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The CB_1 Cannabinoid Receptor Agonist, HU-210, Reduces Levodopa-Induced Rotations in 6-Hydroxydopamine-Lesioned Rats

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Abstract: Parkinson's disease is a chronic neurodegenerative disease of the extrapyramidal system associated with dopaminergic neuronal loss in the basal ganglia. However, several other neurotransmitters, such as serotonin, γ-amino-butyric acid and glutamate, are also related to the symptoms of Parkinson's disease patients and their response to levodopa treatment. The co-expression of cannabinoid and dopamine receptors in the basal ganglia suggests a potential role for endocannabinoids in the control of voluntary movement in Parkinson's disease. In the present study we treated unilaterally 2,4,5-trihydroxyphenethylamine (6-hydroxydopamine)-lesioned rats with the enantiomers of the synthetic cannabinoid 7-hydroxy-Δ^6-tetrahydrocannabinol 1,1-dimethylheptyl. Treatment with its (−)− (3R, 4R) enantiomer (code-name HU-210), a potent cannabinoid receptor type 1 agonist, reduced the rotations induced by levodopa/carbidopa or apomorphine by 34% and 44%, respectively. In contrast, treatment with the (+)− (3S, 4S) enantiomer (code-name HU-211), an N-methyl-D-aspartate antagonist, as well as the psychotropically inactive cannabis constituent: cannabidiol and its primary metabolite, 7-hydroxy-cannabinol, did not show any reduction of rotational behavior. Our results indicate that activation of the CB1 stimulates the dopaminergic system ipsilaterally to the lesion, and may have implications in the treatment of Parkinson's disease.

Cannabinoid components of the marijuana plant (*Cannabis sativa*) are known to exert behavioural and psychotropic effects, but also possess therapeutic properties. The Δ-9-tetrahydrocannabinol is the major psychoactive substance in marijuana. Cannabidiol and cannabinol, as Δ-9-tetrahydrocannabinol, are the most abundant natural components of the marijuana plant. The main effect achieved by these compounds is through activation of the cannabinoid receptors, which are CB_1 (found primarily, but not exclusively in the brain) and CB_2 (found only in peripheral tissues). Other proposed mechanisms of cannabinoids include the increase of cell membrane fluidity, alternation of other neurotransmitters (mainly dopamine and γ-amino butyric acid-GABA) and prostaglandins.

CB_1 receptors are most prevalent in the hippocampus, cerebral cortex, cerebellum and especially in the basal ganglia. The high levels of these receptors in the basal ganglia suggest a potential role for endocannabinoids in the control of voluntary movement and in basal ganglia-related movement disorders such as Parkinson's disease (Di Marzo *et al.* 1998; Self *et al.* 1999). Within the basal ganglia, CB_1 receptors are particularly prominent on the terminals of GABAergic projections from the striatum to the globus pallidus and substantia nigra pars reticulata (the "indirect" and "direct" striatal output pathways respectively). The interplay between these neurotransmitters plays a crucial role in the initiation and severity of the voluntary movements regulated by the dopaminergic nigrostriatal system.

The presence and actions of cannabinoid structure in the central nervous system led us to investigate the potential inhibitory effects of (−)− (3R, 4R)-7-hydroxy-Δ^6-tetrahydrocannabinol 1,1-dimethylheptyl (HU-210), a highly potent synthetic cannabinoid agonist (Mechoulam *et al.* 1988), and its enantiomer (mirror image) (+)− (3S, 4S)-7-hydroxy-Δ^6-tetrahydrocannabinol 1,1-dimethylheptyl (HU-211), an N-methyl-D-aspartate (NMDA) antagonist that lacks psychotropic properties (Mechoulam *et al.* 1988 & 1990; Feigenbaum *et al.* 1989; Eshhar *et al.* 1995; Shohami *et al.* 1996), in a rat model of Parkinson's disease. In view of the known effects of cannabidiol in neurological conditions (Consroe *et al.* 1998), we also investigated in the same model, the effects of this cannabinoid and of its primary metabolite, 7-hydroxy-cannabidiol (Tchilibon & Mechoulam 2000). Since there is accumulating evidence that cannabinoids might also be neuroprotective *in vitro* (Eshhar *et al.* 1995; Hampson *et al.* 1998), we also examined whether HU-210 or HU-211 might have neuroprotective effects against dopamine, 2,4,5-trihydroxyphenethylamine (6-hydroxydopamine), levodopa and 1-methyl-4-phenylpyridinium ion, all well known neurotoxins, in neuroblastoma SH-SY5Y cells. Our data shows that only HU-210, the CB_1 agonist, and none of the other compounds, affect rotation behavior and inhibit its induction by levodopa or apomorphine.

