ORIGINAL ARTICLE

M. Kathmann · U. Bauer · E. Schlicker · M. Göthert

Cannabinoid CB$_1$ receptor-mediated inhibition of NMDA- and kainate-stimulated noradrenaline and dopamine release in the brain

Abstract Guinea-pig hippocampal slices preincubated with [^{3}H]noradrenaline were superfused with medium containing desipramine and rauwolscine and rat striatal slices preincubated with [^{3}H]dopamine were superfused with medium containing nomifensine; the effect of cannabinoid receptor ligands on tritium overflow stimulated by NMDA or kainate was examined. Furthermore, the affinity of the drugs for cannabinoid CB$_1$ receptors was determined in rat brain cortex membranes using [^{3}H]SR 141716.

In *guinea-pig hippocampal slices* preincubated with [^{3}H]noradrenaline, tritium overflow stimulated by NMDA 100 µM and 1000 µM and by kainate 1000 µM was inhibited by the cannabinoid receptor agonists CP-55,940 and/or WIN 55,212-2. The CB$_1$ receptor antagonist SR 141716 increased the NMDA (1000 µM)-stimulated tritium overflow but did not affect tritium overflow stimulated by NMDA 100 µM or kainate 1000 µM. The inhibitory effect of WIN 55,212-2 on the NMDA (100 µM)- and kainate (1000 µM)-evoked tritium overflow was antagonized by SR 141716. In *rat striatal slices* preincubated with [^{3}H]dopamine, WIN 55,212-2 inhibited the NMDA (1000 µM)-stimulated tritium overflow. SR 141716, which, by itself, did not affect tritium overflow, counteracted the inhibitory effect of WIN 55,212-2. *[^{3}H]SR 141716 binding* to rat cortical membranes was inhibited by SR 141716, CP-55,940 and WIN 55,212-2 (pK_i 8.53, 7.34 and 5.93, respectively) but not affected by desipramine, rauwolscine and nomifensine (pK_i < 5).

In conclusion, activation of CB$_1$ receptors inhibits the NMDA- and kainate-stimulated noradrenaline release in guinea-pig hippocampus and the NMDA-stimulated dopamine release in rat striatum. The explanation for the facilitatory effect of SR 141716 might be that it acts as an inverse agonist at CB$_1$ receptors or that these receptors are activated by endogenous cannabinoids.

M. Kathmann · U. Bauer · E. Schlicker (✉) · M. Göthert
Institut für Pharmakologie und Toxikologie der Universität Bonn,
Reuterstrasse 2b, D-53113 Bonn, Germany
Fax: +49-228-735404

Introduction

The effects of Δ^9-tetrahydrocannabinol and chemically related constituents of hashish and marijuana are mediated via cannabinoid CB$_1$ and CB$_2$ receptors, both of which belong to the G protein-coupled receptor superfamily; CB$_1$ receptors are located in the CNS and at lower density in peripheral tissues whereas CB$_2$ receptors are restricted to the periphery (for review, see Pertwee 1997; Childers and Breivogel 1998). Characterization of cannabinoid receptors is facilitated by the availability of potent agonists like WIN 55,212-2 and CP-55,940 (see Pertwee 1997; Childers and Breivogel 1998) and the potent and selective CB$_1$ and CB$_2$ receptor antagonists, SR 141716 and SR 144528, respectively (Rinaldi-Carmona et al. 1994, 1998).

Activation of CB$_1$ receptors causes inhibition of neurotransmitter release from several types of neurones both in the peripheral and in the central nervous system (for review, see Pertwee 1997; Childers and Breivogel 1998). With respect to the CNS, CB$_1$ receptors inhibit, e.g., dopamine release from rat striatal slices (Cadogan et al. 1997) and noradrenaline release from human or guinea-pig hippocampal slices (Schlicker et al. 1997). On the other hand, the release of both monoamines is stimulated by *N*-methyl-D-aspartate (NMDA) in the rat striatum and hippocampus (Krebs et al. 1991; Pittaluga and Raiteri 1992). Long-term potentiation of synaptic transmission in the hippocampus (involved in learning and memory) is induced via NMDA receptors (for review, see Bliss and Collingridge 1993) but inhibited via CB$_1$ receptors (Terranova et al. 1995). The aim of the present study was to examine whether the NMDA receptor-stimulated monoamine release from rat striatal and guinea-pig hippocampal slices

is inhibited via CB_1 receptor activation, as previously shown for the electrically evoked release in these preparations (Cadogan et al. 1997; Schlicker et al. 1997).

