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Protective effects of cannabinoid receptor agonists against cocaine and other convulsant-induced toxic behavioural symptoms

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Abstract

Based on the previously reported co-localization and relationship between cannabinoid and dopamine receptors, the effects of cannabinoid receptor agonists against cocaine-induced toxic behavioural symptoms, including convulsive seizures, were examined in mice. The anticonvulsant effect of several cannabimimetics against seizures induced by other convulsants was also compared. The cannabinoid receptor agonists CP 55940 ((−)-*cis*-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-trans-4-(3-hydroxypropyl)-cyclohexanol) and WIN 55212-2 ((*R*)-(+)-[2.3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone), and the endogenous cannabinoid anandamide were co-administered intraperitoneally with cocaine (75 mg kg^{-1}) or other convulsants such as bicuculline, methyl 6,7-dimethoxy-4-ethyl-β-carboline-carboxylate (DMCM), L-glutamic acid and *N*-methyl-D-aspartate (NMDA). CP 55940 (2.5 mg kg^{-1}) and anandamide (15 mg kg^{-1}) significantly antagonized cocaine-induced lethality, and CP 55940 and WIN 55212-2 (2.5 mg kg^{-1}) significantly attenuated the severity of cocaine-induced convulsive seizures. Furthermore, ataxic hyperactivity, which was observed only in the cocaine-treated group of mice and could be evaluated by their activity counts, was also depressed in the groups of mice co-treated with each of the three cannabinoid agonists. However, none of these agonists protected against bicuculline- or DMCM-induced lethality or convulsive seizures. In contrast, all of the cannabinoid agonists, most notably anandamide, antagonized both L-glutamic acid (2 g kg^{-1})- and NMDA (200 mg kg^{-1})-induced convulsive seizures. These data support the previously reported close correlation between dopamine and cannabinoid receptors, and between cannabinoid agonists, especially anandamide, and glutamate (NMDA) receptors. Furthermore, these results suggest a potential therapeutic role for cannabinoid agonists against cocaine- and other-convulsant-induced toxicities.

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Introduction

The synthesis of high-potency cannabinoid receptor ligands has enabled the identification of cannabinoid receptors in the brain (Herkenham et al 1990, 1991), and the relationship between cannabinoid receptors and other brain receptors has been studied intensively. In particular, the co-localization of cannabinoid receptors with dopamine receptors, the targets of the effects of cocaine, and behavioural interactions between cannabinoid and dopamine ligands have been demonstrated (Devane et al 1988; Malleux & Vanderhaeghen 1992; Anderson et al 1996; Sañudo-Peña et al 1998; Ferrari et al 1999). Furthermore, cannabinoid agonists, which have

been reported to have sedative effects in animals (Stella et al 1997; Meschler et al 2000), have been reported to antagonize the effects of dopamine receptor agonists, including the hyperlocomotion induced by cocaine (Anderson et al 1996; Sañudo-Peña et al 1998; Ferrari et al 1999).

The effects of cannabinoid agonists on cocaine toxicity have not been thoroughly examined. Considering the above antagonistic effects against cocaine-induced excitatory behaviour (Ferrari et al 1999), it can be predicted that cannabinoid agonists may protect against cocaine-induced convulsive seizures. In previous reports, several cannabinoid-receptor-related drugs including cannabinoid agonists caused anticonvulsant effects against the seizures induced by convulsants (Karler et al 1974; Yamamoto et al 1980; Consroe et al 1982; Watanabe et al 1990). Although various correlations have been reported between cannabinoid receptors and brain-seizure-related receptors, such as γ-aminobutyric acid (GABA) (Romero et al 1998; Hajos et al 2000), benzodiazepine (Mokler et al 1986; Sethi et al 1986) and glutamate, including *N*-methyl-D-aspartate (NMDA) (Feigenbaum et al 1989; Akinshola et al 1999; Szabo et al 2000), receptors, the precise mechanisms underlying the possible anticonvulsant effects of cannabinoid drugs have not been elucidated. Therefore, in this study, the behavioural interactions between several cannabinoid agonists with high specificity or potency and a toxic cocaine dose were examined (in mice) and compared with other convulsant–cannabinoid agonist interactions. The possibility of using cannabinoid agonists against the toxicity caused by cocaine and other convulsants was also discussed.