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Materials and Methods

Cells. Neuroblastoma SH-SY5Y cells (ATCC, USA) were maintained in Dulbeco's modified Eagle's medium (DMEM), supplemented with 8% foetal calf serum, 8% horse serum, penicillin (25 μg/ml), streptomycin (25 μg/ml), and 2 mM L-glutamine. Cells (100 μl of 3×10^5 cells/ml) were subcultured in 2% foetal calf serum to poly-L-lysine-coated 96-well microtiter plates (Corning, USA). HU-210/HU-211, cannabidiol and 7-hydroxy-cannabidiol (3–300 μM) were applied to the cells in each well. Four hours later dopamine, 6-hydroxydopamine or levodopa (50–200 μM) or 1-methyl-4-phenylpyridinium ion (0.5–2 mM), dissolved in phosphate buffer saline, were added for 24 hr. Cell viability was assayed by Neutral Red staining as described in Hochman *et al*. (1998).

Animals. Male Sprague-Dawley rats weighing 250–300 g (Harlan, Israel) were housed in standard conditions: constant temperature (22±1°), humidity (relative, 30%) and 12 hr light/dark cycle. The animals were allowed free access to food and water, and surgical procedures were made under the supervision of the Animal Care Committee at the Rabin Medical Center.

Lesioning. The animals were anaesthetized with chloral hydrate, 350 mg/kg intraperitoneally and secured in a stereotaxic frame (Stoelting, USA). 6-Hydroxydopamine hydrobromide (12 μg in 6 μl of saline with 0.01% ascorbate, Sigma, USA) was prepared fresh and in order to prevent autooxidation, kept on ice until injection. A special drill was used to place a single burr hole at the appropriate site with the following coordinates: posterior 4.8 mm, lateral 1.8 mm dorsoventral, 8.1 mm with respect to bregma and dura, based on the Stereotaxis Atlas (Paxinos & Watson 1986). 6-Hydroxydopamine (6 μl, 1 μl/min.) was injected using a Hamilton 10 μl syringe with a 26-gauge needle. At the completion of the injection, the needle was left in place for another 3 min. and then withdrawn at 1 mm/min. in order to prevent vacuum. The burr hole was cleaned and the skin was closed (Perese *et al*. 1989).

Measurement of rotational behavior. Lesioned animals were tested for rotational behaviour induced by a subcutaneous injection of 0.25 mg/kg apomorphine, which is a dopamine agonist, starting 14 days after the 6-hydroxydopamine lesion. Their contraversive turnings were measured visually in a round tool (40 cm diameter), and only animals that demonstrated an average of at least six contraversive turnings/min. over 30 min. in response to apomorphine, were selected for further examination. Finally six animals were chosen and used for the entire study, and for each, a one-week washout period was interposed between each drug treatment.

Drugs. All cannabinoids (HU-210, HU-211, cannabidiol and 7-hydroxy-cannabidiol) were synthesized at the Hebrew University, Jerusalem, Israel, following reported procedures (Mechoulam *et al*. 1999; Tchilibon & Mechoulam 2000). The drugs were first dissolved in 1:1 ethanol: cremophor (Sigma) solution, and diluted to the desired concentration with 0.9% saline to yield a final vehicle of 1:1:18 (ethanol: cremophor: saline respectively). Levodopa/carbidopa 250/50 mg/kg per tablet (Teva, Israel) and apomorphine (Sigma, USA) were dissolved in sterile water.

Locomotor behavioural assay. Locomotion tests were conducted in an open field box (80×80×40 cm), with 20×20 cm squares marked on the floor. Healthy (n=3) and lesioned (n=3) rats were placed for 5 min. inside the chamber in order to habituate. Their locomotion activity, defined as the total number of lines crossed, was observed for 10 min., 30 min. following injection of saline or drug (Hiltunen *et al*. 1988). For each animal, a one-week washout period was interposed between each drug treatment.