Materials and methods

Superfusion experiments. Hippocampal slices (0.3 mm thick, 3 mm in diameter) from male Dunkin-Hartley guinea pigs and striatal slices (0.3 mm thick, 3 mm in diameter) from male Wistar rats were prepared. The hippocampal slices were incubated with physiological salt solution (PSS) containing [^{3}H]noradrenaline 0.1 μM and the striatal slices were incubated with PSS containing [^{3}H]dopamine 0.1 μM, for 30 min each (37°C). Subsequently, the slices were superfused (0.6 ml/min) with PSS for 60 min (37°C); the superfusate was collected in 5-min samples. Tritium overflow was stimulated after 40 min of superfusion by NMDA or kainate (added for 2 min) in guinea-pig hippocampal slices and by NMDA (added for 5 min) in rat striatal slices. The PSS was composed as follows (in mM): NaCl 118, KCl 4.8, NaHCO$_3$ 25, KH$_2$PO$_4$ 1.2, MgCl$_2$ 1.2, CaCl$_2$ 1.3, glucose 11.1, ascorbic acid 0.06, disodium EDTA 0.03; it was aerated with 95% O$_2$ and 5% CO$_2$. In experiments in which NMDA was used for stimulation, MgCl$_2$ was omitted during incubation and superfusion (unless stated otherwise).

Tritium efflux was calculated as the fraction of the tritium content in the slices at the beginning of the respective collection period (fractional rate of tritium efflux). To quantify effects of drugs on basal efflux, the fractional rate was determined in the sample collected from 35 min to 40 min of superfusion (i.e. immediately before stimulation). Stimulation-evoked tritium overflow was calculated by subtraction of basal from total efflux during stimulation and the subsequent 13 min (hippocampal slices) and 10 min (striatal slices); basal tritium efflux was assumed to decline linearly from the 5-min period before to that 15–20 min after onset of stimulation. The difference between total and basal tritium efflux (stimulated tritium overflow) was expressed as a percentage of the tritium content in the slice at the onset of stimulation. The stimulation-evoked overflow shown in Figs. 2, 3 and 4 is given as percent of the average corresponding control overflow (no drug present except desipramine, rauwolscine, nomifensine and the glutamate receptor agonist).

Binding experiments. Binding experiments were carried out according to Rinaldi-Carmona et al. (1996) with slight modifications. Cerebral cortex from male Wistar rats was homogenized (Potter-Elvehjem) in 25 volumes of ice-cold Tris-HCl buffer (Tris 50 mM, pH 7.5; EDTA 5 mM; sucrose 10.27%) and centrifuged at 1000 *g* for 10 min (4°C). The supernatant was centrifuged at 35,000 *g* for 10 min and the pellet was resuspended in ten volumes of Tris-HCl buffer and frozen at –80°C. The binding assay was performed in Tris-HCl buffer (Tris 50 mM, pH 7.5; EDTA 5 mM) in a final volume of 0.5 ml containing 40–80 μg protein. [^{3}H]SR 141716 was used at seven concentrations ranging from 0.05 nM to 8 nM for saturation experiments and at a concentration of 0.5 nM for competition experiments. The incubation (25°C) was terminated after 60 min by filtration through polyethyleneimine (0.3%)-pretreated Whatman GF/C filters. CP-55,940 3 μM was used to determine nonspecific binding (29% of total binding when [^{3}H]SR 141716 was used at 8 nM). Protein was assayed by the method described by Bradford (1976). Data were analyzed using the programme GraphPadPrism (Prism; GraphPad Software, San Diego, Calif., USA).