Materials and Methods

Animals

Male ICR mice (Shizuoka Laboratory Animal Center, Hamamatsu, Japan), 60–90 days old, were housed in a forced-air facility which was maintained at 23°C and 50% relative humidity, with a 12-h light–dark cycle, in accordance with a previous report on cocaine toxicity (Boyer & Petersen 1992). The mice were kept in single cages (23.5 × 16.5 × 12 cm) with wood-chip bedding, and were allowed free access to water and lab chow. The experiments described in this report were conducted in accordance with the Guidelines for Animal Experiments of our institution (1988), which are based on the National Institutes of Health Guide regarding the care and use of animals for experimental procedures. Following these guidelines, if any symptoms of pain were caused by the high dose of cocaine, the experiment was stopped. However, convulsions and lethality were the subjects of the present investigation, and were allowed to develop.

Drug treatments

The doses of cocaine and convulsants were selected based on previous studies (Pericic & Manev 1983; Yoshida et al 1987; Mares & Velisek 1992; Hayase et al 1997; Tsuda et al 1997). The final doses used caused convulsive seizures in over 80% of the mice in a preliminary trial, regardless of lethality and other toxic symptoms: 75 mg kg^{-1} for cocaine hydrochloride (Takeda Chemical Industries Ltd, Osaka, Japan), 6 mg kg^{-1} for bicuculline (Tocris Cookson Inc., Ballwin, MO), 10 mg kg^{-1} for methyl 6,7-dimethoxy-4-ethyl-β-carboline-carboxylate (DMCM; Sigma-Aldrich, Inc., St Louis, MO), 2 g kg^{-1} for L-glutamic acid (Nacalai Tesque, Inc., Kyoto, Japan) and 200 mg kg^{-1} for *N*-methyl-D-aspartate (NMDA) (Nacalai Tesque, Inc., Kyoto, Japan). Since bicuculline and DMCM are not soluble in water, they were initially dissolved in dimethyl sulfoxide (DMSO) (Nacalai Tesque, Inc., Kyoto, Japan) to one-third of the total volume, and were then diluted in distilled water. The other drugs were also dissolved in a mixture of DMSO and distilled water at the same ratio as the bicuculline and DMCM solutions. For the L-glutamic acid solution, a pH 8.1 buffer (Nacalai Tesque, Inc., Kyoto, Japan) was used instead of distilled water considering its solubility. All of the convulsants were administered by intraperitoneal injection in a volume of 10 mL kg^{-1} body weight.

The cocaine and convulsants were given 1 h after intraperitoneal injection of the cannabinoid receptor agonists or a control vehicle solution, in a volume of 5 mL kg^{-1}. All of the cannabinoid agonists were provided by Tocris Cookson Inc. (Ballwin, MO). The doses used were selected from the non-toxic doses that have been previously reported to have some behavioural effects, or that caused some behavioural effect in our preliminary study (Costa et al 1996; Carriero et al 1998; Sulcova et al 1998; Hayase et al 1999): 2.5 mg kg^{-1} for CP 55940 ((−)-*cis*-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-trans-4-(3-hydroxypropyl)cyclohexanol), 2.5 mg kg^{-1} for WIN 55212-2 ((*R*)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone) and 15 mg kg^{-1} for anandamide ((all Z)-*N*-(2-hydroxyethyl)-5,8,11,14-eicosatetraenamide). Even the doses that caused slight ataxia in the preliminary trials were tested,

Table 1 Drug administration protocol, lethality and convulsive seizures in mice given cocaine or convulsants alone or with cannabinoids.

