 and 7. The recent study by Tzavara et al. (2003b) shows that the differential effects of cannabinoids on hippocampal acetylcholine release (Gessa et al. 1998; Carta et al. 1998; Acquas et al. 2000, 2001) are due to the fact that the cannabinoids, depending on the dose, act on different pathways, involving dopamine D_1 or D_2 receptors.

5
Effects of Cannabinoids on Neurotransmission in the Peripheral Nervous System

Effects of cannabinoids on the sympathetic nervous system have been studied in isolated tissues and in pithed animals (Table 4). Sympathetic neurons were usually activated by electrical stimulation. Activation of CB_1 receptors led to inhibition of noradrenaline and/or ATP release and, consequently, to inhibition of the effector responses in the heart, in mesenteric and renal blood vessels and in the vas deferens. Figure 5A shows that cannabinoids inhibit sympathetic neuroeffector transmission in the heart. Sympathetically mediated vasoconstriction was inhibited in many tissues of pithed rats and rabbits. Sympathetic tone is depressed during long-term Δ^9-tetrahydrocannabinol administration in humans; the presynaptic inhibitory effect of cannabinoids on sympathetic axon endings may be the basis of this effect.

Cannabinoids also inhibit transmitter release from cholinergic autonomic neurons (Table 4). As an example, the bradycardia elicited by vagal nerve stimulation is depressed. Figure 5B shows that cannabinoids inhibit parasympathetic neuroeffector transmission in the heart. Electrically evoked contractions of the ileum and urinary bladder can also be inhibited by activation of CB_1 receptors (Table 4).

Finally, cannabinoids inhibit the release of neuropeptides like calcitonin gene-related peptide (CGRP), substance P and somatostatin from sensory neurons (Table 4). Capsaicin or electrical stimulation was used to evoke neuropeptide release. In some of these studies, the endocannabinoid anandamide was used, which has a dual effect on neuropeptide release from sensory neurons. Anandamide possesses an inhibitory effect mediated via CB_1 receptors at low concentrations and

Table 4. Inhibition of neuroeffector transmission in the peripheral nervous system (*continued on next page*)

Neurotransmitter	Species	Tissue	Method	Reference(s)
Noradrenaline	Mouse	Sympathetic neurons (cell culture)	Electrically evoked [^{3}H]noradrenaline release	Göbel et al. 2000
Noradrenaline	Rat	Vas deferens	Electrically evoked contraction	Christopoulos et al. 2001
Noradrenaline	Rat	Vas deferens, heart atrium	Electrically evoked [^{3}H]noradrenaline release	Ishac et al. 1996
Noradrenaline, ATP	Mouse	Vas deferens	Electrically evoked contraction	Pertwee et al. 1992, 2002
ATP	Mouse	Vas deferens	Electrically evoked contraction	Lay et al. 2000
Noradrenaline	Mouse	Vas deferens	Electrically evoked [^{3}H]noradrenaline release	Trendelenburg et al. 2000; Schlicker et al. 2003
Noradrenaline	Rat	Heart	Electrically evoked cardioaccelerator response	Malinowska et al. 2001
Noradrenaline	Rabbit	Heart	Electrically evoked cardioaccelerator response	Szabo et al. 2001
Acetylcholine			Bradycardia evoked by electrical stimulation of the vagus nerve	
Noradrenaline	Man	Heart atrial appendages	Electrically evoked [^{3}H]noradrenaline release	Molderings et al. 1999
Noradrenaline	Rat	Sympathetically innervated blood vessels of many organs	Electrically evoked increase in blood pressure in pithed rats	Malinowska et al. 1997
Noradrenaline	Rat	Sympathetically innervated tissues of many organs	Electrically evoked increase in blood pressure and plasma noradrenaline in pithed rats	Niederhoffer et al. 2003
Noradrenaline	Rabbit	Sympathetically innervated tissues of many organs	Electrically evoked increase in blood pressure and plasma noradrenaline in pithed rabbits	Niederhoffer and Szabo 1999
Noradrenaline	Rat	Mesenterial vessels	Electrically evoked noradrenaline release	Ralevic and Kendall 2002
Noradrenaline	Rat	Renal arteries	K^+-evoked [^{3}H]noradrenaline release	Deutsch et al. 1997
Noradrenaline	Guinea-pig	Lung (bronchi)	Electrically evoked [^{3}H]noradrenaline release	Vizi et al. 2001
Adrenaline	Rabbit	Adrenal medulla	Electrically evoked increase in plasma adrenaline in pithed rabbits Electrically evoked adrenaline release in isolated adrenal medullary slices	Niederhoffer et al. 2001

Table 4. (*continued*)

Neurotransmitter	Species	Tissue	Method	Reference(s)
Acetylcholine, ATP	Mouse	Urinary bladder	Electrically evoked contraction	Pertwee and Fernando 1996
Acetylcholine, NANC-transmitter	Mouse	Colon	Electrically evoked cholinergic and NANC postsynaptic potentials	Storr et al. 2004
Acetylcholine	Guinea-pig	Ileum	Electrically evoked contraction, acetylcholine release, cholinergic postsynaptic potentials	Pertwee et al. 1992, 1996b; Lopez-Redondo et al. 1997; Mang et al. 2001
Acetylcholine, NANC-transmitter	Guinea-pig	Ileum	Electrically evoked contraction	Izzo et al. 1998
Acetylcholine	Man	Ileum	Electrically evoked contraction	Croci et al. 1998
Adenosine	Guinea-pig	Ileum	Electrically evoked adenosine release	Begg et al. 2002
CGRP	Rat	Primary sensory neurons (cell culture)	Basal and capsaicin-evoked CGRP release	Ahluwalia et al. 2003
CGRP, substance P, somatostatin	Rat	Trachea	Capsaicin-evoked CGRP, substance P and somatostatin release	Nemeth et al. 2003
CGRP	Rat	Hind paw skin	Capsaicin-evoked CGRP release	Richardson et al. 1998; Ellington et al. 2002
CGRP	Rat	Spinal cord slices	Electrically evoked CGRP release	Tognetto et al. 2001

CGRP, calcitonin gene-related peptide; NANC, non-adrenergic-non-cholinergic

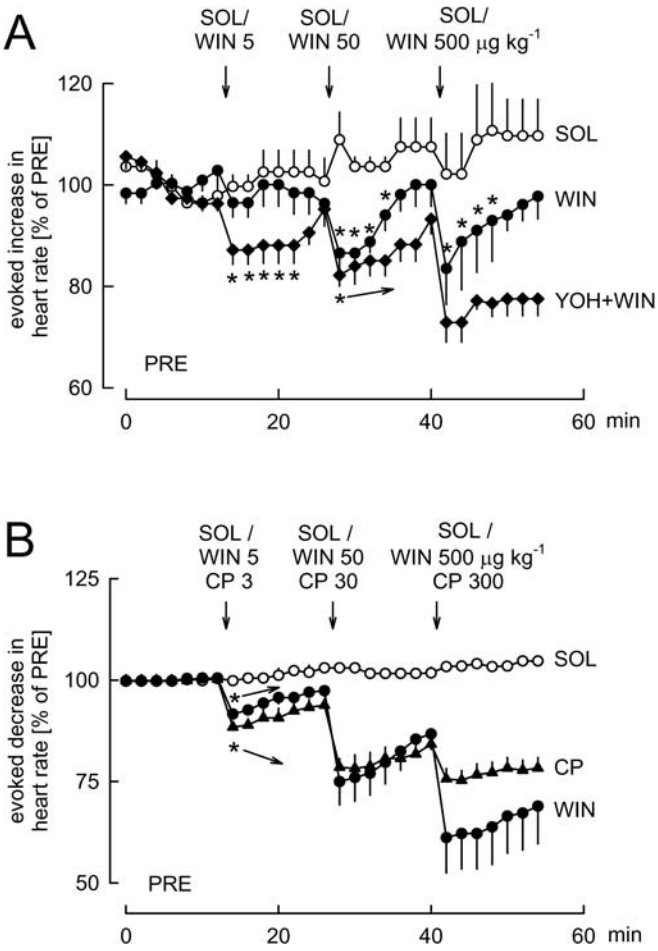

Fig. 5A, B. Cannabinoids inhibit sympathetic and parasympathetic neuroeffector transmission in the heart. **A** Cardiac sympathetic nerves in pithed rabbits were stimulated at a frequency of 1 Hz for 30 s. Solvent (*SOL*) and WIN55212-2 (*WIN*) were administered i.v. as indicated by the *arrows*. One of the WIN groups (*YOH+WIN*) was pretreated with the α_2-adrenoceptor antagonist yohimbine (0.5 mg/kg^{-1}; i.v.) at $t = -14$ min. Cardioaccelerator responses are given as percentages of the initial reference value (*PRE*). WIN inhibited the cardioaccelerator response more strongly in the presence of YOH, probably because YOH prevented concurrent inhibition by endogenous noradrenaline. **B** The right vagus nerve was stimulated at a frequency of 10 Hz for 5 s. SOL, WIN and CP55940 (*CP*) were administered i.v. as indicated by the *arrows*. Cardiodecelerator responses are given as percentages of the initial reference value PRE. *, Significant difference from SOL ($p<0.05$). See Szabo et al. (2001) for details of the experiments

a stimulatory effect mediated via vanilloid receptors (TRPV1, transient receptor potential V1 channel) at high concentrations (Zygmunt et al. 1999; Tognetto et al. 2001; Ahluwalia et al. 2003; Nemeth et al. 2003).