Statistics. Rotational behavioural data, following drug administration and locomotor behavioural assay, were analyzed by the paired, two-tail t-test. In all tests, significance was assigned when $P<0.05$. Results are presented as mean±S.E.

Results

Administration of levodopa/carbidopa (50/5 mg/kg respectively, intraperitoneallly) to 6-hydroxydopamine-lesioned rats (n=6), elicited a high rotation rate contraversive to the lesion site (390±71 for 2 hr). In contrast, injection of HU-210 (0.005 or 0.05 mg/kg, intraperitoneally) 30 min. before levodopa/carbidopa administration markedly reduced the rotations for 2 hr, by 46% and 35% ($P<0.03$ and $P<0.006$, respectively, fig. 1). No statistical significance was demonstrated between the two doses of HU-210. When apomorphine (0.25 mg/kg) was used to induce rotational behaviour, we demonstrated that HU-210 (0.05 mg/kg), given 30 min. before apomorphine, reduced the rotations per 2 hr by 44% ($P<0.02$, fig. 2). To exclude the possibility that the rotation inhibition is an epiphenomenon of sedation, or hypothermia, which is commonly observed with Δ-9-tetrahydrocannabinol and other psychoactive cannabinoids (Ovadia *et al*. 1995), we assayed the locomotion activity in lesioned and non-lesioned rats after challenge with HU-210. We found that HU-210 can reduce the movement in the open field, but only at doses higher than 0.1 mg/kg, which are considerably larger than the dose that showed inhibitory effects in our rotation experiments (0.005 mg/kg, fig. 3). No statistically significant differences were found between lesioned and non-lesioned rats in their locomotion activity (fig. 3). When we injected the psychotropically inactive cannabis constituent: cannabidiol (15 mg/kg) or its primary metabolite 7-hydroxy-cannabinol (15 mg/kg), before the levodopa/carbidopa challenge, we did not find any reduction in rotational behaviour. Similarly, treatment with HU-211 (0.5 mg/kg), an NMDA antagonist, as well as amantadine (100 mg/kg), the NMDA antagonist, did not reduce the rotation rates induced by the levodopa/carbidopa challenge.

In order to examine the possible neuroprotective activity of HU-210 and HU-211, we exposed neuroblastoma cells to various neurotoxins *in vitro*. Using neutral red assay, HU-210 or HU-211 (3–300 μM) did not exhibit any neuroprotective effects, against dopamine, 6-hydroxydopamine, levodopa (50–200 μM) and 1-methyl-4-phenylpyridinium ion (0.5–2 mM) (data not shown).

Discussion

Our study shows that pretreatment with low doses of HU-210, a synthetic, potent CB_1 agonist, markedly reduces the levodopa- and apomorphine-induced contraversive rotations in rats with unilateral 6-hydroxydopamine nigral lesions. By contrast, the non-psychotropic compounds of the cannabinoid family, cannabidiol and 7-hydroxy-cannabidiol did not inhibit the rotation rates. Furthermore, HU-211, the mirror image of HU-210, and amantadine, which are both NMDA antagonists (Eshhar *et al*. 1995; Verhagen *et al*. 1998), did not alter the rotational behaviour.