Statistics. Results are given as means ± SEM of *n* experiments (superfusion experiments) and of *n* experiments in triplicate (binding experiments). Student's *t*-test was used for comparison of mean values and the *F*-test was applied in order to evaluate whether the inhibition of [^{3}H]SR 141716 binding by drugs was better fitted by a one- or two-site model.

Drugs used. D,L-(E)-2-amino-4-methyl-5-phosphono-3-pentanoic acid (CGP 37849), desipramine hydrochloride (Ciba-Geigy, Basel,

Switzerland); 6-cyano-7-nitro-quinoxaline-2,3-dione (CNQX; Tocris-Cookson, Bristol, England); (-)-*cis*-3-[2-hydroxy-4-(1,1-dimethyl-heptyl)phenyl]-*trans*-4-(3-hydroxypropyl)cyclohexanol (CP-55,940; Pfizer, Groton, Conn., USA); nomifensine (base; Hoechst, Frankfurt, Germany); rauwolscine hydrochloride, tetrodotoxin (Roth, Karlsruhe, Germany); *N*-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-3-pyrazole-carboxamide (SR 141716; Sanofi, Montpellier, France); *R*(+)-[2,3-dihydro-5-methyl-3-[(morpholinyl)methyl]pyrrolo[1,2,3-de]-1,4-benzoxazin-yl](1-naphthalenyl)methanone mesylate (WIN 55,212-2; RBI/Biotrend, Cologne, Germany); (-)-[*ring*-2,5,6-^{3}H]-noradrenaline (specific activity 42.0–46.8 Ci/mmol), (-)-[*ring*-2,5,6-^{3}H]-dopamine (specific activity 55.5–57.5 Ci/mmol; NEN, Zaventem, Belgium); [^{3}H]SR 141716 (specific activity 44–60 Ci/mmol; Amersham, Braunschweig, Germany). Drugs were dissolved in DMSO (CNQX, CP-55,940, SR 141716, WIN 55,212-2) or water (other drugs) and diluted with PSS (release experiments) or water (binding experiments) to obtain the concentration required.

Results

Release experiments

In control experiments in guinea-pig hippocampal slices preincubated with [^{3}H]noradrenaline and superfused in the presence of desipramine 1 μM plus rauwolscine 1 μM, the basal tritium efflux, measured in the 5 min of superfusion sampling before stimulation with NMDA (Mg^{2+}-free medium) or kainate (medium with Mg^{2+}), amounted to 0.0017 ± 0.0001 min^{-1} ($n = 8$) and 0.0020 ± 0.0001 min^{-1} ($n = 11$), respectively. In control experiments in rat striatal slices preincubated with [^{3}H]dopamine and superfused in the presence of nomifensine 1 μM, the basal tritium efflux, determined in the 5-min sample before stimulation with NMDA (Mg^{2+}-free medium), was 0.0067 ± 0.0004 min^{-1} ($n = 8$). In guinea-pig hippocampal and rat striatal slices superfused with Mg^{2+}-free medium, basal tritium efflux was increased by omission of Ca^{2+} by 201% and 93%, respectively. The drugs under study did not have marked (less than 45%) and consistent effects on basal tritium efflux (results not shown).

NMDA stimulated tritium overflow in a concentration-dependent manner in guinea-pig hippocampal and rat striatal slices (Fig. 1A,C); in these experiments, Mg^{2+} was omitted from the preincubation and superfusion medium. The effect of NMDA 1000 μM was abolished by addition of Mg^{2+} and markedly attenuated by the NMDA receptor antagonist CGP 37849, by tetrodotoxin or by omission of Ca^{2+} (Fig. 1A,C). In guinea-pig hippocampal slices, kainate also stimulated tritium overflow (Fig. 1B). The effect of kainate 1000 μM was abolished by omission of Ca^{2+} and markedly attenuated by the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid)/kainate receptor antagonist CNQX or by tetrodotoxin (Fig. 1B). The medium used for the subsequent superfusion experiments was Mg^{2+}-free when NMDA was used to stimulate tritium overflow and contained Mg^{2+} when kainate was used.

