Naunyn-Schmiedeberg's Arch Pharmacol (2013) 386:1041–1046
DOI 10.1007/s00210-013-0903-y

ORIGINAL ARTICLE

Do cannabinoids exhibit a tyramine-like effect?

Eman Ilayan · Monika Feliszek · Barbara Malinowska · Eberhard Schlicker

Received: 10 May 2013 / Accepted: 14 July 2013 / Published online: 31 July 2013

Abstract The major constituent of the cannabis plant, Δ^9-tetrahydrocannabinol, has stimulatory and depressant effects on cardiovascular functions. There is evidence from an in vivo study on the urethane-anaesthetized rat that part of the stimulatory effects is related to a tyramine-like activity. In the present study, we examined whether Δ^9-tetrahydrocannabinol induces carrier-mediated noradrenaline release in vitro. The study was extended to another phytocannabinoid, cannabidiol, to the synthetic cannabinoids CP 55,940 and WIN 55,212-2 and to the endocannabinoids anandamide and 2-arachidonoyl glycerol. Tissue pieces of the renal cortex from the mouse and the rat were preincubated with ^{3}H-noradrenaline and superfused. The effect of the cannabinoids on basal ^{3}H-noradrenaline release was studied. Tyramine served as a positive control. In the mouse kidney, basal ^{3}H-noradrenaline release was increased by tyramine 0.1, 1 and 10 μM by 39, 91 and 212 %, respectively, and, in the rat kidney, ^{3}H-noradrenaline release was increased by tyramine 10 μM by 158 %. All effects were abolished by desipramine 1 μM, an inhibitor of the neuronal noradrenaline transporter. The cannabinoids at 0.1, 1 and 10 μM (CP 55,940 at 0.1, 1 and 3.2 μM) did not affect ^{3}H-noradrenaline release in the mouse kidney. The highest concentration of the cannabinoids (10 μM and in the case of CP 55,940 3.2 μM) also failed to affect ^{3}H-noradrenaline release in the rat kidney. In conclusion, the cannabinoids Δ^9-tetrahydrocannabinol, cannabidiol, CP 55,940, WIN 55,212-2, anandamide and 2-arachidonoyl glycerol do not possess a tyramine-like effect on noradrenaline release.

Keywords Tyramine-like effect · Carrier-mediated noradrenaline release · Δ^9-Tetrahydrocannabinol · Cannabinoids · Endocannabinoids · Renal cortex

E. Ilayan · M. Feliszek · E. Schlicker (✉)
Department of Pharmacology and Toxicology, University of Bonn, Sigmund-Freud-Str. 25, 53127 Bonn, Germany
e-mail: e.schlicker@uni-bonn.de

B. Malinowska
Department of Experimental Physiology and Pathophysiology, Medical University of Białystok, Mickiewicz Str. 2A, 15-222 Białystok, Poland

Introduction

Δ^9-Tetrahydrocannabinol (Δ^9-THC), the major psychotropic constituent of the cannabis plant, shows various cardiovascular effects. Depending on the species, the state of wakefulness and other parameters (e.g. disease states), an increase or decrease in heart rate and an increase, decrease or biphasic alteration of blood pressure can occur (for review, see Pacher et al. 2005; Malinowska et al. 2012; Montecucco and Di Marzo 2012). Most of the Δ^9-THC-related cardiovascular alterations are based on the activation of CB_1 or CB_2 receptors located in the central nervous system and/or peripherally. Indeed, it has become increasingly clear during the last two decades that an endogenous cannabinoid system is the target of cardiovascular effects elicited by Δ^9-THC and by endogenously formed cannabinoids and that the latter play a role under physiological and pathophysiological conditions (for review, see Pacher et al. 2005; Malinowska et al. 2008; Montecucco and Di Marzo 2012).

