ELSEVIER

European Journal of Pharmacology 348 (1998) R1–R2

ejp

Rapid communication

Potent effects of a selective cannabinoid receptor agonist on some guinea pig medial vestibular nucleus neurons

David Newsham-West [a], Cynthia L. Darlington [b], Paul F. Smith [a,*]

[a] *Department of Pharmacology, School of Medical Sciences, University of Otago Medical School, Dunedin, New Zealand*
[b] *Department of Psychology and Neuroscience Research Centre, University of Otago, Dunedin, New Zealand*

Received 16 March 1998; accepted 19 March 1998

Abstract

Binding studies have indicated that the density of the cannabinoid CB_1 receptor is very low in the vestibular nucleus complex compared to other areas of the central nervous system (CNS), suggesting that CB_1 receptors may have little functional significance for the vestibular nucleus. However, the dizziness often produced by cannabis suggests that the vestibular system may be implicated. We investigated the effects of the selective CB_1 receptor agonist, CP 55940 (the levorotatory enantiomer of desacetyllevonantradol), on medial vestibular nucleus neurons in guinea pig brainstem slices in vitro. Only 3/18 medial vestibular nucleus neurons tested with 1 μM CP 55940 showed changes in firing rate, however these were decreases with an average magnitude of 72.3%; 3/4 neurons tested with 10 μM CP 55940 showed decreases with an average magnitude of 92.7% ($P < 0.05$ in both cases). In all cases the effects of CP 55940 were long-lasting. These results suggest that despite the low density of CB_1 receptors in the vestibular nucleus complex, they may be of functional significance for the behavioural effects of cannabis use. © 1998 Elsevier Science B.V.

Keywords: Medial vestibular nucleus; Cannabinoid CB_1 receptor; CP 55940

It is clear from numerous receptor binding, in situ hybridization and immunohistochemical studies that the density of the cannabinoid CB_1 receptor is lower in the brainstem than in many other areas of the central nervous system (CNS) (e.g., Herkenham et al., 1991; Tsou et al., 1998). However, some areas of the brainstem such as the vestibular nucleus complex do have a low density of CB_1 binding sites (e.g., Herkenham et al., 1991; Mailleux and Vanderhaegen, 1992; Matsuda et al., 1993), which could potentially contribute to some of the behavioural effects of cannabis (e.g., dizziness). We investigated the effects of the selective CB_1 receptor agonist, CP 55940 (the levorotatory enantiomer of desacetyllevonantradol; Shen et al., 1996), on guinea pig medial vestibular nucleus neurons in brainstem slices in vitro, in an attempt to determine whether the low density of CB_1 receptors in the vestibular nucleus complex might have functional significance.

Data were obtained from 22 medial vestibular nucleus neurons in brainstem slices from 12 labyrinthine-intact guinea pigs which were anesthetized with ether and decapitated. The brainstem was rapidly dissected and coronal slices prepared according to standard in vitro techniques (Darlington and Smith, 1995). Action potentials from single medial vestibular nucleus neurons were recorded extracellularly using glass micropipettes, amplified and displayed as described previously (Darlington and Smith, 1995). The selective CB_1 receptor agonist, CP 55940 (generously gifted by Pfizer, Groton, CT) was initially dissolved in 50% dimethysulphoxide (DMSO)/50% distilled water to a 1 mM stock solution; the final DMSO concentration was 0.05%. CP 55940 (1 or 10 μM) was applied to the slice by superfusion. Concentrations in this range were chosen on the basis of previous in vitro electrophysiological studies which have shown that hippocampal neurons respond to μM concentrations of CP 55940 (Deadwyler et al., 1993). For each neuron, baseline firing rate was recorded for approximately 4 min during superfusion of artificial cerebrospinal fluid (ACSF), then the drug was applied for 4 min, followed by a return to the control ACSF solution. In most cases neurons were recorded for 30 min to 1 h following washout of the drug. Firing frequency was considered to have increased or decreased

* Corresponding author. Tel.: +64-3-479-7253; fax: +64-3-479-9140; e-mail: paul.smith@stonebow.otago.ac.nz

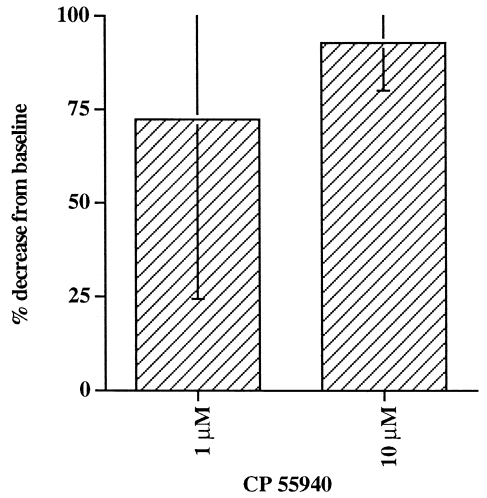

Fig. 1. Average magnitude of the decrease in firing rate in response to 1 ($n = 3$ neurons) or 10 μM CP 55940 ($n = 3$). Bars represent 1 S.D.

from baseline when a change of greater than or equal to 20% of baseline occurred (Darlington and Smith, 1995).

