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Research Report

AM251, a selective antagonist of the CB1 receptor, inhibits the induction of long-term potentiation and induces retrograde amnesia in rats

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ABSTRACT

Long-term potentiation (LTP) has a long history as putative mechanism of memory formation, specially in the hippocampus, a structure essential for memory formation. Endocannabinoids are one of the endogenous systems that modulate this plasticity event: the activation of hippocampal CB1 receptors may inhibit local GABA release. Here, we have studied both (1) the role of the selective CB1 antagonist AM251 upon LTP induction in a hippocampal slice preparation, and (2) the effect of its intrahippocampal administration in the step-down inhibitory avoidance (IA) and the open field habituation tasks (OF). Standard extracellular electrophysiology techniques were used to record field excitatory postsynaptic potentials from the dendritic region of CA1 neurons in response to a high frequency stimulation of Schaffer's collaterals; a micropipette ejected 0.2 μM of AM251 (in DMSO/PBS) 2 min before the stimulus: LTP was induced and lasted more than 30 min in the control, but not in the AM251-treated group. Immediately after training, either in IA (footshock, 0.5 mA) or OF, animals received a bilateral infusion of 0.55 or 5.5 ng/side of AM251 or its vehicle in the CA1 region, and test was performed 24 h later. AM251 has caused a significative decrease in the test step-down latency when compared to the control group, but no differences were detected in the OF task, including the number of crossings, i.e., there were no motor effects. The LTP supression could be caused by AM251 acting over GABAergic interneurons that modulate the LTP-bearing glutamatergic neurons. Endocanabinoids would then be the natural dis-inhibitors of local plasticity in the dorsal hippocampus, and the amnestic action of AM251 would be due to a disruption of this endogenous modulatory system.

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1. Introduction

Cannabinoid receptors CB1 are widely distributed in the CNS, mainly in the hippocampus, cortex, basal ganglia, and cerebellum (Davies et al., 2002; Wilson and Nicoll, 2002). Being one of the most abundant class of metabotropic receptors in the brain, it is specially proeminent in the hippocampus (Ameri, 1999; Hampson and Deadwyler, 1999), a structure both essential for memory formation (Izquierdo and Medina, 1995; Squire, 1992) and extensively studied in LTP experiments (Bliss and Collingridge, 1993).

CB1 receptors couple to $G_{i/o}$ in order to inhibit cAMP formation, decrease Ca^{++} conductance (specially through N-type voltage-gated calcium channels) and increase both K^{+} conductance and MAPK activity (Ameri, 1999; Davies et al., 2002; Mackie et al., 1995; Pertwee and Ross, 2002; Wilson and Nicoll, 2002). In the hippocampus, CB1 receptors are located in the presynaptic portion of GABAergic axon terminals (Herkenham et al., 1991), upon which endocannabinoids may be acting in order to inhibit the release of GABA (Katona et al., 1999), leading to a facilitation of any subsequent glutamatergic plasticity event.

Many studies have shown that the administration of CB1 agonists impairs memory (Davies et al., 2002; Hampson and Deadwyler, 1999; Hernandez-Tristan et al., 2000; Lichtman et al., 1995); antagonists otherwise, may improve it (Lichtman, 2000; Takahashi et al., 2005; Terranova et al., 1996; Wolff and Leander, 2003) or simply have no effect (Da Silva and Takahashi, 2002; Davies et al., 2002). Since most of these studies have investigated only the systemic effect, the ubiquity of CB1 receptors in the CNS may explain the diversity of cognitive effects (Alvares et al., 2005). Accordingly, we have previously reported a memory deficit with the direct intrahippocampal infusion on the selective CB1 antagonist AM251 (Alvares et al., 2005), a result not found elsewhere and contrasting with only two previous reports (Egashira et al., 2002; Lichtman et al., 1995), that (also different from us) investigated distinct types of memory or employed different pharmacological tools.