Although cannabinoid receptors are frequently involved in Δ^9-THC-related cardiovascular effects, other sites of action have to be considered as well. In an in vivo study on urethane-anaesthetized rats, intravenously administered Δ^9-THC increased the mean arterial blood pressure (Adams et al. 1976). In an attempt to determine the mechanism, Δ^9-THC was also administered intraarterially into the perfused hindquarters of rats in that study. Δ^9-THC like tyramine and noradrenaline increased the perfusion pressure. After treatment of the rats with reserpine (to deplete the vesicles in the noradrenergic neurones from noradrenaline) the effect of Δ^9-THC, like that of tyramine, was attenuated, whereas the effect of noradrenaline was not affected. These data are compatible with the explanation that Δ^9-THC releases noradrenaline from the vesicles by carrier-mediated release (Adams et al. 1976), i.e. the neuronal noradrenaline transporter usually transporting noradrenaline from the synaptic cleft to the inner of the neurone is operating in the reverse direction.

The present study was carried out in order to further examine this mechanism in an in vitro model in which the carrier-

mediated ^{3}H-noradrenaline release can be determined directly. For this purpose, superfused tissue pieces of the renal cortex were prepared from rats and mice; tyramine served as a positive control. The study was extended to another plant-derived cannabinoid, namely cannabidiol, to the synthetic cannabinoids CP 55,940 and WIN 55,212-2 and to the endocannabinoids anandamide and 2-arachidonoyl glycerol (for chemical structures, see Fig. 1). The results of the present study have been communicated in preliminary form to the 79th Annual Meeting of the German Society of Experimental and Clinical Pharmacology and Toxicology in Halle/Saale (Ilayan et al. 2013).

Material and methods

Superfusion studies

Pieces from the renal cortex (dimensions of approximately 1×1×1 mm) were prepared from male C57BL/6J mice and male Sprague–Dawley rats (Charles-River, Sulzfeld, Germany) and then incubated for 60 min with physiological salt solution containing ^{3}H-noradrenaline 0.1 μM. Subsequently, the renal tissues were transferred to superfusion chambers and superfused with physiological salt solution for 110 min at a flow rate of 1 mL/min (37 °C). The superfusate was collected in 5-min samples. Tritium overflow was evoked by two 2-min periods of electrical field stimulation (S_1 and S_2) after 40 and 90 min of superfusion. The stimulation parameters were 3 Hz, 200 mA and 2 ms. The cannabinoids under study or tyramine (which served as a positive control) were added to the medium from 62 min of superfusion onward. In some experiments, desipramine 1 μM (an inhibitor of the neuronal noradrenaline transporter) was present in the medium throughout superfusion. At the end of the experiments, the renal pieces were solubilized with Soluene^{R} (Perkin-Elmer, Meriden, CT, USA), and the radioactivity of the renal pieces and superfusate samples was determined by liquid scintillation counting.

The physiological salt solution had the following composition (mmol/L): NaCl 118; KCl 4.8; KH_2PO_4, 1.2; $MgSO_4$ 1.2; $NaHCO_3$ 25; ascorbic acid 0.06; disodium EDTA 0.03; glucose 10; the solution was gassed continuously with 95 % O_2 and 5 % CO_2, at 37 °C and pH 7.4. The concentration of $CaCl_2$, which was 1.3 mM during incubation, had to be increased to 3.25 mM during superfusion in order to allow for a