The effect of cannabinoids on peripheral autonomic transmission has been extensively reviewed by Ralevic (2003).

6
Mechanism of the Presynaptic Inhibition

Information regarding the mechanism of presynaptic inhibition is included in Tables 1 and 2. As expected for a $G\alpha_{i/o}$ protein-coupled receptor, the presynaptic inhibition mediated by the CB_1 receptor was sensitive to pertussis toxin in the few cases where this interaction was studied. Moreover, in isolated hippocampal neurons, presynaptic inhibition of excitatory neurotransmission elicited by CB_1 receptor activation could be mediated by several subtypes of $G\alpha_{i/o}$ proteins: $G\alpha_{o1}$, $G\alpha_{i2}$ and $G\alpha_{i3}$ (Straiker et al. 2002). Information on the involvement of second messengers in the presynaptic inhibition by cannabinoids is sparse. For example, the role of $G\beta\gamma$ proteins is not known. Data on the role of the cyclic adenosine monophosphate (cAMP)–protein kinase A messenger system are contradictory (see Tables 1 and 2). After activation of $G\alpha_{i/o}$ protein-coupled receptors, several final mechanisms may lead to inhibition of transmitter release (for review see Thompson et al. 1993; Wu and Saggau 1997; see Fig. 8). Most often, presynaptic inhibition is attributed to inhibition of voltage-dependent calcium channels. In addition, activation of potassium channels and direct interference with the vesicle release machinery can also play a role in presynaptic inhibition. It seems that cannabinoids can use all three mechanisms for producing presynaptic depression (see Tables 1 and 2). Since it is extremely difficult to obtain electrophysiological access to mammalian axon terminals, direct evidence for cannabinoid-evoked modulation of axon terminal ion channels is lacking. Therefore, most of the evidence regarding the mechanism of cannabinoid-evoked presynaptic inhibition is indirect.

6.1
Inhibition of Calcium Channels

As mentioned above, cannabinoids inhibit voltage-dependent calcium channels in somadendritic regions of neurons (see Sect. 2.1.1). It is assumed that such an inhibition also operates in axon terminals and is responsible for presynaptic inhibition. Using microfluorometric methods, it was indeed shown that the action potential-evoked increase in axon terminal calcium concentration is depressed by exogenous and endogenous cannabinoids (Kreitzer and Regehr 2001; Diana et al. 2002; Daniel and Crepel 2001; Brown et al. 2003a; Diana and Marty 2003). Based on the interaction between cannabinoids and calcium channel blockers, Sullivan (1999) concluded that calcium channel inhibition is responsible for the cannabinoid-evoked depression of synaptic transmission.

6.2
Activation of Potassium Channels

As mentioned above, cannabinoids activate several types of potassium channels in the somadendritic region of neurons (see Sect. 2.1.2). Cannabinoid-evoked open-

ing of potassium channels will hyperpolarise axon terminals and shorten action potentials. As a consequence, invasion of axon terminals by action potentials and the activation of calcium channels can be impeded. The duration of calcium influx during the action potential may also decrease. Evidence for the involvement of potassium channels in presynaptic inhibition was obtained by using potassium channel blockers. Thus, potassium channel blockers prevented cannabinoid-evoked presynaptic inhibition (Daniel and Crepel 2001; Robbe et al. 2001; Diana and Marty 2003; Azad et al. 2003) and cannabinoid-evoked inhibition of the action potential-triggered increase in axon terminal calcium concentration (Daniel and Crepel 2001). In contrast, since potassium channel blockers did not affect cannabinoid-evoked presynaptic inhibition, Hoffman and Lupica (2000) excluded a role of potassium channels in presynaptic inhibition.

6.3
Direct Inhibition of the Vesicle Release Machinery

In most nerve terminals, spontaneous and asynchronous quantal transmitter release occurs also in the absence of calcium influx through voltage-dependent calcium channels. Such release events are recorded in electrophysiological experiments either in the presence of tetrodotoxin or calcium channel blockers. The recorded postsynaptic events are called miniature excitatory or inhibitory postsynaptic currents (mEPSCs or mIPSCs). There are many examples for the lowering of the frequency of mEPSCs and mIPSCs by cannabinoids (Tables 1 and 2), including GABAergic synaptic transmission between basket and Purkinje cells in the rat cerebellar cortex (Fig. 3). These observations indicate that cannabinoids are capable of inhibiting neurotransmitter release at a site downward of calcium entry into axon terminals, most probably at the level of the vesicular release machinery. However, it is also clear from Tables 1 and 2 that at many synapses cannabinoids produce presynaptic inhibition without directly interfering with vesicular release.

In conclusion, there are examples for presynaptic inhibition by all three mechanisms: inhibition of voltage-dependent calcium channels, activation of potassium channels and inhibition of the vesicle-release machinery. The inhibitory mechanisms vary in different types of axon terminals. One axon terminal can possess several inhibitory mechanisms (for example, calcium channels and vesicle release can be inhibited simultaneously).

7
Endogenous Tone at Presynaptic Cannabinoid Receptors

There is now increasing evidence that cannabinoid receptors involved in the inhibition of neuroeffector transmission are subject to an endogenous tone (Table 5). A typical example is the presynaptic CB_1 receptors on GABAergic neurons synapsing with the pyramidal neurons in the rat hippocampus (Wilson and Nicoll 2001). Depolarisation of the latter neurons causes an increase in formation of endo-

Table 5. Endogenous tone at CB_1 receptors inhibiting neuroeffector transmission (*continued on next page*)

Neurotransmitter	Species	Tissue	Method	Identification of endogenous tone[1]	Reference(s)
Glutamate	Rat	Cortex	Electrophysiology (patch clamp)	Inverse agonist (SR 141716)	Auclair et al. 2000
Glutamate	Rat	Caudate-putamen	Electrophysiology (patch clamp)	Inverse agonist (AM 281)	Huang et al. 2001
Glutamate	Rat	Hippocampus	Electrophysiology (extracellular recording)	Inverse agonist (SR 141716)	Ameri et al. 1999
GABA	Rat	Hippocampus	Electrophysiology (patch clamp)	Inhibitor of endocannabinoid reuptake (AM 404)	Wilson and Nicoll 2001
Noradrenaline	Guinea-pig	Hippocampus	[^{3}H]Noradrenaline release	Inverse agonists (SR 141716, AM 251, AM 281)	Schlicker et al. 1997, 2002
Noradrenaline	Rat	Vas deferens	Contraction	Inverse agonists (SR 141716, LY 320135), inhibitor of endocannabinoid degradation (phenylmethylsulfonyl fluoride, PMSF)	Christopoulos et al. 2001
Noradrenaline, ATP	Mouse	Vas deferens	Contraction	Inverse agonist (SR 141716)	Pertwee et al. 1996a
Noradrenaline	Mouse	Vas deferens	[^{3}H]Noradrenaline release	Inverse agonist (SR 141716), knockout mouse generated by Zimmer et al. 1999	Schlicker et al. 2003
Dopamine	Guinea-pig	Retina	[^{3}H]Dopamine release	Inverse agonist (SR 141716)	Schlicker et al. 1996
Acetylcholine	Man	Cortex	[^{3}H]Acetylcholine release	Inverse agonist (SR 141716), partial agonist (O-1184), inhibitor of endocannabinoid reuptake (AM 404)	Steffens et al. 2003
Acetylcholine	Rat	Hippocampus	[^{3}H]Acetylcholine release	Inverse agonists (SR 141716, AM 281)	Gifford and Ashby 1996; Gifford et al. 1997b, 2000
Acetylcholine	Mouse	Hippocampus	[^{3}H]Acetylcholine release	Inverse agonist (SR 141716), knockout mouse generated by Zimmer et al. 1999	Kathmann et al. 2001a,b
Acetylcholine	Guinea-pig	Hippocampus	[^{3}H]Acetylcholine release	Inverse agonist (SR 141716)	Schultheiß et al. 2004
Acetylcholine, ATP	Mouse	Urinary bladder	Contraction	Inverse agonist (SR 141716)	Pertwee and Fernando 1996

Table 5. (*continued*)