In guinea-pig hippocampal slices preincubated with [^{3}H]noradrenaline, the NMDA (1000 μM)-stimulated tritium overflow was inhibited by the cannabinoid receptor agonists CP-55,940 and WIN 55,212-2 by maximally
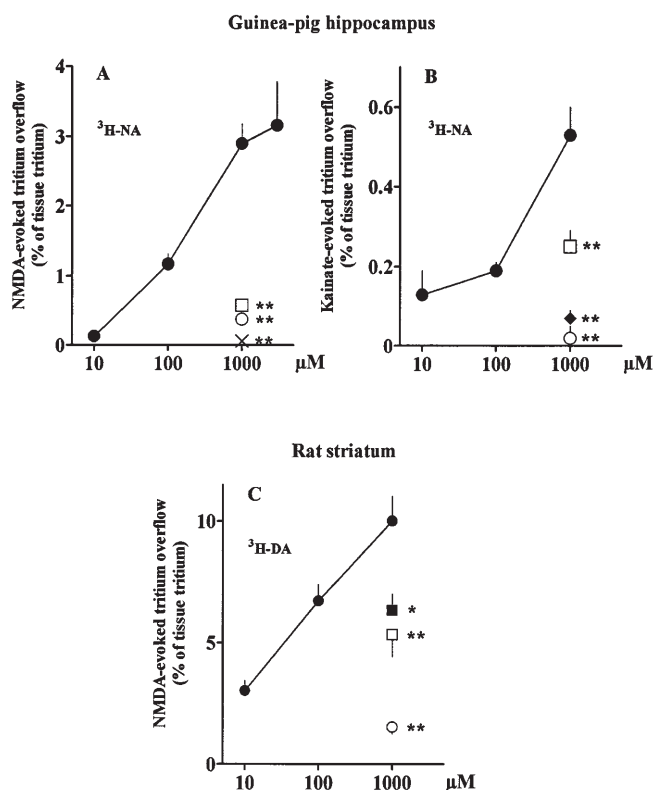
Guinea-pig hippocampus

Rat striatum

Fig. 1 Tritium overflow evoked by NMDA (**A**) or kainate (**B**) from guinea-pig hippocampal slices preincubated with [³H]noradrenaline *([³H]NA)* and NMDA-evoked tritium overflow from rat striatal slices preincubated with [³H]dopamine (*[³H]DA*; **C**). Guinea-pig hippocampal slices were superfused with medium containing desipramine 1 μM plus rauwolscine 1 μM; NMDA (Mg²⁺ omitted from the medium unless stated otherwise) or kainate was added for 2 min after 40 min of superfusion. Rat striatal slices were superfused with Mg²⁺-free medium containing nomifensine 1 μM; NMDA was added for 5 min after 40 min of superfusion. ● concentration-response curves without further drugs or changes in ionic composition, □ tetrodotoxin 0.3 μM present from 20 min of superfusion onward, ○ omission of Ca²⁺ ions from the medium throughout superfusion, × Mg²⁺ present in the medium throughout superfusion, ◆ CNQX 30 μM present from 20 min of superfusion onward, ■ CGP 37849 30 μM present from 20 min of superfusion onward. Note that scales of ordinates differ in **A–C**. Means ± SEM of 6–15 experiments (in some instances, SEM is contained within the symbol). *$P < 0.05$, **$P < 0.01$, compared to the corresponding control

40% (Fig. 2). The CB₁ receptor antagonist SR 141716 did not affect the evoked tritium overflow at 0.03 μM but increased it by about 50% at 0.3 μM and 3 μM (Fig. 2). Tritium overflow evoked by a lower concentration of NMDA (100 μM) was inhibited by WIN 55,212-2 as well; SR 141716 antagonized this effect but did not affect the evoked tritium overflow by itself (Fig. 3A).