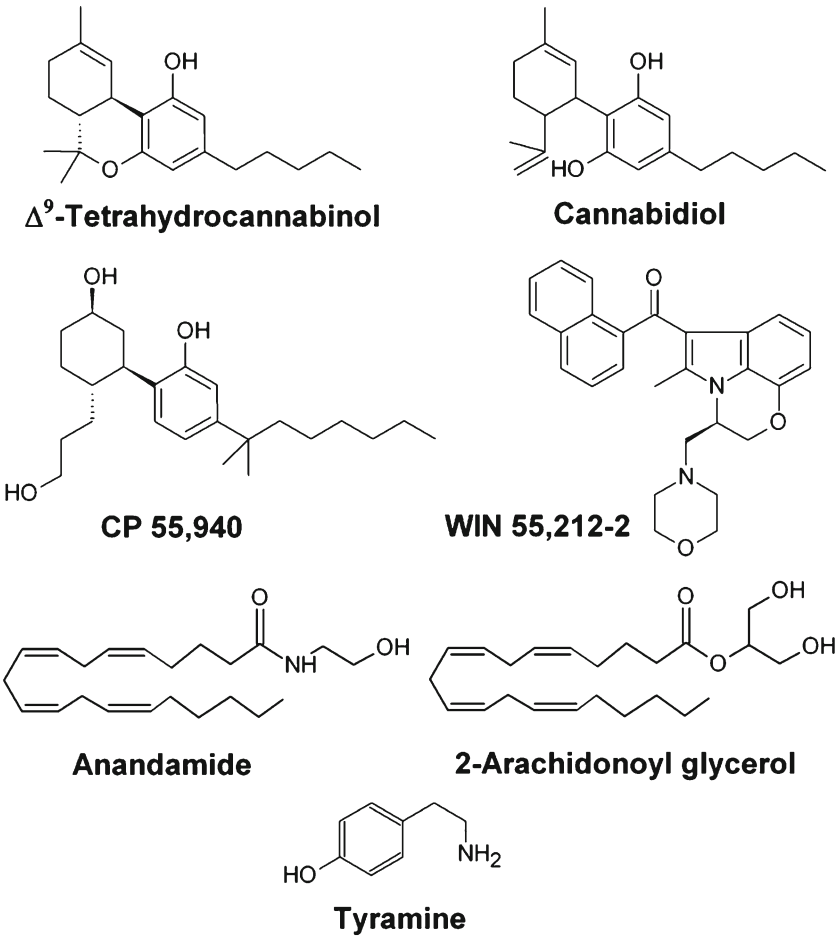

Fig. 1 Chemical structures of the six cannabinoids under study and of tyramine, which served as a positive control

minimum amount of the electrically evoked tritium overflow under the experimental conditions of the present study.

Drugs used

(R)-(−)-[ring-2,5,6-^{3}H]-noradrenaline (specific activity 48.4–57.9 Ci/mmol) (Perkin-Elmer, Zaventem, Belgium); anandamide, CP 55,940 ((−)-cis-3-[2-hydroxy-4-(1,1-dimethylheptyl) phenyl]-trans-4-[3-hydroxypropyl)cyclohexanol]) (Tocris, Bristol, UK); arachidonoyl glycerol, cannabidiol (Biotrend, Köln, Germany); desipramine hydrochloride, Δ^9-tetrahydrocannabinol (Δ^1-tetrahydrocannabinol according to another nomenclature), WIN 55,212-2 (R-(+)-[2,3-dihydro-5-methyl-[(3-morpholinyl) methyl]-pyrrolo[1,2,3-de]1,4-benzoxazinyl](1-naphthalenyl) methanone mesylate) (Sigma, Munich, Germany); tyramine hydrochloride (Merck, Darmstadt, Germany). Stock solutions of the drugs were prepared with DMSO (CP 55,940, WIN 55,212-2), ethanol (anandamide, arachidonoyl glycerol, cannabidiol, Δ^9-tetrahydrocannabinol) or water (desipramine, tyramine). The stock solutions were further diluted with deionized water to the concentration required. The organic solvent in the superfusion medium did not exceed 0.1 %*v*/*v*.

Calculations and statistical analysis

The tritium remaining in a given tissue piece and the tritium of all superfusion samples collected from this preparation were added up to allow for the determination of the tritium content at any time of the superfusion experiment (35 to 110 min of superfusion). However, during the time period lasting from 60 to 85 min the superfusate was collected only from 70 to 75 min and the radioactivity in this sample was multiplied by 5. Tritium efflux was calculated as the fraction of the tritium content in the tissue pieces at the beginning of the respective collection period (fractional rate of tritium efflux). t_1 and t_2 denote the fractional rate in the samples collected from 55 to 60 and from 85 to 90 min, respectively; for quantification of the effects of the test drugs and of tyramine on basal tritium efflux, the ratio of t_2 over t_1 was determined. The electrically evoked tritium overflow was calculated by subtraction of basal from total tritium efflux during stimulation (S_1 or S_2) and the subsequent 13 min and expressed as percent of the tritium present in the preparation at the onset of stimulation. To quantify the effect of desipramine on the evoked overflow, the S_1 values obtained in the presence and absence of the drug were compared. The tritium overflow evoked by S_2 was not systematically examined since the ratio of the overflow evoked by S_2 over that evoked by S_1 is extremely variable if the amount of S_1 is low (for this reason a limit of 0.9 % was chosen for S_1 in the study by Kurz et al. 2008) and since the electrically evoked tritium overflow was only of marginal interest in the present study.