Neurotransmitter	Species	Tissue	Method	Identification of endogenous tone[1]	Reference(s)
Acetylcholine	Mouse	Colon	Electrophysiology (intracellular recording)	Inverse agonist (SR 141716), knockout mouse generated by Marsicano et al. 2002	Storr et al. 2004
Acetylcholine, substance P	Guinea-pig	Small intestine	Contraction	Inverse agonist (SR 141716)	Pertwee et al. 1996b; Coutts and Pertwee 1997; Izzo et al. 1998
Acetylcholine	Guinea-pig	Ileum	[^{3}H]Acetylcholine release	Inverse agonist (SR 141716)	Mang et al. 2001
Substance P	Mouse	Spinal cord	Substance P release	Inverse agonist (SR 141716)	Lever and Malcangio 2002

[1] Inverse and partial agonists and CB_1 receptor disruption increase, whereas inhibition of endocannabinoid reuptake or degradation decreases, transmitter release.

cannabinoids, which in turn activate the presynaptic inhibitory CB_1 receptors on the GABAergic neurons (Fig. 8; see also the chapter by Vaughan and Christie, this volume). The inhibitory effect is mimicked by a blocker of endocannabinoid reuptake, i.e. AM 404 (in a manner sensitive to the CB_1 receptor inverse agonist SR 141716), suggesting that endocannabinoids are accumulating. This has also been shown in some other paradigms (Table 5) and even in human tissue (Steffens et al. 2003). The same conclusion was reached from experiments in which a blocker of the degradation of the endocannabinoids, i.e. phenylmethylsulfonyl fluoride (PMSF), mimicked the inhibitory effect of the endocannabinoids (Table 5). The third approach was the use of a partial CB_1 receptor agonist, O-1184, which led to an increase in transmitter release, probably by interrupting the inhibition caused by accumulating endocannabinoids (Steffens et al. 2003).

In many studies, SR 141716 or other antagonists/inverse agonists increased transmitter release (Fig. 4; Table 5). Although the reason for their facilitatory effect might be the same as in the case of O-1184, an entirely different explanation has to be considered as well. Thus, presynaptic CB_1 receptors may be constitutively active, i.e. inhibit transmitter release even if they are not activated by endocannabinoids, and in this case inverse agonists would be expected to increase transmitter release as well. Constitutive activity frequently occurs with G protein-coupled receptors expressed in high densities (Seifert and Wenzel-Seifert 2002) and CB_1 receptors are expressed in relatively high densities when compared to other G protein-coupled receptors (Wilson and Nicoll 2002). In at least one of the paradigms shown in Table 5, constitutive activity seems to be the only possible explanation. Thus, SR 141716 increased the Ca^{2+}-induced [^{3}H]acetylcholine release in rat hippocampal synaptosomes (Gifford et al. 2000). In synaptosomes as opposed to isolated tissues (used in most of the other studies shown in Table 5), accumulation of endogenously released ligands cannot occur, since the latter are efficiently removed by the superfusion stream (Starke et al. 1989). For further clarification, neutral CB_1 receptor antagonists (which have become available only recently; Hurst et al. 2002; Ruiu et al. 2003) will be useful, since they are expected to facilitate transmitter release if endocannabinoids are accumulating but should be without effect if CB_1 receptors are constitutively active.

The facilitatory effect of inverse agonists on transmitter release was mimicked in some paradigms by the disruption of CB_1 receptors, i.e. transmitter release was higher in tissues from CB_1 receptor-deficient mice when compared to wild-type animals (Table 5). This experimental approach does not allow one to reach a conclusion as to whether the endogenous tone is related to accumulation of endocannabinoids or constitutively active CB_1 receptors; yet it is remarkable that blockade of, or inverse agonism at, CB_1 receptors during the course of the experiment and complete lack of CB_1 receptors have the same consequence.

The fact that presynaptic CB_1 receptors at many sites are activated by endogenous compounds lends further support to the view that the cannabinoid system plays an important regulatory role. It has also great practical relevance since CB_1 receptor antagonists/inverse agonists may be used for therapeutic purposes (for further discussion, see the chapter by Robson, this volume).

8
What Is the Functional Role of Presynaptic Cannabinoid Receptors?

It is evident from Sects. 4 and 5 that presynaptic CB_1 receptors are ubiquitous in the central and peripheral nervous system. Even within one functional system, several components of the neuronal circuitry are equipped with CB_1 receptors. This will be illustrated in two functional systems: the extrapyramidal motor control system (Fig. 6) and the cerebellum (Fig. 7).

Figure 6 shows the most important glutamatergic, GABAergic and dopaminergic neuronal connections within the extrapyramidal motor control system. Glutamatergic and GABAergic neurotransmission is inhibited at several sites by cannabinoids. In contrast, dopaminergic transmission may not be influenced. A typical motor effect of high doses of cannabinoids is catalepsy (Compton et al. 1996; Sanudo-Pena et al. 1999). Catalepsy is thought to occur if the GABAergic neurons in the output nucleus of the basal ganglia, the substantia nigra pars reticulata, are firing at a high rate (Kolasiewicz et al. 1988). Among the 11 sites where cannabinoids can act presynaptically, an action at 5 sites would indirectly enhance the firing rate of substantia nigra pars reticulata neurons, and thus would lead to

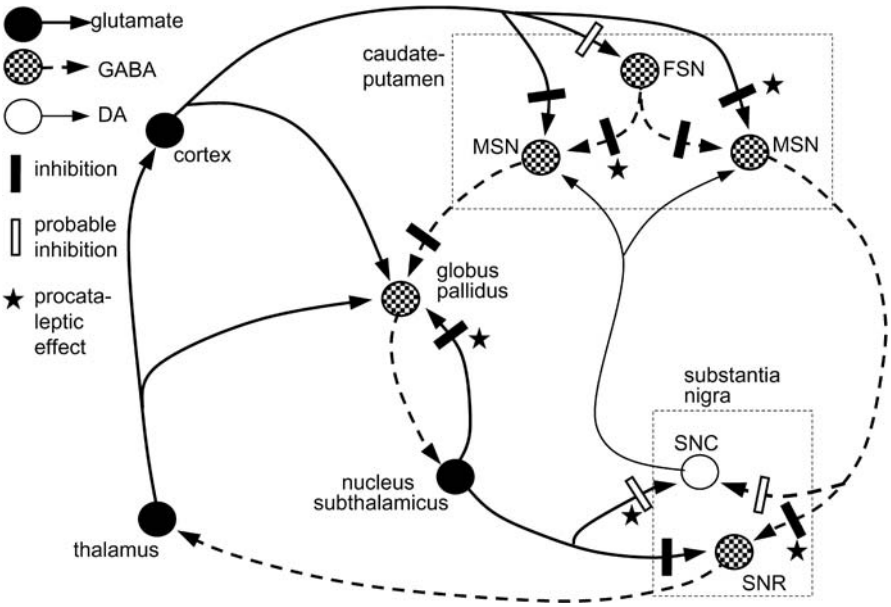

Fig. 6. Effects of cannabinoids on synaptic transmission in nuclei belonging to the extrapyramidal motor control system. *DA*, dopamine; *FSN*, fast spiking neuron; *MSN*, medium spiny neuron; *SNC*, substantia nigra pars compacta; *SNR*, substantia nigra pars reticulata. CB_1 receptor-mediated inhibition of neurotransmission was demonstrated at many synapses of this motor control system. In addition to the proved sites of inhibition, inhibition is very probable at additional sites (based on the localisation of the CB_1 receptor). For the sake of simplicity, the pathway including the entopeduncular nucleus (globus pallidus medialis/internus) is not shown

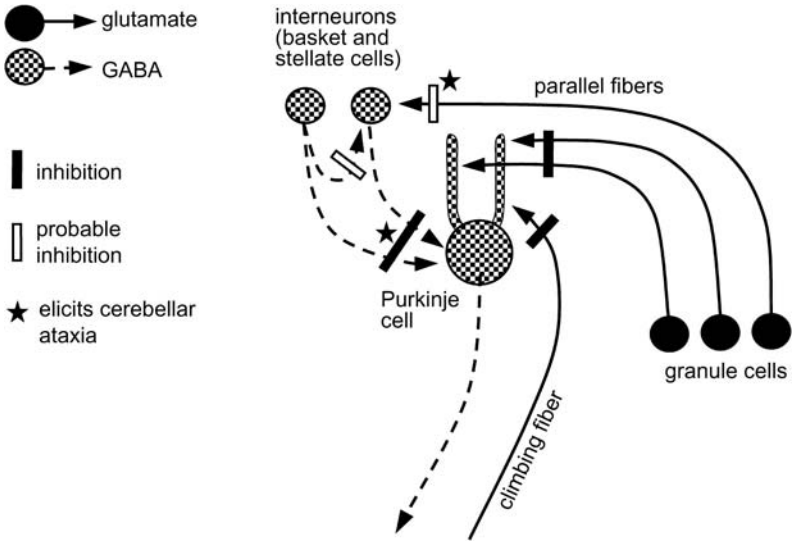

Fig. 7. Effects of cannabinoids on synaptic transmission in the cerebellar cortex. CB_1 receptor-mediated inhibition of neurotransmission was demonstrated at several synapses in the cerebellar cortex. In addition to the proven sites of inhibition, inhibition is very probable at additional sites (based on the localisation of the CB_1 receptor). In addition to synaptic inhibition, activation of CB_1 receptors can also directly decrease the firing rate of interneurons (not shown)

catalepsy. Action at the remaining sites would lead to the opposite effect, i.e. the firing rate of substantia nigra pars reticulata neurons would decrease, which would be an "anticataleptic" effect. In vivo, the balance of all effects obviously favours catalepsy.