The kainate (1000 μM)-evoked tritium overflow in guinea-pig hippocampal slices preincubated with [³H]noradrenaline was inhibited by CP-55,940 and WIN 55,212-2 by up to 50% (Fig. 4). SR 141716 3 μM did not affect the evoked tritium overflow by itself but abolished the inhibitory effect of WIN 55,212-2 1, 3 and 10 μM (Fig. 4).
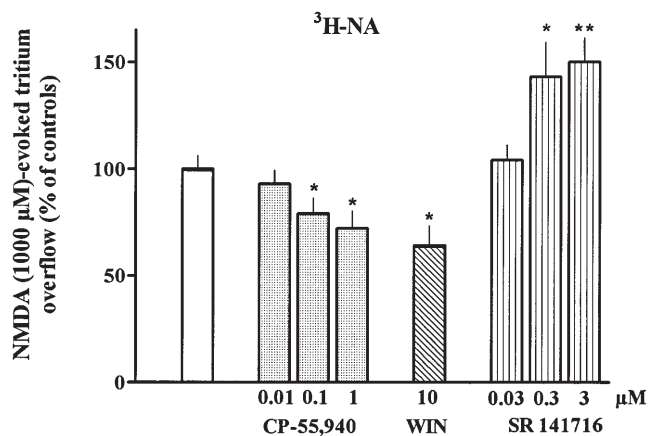

Fig. 2 Effects of CP-55,940, WIN 55,212-2 and SR 141716 on the NMDA (1000 μM)-evoked tritium overflow from superfused guinea-pig hippocampal slices preincubated with [³H]noradrenaline (*[³H]NA*). The slices were superfused with medium containing desipramine 1 μM plus rauwolscine 1 μM, and Mg²⁺ ions were omitted from the medium. CP-55,940, WIN 55,212-2 (*WIN*) or SR 141716 was added to the medium from 20 min of superfusion onward. NMDA was added for 2 min after 40 min of superfusion. Means ± SEM of 7–22 experiments. *$P < 0.05$, **$P < 0.01$, compared to the control
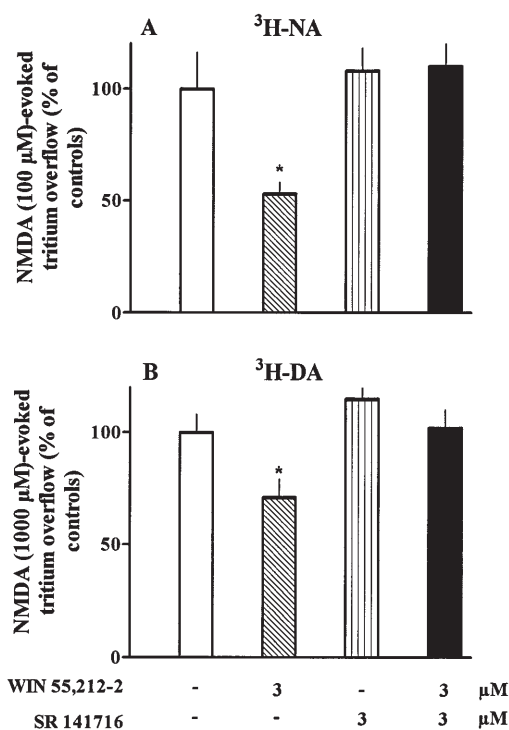