Results are expressed as mean±SEM of *n* experiments; *n* refers to the number of animals. Student's *t* test was used for comparison of mean values; the Bonferroni correction was used when two or more values were compared to the same control. Differences were considered as significant when $P<0.05$.

Results

Basal and electrically evoked tritium overflow were determined in superfused pieces of the renal cortex (preincubated with ^{3}H-noradrenaline) from mice and rats. Basal tritium efflux was quantified in the 5-min collection periods from 55 to 60 (t_1) and from 85 to 90 min (t_2) of superfusion, i.e. shortly before and about 25 min after the addition of the test drugs to the medium. Tritium efflux (t_1) expressed as fractional rate of tritium efflux was about 0.004–0.005 min^{-1} in tissues from either species and was not affected by desipramine 1 μM (Table 1). To quantify the effect of the test drugs on basal tritium efflux, the ratio of t_2 over t_1 was determined (see later). The electrically evoked tritium overflow evoked by the first period of electrical stimulation after 40 min of superfusion (S_1) was lower than 1 % of tissue tritium in either species; this value was increased by desipramine 1 μM (Table 1).

With respect to the basal tritium efflux, the suitability of tyramine as a positive control was studied first; tyramine was added to the medium before t_2. In tissues from the mouse, tyramine 0.1, 1 and 10 μM concentration-dependently increased t_2/t_1 by 39, 91 and 212 %, respectively. The shape of the time–effect curve under tyramine 0.1, 1 and 10 μM is presented in Fig. 2a; the statistical evaluation of the t_2/t_1 values is shown in Fig. 3a. The effect of tyramine 0.1–10 μM was abolished by desipramine 1 μM. The time–effect curve for the interaction of tyramine 10 μM with desipramine 1 μM in a representative experiment is shown in Fig. 2a; the t_2/t_1 values obtained from five experiments (each) were 0.70±0.02 (control), 0.73±0.04 (tyramine 0.1 μM), 0.73±0.05 (tyramine 1 μM) and 0.82±0.04 (tyramine 10 μM). In tissues from the rat, tyramine was studied at 10 μM only. This concentration led to an increase of t_2/t_1 by 158 %; the time–effect curve of a representative experiment is depicted in Fig. 2b, and the statistical evaluation is shown in Fig. 3b. Again the effect of tyramine was abolished by desipramine 1 μM. The time–effect curve of one experiment is shown in Fig. 2b; the t_2/t_1 values obtained from five experiments (each) were 0.63±0.04 (control) and 0.75±0.04 (tyramine 10 μM).

Next, the effect of the six cannabinoids on basal tritium efflux was determined in tissues from the mouse and the rat. The cannabinoid under study was added to the medium before t_2. In tissues from the mouse, three concentrations were studied (0.1, 1 and 10 and, in the case of CP 55,940, 0.1, 1 and 3.2 μM), whereas only the highest concentration was examined in the rat renal cortex. The cannabinoids did not affect

Table 1 Basal and stimulation-evoked tritium overflow in pieces of the renal cortex from mice and rats

	Mouse		Rat	
	–	Desipramine 1 μM throughout superfusion	–	Desipramine 1 μM throughout superfusion
Basal tritium efflux (fractional rate of tritium efflux in the collection period from 55 to 60 min (t_1; min^{-1})	0.0052±0.0004	0.0053±0.0004	0.0042±0.0006	0.0039±0.0005
Tritium overflow evoked by the first period of electrical stimulation (S_1, after 40 min of superfusion; percentage of tissue tritium)	0.70±0.02	0.82±0.04*	0.24±0.04	0.56±0.13*

Tissues were preincubated with ^{3}H-noradrenaline and then superfused with physiological salt solution with or without desipramine 1 μM. Mean±SEM from five animals each

*$P<0.05$, compared to the corresponding value without desipramine

basal efflux (t_2/t_1) in either species (Fig. 3a, mouse and Fig. 3b, rat).