Figure 7 shows neuronal connections in the cortex of the cerebellum and the action of cannabinoids on these connections. Activation of CB_1 receptors inhibits glutamatergic as well as GABAergic neurotransmission at altogether five sites. Cannabinoids cause static and gait ataxia, and this is attributed to cerebellar dysfunction (Fränkel 1903; Patel and Hillard 2001). It is thought that the firing rate of Purkinje cells is increased during cerebellar ataxia. Two of the presynaptic cannabinoid effects shown in Fig. 7 would indirectly enhance the firing rate of Purkinje cells; these effects could be the primary events behind cerebellar ataxia. As in the extrapyramidal motor control system, however, inhibitory CB_1 presynaptic receptors are also localised on neurons that play opposite roles in the function of the cortex of the cerebellum.

Further examples for the simultaneous inhibitory effects of cannabinoids on antagonistic components of functional systems can be easily found. For example, cannabinoids inhibit the glutamatergic as well as the GABAergic input of ventral tegmental area dopaminergic neurons (Szabo et al. 2002; Melis et al. 2004) and the sympathetic as well as the parasympathetic input of the heart (Szabo et al. 2001).

What is the physiological role of CB_1 receptors—receptors that are so widely distributed and that simultaneously influence antagonistic components of a given

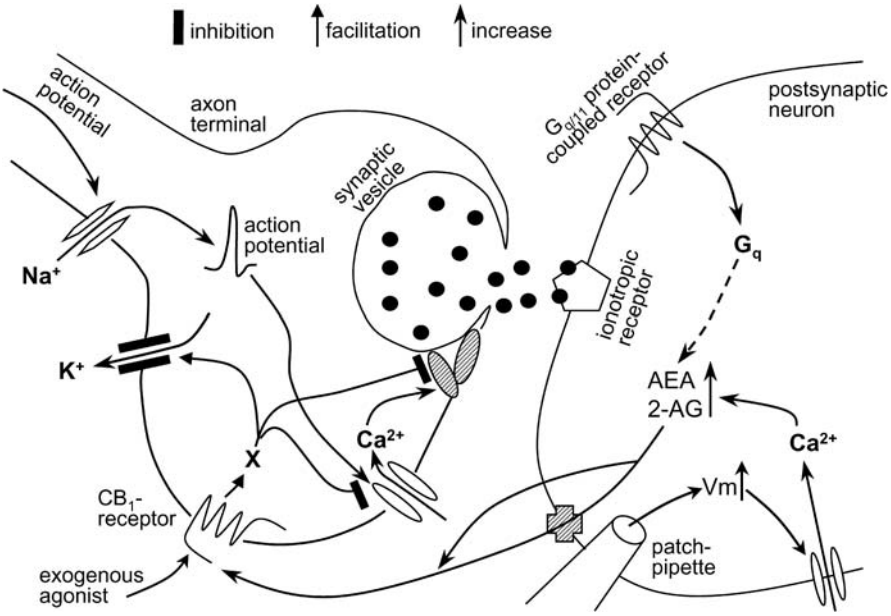

Fig. 8. Effects of cannabinoids on synaptic transmission. Activation of the CB_1 receptor at the presynaptic axon terminal inhibits transmitter release from the synaptic vesicle. Three mechanisms can be involved in presynaptic inhibition (*X* refers to unknown second messengers): inhibition of voltage-dependent calcium channels, activation of potassium channels and direct interference with the vesicle release machinery. The CB_1 receptor can be activated by exogenous agonists, but also by the endocannabinoids anandamide (*AEA*) and 2-arachidonoylglycerol (*2-AG*), which are released from the postsynaptic neuron by passive and/or facilitated diffusion. The synthesis of endocannabinoids is triggered by a depolarisation-induced (V_m, membrane potential) calcium influx or by activation of $G_{q/11}$ protein-coupled receptors

functional system? One functional role of CB_1 receptors is their participation in retrograde signalling, at least with respect to fast excitatory and inhibitory transmission. Endogenous cannabinoids released from postsynaptic neurons can diffuse to presynaptic axon terminals where they produce presynaptic inhibition (Ohno-Shosaku et al. 2001; Wilson and Nicoll 2001). The trigger for synthesis of endocannabinoids is depolarisation of postsynaptic neurons or activation of $G\alpha_{q/11}$ protein-coupled receptors of postsynaptic neurons (see Fig. 8). This phenomenon is called depolarisation-induced suppression of inhibition (DSI; if inhibitory neurotransmission is suppressed by endocannabinoids) or depolarisation-induced suppression of excitation (DSE; if excitatory neurotransmission is suppressed by endocannabinoids). This new research field was reviewed by Wilson and Nicoll (2002) and Freund et al. (2003) and is also reviewed in the chapter by Vaughan and Christie (this volume).

References

Acquas E, Pisanu A, Marrocu P, Di Chiara G (2000) Cannabinoid CB_1 receptor agonists increase rat cortical and hippocampal acetylcholine release in vivo. Eur J Pharmacol 401:179–185

Acquas E, Pisanu A, Marrocu P, Goldberg SR, Di Chiara G (2001) Δ^9-Tetrahydrocannabinol enhances cortical and hippocampal acetylcholine release in vivo: a microdialysis study. Eur J Pharmacol 419:155–161

Ahluwalia J, Urban L, Bevan S, Nagy I (2003) Anandamide regulates neuropeptide release from capsaicin-sensitive primary sensory neurons by activating both the cannabinoid 1 receptor and the vanilloid receptor 1 in vitro. Eur J Neurosci 17:2611–2618

Akinshola BE, Taylor RE, Ogunseitan AB, Onaivi ES (1999) Anandamide inhibition of recombinant AMPA receptor subunits in Xenopus oocytes is increased by forskolin and 8-bromo-cyclic AMP. Naunyn–Schmiedeberg's Arch Pharmacol 360:242–248

Al-Hayani A, Davies SN (2000) Cannabinoid receptor mediated inhibition of excitatory synaptic transmission in the rat hippocampal slice is developmentally regulated. Br J Pharmacol 131:663–665

Ameri A, Simmet T (2000) Effects of 2-arachidonoylglycerol, an endogenous cannabinoid, on neuronal activity in rat hippocampal slices. Naunyn–Schmiedeberg's Arch Pharmacol 361:265–272

Ameri A, Wilhelm A, Simmet T (1999) Effects of the endogenous cannabinoid, anandamide, on neuronal activity in rat hippocampus slices. Br J Pharmacol 126:1831–1839

Auclair N, Otani S, Soubrie P, Crepel F (2000) Cannabinoids modulate synaptic strength and plasticity at glutamatergic synapses of rat prefrontal cortex pyramidal neurons. J Neurophysiol 83:3287–3293

Azad SC, Eder M, Marsicano G, Lutz B, Zieglgänsberger W, Rammes G (2003) Activation of the cannabinoid receptor type 1 decreases glutamatergic and GABAergic synaptic transmission in the lateral amygdala of the mouse. Learn Mem 10:116–128

Barann M, Molderings G, Brüss M, Bönisch H, Urban BW, Göthert M (2002) Direct inhibition by cannabinoids of human $5\text{-}HT_{3A}$ receptors: probable involvement of an allosteric modulatory site. Br J Pharmacol 137:589–596

Begg M, Dale N, Llaudet E, Molleman A, Parsons ME (2002) Modulation of the release of endogenous adenosine by cannabinoids in the myenteric plexus-longitudinal muscle preparation of the guinea-pig ileum. Br J Pharmacol 137:1298–1304

Brown SP, Brenowitz SD, Regehr WG (2003a) Brief presynaptic bursts evoke synapse-specific retrograde inhibition mediated by endogenous cannabinoids. Nat Neurosci 6:1048–1057

Brown TM, Brotchie JM, Fitzjohn SM (2003b) Cannabinoids decrease corticostriatal synaptic transmission via an effect on glutamate uptake. J Neurosci 23:11073–11077

Cadogan A-K, Alexander SPH, Boyd AE, Kendall DA (1997) Influence of cannabinoids on electrically evoked dopamine release and cyclic AMP generation in the rat striatum. J Neurochem 69:1131–1137

Carta G, Nava F, Gessa GL (1998) Inhibition of hippocampal acetylcholine release after acute and repeated Δ^9-tetrahydrocannabinol in rats. Brain Res 809:1–4