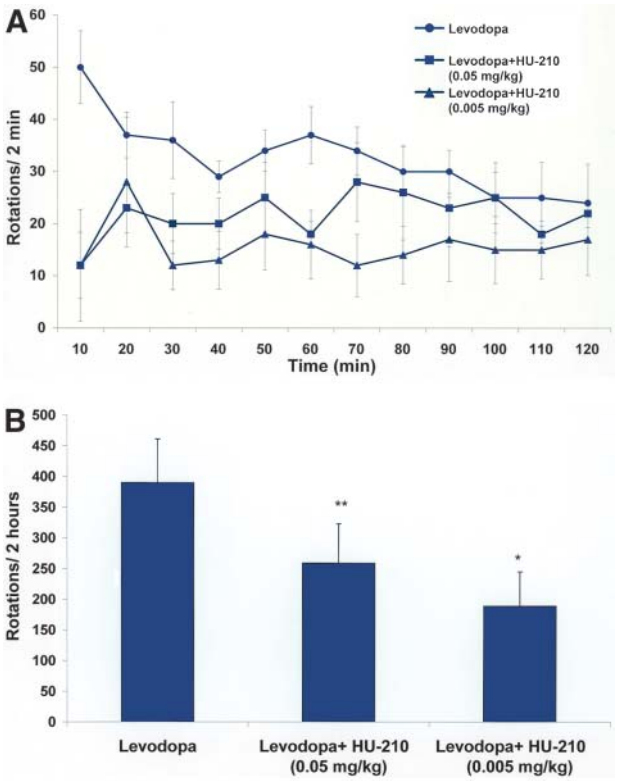

Fig. 1. HU-210 (0.005 or 0.05 mg/kg) inhibits levodopa/carbidopa (50/5 mg/kg, intraperitoneally respectively) induced-rotations in 6-OHDA lesioned rats (n=6) (A). Histograms of the total measured levodopa-induced rotations in 2 hr (B). The rotations were measured for 2 hr in a round tool (*P<0.03, **P<0.006, Student's t-test).

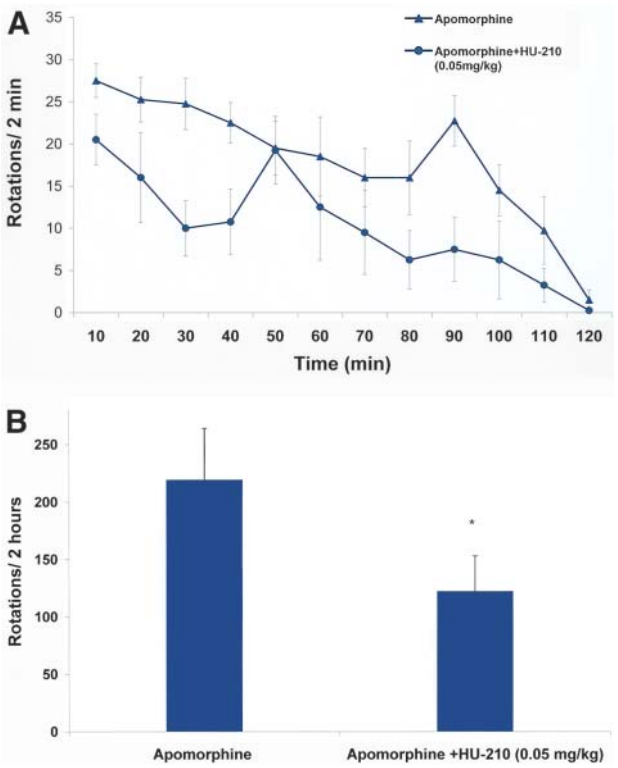

Fig. 2. HU-210 (0.05 mg/kg) reduces apomorphine (0.25 mg/kg, intraperitoneally)-induced rotations in 6-OHDA lesioned rats (n=6) (A). Histograms of the total measured apomorphine-induced rotations in 2 hr (B). The rotations were measured for 2 hr in a round tool. *P<0.02, Student's t-test.

In the 6-hydroxydopamine rat model of Parkinson's disease, apomorphine induces rotations only when there is massive (over 90%) unilateral destruction of the dopaminergic nigrostriatal projections in the striatum (Hudson *et al*. 1993). Following exogenous levodopa challenge, dopamine is generated in the striatum, predominantly in dopa-decarboxylase containing non-dopaminergic cells (Hefti *et al*. 1980; Melamed *et al*. 1980). In contrast with the dopaminergic nerve terminals, these neuronal and non-neuronal cells do not contain dopamine vesicular storage sites and the formed dopamine molecules rapidly leak and stimulate receptors in a non-physiologic pulsatile fashion (Davis *et al*. 1991). The unilateral destruction of the dopaminergic cells induces supersensitivity of the striatal dopamine receptors. It is believed that the contraversive-circling behaviour following exogenous administration of levodopa is due to overstimulation of the supersensitive receptors by the unregulated release of the unstored dopamine (Crossman *et al*. 1990). However, apomorphine causes contraversive circling by direct receptor stimulation of the lesioned hemisphere (Perese *et al*. 1989). Basal ganglia are likely sites of action for the effects of cannabinoids on D_1-mediated rotation, since they have among the highest densities of cannabinoid receptor binding in the brain. Cannabinoid receptors are present in the striatum and on the terminals of striatal output neurones in the substantia nigra pars reticulata and the globus pallidus (Herkenham *et al*. 1990 & 1991).