Discussion

The aim of the present study was to examine whether Δ^9-THC, for which a tyramine-like effect was suggested by Adams et al. (1976) on the basis of findings from an in vivo study, is capable to induce carrier-mediated noradrenaline release in vitro. For this purpose, the renal cortex was used since this sympathetically innervated tissue has been used frequently for the study of presynaptic mechanisms including the neuronal noradrenaline transporter (e.g. Rump et al. 1992; Günther et al. 2010; Schulte et al. 2011) and since many individual tissue pieces can be prepared from one animal. Renal cortex was obtained from Sprague–Dawley rats in which the in vivo experiments by Adams et al. (1976) had been carried out. Most of the experiments have been performed on kidney tissue pieces from mice since in the case of positive results additional experiments with the knockout mouse deficient of the neuronal noradrenaline transporter (Xu et al. 2000) would be possible. Renal cortex tissue pieces were preincubated with ^{3}H-noradrenaline, which is transported via

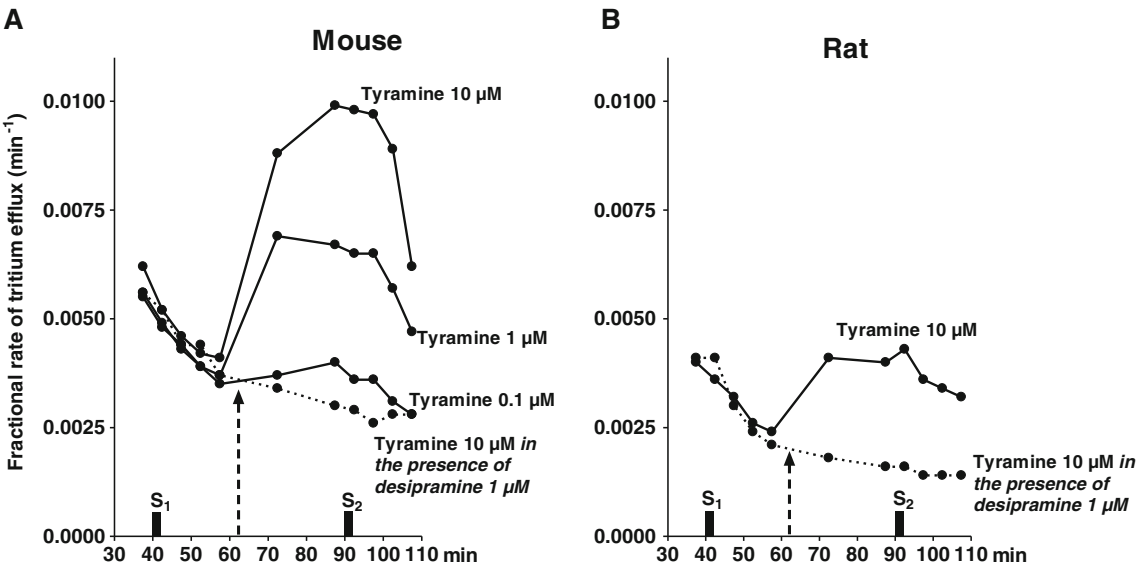

Fig. 2 Time course of tritium efflux from tissue pieces of the mouse (**a**) and rat renal cortex (**b**) under the influence of tyramine alone or in the presence of desipramine. Tissues preincubated with ^{3}H-noradrenaline were superfused with physiological salt solution and tritium overflow was evoked by two 2-min periods of electrical field stimulation (S_1, S_2, as indicated). The superfusate was collected in 5-min samples from 35 to 60, from 70 to 75 and from 85 to 110 min. Tritium efflux was expressed as fractional rate, i.e. as fraction of the tritium present in the tissue at the beginning of the respective 5-min sample, divided by 5. Tyramine was present in the medium from 62 min of superfusion onward (as indicated by the *arrows*), whereas desipramine (when necessary) was present throughout superfusion. The control curve (no tyramine, no desipramine) was virtually identical with the curve obtained in the presence of tyramine plus desipramine and is not shown for the sake of clarity. The stimulation-evoked increase in tritium overflow was very small and cannot easily be recognized in each curve (exceptions are S_1, *dashed line* and S_2, *solid line* in **b**). The curves are representative experiments which were repeated five times

