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Correlation between cannabinoid mediated effects on paired pulse depression and induction of long term potentiation in the rat hippocampal slice

Gaynor S. Paton, Roger G. Pertwee, Stephen N. Davies *

Department of Biomedical Sciences, Institute of Medical Sciences, University of Aberdeen, Aberdeen AB25 2ZB, UK

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Abstract

Cannabinoids cause an increase in synaptic transmission via γ-aminobutyric acid (GABA) receptors and this may be the mechanism by which activation of CB1 receptors blocks the induction of long-term potentiation (LTP). To test this hypothesis, we used paired pulse depression (PPD) of CA1 population spike responses recorded in the rat hippocampal slice as an index of GABA-ergic feedback inhibition, to establish whether the effects of a stereoselective CB1 receptor agonist on GABA-ergic transmission and LTP were correlated. The active isomer, WIN55212-2, blocked the induction of LTP and suppressed PPD over the concentration range 250 nM–5 μM, whereas the inactive isomer, WIN55212-3, was inactive at 5 μM. The effects of 5 μM WIN55212-2 on both LTP and PPD were completely blocked by the CB1 receptor antagonist SR141716A (5 μM). The results show that the effects are correlated in that both suppression of PPD and blockade of induction of LTP are probably mediated by CB1 receptors. However, the suppression in PPD suggests that WIN55212-2 caused a decrease in GABA-ergic feedback transmission which would be expected to facilitate, rather than block, the induction of LTP. We therefore conclude that the blockade of LTP by cannabinoids is not via upregulation of GABA-ergic synaptic transmission. © 199X Elsevier Science Ltd. All rights reserved.

Keywords: WIN55212-2; SR141716A; Cannabinoids; Paired pulse depression; γ-Aminobutyric acid

1. Introduction

Cannabinoids have been shown to inhibit synaptic long-term potentiation (LTP) (Nowicky et al., 1987) and this appears to be a receptor mediated effect, i.e. it is stereoselective (Collins et al., 1994; Terranova et al., 1995) and is sensitive to CB1 receptor antagonists (Collins et al., 1995; Terranova et al., 1995). However, the mechanism by which activation of cannabinoid receptors inhibits LTP is not known.

There is much indirect evidence showing that cannabinoids affect GABA-ergic transmission. Drugs which facilitate GABA-ergic transmission show a synergism with Δ^9-tetrahydrocannabinol (THC) in abolishing the righting reflex in mice, and producing catalepsy in mice and rats (Pertwee and Greentree, 1988; Pertwee et al., 1988; Pertwee and Wickens, 1991; Wickens and Pertwee, 1993), and in causing circling behaviour in rats (Wickens and Pertwee, 1993). Paired pulse depression (PPD) is a form of synaptic transmission used as an index of the strength of GABA-ergic feedback inhibition (Schwartzkroin and Knowles, 1983) and is increased by the application of THC both in vitro (Weisz et al., 1982), and in vivo (Vardaris et al., 1977). Cannabinoids have also been shown to potentiate responses to exogenous GABA but nor to muscimol (Coull et al., 1997), and to inhibit the GABA uptake in synaptosomes (Banerjee et al., 1975; Hershkowitz et al., 1977) and brain slices (Maneuf and Brotchie, 1995).

Most of these findings indicate that cannabinoids cause an increase in synaptic transmission mediated by GABA receptors. Since concurrent GABA-ergic synaptic transmission can block the induction of LTP (Douglas et al., 1983), it is reasonable to hypothesise that upregulation of GABA-ergic transmission may form

* Corresponding author. Tel.: +44 1224 273086; fax: +44 1224 273019.

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the mechanism underlying the blockade of LTP by cannabinoids. If this hypothesis were correct, it would demand that the effects of cannabinoids on GABA-ergic transmission would also be receptor mediated, and hence that the effective concentrations required to block LTP and to modulate GABA-ergic transmission should be similar, production of both effects should be stereoselective, and both effects should be blocked by an appropriate antagonist. In order to test this, we have used paired pulse inhibition of CA1 population spike responses recorded in the rat hippocampal slice as an index of GABA-ergic feedback inhibition (Schwartzkroin and Knowles, 1983) to assess whether the effects of the synthetic cannabinoid WIN55212-2 and its inactive stereoisomer WIN55212-3 on LTP and on GABA-ergic transmission are correlated.