Fig. 3 Effect of WIN 55,212-2 and/or SR 141716 on the NMDA-evoked tritium overflow from superfused brain slices preincubated with [³H]noradrenaline (*[³H]NA*) or [³H]dopamine (*[³H]DA*). WIN 55,212-2 and/or SR 141716 were/was present in the medium from 20 min of superfusion onward. **A** Guinea-pig hippocampal slices preincubated with [³H]NA were superfused with Mg²⁺-free medium containing desipramine 1 μM plus rauwolscine 1 μM. NMDA was added for 2 min after 40 min of superfusion. **B** Rat striatal slices preincubated with [³H]DA were superfused with Mg²⁺-free medium containing nomifensine 1 μM. NMDA was added for 5 min after 40 min of superfusion. Means ± SEM of 11–16 experiments. *$P < 0.05$, compared to the corresponding control (i.e. the value without WIN 55,212-2 or SR 141716)
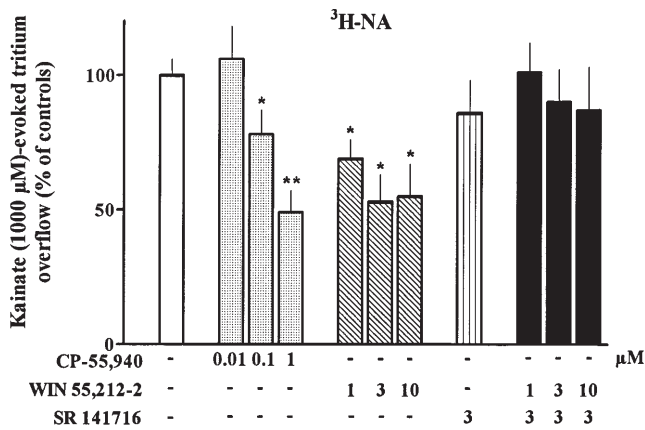
Fig. 4 Effect of CP-55,940, WIN 55,212-2 and/or SR 141716 on the kainate (1000 μM)-evoked tritium overflow from superfused guinea-pig hippocampal slices preincubated with [³H]noradrenaline ([³H]NA). The slices were superfused with medium containing desipramine 1 μM plus rauwolscine 1 μM. CP-55,940, WIN 55,212-2 and/or SR 141716 were/was added to the medium from 20 min of superfusion onward. Kainate was added for 2 min after 40 min of superfusion. Means ± SEM of 9–16 experiments. *$P < 0.05$, **$P < 0.01$, compared to the corresponding control
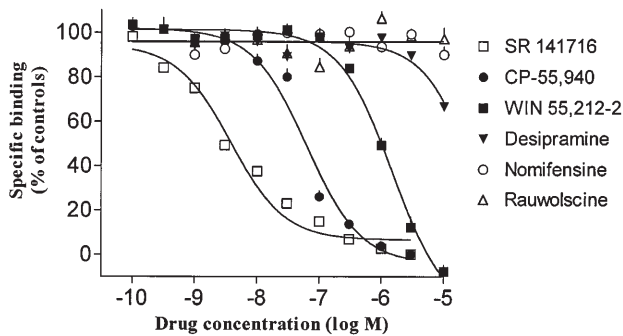

Fig. 5 Effect of CB₁ receptor ligands and auxiliary drugs used in this study on specific [³H]SR 141716 binding to rat brain cortex membranes. Membranes were incubated (25°C) for 60 min with [³H]SR 141716 0.5 nM and 9–11 concentrations of the drugs under study. Means ± SEM from four experiments in triplicate are shown (for some data points, SEM is contained within the symbol)

Finally, in rat striatal slices preincubated with [³H]dopamine, WIN 55,212-2 3 μM inhibited the NMDA (1000 μM)-evoked tritium overflow; this effect was abolished by SR 141716 3 μM, which by itself did not affect the evoked tritium overflow (Fig. 3B).

Binding experiments

In rat brain cortex membranes, [³H]SR 141716 at concentrations from 0.05 nM to 8.0 nM was used for saturation binding experiments. The dissociation constant (K_d) was 1.55 ± 0.10 nM and the maximum number of binding sites (B_{max}) was 0.51 ± 0.03 pmol/mg protein ($n = 4$). Scatchard analysis (not shown) of the data revealed a straight line with a Hill coefficient (n_H) of unity.