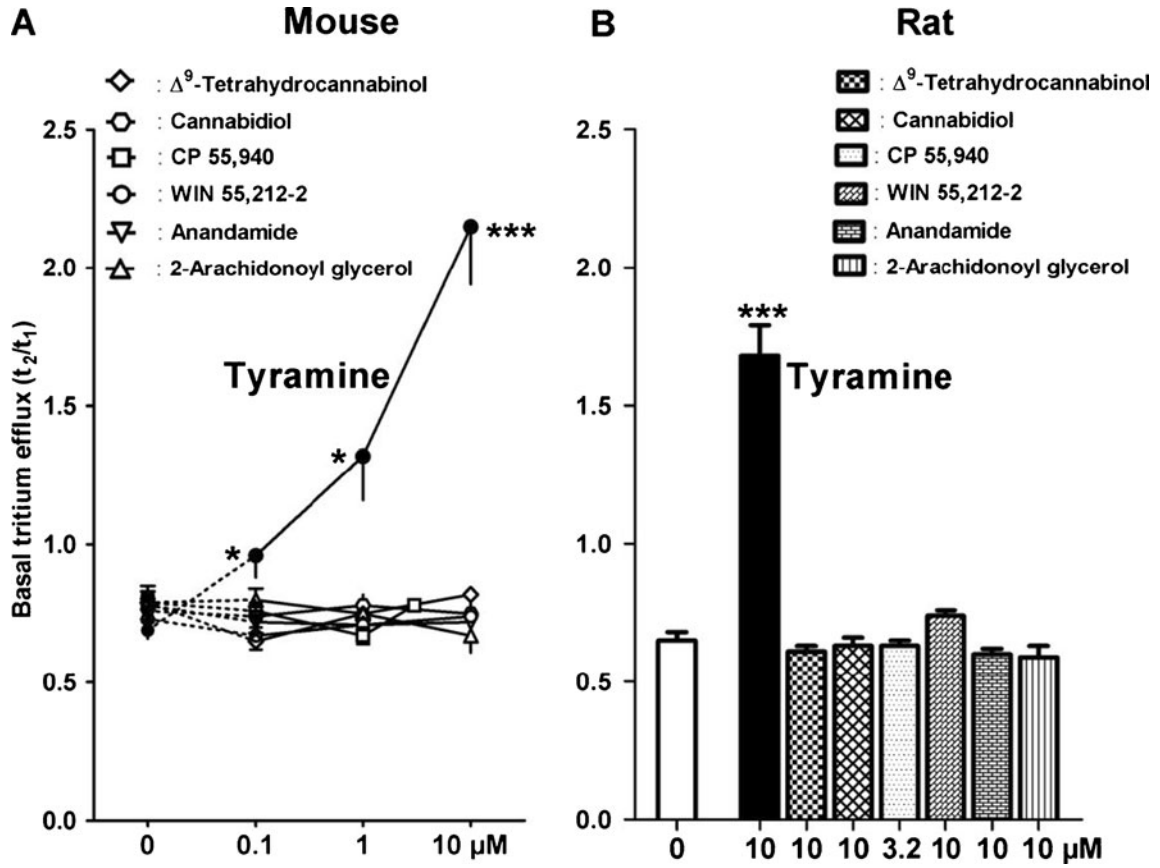

Fig. 3 Effect of six cannabinoids and of tyramine (positive control) on basal tritium efflux from superfused mouse (**a**) and rat renal cortex tissue pieces (**b**) preincubated with ^{3}H-noradrenaline. The drugs under study were added to the medium from 62 min of superfusion onward. Basal tritium efflux was determined as the ratio of the fractional rate of tritium efflux in the 5-min sample collected from 85 to 90 min (t_2) over that collected from 55 to 60 min (t_1). Mean±SEM of five to eight experiments. *P<0.05, ***P<0.001, compared to the corresponding drug-free control

the neuronal noradrenaline transporter and stored in the vesicles of noradrenergic neurones. In order to check whether ^{3}H-noradrenaline can be released in a tyramine-like manner, tyramine itself served as a positive control. The fact that desipramine, an inhibitor of the neuronal noradrenaline transporter, abolished the effect of tyramine in our study further supports the view that the increased tritium efflux indeed represents ^{3}H-noradrenaline.