Caulfield MP, Brown DA (1992) Cannabinoid receptor agonists inhibit Ca current in NG108-15 neuroblastoma cells via a pertussis toxin-sensitive mechanism. Br J Pharmacol 106:231–232

Chan PKY, Yung W-H (1998) Occlusion of the presynaptic action of cannabinoids in rat substantia nigra pars reticulata by cadmium. Neurosci Lett 249:57–60

Chan PKY, Chan SCY, Yung W-H (1998) Presynaptic inhibition of GABAergic inputs to rat substantia nigra pars reticulata neurones by a cannabinoid agonist. Neuroreport 9:671–675

Chemin J, Monteil A, Perez-Reyes E, Nargeot J, Lory P (2001) Direct inhibition of T-type calcium channels by the endogenous cannabinoid anandamide. EMBO J 20:7033–7040

Christopoulos A, Coles P, Lay L, Lew MJ, Angus JA (2001) Pharmacological analysis of cannabinoid receptor activity in the rat vas deferens. Br J Pharmacol 132:1281–1291

Compton DR, Harris LS, Lichtman AH Martin BR (1996) Marihuana. Pharmacological aspects of drug dependence. In: Schuster CR, Kuhar MJ (eds) Handbook of Experimental Pharmacology. Springer, Heidelberg, pp 83–158

Coutts AA, Pertwee RG (1997) Inhibition by cannabinoid receptor agonists of acetylcholine release from the guinea-pig myenteric plexus. Br J Pharmacol 121:1557–1566

Croci T, Manara L, Aureggi G, Guagnini F, Rinaldi-Carmona M, Maffrand J-P, Le Fur G, Mukenge S, Ferla G (1998) In vitro functional evidence of neuronal cannabinoid CB1 receptors in human ileum. Br J Pharmacol 125:1393–1395

Daniel H, Crepel F (2001) Control of Ca^{2+} influx by cannabinoid and metabotropic glutamate receptors in rat cerebellar cortex requires K^+ channels. J Physiol (Lond) 537:793–800

Deadwyler SA, Hampson RE, Mu J, Whyte A, Childers S (1995) Cannabinoids modulate voltage sensitive potassium A-current in hippocampal neurons via a cAMP-dependent process. J Pharmacol Exp Ther 273:734–743

Deutsch DG, Goligorsky MS, Schmid PC, Krebsbach RJ, Schmid HHO, Das SK, Dey SK, Arreaza G, Thorup C, Stefano G, Moore L (1997) Production and physiological actions of anandamide in the vasculature of the rat kidney. J Clin Invest 100:1538–1546

Diana MA, Marty A (2003) Characterization of depolarization-induced suppression of inhibition using paired interneuron-Purkinje cell recordings. J Neurosci 23:5906–5918

Diana MA, Levenes C, Mackie K, Marty A (2002) Short-term retrograde inhibition of GABAergic synaptic currents in rat Purkinje cells is mediated by endogenous cannabinoids. J Neurosci 22:200–208

Ellington HC, Cotter MA, Cameron NE, Ross RA (2002) The effect of cannabinoids on capsaicin-evoked calcitonin gene-related peptide (CGRP) release from the isolated paw skin of diabetic and non-diabetic rats. Neuropharmacology 42:966–975

Engler B, Szabo B (2003) Cannabinoids inhibit striatopallidal neurotransmission in mice. Naunyn–Schmiedeberg's Arch Pharmacol 367:R85

Engler B, Szabo B (2004) Characterization of the effects of cannabinoids on synaptic transmission between caudate-putamen and globus pallidus. Naunyn–Schmiedeberg's Arch Pharmacol 369:R80

Fan P (1995) Cannabinoid agonists inhibit the activation of 5-HT_3 receptors in rat nodose ganglion neurons. J Neurophysiol 73:907–910

Ferraro L, Tomasini MC, Gessa GL, Bebe BW, Tanganelli S, Antonelli T (2001) The cannabinoid receptor agonist WIN 55,212–2 regulates glutamate transmission in rat cerebral cortex: an in vivo and in vitro study. Cerebral Cortex 11:728–733

Fränkel S (1903) Chemie und Pharmakologie des Haschisch. Naunyn–Schmiedeberg's Arch Exp Pathol Pharmakol 49:266–284

Freund TF, Katona I, Piomelli D (2003) Role of endogenous cannabinoids in synaptic signaling. Physiol Rev 83:1017–1066

Garcia DE, Brown S, Hille B, Mackie K (1998) Protein kinase C disrupts cannabinoid actions by phosphorylation of the CB1 cannabinoid receptor. J Neurosci 18:2834–2841

Gerdeman G, Lovinger DM (2001) CB1 cannabinoid receptor inhibits synaptic release of glutamate in rat dorsolateral striatum. J Neurophysiol 85:468–471

Gessa GL, Casu MA, Carta G, Mascia MS (1998) Cannabinoids decrease acetylcholine release in the medial-prefrontal cortex and hippocampus, reversal by SR 141716A. Eur J Pharmacol 355:119–124

Gifford AN, Ashby Jr CR (1996) Electrically evoked acetylcholine release from hippocampal slices is inhibited by the cannabinoid receptor agonist, WIN 55212–2, and is potentiated by the cannabinoid antagonist, SR 141716A. J Pharmacol Exp Ther 277:1431–1436

Gifford AN, Samiian L, Gatley JS, Ashby Jr CR (1997a) Examination of the effect of the cannabinoid receptor agonist, CP 55,940, on electrically evoked transmitter release from rat brain slices. Eur J Pharmacol 324:187–192

Gifford AN, Tang Y, Gatley SJ, Volkow ND, Lan R, Makriyannis A (1997b) Effect of the cannabinoid receptor SPECT agent, AM 281, on hippocampal acetylcholine release from rat brain slices. Neurosci Lett 238:84–86

Gifford AN, Bruneus M, Gatley SJ, Volkow ND (2000) Cannabinoid receptor-mediated inhibition of acetylcholine release from hippocampal and cortical synaptosomes. Br J Pharmacol 131:645–650

Glass M, Dragunow M, Faull RLM (2000) The pattern of neurodegeneration in Huntington's disease: a comparative study of cannabinoid, dopamine, adenosine and $GABA_A$ receptor alterations in the human basal ganglia in Huntington's disease. Neuroscience 97:505–519

Göbel I, Trendelenburg AU, Cox SL, Meyer A, Starke K (2000) Electrically evoked release of [^{3}H]noradrenaline from mouse cultured sympathetic neurons: release-modulating heteroreceptors. J Neurochem 75:2087–2094

Hájos N, Freund TF (2002) Pharmacological separation of cannabinoid sensitive receptors on hippocampal excitatory and inhibitory fibers. Neuropharmacology 43:503–510

Hájos N, Katona I, Naiem SS, Mackie K, Ledent C, Mody I, Freund TF (2000) Cannabinoids inhibit hippocampal GABAergic transmission and network oscillations. Eur J Neurosci 12:3239–3249

Hájos N, Ledent C, Freund TF (2001) Novel cannabinoid-sensitive receptor mediates inhibition of glutamatergic synaptic transmission in the hippocampus. Neuroscience 106:1–4

Hampson RE, Mu J, Deadwyler SA (2000) Cannabinoid and kappa opioid receptors reduce potassium K current via activation of G_s proteins in cultured hippocampal neurons. J Neurophysiol 84:2356–2364

Henry DJ, Chavkin C (1995) Activation of inwardly rectifying potassium channels (GIRK1) by co-expressed rat brain cannabinoid receptors in Xenopus oocytes. Neurosci Lett 186:91–94

Herkenham M, Lynn AB, De Costa BR, Richfield EK (1991) Neuronal localization of cannabinoid receptors in the basal ganglia of the rat. Brain Res 547:267–274

Himmi T, Perrin J, El Ouazzani T, Orsini J-C (1998) Neuronal responses to cannabinoid receptor ligands in the solitary tract nucleus. Eur J Pharmacol 359:49–54

Hoffman AF, Lupica CR (2000) Mechanisms of cannabinoid inhibition of GABAA synaptic transmission in the hippocampus. J Neurosci 20:2470–2479

Hoffman AF, Lupica CR (2001) Direct actions of cannabinoids on synaptic transmission in the nucleus accumbens: a comparison with opioids. J Neurophysiol 85:72–83

Hoffman AF, Oz M, Caulder T, Lupica CR (2003a) Functional tolerance and blockade of long-term depression at synapses in the nucleus accumbens after chronic cannabinoid exposure. J Neurosci 23:4815–4820

Hoffman AF, Riegel AC, Lupica CR (2003b) Functional localization of cannabinoid receptors and endogenous cannabinoid production in distinct neuron populations of the hippocampus. Eur J Neurosci 18:524–534

Huang C-C, Lo S-W, Hsu K-S (2001) Presynaptic mechanisms underlying cannabinoid inhibition of excitatory synaptic transmission in rat striatal neurons. J Physiol (Lond) 532:731–748