Groups	Mortality rate (%)	Seizure score
Cocaine (75 mg kg^{-1}) groups		
Cocaine only (n = 16)	75.0	3.2 ± 0.7
Cocaine + CP 55940 (2.5 mg kg^{-1}) (n = 9)	22.2*	1.0 ± 0.8*
Cocaine + WIN 55212-2 (2.5 mg kg^{-1}) (n = 9)	33.3	1.2 ± 0.8*
Cocaine + anandamide (15 mg kg^{-1}) (n = 9) (10-min interval group)	22.2*	2.8 ± 0.9
Cocaine + anandamide (15 mg kg^{-1}) (n = 9) (1-h interval group)	22.2*	2.7 ± 0.9
Bicuculline (6 mg kg^{-1}) groups		
Bicuculline only (n = 12)	66.7	3.1 ± 0.9
Bicuculline + CP 55940 (2.5 mg kg^{-1}) (n = 10)	60.0	2.9 ± 0.7
Bicuculline + WIN 55212-2 (2.5 mg kg^{-1}) (n = 12)	66.7	3.0 ± 0.8
Bicuculline + anandamide (15 mg kg^{-1}) (n = 10) (10-min interval group)	60.0	2.9 ± 0.8
Bicuculline + anandamide (15 mg kg^{-1}) (n = 11) (1-h interval group)	63.6	2.9 ± 0.8
DMCM (10 mg kg^{-1}) groups		
DMCM only (n = 11)	63.6	3.0 ± 0.9
DMCM + CP 55940 (2.5 mg kg^{-1}) (n = 12)	66.7	2.5 ± 1.0
DMCM + WIN 55212-2 (2.5 mg kg^{-1}) (n = 12)	66.7	2.6 ± 0.9
DMCM + anandamide (15 mg kg^{-1}) (n = 10) (10-min interval group)	60.0	3.0 ± 0.8
DMCM + anandamide (15 mg kg^{-1}) (n = 10) (1-h interval group)	60.0	2.7 ± 0.9
NMDA (200 mg kg^{-1}) groups		
NMDA only (n = 13)	69.2	3.2 ± 1.1
NMDA + CP 55940 (2.5 mg kg^{-1}) (n = 9)	33.3	1.6 ± 1.1*
NMDA + WIN 55940 (2.5 mg kg^{-1}) (n = 9)	44.4	1.7 ± 0.8*
NMDA + anandamide (15 mg kg^{-1}) (n = 9) (10-min interval group)	33.3	1.3 ± 0.9*
NMDA + anandamide (15 mg kg^{-1}) (n = 9) (1-h interval group)	33.3	1.2 ± 1.0*
L-Glutamic acid (2 g kg^{-1}) groups		
L-Glutamic acid only (n = 11)	63.6	3.0 ± 0.7
L-Glutamic acid + CP 55940 (2.5 mg kg^{-1}) (n = 9)	33.3	1.0 ± 0.7*
L-Glutamic acid + WIN 55212-2 (2.5 mg kg^{-1}) (n = 9)	22.2	1.2 ± 0.8*
L-Glutamic acid + anandamide (15 mg kg^{-1}) (n = 9) (10-min interval group)	22.2	0.9 ± 0.7*
L-Glutamic acid + anandamide (15 mg kg^{-1}) (n = 9) (1-h interval group)	22.2	0.9 ± 0.6*

The number of surviving mice is shown in Table 2 and was used for the statistical analysis. The data for the seizure scores represent means ± s.d. *$P < 0.05$, compared with the cocaine- or convulsant-only groups.

but doses that caused any observable toxic effects, including severe catalepsy, were not selected. Effects of these agonists, such as the potency and specificity, have been described in previous studies (Rinaldi-Carmona et al 1996; Burkey et al 1997; Carriero et al 1998). The time-interval between administration of the cannabinoid agonists and the convulsant (1 h) was determined from the time course of the effects of each drug (Romero et al 1995; Niederhoffer & Szabo 2000). For anandamide, the administration was also performed with a short interval (10 min) between the anandamide and the convulsant (10-min interval group), as the early disappearance of the effects of anandamide has been reported due to its rapid metabolism (Romero et al 1995). Since

CP 55940 and WIN 55212-2 are not soluble in water, each drug was initially dissolved in DMSO to one-third of the total volume, and then diluted in distilled water. As a control solution, a mixture of DMSO and distilled water at the same ratio as the cannabinoid solutions was prepared and administered in the cocaine- and convulsant-only groups.

In the behavioural analysis study, a control group of mice in which the above DMSO–water vehicle was injected instead of the convulsants and cannabinoid agonists was prepared, and the activity counts were measured in the same manner as the other groups.

Behavioural analysis

Modifications in the cocaine- or convulsant-induced lethality, convulsive seizures and toxic behavioural alterations were investigated. The lethality was evaluated by the total mortality rate at 24 h after cocaine administration. The convulsive seizures were scored for all mice based on their severity, using previously-reported evaluation methods and common features of the seizures induced by each convulsant (Piredda & Gale 1986; Przewlocka et al 1994): score 0 = no convulsive seizures, score 1 = short-lasting mild episodes of clonic convulsions, score 2 = short-lasting episodes of clonic convulsions that caused a loss of the righting reflex, score 3 = episodic convulsive seizures accompanied by continuous severe clonus or rearing and score 4 = episodic convulsive seizures continuous and violent enough to cause fatal respiratory disorders. Nine mice were examined in total for each administration group, but in the groups with a high mortality rate, a larger number of mice (Table 1) were actually tested to examine the toxic behavioural alterations in a sufficient number of surviving mice (Table 2).