Unlike tyramine, the six cannabinoids failed to induce carrier-mediated ^{3}H-noradrenaline release although they were examined in high concentrations. In the case of Δ^{9}-THC, this lack of effect may be interpreted as a discrepancy to the results obtained by Adams et al. (1976). However, in the latter study (1) an in vivo design was chosen, (2) noradrenaline release was not determined directly, (3) the authors provided evidence that the major part of the increase in perfusion pressure elicited by Δ^{9}-THC was related to a direct contractile effect on the vessels and (4) part of the effect of Δ^{9}-THC might be related to the blockade of the noradrenaline transporter. Δ^{9}-THC possesses a tenth of the activity as an inhibitor of the neuronal noradrenaline transporter compared to cocaine in the isolated rat heart (Graham et al. 1974a). A more direct approach was chosen by Graham et al. (1974b) on the isolated rat vas deferens. In their study, ^{3}H-Δ^{9}-THC entered the noradrenergic neurones and could be released upon electrical stimulation; the release was markedly decreased when the tissues had been pretreated with 6-hydroxydopamine, a tool that destroys the noradrenergic neurones. Even those data do not necessarily speak against our own findings since in the study by Graham et al. (1974b) ^{3}H-Δ^{9}-THC may have entered the noradrenergic neurones by a mechanism different from the neuronal noradrenaline transporter. Our data are compatible with the results obtained by Ishac et al. (1996) on the isolated rat atrium and vas deferens, although the experimental design differed between both studies. In our hands, Δ^{9}-THC and anandamide did not elicit carrier-mediated ^{3}H-noradrenaline release per se, whereas in the study by Ishac et al. (1996), the two cannabinoids had no influence on the tyramine-induced ^{3}H-noradrenaline release.

The structural requirement necessary that a given compound will be handled as a substrate by the neuronal noradrenaline transporter has been given by Graefe and Bönisch (1988): "The only common denominator in the structures of all known substrates appears to be the presence of an ionizable

nitrogen not incorporated into an aromatic ring system." Since the nitrogen in the anandamide molecule is not ionizable and Δ^9-THC, cannabidiol, CP 55,940 and 2-arachidonoyl glycerol do not contain a nitrogen at all (Fig. 1), the failure of the latter five compounds to induce carrier-mediated noradrenaline release is not surprising. On the other hand, the nitrogen in the morpholine ring system in the WIN 55,212-2 molecule is ionizable. Moreover, this compound was shown to interfere with the uptake of another two monoamines, i.e. ^{3}H-serotonin and ^{3}H-dopamine, by rat neocortical synaptosomes in the concentration range used in the present study (Steffens and Feuerstein 2004). However, also WIN 55,212-2 failed to induce carrier-mediated ^{3}H-noradrenaline release. In this context, the study by Reyes et al. (2009) is of interest, in which a single intraperitoneal administration of WIN 55,212-2 to rats led to a decrease in the expression of the neuronal noradrenaline transporter (quantified by Western blots) in the frontal cerebral cortex. The discrepancy between the latter study and our own results may be related to the fact that in the paper by Reyes et al. (2009) complex in vivo alterations may have occurred following administration of WIN 55,212-2.

The superfusion protocol of the present study was essentially that used by Günther et al. (2010) and Schulte et al. (2011) on mouse and rat renal tissues, respectively. In the latter two studies, the focus was on the electrically evoked tritium overflow, i.e. the *exocytotic* (as opposed to the carrier-mediated) noradrenaline release. Since the auxiliary drugs used in the latter two studies (the α_2-adrenoceptor antagonist rauwolscine or the K^+ channel blocker tetraethylammonium) might interfere with the carrier-mediated noradrenaline release, they were omitted in the present study, and this explains why the electrically evoked tritium overflow was extremely low. Desipramine, which prevents the re-uptake of noradrenaline, as expected increased the amount of the electrically ^{3}H-noradrenaline overflow. The possibility that the lack of effect is related to the fact that the putative facilitatory effect of a given cannabinoid on the carrier-mediated noradrenaline release is set off by an inhibitory effect on the exocytotic noradrenaline release (Ishac et al. 1996; Kurz et al. 2008; Malinowska et al. 2012) can be excluded. So, the effect of the drugs on the carrier-mediated noradrenaline release was studied during the time period from 55 to 90 min of superfusion, whereas the exocytotic noradrenaline release was examined before 55 min and after 90 min of superfusion (see Fig. 2).