Of 18 medial vestibular nucleus neurons which were tested with 1 μM CP 55940, 3/18 showed a change in firing rate of $> 20\%$, and all of these responses were decreases. In general, the effects of the CP 55940 were long-lasting. In some cases, even 40 min following washout, baseline firing rate had not totally recovered. The average magnitude of the decreases in firing rate was 72.3% (± 47.9 (S.D.), $n = 3$; $P < 0.05$, two-tailed *t*-test; Fig. 1). The average baseline discharge was 10.6 spikes/s (± 10.5, $n = 18$). Four neurons were tested with the higher concentration of 10 μM, and 3/4 showed a decrease in firing rate of $> 20\%$; the average magnitude of the decrease was 92.7% (± 12.7, $n = 3$; $P < 0.05$; Fig. 1). In none of these cases did the firing rate completely return to baseline even 40–50 min following washout. The average baseline firing rate for these neurons was 12.3 spikes/s (± 4.8, $n = 4$).

These data suggest, for the first time, that despite the apparently low density of CB_1 receptors in the vestibular nucleus complex, at least some medial vestibular nucleus neurons respond to the selective cannabinoid receptor agonist, CP 55940, and therefore may have functional CB_1 receptors. Using a 1 μM CP 55940 concentration, which had potent effects on hippocampal neurons in other studies (Deadwyler et al., 1993; Cohen, Smith and Darlington, unpublished observation), only 3/18 medial vestibular nucleus neurons showed a response. Nonetheless, some large changes in firing frequency were observed, and this became more noticeable with the higher CP 55940 concentration. Although many neurotransmitter and neuromodulator receptors have been studied in the medial vestibular nucleus, the effects of CP 55940 were probably most similar to those of the metabotropic glutamate receptor agonist, 1*S*,3*R*-amino-cyclopentyl-1,3-dicarboxylate (1*S*,3*R*-ACPD), which produced similar decreases in firing rate at a 1 μM concentration and also exerted its effects for 20–30 min following washout (Darlington and Smith, 1995; Smith and Darlington, 1996). The longevity of the effects of CP 55940 was striking, and suggests that despite the lower density of CB_1 receptors in the vestibular nucleus complex, they could be of functional significance in the development of dizziness following cannabis use. We believe that further studies of CB_1 receptors in the vestibular nucleus complex are merited.

Acknowledgements

We are grateful to Dr. Saul B. Kadin of the Central Research Division, Pfizer, Groton, CT, USA, for generously providing the CP 55940 used in this study. This research was supported by a Project Grant (to CD and PS) from the Health Research Council of New Zealand.

References

Darlington, C.L., Smith, P.F., 1995. Metabotropic glutamate receptors in the guinea pig medial vestibular nucleus in vitro. NeuroReport 6, 1799–1802.

Deadwyler, S.A., Hampson, R.E., Bennet, B.A., Edwards, T.A., Mu, J., Pacheco, M.A., Ward, S.J., Childers, S.R., 1993. Cannabinoids modulate potassium channels in cultured hippocampal neurons. Recept. Channels 1, 121–134.

Herkenham, M., Lynn, A.B., Johnson, M.R., Melvin, L.S., DeCosta, B.R., Rice, K.C., 1991. Characterization and localization of cannabinoid receptors in rat brain: a quantitative in vitro autoradiographic study. J. Neurosci. 11, 563–583.

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

Matsuda, L.A., Bonner, T.I., Lolait, S.J., 1993. Localization of cannabinoid receptor mRNA in rat brain. J. Comp. Neurol. 327, 535–550.

Shen, M., Piser, T.M., Seybold, V.S., Thayer, S.A., 1996. Cannabinoid receptor agonists inhibit glutamatergic synaptic transmission in rat hippocampal cultures. J. Neurosci. 16, 4322–4334.

Smith, P.F., Darlington, C.L., 1996. Recent advances in the pharmacology of the vestibulo-ocular reflex system. Trends Pharmacol. Sci. 17, 421–427.

Tsou, K., Brown, S., Sanudo-Pena, M.C., Mackie, K., Walker, J.M., 1998. Immunohistochemical distribution of cannabinoid CB_1 receptors in the rat central nervous system. Neuroscience 83, 393–411.