Quantitative alterations in the toxic behavioural symptoms were evaluated by activity counts using the counting instrument Supermex (Muromachi Kikai Co. Ltd, Tokyo, Japan) connected to the behaviour analysing system CompACT AMS (Muromachi Kikai Co. Ltd) (Masuo et al 1997). This analysis was performed for all mice in each administration group. The Supermex instrument can monitor even minute movements in all three planes of motion (sagittal, coronal and horizontal) as one value, since its infrared sensor with multiple Fresnel lenses can be moved close enough to the cage to capture multi-directional locomotor alterations of a single mouse as infrared signals. Therefore, in combination with the CompACT AMS, vertical movements such as jumping, horizontal movements such as walking and running, and smaller movements of the limbs, head and tail accompanying the convulsive seizures could be quantitatively scored as activity counts. The total activity counts for the first hour in the surviving mice are summarized in Table 2. For the dead mice, the trends in

Table 2 Activity counts for the surviving mice after administration of cocaine or convulsants alone or with cannabinoids.

Groups	Number of tested survivors (total)	Activity counts
Control group	4 (4)	2398 ± 635
Cocaine groups		
Cocaine only	4 (16)	5155 ± 717 #
Cocaine + CP 55940	7 (9)	3239 ± 439* #
Cocaine + WIN 55212-2	6 (9)	3424 ± 60* #
Cocaine + anandamide (10-min interval group)	7 (9)	4037 ± 580* #
Cocaine + anandamide (1-h interval group)	7 (9)	4255 ± 607* #
Bicuculline groups		
Bicuculline only	4 (12)	2912 ± 387
Bicuculline ± CP 55940	4 (10)	3015 ± 296
Bicuculline + WIN 55212-2	4 (12)	2665 ± 227
Bicuculline + anandamide (10-min interval group)	4 (10)	2806 ± 263
Bicuculline + anandamide (1-h interval group)	4 (11)	2682 ± 265
DMCM groups		
DMCM only	4 (11)	2946 ± 303
DMCM + CP 55940	4 (12)	3027 ± 330
DMCM + WIN 55212-2	4 (12)	2702 ± 288
DMCM + anandamide (10-min interval group)	4 (10)	2722 ± 218
DMCM + anandamide (1-h interval group)	4 (10)	2631 ± 250
NMDA groups		
NMDA only	4 (13)	3155 ± 378
NMDA + CP 55940	6 (9)	2659 ± 364*
NMDA + WIN 55212-2	5 (9)	2225 ± 272*
NMDA + anandamide (10-min interval group)	6 (9)	2143 ± 227*
NMDA + anandamide (1-h interval group)	6 (9)	2228 ± 287*
L-Glutamic acid groups		
L-Glutamic acid only	4 (11)	3107 ± 323
L-Glutamic acid + CP 55940	6 (9)	2316 ± 287*
L-Glutamic acid + WIN 55212-2	7 (9)	2208 ± 334*
L-Glutamic acid + anandamide (10-min interval group)	7 (9)	2110 ± 243*
L-Glutamic acid + anandamide (1-h interval group)	7 (9)	2095 ± 246*

Values represent counts for the first hour of activity after drug administration in the surviving mice. The number of survivors in each group against the total number of mice (in parentheses) is shown. The data represent means ± s.d. *$P < 0.05$, compared with the cocaine- or convulsant-only groups; #$P < 0.05$, compared with the control group.

the counted activity are briefly summarized in the results section.

Statistical analysis

Fisher's exact test was used to compare the frequency of lethality in each cannabinoid agonist co-treatment group with the corresponding cocaine- or convulsant-only group (Matsumoto et al 2001). For the seizure scores, the Mann-Whitney *U*-test was performed to evaluate the effects of each cannabinoid drug, after the data were subjected to a Kruskal-Wallis analysis of variance (Sañudo-Peña et al 2000). For the activity-count values, a two sample *t*-test with Welch's correction was performed to evaluate the effects of each cannabinoid drug, after the data were subjected to a one-way analysis of variance (Derlet et al 1990; Sañudo-Peña et al 2000). All of the comparisons were performed using statistical software packages and their manuals (Shakai Johou Service, Tokyo, Japan; OMS Publication, Saitama, Japan). Unless otherwise noted, $P < 0.05$ was concluded to be statistically significant.