In conclusion, two phytocannabinoids (Δ^9-tetrahydrocannabinol and cannabidiol), two synthetic cannabinoids (CP 55,940 and WIN 55,212-2) and two endocannabinoids (anandamide and 2-arachidonoyl glycerol), unlike tyramine, do not elicit carrier-mediated noradrenaline release in the renal cortex from the mouse and the rat.

Acknowledgments This work was supported by a grant from the Deutsche Forschungsgemeinschaft to E.S. (Schl 266/9-2) within the "Forschergruppe 926". The authors would like to thank Mrs. Doris Petri for her skilled technical assistance.

References

Adams M, Ernhardt J, Dewey W, Harris L (1976) Vasoconstrictor actions of Δ8- and Δ9-tetrahydrocannabinol in the rat. J Pharmacol Exp Ther 196:649–656

Graefe KH, Bönisch H (1988) The transport of amines across the axonal membranes of noradrenergic and dopaminergic neurones. Handb Exp Pharmacol 90/I:193–245

Graham JDP, Lewis MJ, Li DMF (1974a) The effect of Δ^1-tetrahydrocannabinol on the uptake of [^{3}H]-(−)-noradrenaline by the isolated perfused heart of the rat. Brit J Pharmacol 51:465–466

Graham JDP, Lewis MJ, Li DMF (1974b) The effect of Δ^1-tetrahydrocannabinol on the release of [^{3}H]-(−)-noradrenaline from the isolated vas deferens of the rat. Brit J Pharmacol 52:233–236

Günther J, Schulte K, Wenzel D, Malinowska B, Schlicker E (2010) Prostaglandins of the E series inhibit monoamine release via EP_3 receptors: proof with the competitive EP_3 receptor antagonist L-826,266. Naunyn-Schmiedeberg's Arch Pharmacol 381:21–31

Ilayan E, Feliszek M, Schlicker E (2013) Do cannabinoids exhibit a tyramine-like effect? Naunyn-Schmiedeberg's Arch Pharmacol 386(Suppl 1):S21

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. Brit J Pharmacol 118:2023–2028

Kurz CM, Gottschalk C, Schlicker E, Kathmann M (2008) Identification of a presynaptic cannabinoid CB_1 receptor in the guinea-pig atrium and sequencing of the guinea-pig CB_1 receptor. J Physiol Pharmacol 59:3–15

Malinowska B, Lupinski S, Godlewski G, Baranowska U, Schlicker E (2008) Role of endocannabinoids in cardiovascular shock. J Physiol Pharmacol 59(Suppl 8):91–107

Malinowska B, Baranowska-Kuczko M, Schlicker E (2012) Triphasic blood pressure responses to cannabinoids: do we understand the mechanism? Brit J Pharmacol 165:2073–2088

Montecucco F, Di Marzo V (2012) At the heart of the matter: the endocannabinoid system in cardiovascular function and dysfunction. Trends Pharmacol Sci 33:331–340

Pacher P, Bátkai S, Kunos G (2005) Cardiovascular pharmacology of cannabinoids. Handb Exp Pharmacol 168:599–625

Reyes BAS, Rosario JC, Piana PMT, Van Bockstaele EJ (2009) Cannabinoid modulation of cortical adrenergic receptors and transporters. J Neurosci Res 87:3671–3678

Rump LC, Schuster MJ, Schollmeyer P (1992) Activation of ß$_2$-adrenoceptors by isoprenaline and adrenaline enhances noradrenaline release in cortical kidney slices of young spontaneously hypertensive rats. Naunyn-Schmiedeberg's Arch Pharmacol 345:25–32

Schulte K, Kumar M, Zajac JM, Schlicker E (2011) Noradrenaline release in rodent tissues is inhibited by interleukin-1ß but is not affected by urotensin II, MCH, NPW and NPFF. Pharmacol Rep 63:102–111

Steffens M, Feuerstein TJ (2004) Receptor-independent depression of DA and 5-HT uptake by cannabinoids in rat neocortex — involvement of Na^+/K^+-ATPase. Neurochem Int 44:529–538

Xu F, Gainetdinov RR, Wetsel WC, Jones SR, Bohn LM, Miller GW, Wang YM, Caron MG (2000) Mice lacking the norepinephrine transporter are supersensitive to psychostimulants. Nat Neurosci 3:465–471