The cannabinoid and dopamine receptors have a close functional relationship and apparently interact with each other (Muller-Vahl *et al*. 1999). Indeed, Sanudo-Pena *et al*. (1998) have shown that dopamine depletion greatly potentiated the contralateral turning produced by administration of CP 55,940, a CB_1 receptor agonist, into the substantia nigra pars reticulata. Furthermore, stimulation of the CB_1 receptor at one or several of these sites, counteracts the ef-

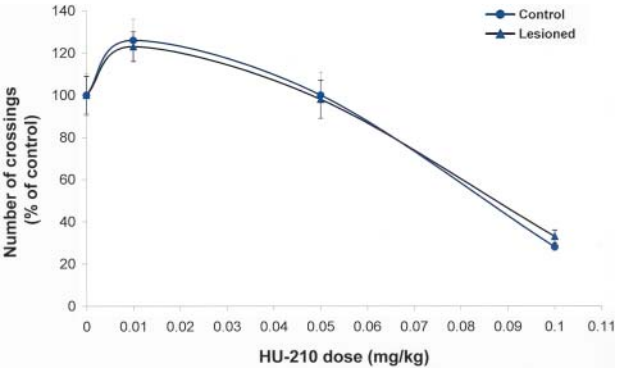

Fig. 3. Locomotor activity in control and non-lesioned rats was measured in an open field box following HU-210 treatment.

fect of dopamine (Piomelli *et al*. 2000). Similarly, Mailleux & Vanderhaeghen (1993) showed that loss of dopaminergic neurones in the 6-hydroxydopamine lesioned rats, increased by 45% the cannabinoid receptor mRNA in homolateral striatum. Moreover, the dopamine antagonists, SCH-23390, haloperidol and sulpiride, also significantly upregulate the cannabinoid receptor mRNA. These studies indicate negative regulation of the cannabinoid receptor by the dopamine receptor activation.

Stimulation of the CB_1 receptor, by HU-210, may oppose dopamine activation and reduce the glutamate release from the subthalamic terminals to the internal globus pallidus and the substantia nigra pars reticulata. Downstream, it may lead to decreased activity of thalamic nuclei and the GABAergic terminals in the brain stem, which may reduce motor disturbances (Sanudo-Pena *et al*. 1996 & 1998; Sanudo-Pena & Walker 1997).

Although HU-210 effectively inhibited levodopa induced-rotation, it did not show any neuroprotective effects. This indicates that the inhibition is not through reduction of the direct or indirect toxicity of levodopa. Interestingly, it was already shown that levodopa is highly toxic in neuronal culture, while its toxicity could not be demonstrated *in vivo*, both in animal experiments and as therapeutic drug for Parkinson's disease (Melamed *et al*. 2000). The inhibition of the levodopa induced-rotation by HU-210 rather reflects functional changes of the GABA, dopamine or CB_1 receptors. The possibility that the effects observed in HU-210-treated rats was due to a sedative action or hypothermia was excluded in our data (Ovadia *et al*. 1995), since such behaviour in the locomotion study was seen only at much higher doses than those causing the rotation inhibition (0.005 versus 0.1 mg/kg).

Our study supports previous experiments showing that the CB_1 receptor agonists WIN 55,212-2 and CP 55,940 attenuate the rotational behaviour induced by a dopamine D_1 agonist in rats with unilateral lesions of the nigrostriatal pathway (Anderson *et al*. 1995). Moreover, in a double-blind placebo-controlled cross-over study in seven Parkinson's disease patients, it was demonstrated that oral administration of nabilone, a CB_1 agonist, reduces levodopa-induced dyskinesia without aggravating the parkinsonian motor signs (Sieradzan *et al*. 2001). Since 6-hydroxydopamine-lesioned rats display increased contraversive circling in long-term treatment of levodopa or apomorphine, Henry *et al*. (1998) suggested that this model can be regarded as an analogue to levodopa-induced dyskinesia in Parkinson's disease patients. Therefore, our findings support recent studies suggesting that treatment with cannabinoid agonists may become a new strategy for the treatment of levodopa-induced dyskinesia. Further research is needed in order to determine the interactions between dopamine and the CB_1 receptors in the brain, and their dual association in movement regulation.