Results

Lethality

The total mortality rate due to cocaine was significantly attenuated by CP 55940 and anandamide (Table 1). These cannabinoid agonists did not, however, provide any protective effects in the bicuculline and DMCM groups. The mortality rate due to L-glutamic acid and NMDA was attenuated by CP 55940, WIN 55212-2 and anandamide, but these effects were not statistically significant. All of the cocaine- and convulsant-induced deaths were observed within 24 h after drug administration and, except for the cocaine-only group (two mice died after the 1-h time point), all of the cocaine- and convulsant-induced deaths were observed within 1 h of drug administration.

Convulsive seizures

The scores of the cocaine-induced seizures were significantly reduced by CP 55940 and WIN 55212-2 (Table 1), but none of the cannabinoid agonists produced any significant anticonvulsant effect in the bicuculline and DMCM groups. Anandamide did not significantly attenuate the severity of the cocaine-, bicuculline- or DMCM-induced seizures, in either the 10-min or the 1-h interval group. The scores for the L-glutamic acid- and NMDA-induced seizures were significantly reduced by CP 55940, WIN 55212-2 and anandamide, and the strongest anticonvulsant effect was provided by anandamide.

Behavioural alterations

The activity counts for the surviving mice over the first hour immediately after cocaine or convulsant administration are shown in Table 2. Although the slight hyperlocomotion had not disappeared yet by one hour in the cocaine groups, the observable convulsive seizures had disappeared in all groups, even in the cocaine groups, by that time point. In the cocaine-only group, a remarkable increase in the activity counts as compared with the control group was observed. Although anandamide did not significantly attenuate the severity of the cocaine-induced seizures (Table 1), the cocaine-induced morbid increase in the activity counts was normalized by anandamide in the survivors, in both the 10-min and the 1-h interval groups. CP 55940, a cannabinoid agonist with high potency and selectivity, as well as WIN 55212-2, attenuated the cocaine-increased activity counts. Even in the dead mice, attenuated activity counts and an apparently delayed onset of death were observed in the cannabinoid agonist co-treated groups, although the count values varied depending on the different times of death (data not shown). For both survivors and dead mice, the morbid hyperactivity accompanied by increased ambulation was observed only in the cocaine group. Due to the convulsive seizures, an increase in the activity counts as compared with the control group was also predicted in the bicuculline, DMCM, L-glutamic acid and NMDA groups. However, in these groups, unlike in the cocaine group, the 1-h count value was not significantly different from the control value, which was increased as compared with the baseline due to the excitement from the injection. In the L-glutamic acid and NMDA groups (even in the dead mice, data not shown), the activity counts were attenuated by the cannabinoid agonists, corresponding to an amelioration of the convulsive seizures (Table 1).

Discussion

Some cannabinoid agonists have been reported to have various effects on receptors other than cannabinoid receptors (e.g. dopamine receptors), depending on their structural differences (Hampson et al 1998; Kimura et al 1998; Sañudo-Peña et al 1998; Auclair et al 2000). Judging by the strong protective effect of the potent and selective cannabinoid agonist CP 55940 against the toxic

effects of cocaine observed in this study, and previous studies of the activation of dopamine receptors by cannabinoid agonists, which were antagonized by the selective cannabinoid antagonist SR 141716 (Diana et al 1998). Therefore the co-localization of, and the accompanying close relationship between, cannabinoid and dopamine receptors (Devane et al 1988; Malleux & Vanderhaeghen 1992) seemed to contribute greatly to the protective effects of the cannabinoid agonists against the cocaine-induced lethality and convulsive seizures, which were also closely correlated with dopamine receptors and were antagonized by a dopamine antagonist (Shimosato et al 1995). However, a functional correlation between cannabinoid agonists and dopamine receptors cannot be proven directly from these results, although a simple structural relationship cannot account for these effects, based on the reported lack of activity for stereoisomers such as WIN 55212-3 (Song & Slowey 2000). Furthermore, a strong affinity for cannabinoid receptors did not seem to be a necessary prerequisite for the protective effects against cocaine-induced lethality, judging from the effectiveness of anandamide, which has a weak affinity.