The local, intrahippocampal amnestic effect described by us was consistent with three facts: (1) in the hippocampus, CB1 receptors seem to be located basically in the presynaptic portions of the GABAergic axon terminals, mostly on CCK-releasing basket cells, which should explain the inhibition of GABA release by CB1 agonists (Katona et al., 1999; Wilson and Nicoll, 2002); (2) in DSI (depolarization-induced suppression of inhibition), endocannabinoids may be acting as retrograde messengers mediating down-regulation of GABA release in the hippocampus (Kreitzer and Regehr, 2001; Ohno-Shosaku and Kano, 2001; Wilson and Nicoll, 2001, 2002); (3) LTP, a phenomenon itself reinforced by DSI, was shown to be indirectly modulated by endocannabinoids that reduce presynaptic neurotransmiter release, suppressing the postsynaptic membrane depolarization necessary to activate NMDA receptors (Carlson et al., 2002; Wilson and Nicoll, 2002).

Long-term potentiation (LTP) has a long history as putative mechanism of memory formation, but even if it is not exactly "the" mechanism, its close scrutiny has brought us a great load of knowledge about synaptic plasticity, the phenomenon that may explain the engram register into brain neural networks (Bliss and Collingridge, 1993; Frankland and Bontempi, 2005; Izquierdo and Medina, 1995; Lamprecht and LeDoux, 2004). With one exception (Carlson et al., 2002), most studies show that cannabinomimetics inhibit the induction of LTP (Collins et al., 1995; Davies et al., 2002; Terranova et al., 1995), and there is evidence that mice lacking cannabinoid CB1 receptors exhibit an enhanced long-term potentiation (Bohme et al., 2000). Consistently, cannabinoids acting upon CB1 receptors have been shown to inhibit the release of glutamate in hippocampal preparations (Davies et al., 2002).

In this work, we have studied both (1) the role of the selective CB1 receptor antagonist AM251 upon LTP induction in a hippocampal slice preparation, and (2) the effect of its intrahippocampal administration in the step-down inhibitory avoidance and the open field habituation task.

2. Results

2.1. *Electrophysiological effects: long-term potentiation*

Slices from 7 out of 10 dissected animals were used to record fEPSPs. Data from pretetanic (−10, −5 and 0 min, or HFS) and posttetanic (5, 10, 15, 20, 25, 30, 35, 40, 45, and 50 min) moments were analyzed by Repeated Measure ANOVA to compare recordings from AM251 (0.2 μM) and vehicle (8% DMSO) groups: there was a significant between-subjects Drug effect ($F_{1,7}$ = 14.039, P = 0.010) and a within-subjects Time ($F_{1,7}$ = 9.827, P = 0.000), and Time vs. Drug interaction ($F_{1,7}$ = 9.303, P = 0.000).

Since the DMSO-treated (or control) group develops (1) a fEPSP potentiation response of 207.4 ± 4.9% that (2) lasts more than 30 min, the Δ-curve seen in Fig. 1 can be considered to be a long-term potentiation response (Bliss and Collingridge, 1993). Except for the short posttetanic potential peak, the AM251 treatment (◇) seems to have prevented the onset of any long-lasting potentiation, as confirmed by the near-baseline 103.3 ± 1.1% response.

Fig. 2 shows the percentage change of fEPSP% amplitude in pretetanic ($\langle t_{-9\text{–}0\ \mathrm{min}}\rangle$), and two posttetanic time windows ($\langle t_{26\text{–}30\ \mathrm{min}}\rangle$ and $\langle t_{56\text{–}50\ \mathrm{min}}\rangle$). The average fEPSPs for each posttetanic group in each of the two posttetanic time windows ($\langle t_{26\text{–}30\ \mathrm{min}}\rangle$ and $\langle t_{56\text{–}50\ \mathrm{min}}\rangle$) were significantly different (both with a P = 0.000, Student's t test). To confirm that the recording was being performed on hippocampal CA1 neurons, some cells were filled with biocytin, as shown in Fig. 2B.

2.2. *Behavioral effects: step-down inhibitory avoidance*

Behavioral results are shown in Figs. 3 and 4. In Inhibitory Avoidance task (Fig. 3, n = 10 in each group), comparisons among test latencies were possible since there was no statistically significant difference among the training session latencies (P = 0.155; Kruskal–Wallis ANOVA); test latencies, however, exhibited a difference (P = 0.020; Kruskal–Wallis ANOVA). Post hoc Dunn's All Pairwise Multiple Comparison Procedure has shown that only the 5.5 ng/side of AM251 is significantly smaller than the control group (P < 0.05), the other groups being not different among themselves (P > 0.050). Each

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