In competition experiments, binding of [³H]SR 141716 0.5 nM was inhibited monophasically by CP-55,940,

WIN 55,212-2 and SR 141716 (Fig. 5; n_H values near unity), yielding pK_i values of 7.34 ± 0.08, 5.93 ± 0.10 and 8.53 ± 0.12, respectively. The three auxiliary drugs desipramine, rauwolscine and nomifensine were studied at concentrations up to 10 μM; desipramine affected binding only marginally and the other two drugs did not affect it at all (Fig. 5; $pK_i < 5$).

Discussion

Tritium overflow evoked by NMDA and kainate in guinea-pig hippocampal slices (preincubated with [³H]noradrenaline) and by NMDA in rat striatal slices (preincubated with [³H]dopamine) reflects exocytotic noradrenaline and dopamine release, respectively, as suggested by the strong Ca^{2+} dependence. The effects induced by NMDA are mediated via NMDA receptors (since they were abolished by Mg^{2+} or attenuated by the competitive NMDA receptor antagonist CGP 37849) whereas the effect evoked by kainate involves non-NMDA receptors (since it was attenuated by the AMPA/kainate receptor antagonist CNQX). A substantial part of the NMDA and non-NMDA receptors involved is probably located on interneurones since the effects of NMDA and kainate were greatly attenuated by tetrodotoxin (for further discussion of this issue, see Fink et al. 1992). Superfusion experiments were performed in the presence of desipramine or nomifensine to study the effects of cannabinoid receptor ligands undisturbed by the function of the neuronal noradrenaline and dopamine transporter, respectively. In the superfusion experiments on guinea-pig hippocampal slices, the α₂-adrenoceptor antagonist rauwolscine was present as well because the CB₁ receptor-mediated inhibition of (electrically evoked) noradrenaline release in this tissue is increased by simultaneous blockade of the α₂-autoreceptors (Schlicker and Göthert 1998). We can exclude that desipramine, nomifensine and rauwolscine directly interacted with CB₁ receptors since they did not inhibit binding of the CB₁ receptor radioligand [³H]SR 141716 to rat cortical membranes. On the other hand, (unlabelled) SR 141716, CP-55,940 and WIN 55,212-2 inhibited binding, exhibiting the same order of potencies as in a previous study on membranes from whole rat brain minus cerebellum (Rinaldi-Carmona et al. 1996).

NMDA- and kainate-evoked noradrenaline release in guinea-pig hippocampal slices and NMDA-evoked dopamine release in rat striatal slices were inhibited by the cannabinoid receptor agonists WIN 55,212-2 and/or CP-55,940. The inhibitory effect of WIN 55,212-2 on the NMDA (100 μM)- and kainate-evoked noradrenaline release and on the NMDA-evoked dopamine release was counteracted by the CB₁ receptor antagonist SR 141716. Thus, CB₁ receptor-mediated inhibition of monoamine release in the guinea-pig hippocampus and rat striatum not only occurs when release is stimulated by electrical pulses (Cadogan et al. 1997; Schlicker et al. 1997) but also when it is evoked by NMDA and/or kainate.

SR 141716 by itself increased the release of noradrenaline stimulated by 1000 μM NMDA in guinea-pig hippocampal slices but failed to affect the release of noradrenaline evoked by 1000 μM kainate in this tissue and the release of dopamine induced by 1000 μM NMDA in rat striatal slices. SR 141716 also did not affect the noradrenaline release evoked by 100 μM NMDA in guinea-pig hippocampal slices; this lower concentration of NDMA stimulated noradrenaline release to a comparable extent as kainate 1000 μM (only 2 instead of 5.5 times more pronounced stimulation than by 1000 μM kainate). The reason for the facilitatory effect of SR 141716 on noradrenaline release stimulated by 1000 μM NMDA may be that in the hippocampus this strong stimulus induces the formation of endogenous cannabinoids which, in turn, activate CB_1 receptors and that this tonical inhibition is interrupted by SR 141716. Alternatively, SR 141716, which has been shown to be an inverse CB_1 receptor agonist at recombinant CB_1 receptors (see MacLennan et al. 1998; Pan et al. 1998), may behave as an inverse agonist also at CB_1 receptors in isolated tissue slices (for detailed discussion, see Pertwee 1997).