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References

Anderson, L. A., J. J. Anderson, T. N. Chase & J. R. Walters: The cannabinoid agonists WIN 55,212-2 and CP 55,940 attenuate rotational behavior induced by a dopamine D_1 but not a D_2 agonist in rats with unilateral lesions of the nigrostriatal pathway. *Brain Res.* 1995, **691**, 106–114.

Consroe, P.: Brain cannabinoid system as target for the therapy of neurological disorders. *Neurobiol Dis.* 1998, **5**, 534–551.

Crossman, A. R.: A hypothesis on the pathophysiological mechanisms that underlie levodopa- or dopamine agonist-induced dyskinesia in Parkinson's disease: implications for future strategies in treatment. *Mov. Disord.* 1990, **5**, 100–108.

Davis, T. L., G. Brughitta, F. Baronti & M. M. Mouradian: Acute effects of pulsatile levodopa administration on central dopamine pharmacodynamics. *Neurology* 1991, **41**, 630–633.

Di Marzo, V., D. Meleck, T. Bisogno & L. De petrocellis: Endocannabinoids: endogenous cannabinoid receptor ligands with neuromodulatory action. *Trends in Neuroscience* 1998, **21**, 521–528.

Eshhar, N., S. Striem, R. Kohen, O. Tirosh & A. Biegon: Neuroprotective and antioxidant activities of HU-211, a novel NMDA receptor antagonist. *Eur. J. Pharmacol.* 1995, **283**, 19–29.

Feigenbaum, J. J., F. Bergman, S. A. Richmond, R. Mechoullam, V. Nadler, Y. Kloog & M. Sokolovsky: Nonpsychotrophic cannabinoid acts as a functional N-methl-D-aspartate receptor blocker. *Proc. Natl. Acad. Sci. USA* 1989, **86**, 9584–9587.

Hampson, A. J., M. Grimaldi, J. Axelrod & D. Wink: Cannabidiol and (-)Δ^9-tetrahydrocannabinol are neuroprotective antioxidants. *Proc. Natl. Acad. Sci. USA* 1998, **95**, 8268–8273.

Hefti, F., E. Melamed & R. J. Wurtman: The decarboxylation of DOPA in the parkinsonian brain: *in vivo* studies in animal models. *J. Neural Transm.* 1980, **Suppl 16**, 95–101.

Henry, B., A. R. Crossman & J. M. Brotchie: Characterization of enhanced behavioral response to levodopa following repeated administration in the 6-hydroxydopamine-lesioned rat model of Parkinson's disease. *Exp. Neurol.* 1998, **151**, 334–342.

Herkenham, M., A. B. Lynn, B. R. Costa & E. K. Richfield: Neuronal localization of cannabinoid receptors in the basal ganglia of the rat. *Brain Res.* 1991, **547**, 267–274.

Hiltunen, A. G., T. U. Jarbe & K. Wangdahl: Cannabinol and cannabidiol in combination: temperature, open-field activity, and vocalization. *Pharmacol. Biochem. Behav.* 1988, **30**, 675–678.

Hochman, A., H. Sternin, S. Gorodin, S. Korsmeyer, I. Ziv, E. Melamed & D. Offen: Enhanced oxidative stress and altered antioxidants in brains of bcl-2 deficient mice. *J. Neurochem.* 1998, **71**, 741–748.

Hudson, J. L., V. H. G. Craig, I. Stromberg, S. Brock, J. Clayton, J. Masserano, B. J. Hoffer & G. A. Gerhardt: Correlation of apomorphine and amphetamine-induced turning with nigrostriatal dopamine content in inilateral 6-hydroxydopamine lesioned rats. *Brain Res.* 1993, **626**, 167–174.

Mailleux, P. & J. J. Vanderhaeghen: Dopaminergic regulation of cannabinoid receptor mRNA levels in the rat caudate-putamen: an in situ hybridization study. *J. Neurochem.* 1993, **61**, 1705–1712.