Huang C-C, Chen Y-L, Lo S-W, Hsu K-S (2002) Activation of cAMP-dependent protein kinase suppresses the presynaptic cannabinoid inhibition of glutamatergic transmission at corticostriatal synapses. Mol Pharmacol 61:578–585

Hurst DP, Lynch DL, Barnett-Norris J, Hyatt SM, Seltzman HH, Zhong M, Song ZH, Nie J, Lewis D, Reggio PH (2002) N-(Piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide (SR141716A) interaction with LYS 3.28 (192) is crucial for its inverse agonism at the cannabinoid CB1 receptor. Mol Pharmacol 62:1274–1287

Irving AJ, Coutts AA, Harvey J, Rae MG, Mackie K, Bewick GS, Pertwee RG (2000) Functional expression of cell surface cannabinoid CB_1 receptors on presynaptic inhibitory terminals in cultured rat hippocampal neurons. Neuroscience 98:253–262

Ishac EJN, Jiang L, Lake KD, Varga K, Abood ME, Kunos G (1996) Inhibition of exocytotic noradrenaline release by presynaptic cannabinoid CB_1 receptors on peripheral sympathetic nerves. Br J Pharmacol 118:2023–2028

Izzo AA, Mascolo N, Borrelli F, Capasso F (1998) Excitatory transmission to the circular muscle of the guinea-pig ileum: evidence for the involvement of cannabinoid CB_1 receptors. Br J Pharmacol 124:1363–1368

Jennings EA, Vaughan CW, Christie MJ (2001) Cannabinoid actions on rat superficial medullary dorsal horn neurons in vitro. J Physiol 534:805–812

Kathmann M, Bauer U, Schlicker E, Göthert M (1999) Cannabinoid CB_1 receptor-mediated inhibition of NMDA- and kainate-stimulated noradrenaline and dopamine release in the brain. Naunyn–Schmiedeberg's Arch Pharmacol 359:466–470

Kathmann M, Weber B, Schlicker E (2001a) Cannabinoid CB_1 receptor-mediated inhibition of acetylcholine release in the brain of NMRI, CD-1 and C57BL/6 J mice. Naunyn–Schmiedeberg's Arch Pharmacol 363:50–56

Kathmann M, Weber B, Zimmer A, Schlicker E (2001b) Enhanced acetylcholine release in the hippocampus of cannabinoid CB_1 receptor-deficient mice. Br J Pharmacol 132:1169–1173

Katona I, Sperlagh B, Sik A, Köfalvi A, Vizi ES, Mackie K, Freund TF (1999) Presynaptically located CB1 cannabinoid receptors regulate GABA release from axon terminals of specific hippocampal interneurons. J Neurosci 19:4544–4558

Katona I, Sperlagh B, Magloczky Z, Santha E, Köfalvi A, Czirjak S, Mackie K, Vizi ES, Freund TF (2000) GABAergic interneurons are the targets of cannabinoid actions in the human hippocampus. Neuroscience 100:797–804

Katona I, Rancz EA, Acsady L, Ledent C, Mackie K, Hajos N, Freund TF (2001) Distribution of CB1 cannabinoid receptors in the amygdala and their role in the control of GABAergic transmission. J Neurosci 21:9506–9518

Kim DJ, Thayer SA (2000) Activation of CB1 cannabinoid receptors inhibits neurotransmitter release from identified synaptic sites in rat hippocampal cultures. Brain Res 852:398–405

Köfalvi A, Vizi ES, Ledent C, Sperlagh B (2003) Cannabinoids inhibit the release of [^{3}H]glutamate from rodent hippocampal synaptosomes via a novel CB_1 receptor-independent action. Eur J Neurosci 18:1973–1978

Kolasiewicz W, Wolfarth S, Ossowska K (1988) The role of the ventromedial thalamic nucleus in the catalepsy evoked from the substantia nigra pars reticulata in rats. Neurosci Lett 90:219–223

Kouznetsova M, Kelley B, Shen M, Thayer SA (2002) Desensitization of cannabinoid-mediated presynaptic inhibition of neurotransmission between rat hippocampal neurons in culture. Mol Pharmacol 61:477–485

Kreitzer AC, Regehr WG (2001) Retrograde inhibition of presynaptic calcium influx by endogenous cannabinoids at excitatory synapses onto Purkinje cells. Neuron 29:717–727

Kreitzer AC, Carter AG, Regehr WG (2002) Inhibition of interneuron firing extends the spread of endocannabinoid signaling in the cerebellum. Neuron 34:787–796

Lay L, Angus JA, Wright CE (2000) Pharmacological characterisation of cannabinoid CB_1 receptors in the rat and mouse. Eur J Pharmacol 391:151–161

Levenes C, Daniel H, Soubrie P, Crepel F (1998) Cannabinoids decrease excitatory synaptic transmission and impair long-term depression in rat cerebellar Purkinje cells. J Physiol (Lond) 510:867–879

Lever IJ, Malcangio M (2002) CB1 receptor antagonist SR141716A increases capsaicin-evoked release of Substance P from the adult mouse spinal cord. Br J Pharmacol 135:21–24

Lopez-Redondo F, Lees GM, Pertwee RG (1997) Effects of cannabinoid receptor ligands on electrophysiological properties of myenteric neurones of the guinea-pig ileum. Br J Pharmacol 122:330–334

Mackie K, Hille B (1992) Cannabinoids inhibit N-type calcium channels in neuroblastoma-glioma cells. Proc Natl Acad Sci USA 89:3825–3829

Mackie K, Devane WA, Hille B (1993) Anandamide, an endogenous cannabinoid, inhibits calcium currents as a partial agonist in N 18 neuroblastoma cells. Mol Pharmacol 44:498–503

Mackie K, Lai Y, Westenbroek R, Mitchell R (1995) Cannabinoids activate an inwardly rectifying potassium conductance and inhibit Q-type calcium currents in AtT20 cells transfected with rat brain cannabinoid receptor. J Neurosci 15:6552–6561

Maejima T, Hashimoto K, Yoshida T, Aiba A, Kano M (2001) Presynaptic inhibition caused by retrograde signal from metabotropic glutamate to cannabinoid receptors. Neuron 31:463–475

Mailleux P, Vanderhaeghen J-J (1992) Distribution of neuronal cannabinoid receptor in the adult rat brain: a comparative receptor binding radioautography and in situ hybridization histochemistry. Neuroscience 48:655–668

Maingret F, Patel AJ, Lazdunski M, Honore E (2001) The endocannabinoid anandamide is a direct and selective blocker of the background K+ channel TASK-1. EMBO J 20:47–54

Malinowska B, Godlewski G, Bucher B, Schlicker, E (1997) Cannabinoid CB_1 receptor-mediated inhibition of the neurogenic vasopressor response in the pithed rat. Naunyn–Schmiedeberg's Arch Pharmacol 356:197–202

Malinowska B, Piszcz J, Koneczny B, Hryniewicz A, Schlicker E (2001) Modulation of the cardiac autonomic transmission of pithed rats by presynaptic opioid OP_4 and cannabinoid CB_1 receptors. Naunyn–Schmiedeberg's Arch Pharmacol 364:233–241

Malone DT, Taylor DA (1999) Modulation by fluoxetine of striatal dopamine release following Δ^9-tetrahydrocannabinol: a microdialysis study in conscious rats. Br J Pharmacol 128:21–26

Mang CF, Erbelding D, Kilbinger H (2001) Differential effects of anandamide on acetylcholine release in the guinea-pig ileum mediated via vanilloid and non-CB_1 receptors. Br J Pharmacol 134:161–167

Manzoni OJ, Bockaert J (2001) Cannabinoids inhibit GABAergic synaptic transmission in mice nucleus accumbens. Eur J Pharmacol 412:R3–R5

Marsicano G, Wotjak CT, Azad SC, Bisogno T, Rammes G, Cascio MG, Hermann H, Tang J, Hofmann C, Zieglgänsberger W, Di Marzo V, Lutz B (2002) The endogenous cannabinoid system controls extinction of aversive memories. Nature 418:530–534

Matsuda LA, Bonner TI, Lolait SJ (1993) Localization of cannabinoid receptor mRNA in rat brain. J Comp Neurol 327:535–550

McAllister SD, Griffin G, Satin LS, Abood ME (1999) Cannabinoid receptors can activate and inhibit G protein-coupled inwardly rectifying potassium channels in a Xenopus oocyte expression system. J Pharmacol Exp Ther 291:618–626

Melis M, Pistis M, Perra S, Muntoni AL, Pillolla G, Gessa GL (2004) Endocannabinoids mediate presynaptic inhibition of glutamatergic transmission in rat ventral tegmental area dopamine neurons through activation of CB1 receptors. J Neurosci 24:53–62

Mishima K, Egashira N, Matsumoto Y, Iwasaki K, Fujiwara M (2002) Involvement of reduced acetylcholine release in Δ^9-tetrahydrocannabinol-induced impairment of spatial memory in the 8-arm radial maze. Life Sci 72:397–407