The weaker anticonvulsant effects of anandamide against cocaine as compared with the other cannabinoid agonists seemed to be related to its weaker affinity for cannabinoid receptors (Rinaldi-Carmona et al 1996; Burkey et al 1997). In our preliminary study, high doses of anandamide (> 20 mg kg^{-1}) suppressed cocaine-induced convulsive seizures, but increased mortality rate. However, in spite of its weaker anticonvulsant effect, the mortality rate in the anandamide co-treated group was attenuated to the same extent as in the CP 55940 co-treated group. The endogenous cannabinoid ligand anandamide has been reported to act as an agonist at cannabinoid receptors (Fride & Mechoulam 1993; Ueda 1995), but has also been reported to act as a potent analgesic via mechanisms related to other brain receptor sites, either directly or indirectly, in a manner that cannot be mimicked by other agonists (Hampson et al 1998; Akinshola et al 1999; Houser et al 2000). Such a mechanism may contribute to the protective effects of anandamide. Furthermore, it is possible that the metabolites of anandamide may have contributed to the protective effects, judging from the long-lasting effectiveness and the reported neuroprotective effects of arachidonic acid, a metabolite of anandamide (Laborit et al 1975). It has been shown that anandamide itself provides a strong neuroprotective effect during the early period (within 1 h after administration) (Romero et al 1995; Sinor et al 2000), and these neuroprotective effects have been reported to be due to its structure, in experiments using methanandamide, a stable analogue of anandamide (Abadji et al 1994).

The cannabinoid agonists relieved neither the lethality, the convulsive seizures nor the toxic behavioural alterations induced by the GABA receptor-related convulsant drug bicuculline or the benzodiazepine receptor-related convulsant drug DMCM. Nevertheless, some functional correlations have been reported between cannabinoid and GABA receptors (Romero et al 1998; Hajos et al 2000), and between cannabinoid and benzodiazepine receptors (Mokler et al 1986; Sethi et al 1986). On the other hand, all of the cannabinoid agonists examined in this study protected against the toxic effects, especially the convulsive seizures, induced by L-glutamic acid and NMDA. Furthermore, these protective effects were most notable for anandamide despite it having the lowest affinity for cannabinoid receptors among the three agonists studied (Rinaldi-Carmona et al 1996; Burkey et al 1997). The strength of the direct effects on glutamate (NMDA) receptors provided by the present three agonists has not been investigated and compared. Nevertheless, as compared with the effects on GABA and benzodiazepine receptors, stronger direct effects for the cannabinoid agonists (especially anandamide) on NMDA and other glutamate receptors have been demonstrated by in-vitro studies (Hampson et al 1998; Auclair et al 2000). In particular, modifications of the functions of NMDA receptors at the gene level have been suggested for anandamide (Hampson et al 1998).

Some of the results from this study suggest the possible therapeutic use of cannabinoid agonists against cocaine and convulsant toxicities. In particular, the protective effect against cocaine toxicity, which was characteristically accompanied by relief from the cocaine-induced hyperlocomotion, seems to support the validity of using these cannabinoid agonists. The protective effect of the cannabinoid agonists against cocaine toxicity seems to be most strongly influenced by direct drug–receptor effects, since CP 55940, which has the strongest affinity for cannabinoid receptors, had the strongest protective effect (Table 1). However, the predictable direct effects of the three cannabinoid agonists on dopamine receptors have not been compared. In this study, in addition to the lethality and convulsive seizures, the cocaine-induced hyperlocomotion was also relieved by the cannabinoid agonists. This reduction in the activity counts seems to indicate a good prognosis, since the relief from cocaine-induced hyperlocomotion has been reported to be directly correlated with dopamine receptors, and the prognosis of the cocaine toxicity has been reported to be partially dependent on the severity of the cocaine-induced hyperlocomotion (O'Neill & Shaw 1999).

It can be concluded that cannabinoid agonists protected against cocaine toxicity in mice effectively. Furthermore, the cannabinoid agonists also antagonized the toxic effects of convulsants related to glutamate (NMDA) receptors. However, the receptor sites related to the protective effects of anandamide cannot be explained simply by the interactions between the dopamine– and glutamate (NMDA)–cannabinoid receptor systems. Nevertheless, the protective effects of cannabinoid agonists with high potency and specificity against the toxic stimulant effects of cocaine support the validity of the therapeutic usage of cannabinoid agonists such as CP 55940.

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