References

1. Bliss TVP, Collingridge GL (1993) A synaptic model of memory: long-term potentiation in the hippocampus. Nature 361:31–39
2. Bradford MM (1976) A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. Anal Biochem 72:248–254
3. Cadogan AK, Alexander SPH, Boyd EA, Kendall DA (1997) Influence of cannabinoids on electrically evoked dopamine release and cyclic AMP generation in the rat striatum. J Neurochem 69:1131–1137
4. Childers SR, Breivogel CS (1998) Cannabis and endogenous cannabinoid systems. Drug Alcohol Depend 51:173–187
5. Fink K, Schultheiß R, Göthert M (1992) Stimulation of noradrenaline release in human cerebral cortex mediated by N-methyl-D-aspartate (NMDA) and non-NMDA receptors. Br J Pharmacol 106:67–72
6. Krebs MO, Desce JM, Kemel ML, Gauchy C, Godeheu G, Cheramy A, Glowinski J (1991) Glutamatergic control of dopamine release in the rat striatum: evidence for presynaptic N-methyl-D-aspartate receptors on dopaminergic nerve terminals. J Neurochem 56:81–85
7. MacLennan SJ, Reynen PH, Kwan J, Bonhaus DW (1998) Evidence for inverse agonism of SR141716A at human recombinant cannabinoid CB_1 and CB_2 receptors. Br J Pharmacol 124:619–622
8. Pan X, Ikeda SR, Lewis DL (1998) SR 141716A acts as an inverse agonist to increase neuronal voltage-dependent Ca^{2+} currents by reversal of tonic CB1 cannabinoid receptor activity. Mol Pharmacol 54:1064–1072
9. Pertwee RG (1997) Pharmacology of cannabinoid CB_1 and CB_2 receptors. Pharmacol Ther 74:129–180
10. Pittaluga A, Raiteri M (1992) N-Methyl-D-aspartic acid (NMDA) and non-NMDA receptors regulating hippocampal norepinephrine release. I. Location on axon terminals and pharmacological characterization. J Pharmacol Exp Ther 260:232–237
11. Rinaldi-Carmona M, Barth F, Héaulme M, Shire D, Calandra B, Congy C, Martinez S, Maruani J, Néliat G, Caput D, Ferrara P, Soubrié P, Brelière JC, Le Fur G (1994) SR141716, a potent and selective antagonist of the brain cannabinoid receptor. FEBS Lett 350:240–244
12. Rinaldi-Carmona M, Pialot F, Congy C, Redon E, Barth F, Bachy A, Brelière JC, Soubrié P, Le Fur G (1996) Characterization and distribution of binding sites for [^{3}H]-SR 141716A, a selective brain (CB1) cannabinoid receptor antagonist in rodent brain. Life Sci 58:1239–1247
13. Rinaldi-Carmona M, Barth F, Millan J, Derocq JM, Casellas P, Congy C, Oustric D, Sarran M, Bouaboula M, Calandra B, Portier M, Shire D, Brelière JC, Le Fur G (1998) SR 144528, the first potent and selective antagonist of the CB2 cannabinoid receptor. J Pharmacol Exp Ther 284:644–650
14. Schlicker E, Göthert M (1998) Interactions between the presynaptic α_2-autoreceptor and presynaptic inhibitory heteroreceptors on noradrenergic neurones. Brain Res Bull 47:129–132
15. Schlicker E, Timm J, Zentner J, Göthert M (1997) Cannabinoid receptor-mediated inhibition of noradrenaline release in the human and guinea-pig hippocampus. Naunyn-Schmiedeberg's Arch Pharmacol 356:583–589
16. Terranova JP, Michaud JC, Le Fur G, Soubrié P (1995) Inhibition of long-term potentiation in rat hippocampal slices by anandamide and WIN55212-2: reversal by SR141716A, a selective antagonist of CB1 cannabinoid receptors. Naunyn-Schmiedeberg's Arch Pharmacol 352:576–579