Misner DL, Sullivan JM (1999) Mechanism of cannabinoid effects on long-term potentiation and depression in hippocampal CA1 neurons. J Neurosci 19:6795–6805

Molderings GJ, Likungu J, Göthert M (1999) Presynaptic cannabinoid and imidazoline receptors in the human heart and their potential relationship. Naunyn–Schmiedeberg's Arch Pharmacol 360:157–164

Morisset V, Urban L (2001) Cannabinoid-induced presynaptic inhibition of glutamatergic EPSCs in substantia gelatinosa neurons of the rat spinal cord. J Neurophysiol 86:40–48

Mu J, Zhuang S-Y, Hampson RE, Deadwyler SA (2000) Protein kinase-dependent phosphorylation and cannabinoid receptor modulation of potassium A current (I_A) in cultured rat hippocampal neurons. Pflügers Arch 439:541–546

Nakatsuka T, Chen H-X, Roper SN, Gu JG (2003) Cannabinoid receptor-1 activation suppresses inhibitory synaptic activity in human dentate gyrus. Neuropharmacology 45:116–121

Nakazi M, Bauer M, Nickel T, Kathmann M, Schlicker E (2000) Inhibition of serotonin release in the mouse brain via presynaptic cannabinoid CB_1 receptors. Naunyn–Schmiedeberg's Arch Pharmacol 361:19–24

Nemeth J, Helyes Z, Than M, Jakab B, Pinter E, Szolcsanyi J (2003) Concentration-dependent dual effect of anandamide on sensory neuropeptide release from isolated rat tracheae. Neurosci Lett 336:89–92

Nicholson RA, Liao C, Zheng J, David LS, Coyne L, Errington AC, Singh G, Lees G (2003) Sodium channel inhibition by anandamide and synthetic cannabimimetics in brain. Brain Res 978:194–204

Niederhoffer N, Szabo B (1999) Effect of the cannabinoid receptor agonist WIN55212–2 on sympathetic cardiovascular regulation. Br J Pharmacol 126:457–466

Niederhoffer N, Hansen HH, Fernandez-Ruiz JJ, Szabo B (2001) Effects of cannabinoids on adrenaline release from adrenal medullary cells. Br J Pharmacol 134:1319–1327

Niederhoffer N, Schmid K, Szabo B (2003) The peripheral sympathetic nervous system is the major target of cannabinoids in eliciting cardiovascular depression. Naunyn–Schmiedeberg's Arch Pharmacol 367:434–443

Nogueron IM, Porgilsson B, Schneider WE, Stucky CL, Hillard CJ (2001) Cannabinoid receptor agonists inhibit depolarization-induced calcium influx in cerebellar granule neurons. J Neurochem 79:371–381

Ohno-Shosaku T, Maejima T, Kano M (2001) Endogenous cannabinoids mediate retrograde signals from depolarized postsynaptic neurons to presynaptic terminals. Neuron 29:729–738

Oz M, Ravindran A, Diaz-Ruiz O, Zhang L, Morales M (2003) The endogenous cannabinoid anandamide inhibits $\alpha 7$ nicotinic acetylcholine receptor-mediated responses in Xenopus oocytes. J Pharmacol Exp Ther 306:1003–1010

Pan X, Ikeda SR, Lewis DL (1996) Rat brain cannabinoid receptor modulates N-type Ca^{2+} channels in a neuronal expression system. Mol Pharmacol 49:707–714

Patel S, Hillard CJ (2001) Cannabinoid CB1 receptor agonists produce cerebellar dysfunction in mice. J Pharmacol Exp Ther 297:629–637

Pertwee RG, Fernando SR (1996) Evidence for the presence of cannabinoid CB_1 receptors in mouse urinary bladder. Br J Pharmacol 118:2053–2058

Pertwee RG, Stevenson LA, Elrick DB, Mechoulam R, Corbett AD (1992) Inhibitory effects of certain enantiomeric cannabinoids in the mouse vas deferens and the myenteric plexus preparation of guinea-pig small intestine. Br J Pharmacol 105:980–984

Pertwee RG, Fernando SR, Griffin G, Ryan W, Razdan RK, Compton DR, Martin BR (1996a) Agonist-antagonist characterization of 6'-cyanohex-2'-yne-Δ^8-tetrahydrocannabinol in two isolated tissue preparations. Eur J Pharmacol 315:195–201

Pertwee RG, Fernando SR, Nash JE, Coutts AA (1996b) Further evidence for the presence of cannabinoid CB_1 receptors in guinea-pig small intestine. Br J Pharmacol 118:2199–2205

Pertwee RG, Ross RA, Craib S, Thomas A (2002) (–)-Cannabidiol antagonizes cannabinoid receptor agonists and noradrenaline in the mouse vas deferens. Eur J Pharmacol 456:99–106

Ralevic V (2003) Cannabinoid modulation of peripheral autonomic and sensory neurotransmission. Eur J Pharmacol 472:1–21

Ralevic V, Kendall DA (2001) Cannabinoid inhibition of capsaicin-sensitive sensory neurotransmission in the rat mesenteric arterial bed. Eur J Pharmacol 418:117–125

Ralevic V, Kendall DA (2002) Cannabinoids inhibit pre- and postjunctionally sympathetic neurotransmission in rat mesenteric arteries. Eur J Pharmacol 444:171–181

Richardson JD, Kilo S, Hargreaves KM (1998) Cannabinoids reduce hyperalgesia and inflammation via interaction with peripheral CB1 receptors. Pain 75:111–119

Riegel AC, Williams JT, Lupica CR (2003) Cannabinoid receptor activation depresses $GABA_B$-mediated synaptic responses in dopamine neurons. In: 2003 Symposium on the cannabinoids. International Cannabinoid Research Society, Burlington, p 23

Robbe D, Alonso G, Duchamp F, Bockaert J, Manzoni OJ (2001) Localization and mechanisms of action of cannabinoid receptors at the glutamatergic synapses of the mouse nucleus accumbens. J Neurosci 21:109–116

Rodriguez JJ, Mackie K, Pickel VM (2001) Ultrastructural localization of the CB1 cannabinoid receptor in μ-opioid receptor patches of the rat caudate putamen nucleus. J Neurosci 21:823–833

Rubovitch V, Gafni M, Sarne Y (2002) The cannabinoid agonist DALN positively modulates L-type voltage-dependent calcium-channels in N18TG2 neuroblastoma cells. Mol Brain Res 101:93–102

Ruiu S, Pinna GA, Marchese G, Mussinu JM, Saba P, Tambaro S, Casti P, Vargiu R, Pani L (2003) Synthesis and characterization of NESS 0327: a novel putative antagonist of the CB_1 cannabinoid receptor. J Pharmacol Exp Ther 306:363–370

Sanudo-Pena MC, Tsou K, Walker JM (1999) Motor actions of cannabinoids in the basal ganglia output nuclei. Life Sci 65:703–713

Schlicker E, Kathmann M (2001) Modulation of transmitter release via presynaptic cannabinoid receptors. Trends Pharmacol Sci 22:565–572

Schlicker E, Timm J, Göthert M (1996) Cannabinoid receptor-mediated inhibition of dopamine release in the retina. Naunyn–Schmiedeberg's Arch Pharmacol 354:791–795

Schlicker E, Timm J, Zentner J, Göthert M (1997) Cannabinoid CB_1 receptor-mediated inhibition of noradrenaline release in the human and guinea-pig hippocampus. Naunyn–Schmiedeberg's Arch Pharmacol 356:583–589

Schlicker E, Liedtke S, Flau K, Kathmann M (2002) Further evidence that the cannabinoid receptor inhibiting noradrenaline release in the guinea-pig brain belongs to the CB_1 subtype and is subject to an endogenous tone. Pharmacologist 44(Suppl 1):A112

Schlicker E, Redmer A, Werner A, Kathmann M (2003) Lack of CB_1 receptors increases noradrenaline release in vas deferens without affecting atrial noradrenaline release or cortical acetylcholine release. Br J Pharmacol 140:323–328

Schultheiß T, Flau K, Redmer A, Kathmann M, Reggio PH, Seltzman HH, Schlicker E (2004) The facilitatory effect of SR141716 on transmitter release in guinea-pig hippocampus is due to its inverse agonist activity at cannabinoid CB_1 receptors. Naunyn–Schmiedeberg's Arch Pharmacol 369 (Suppl 1):R84

Schweitzer P (2000) Cannabinoids decrease the K^+ M-current in hippocampal CA1 neurons. J Neurosci 20:51–58

Seifert R, Wenzel-Seifert K (2002) Constitutive activity of G-protein-coupled receptors: cause of disease and common property of wild-type receptors. Naunyn–Schmiedeberg's Arch Pharmacol 366:381–416

Shen M, Thayer SA (1999) Δ^9-Tetrahydrocannabinol acts as a partial agonist to modulate glutamatergic synaptic transmission between rat hippocampal neurons in culture. Mol Pharmacol 55:8–13