Mechoulam, R., J. J. Feigenbaum, M. Lander, M. Segal, T. U. Jarbe, A. J. Hiltunen & P. Consroe: Enantiomeric cannabinoids: stereospecificity of psychotrophic activity. *Experientia* 1988, **44**, 762–764.

Mechoulam, R., N. Lauder, A. Breuer & J. Zahalaka: Synthesis of the individual pharmacologically distinct enantiomers of tetrahydrocannabinol derivatives. *Tetrahedron: Assymetry* 1990, **1**, 315–319.

Mechoulam, R. & S. Ben-Shabat: From Gan-Zi-Gun-Nu to anandamide and 2-arachidonoyl-glycerol, the ongoing story of cannabis. *Nat. Prod. Rep.* 1999, **16**, 131–143.

Melamed, E., D. Offen, A. Shirvan & I. Ziv: Levodopa- an exotoxin or a therapeutic drug. *J. Neurol.* 2000, **247** Suppl 2, II135–139.

Melamed, E., F. Hefti & R. J. Wurtman: Nonaminergic striatal neurons convert exogenous L-DOPA to dopamine in Parkinsonism. *Ann. Neurol.* 1980, **8**, 558–563.

Muller-Vahl, K. R., H. Kolbe, U. Schneider & H. M. Emrich: Cannabis in movement disorders. *Res. in Complement Med.* 1996, **6**, 23–27.

Ovadia, H., A. Wohlman, R. Mechoulam & R. Weidenfeld: Characterization of the hypothermic effect of the synthetic cannabinoid HU-210 in the rat. Relation to the adrenergic system and endogenous pyrogens. *Neuropharmacology* 1995, **34**, 175–180.

Paxinos, G. & C. Watson: *The rat brain in stereotaxic coordinate*. New York, Academic Press, 1986.

Perese, D. A., J. Ulman, J. Viola, S. E. Ewing & K. S. Bankiewicz: A 6-hydroxydopamine-induced selective parkinsonian rat model. *Brain Res.* 1989, **494**, 285–293.

Piomelli, D., A. Giuffrida, A. Calignano & F. Rodriguez de Fonseca: The endocannabinoids system as a target for therapeutic drugs. *TIPS* 2000, **21**, 482–486.

Sanudo-pena, M. C., S. L. Patrick, R. L. Patrick & J. M. Walker: Effects of intranigral cannabinoids on rotational behavior in rats: interactions with the dopaminergic system. *Neurosci. Letters* 1996, **206**, 21–24.

Sanudo-pena, M. C. & J. M. Walker: Role of the subthalamic nucleus on cannabinoid actions in the substantia nigra of the rat. *J. Neurophysiol.* 1997, **77**, 1635–1638.

Sanudo-pena, M. C., S. L. Patrick, S. Khen, R. L. Patrick, K. Tsou & J. M. Walker: Cannabinoid effects in basal ganglia in rat model of Parkinson's disease. *Neurosci. Letters* 1998, **248**, 171–174.

Self, D. W.: Anandamide: a candidate neurotransmitter heads for the big leagues. *Nature Neuroscience* 1999, **2**, 303–304.

Shohami, E., J. Weidenfeld, H. Ovadia, Z. Vogel, L. Hanus, E. Fride, A. Breuer, S. Ben-shabat, T. Sheskin & R. Mechoulam: Endogenous and synthetic cannabinoids: recent advances. *CNS Drug Reviews* 1996, **2**, 429–451.

Sieradzan, K. A., S. H. Fox, M. Hill, J. Dick, A. R. Crossman & J. M. Brotzhie: Cannabinoids reduce levodopa-induced dyskinesia in Parkinson's disease: A pilot study. *Neurology* 2001, **57**, 2108–2111.

Tchilibon, S. & R. Mechoulam: Synthesis of a primary metabolite of cannabidiol. *Org Letters* 2000, **2**, 3301–3303.

Verhagen, M. L., P. Del dotto, P. Van den Munckhof, J. Fang, M. M. Mouradian & T. N. Chase: Amantadine as treatment for dyskinesias and motor fluctuations in Parkinson disease. *Neurology* 1998, **50**, 1323–1326.