Shen M, Piser TM, Seybold VS, Thayer SA (1996) Cannabinoid receptor agonists inhibit glutamatergic synaptic transmission in rat hippocampal cultures. J Neurosci 16:4322–4334

Starke K, Göthert M, Kilbinger H (1989) Modulation of neurotransmitter release by presynaptic autoreceptors. Physiol Rev 69:864–989

Steffens M, Szabo B, Klar M, Rominger A, Zentner J, Feuerstein TJ (2003) Modulation of electrically evoked acetylcholine release through cannabinoid CB_1 receptors: evidence for an endocannabinoid tone in the human neocortex. Neuroscience 120:456–465

Storr M, Sibaev A, Marsicano G, Lutz B, Schusdziarra V, Timmermans JP, Allescher HD (2004) Cannabinoid receptor type 1 modulates excitatory and inhibitory neurotransmission in mouse colon. Am J Physiol Gastrointest Liver Physiol 286:G110–G117

Straiker A, Sullivan JM (2003) Cannabinoid receptor activation differentially modulates ion channels in photoreceptors of the tiger salamander. J Neurophysiol 89:2647–2654

Straiker AJ, Borden CR, Sullivan JM (2002) G-protein alpha subunit isoforms couple differentially to receptors that mediate presynaptic inhibition at rat hippocampal synapses. J Neurosci 22:2460–2468

Sullivan JM (1999) Mechanisms of cannabinoid-receptor-mediated inhibition of synaptic transmission in cultured hippocampal pyramidal neurons. J Neurophysiol 82:1286–1294

Szabo B, Dörner L, Pfreundtner C, Nörenberg W, Starke K (1998) Inhibition of GABAergic inhibitory postsynaptic currents by cannabinoids in rat corpus striatum. Neuroscience 85:395–403

Szabo B, Müller T, Koch H (1999) Effects of cannabinoids on dopamine release in the corpus striatum and the nucleus accumbens in vitro. J Neurochem 73:1084–1089

Szabo B, Wallmichrath I, Mathonia P, Pfreundtner C (2000) Cannabinoids inhibit excitatory neurotransmission in the substantia nigra pars reticulata. Neuroscience 97:89–97

Szabo B, Nordheim U, Niederhoffer N (2001) Effects of cannabinoids on sympathetic and parasympathetic neuroeffector transmission in the rabbit heart. J Pharmacol Exp Ther 297:819–826

Szabo B, Siemes S, Wallmichrath I (2002) Inhibition of GABAergic neurotransmission in the ventral tegmental area by cannabinoids. Eur J Neurosci 15:2057–2061

Szabo B, Than M, Wallmichrath I, Thorn D (2004) Analysis of the effects of cannabinoids on synaptic transmission between basket and Purkinje cells in the cerebellar cortex of the rat. J Pharmacol Exp Ther 310:915–925

Takahashi KA, Linden DJ (2000) Cannabinoid receptor modulation of synapses received by cerebellar Purkinje cells. J Neurophysiol 83:1167–1180

Thompson SM, Capogna M, Scanziani M (1993) Presynaptic inhibition in the hippocampus. Trends Neurosci 16:222–227

Timm J, Marr I, Werthwein S, Elz S, Schunack W, Schlicker E (1998) H_2 receptor-mediated facilitation and H3 receptor-mediated inhibition of noradrenaline release in the guinea-pig brain. Naunyn–Schmiedeberg's Arch Pharmacol 357:232–239

Tognetto M, Amadesi S, Harrison S, Creminon C, Trevisani M, Carreras M, Matera M, Geppetti P, Bianchi A (2001) Anandamide excites central terminals of dorsal root ganglion neurons via vanilloid receptor-1 activation. J Neurosci 21:1104–1109

Trendelenburg AU, Cox SL, Schelb V, Klebroff W, Khairallah L, Starke K (2000) Modulation of 3H-noradrenaline release by presynaptic opioid, cannabinoid and bradykinin receptors and ß-adrenoceptors in mouse tissues. Br J Pharmacol 130:321–330

Trettel J, Levine ES (2002) Cannabinoids depress inhibitory synaptic inputs received by layer 2/3 pyramidal neurons of the neocortex. J Neurophysiol 88:534–539

Trettel J, Levine ES (2003) Endocannabinoids mediate rapid retrograde signaling at interneuron→pyramidal neuron synapses of the neocortex. J Neurophysiol 89:2334–2338

Tsou K, Brown S, Sanudo-Pena MC, Mackie K, Walker JM (1998) Immunohistochemical distribution of cannabinoid CB1 receptors in the rat central nervous system. Neuroscience 83:393–411

Turkanis SA, Partlow LM, Karler R (1991) Delta-9-tetrahydrocannabinol depresses inward sodium current in mouse neuroblastoma cells. Neuropharmacology 30:73–77

Twitchell W, Brown S, Mackie K (1997) Cannabinoids inhibit N- and P/Q-type calcium channels in cultured rat hippocampal neurons. J Neurophysiol 78:43–50

Tzavara ET, Perry KW, Rodriguez DE, Bymaster F, Nomikos GG (2001) The cannabinoid CB1 receptor antagonist SR141716A increases norepinephrine outflow in the rat anterior hypothalamus. Eur J Pharmacol 426:R3–R4

Tzavara ET, Davis RJ, Perry KW, Li X, Salhoff C, Witkin JM, Bymaster F, Nomikos GG (2003a) The CB_1 receptor antagonist SR141716A selectively increases monoaminergic neurotransmission in the medial prefrontal cortex: implications for therapeutic actions. Br J Pharmacol 138:544–553

Tzavara ET, Wade M, Nomikos GG (2003b) Biphasic effects of cannabinoids on acetylcholine release in the hippocampus: site and mechanism of action. J Neurosci 23:9374–9384

Van Vliet BJ, Nievelstein HNMW, Long SK, Kruse CG (2000) CB_1 receptor-mediated effects on brain neurotransmitter systems. Eur Neuropsychopharmacol 10 (Suppl 3):S182–S183

Vaughan CW, McGregor IS, Christie McDJ (1999) Cannabinoid receptor activation inhibits GABAergic neurotransmission in rostral ventromedial medulla neurons in vitro. Br J Pharmacol 127:935–940

Vaughan CW, Connor M, Bagley EE, Christie MJ (2000) Actions of cannabinoids on membrane properties and synaptic transmission in rat periaqueductal gray neurons in vitro. Mol Pharmacol 57:288–295

Verrico CD, Jentsch JD, Dazzi L, Roth RH (2003) Systemic, but not local, administration of cannabinoid CB1 receptor agonists modulate prefrontal cortical acetylcholine efflux in the rat. Synapse 48:178–183

Vizi ES, Katona I, Freund TF (2001) Evidence for presynaptic cannabinoid CB_1 receptor-mediated inhibition of noradrenaline release in the guinea pig lung. Eur J Pharmacol 431:237–244

Wallmichrath I, Szabo B (2002a) Analysis of the effect of cannabinoids on GABAergic neurotransmission in the substantia nigra pars reticulata. Naunyn–Schmiedeberg's Arch Pharmacol 365:326–334

Wallmichrath I, Szabo B (2002b) Cannabinoids inhibit striatonigral GABAergic neurotransmission in the mouse. Neuroscience 113:671–682

Wallmichrath I, Szabo B (2003) Effects of cannabinoids on the glutamatergic neurotransmission between nucleus subthalamicus and globus pallidus. Naunyn–Schmiedeberg's Arch Pharmacol 367:R83

Wang S-J (2003) Cannabinoid CB_1 receptor-mediated inhibition of glutamate release from rat hippocampal synaptosomes. Eur J Pharmacol 469:47–55

Wilson RI, Nicoll RA (2001) Endogenous cannabinoids mediate retrograde signalling at hippocampal synapses. Nature 410:588–592

Wilson RI, Nicoll RA (2002) Endocannabinoid signaling in the brain. Science 296:678–682

Wu L-G, Saggau P (1997) Presynaptic inhibition of elicited neurotransmitter release. Trends Neurosci 20:204–212

Yoshida T, Hashimoto K, Zimmer A, Maejima T, Araishi K, Kano M (2002) The cannabinoid CB1 receptor mediates retrograde signals for depolarization-induced suppression of inhibition in cerebellar Purkinje cells. J Neurosci 22:1690–1697

Zimmer A, Zimmer AM, Hohmann AG, Herkenham M, Bonner TI (1999) Increased mortality, hypoactivity, and hypoalgesia in cannabinoid CB1 receptor knockout mice. Proc Natl Acad Sci USA 96:5780–5785

Zygmunt PM, Petersson J, Andersson DA, Chuang H, Sorgard M, Di Marzo V, Julius D, Högestätt ED (1999) Vanilloid receptors on sensory nerves mediate the vasodilator action of anandamide. Nature 400:452–457