2. Methods

Female Sprague-Dawley rats (120–150 g) were anaesthetised with halothane and decapitated. The skull was opened to reveal the brain which was removed and sectioned along the midline to separate the two hemispheres. The hippocampi were dissected out and placed on moistened filter paper on a McIlwain tissue chopper and chopped transversely forming slices 400 μm thick. The slices were maintained in a humidified and oxygenated holding chamber at room temperature for at least 1 h, or until they were required. Slices were then transferred to a standard interface chamber and constantly perfused with oxygenated artificial cerebrospinal fluid (aCSF) at a constant temperature of approximately 28°C. The aCSF was made up with the following concentrations (mM) in distilled water: NaCl (24.8), KCl (0.6), $NaHCO_3$ (5.2), NaH_2PO_4 (0.25), D-glucose (2), $CaCl_2.2H_2O$ (2), $MgSO_4.7H_2O$ (1). Stimulation of the Schaffer collateral-commissural fibres was achieved using a bipolar stimulating electrode connected to an isolated stimulator unit (Digitimer UK) and the evoked population spike was recorded from the cell body layer of the CA1 region using a pulled glass capillary microelectrode (Clark Electrotnedical Instruments, UK) filled with 3 M NaCl. Stimulation protocols were controlled using the LTP0911 3 program (Anderson and Collingridge, 1997). All drugs were stored in ethanol until required and then mixed with Tween SO (two parts Tween:one part drug). The alcohol was then evaporated off with nitrogen and saline added in aliquots. The saline was then diluted in aCSF until the required concentration was obtained. WIN552 12-2 and WIN552 12-3 were obtained from Research Biochemicals (Herts, UK). Each paired pulse trial consisted of three consecutive responses recorded at 30 s intervals over 16 different interpulse intervals (IPI) between 4 and 200 ms. The cannabinoids were applied for 20 min after the first paired pulse trial and immediately followed by the second paired pulse trial. Previous studies have shown that the recovery from cannabinoid mediated effects is virtually irreversible (Pertwee et al., 1992) and therefore washout over the course of these experiments is highly unlikely. In all cases statistical analysis was performed using a paired Student's *t*-test and results were judged significant when $P < 0.05$.

3. Results

To determine the most effective stimulus strength, a voltage trial was performed to establish the effect of high and low stimulus strengths on PPD. Two paired pulse trials were carried out with the stimulus strength set at 25 and 75% of the maximum evoked response (Fig. 1 A). Low stimulus strengths produced a sustained depression followed by a marked facilitation (at an IPI of 80–200 ms) of the second (test) response whereas a high stimulus strength resulted in depression, although to a lesser extent, and very little facilitation. Subsequent experiments were performed using approximately half maximum stimulus strength so as to obtain significant, but not maximal PPD.

In control slices ($n = 11$) PPD of the population spike amplitude was observed over an IPI range of 4-80 ms, with a maximum test-response inhibition at an IPI of 4 ms. This recovered in a sigmoidal manner as the IPI increased. There was no significant paired pulse facilitation at any of the IPIs tested, nor was there a significant difference between the first paired pulse trial, and a second trial carried out 20 min later (Fig. 1B).

Perfusion of 250 nM ($n = 9$), 500 nM ($n = 5$) or 5 μM ($n = 7$) WIN55212-2 for 20 min had no effect on the amplitude of the conditioning response (102 ± 9, 94 ± 17 and $105 \pm 10\%$ (mean ± S.E.) of control, respectively) but significantly decreased the PPD observed. 250 nM WIN55212-2 caused significant attenuation of the PPD at an IPI of only 10 ms, whereas 500 nM had a significant effect at 6–10 and 20 ms, and 5 μM an effect over most of the range from 5 to 150 ms (Fig. 2). There was no significant effect at any concentration when 5 μM WIN5521 2-2 was applied in the presence of 5 μM SR141716A, a selective cannabinoid receptor antagonist (Rinaldi-Carmona et al., 1994) ($n = 6$, Fig. 3A). The antagonist was applied for 30 min prior to, and throughout, the 20 min perfusion of WIN55212-2. Perfusion of both drugs was stopped before the second paired pulse trial. Curiously, when SR1417 16A was applied on its own, it mimicked the effects of the agonist and suppressed PPD over most intervals though this only reached significant levels at an IPI of 10 ms ($n = 7$, Fig. 3B).

Addition of the inactive isomer, WIN55212-3, at concentrations of 5 μM ($n = 6$) or 500 nM ($n = 4$) for

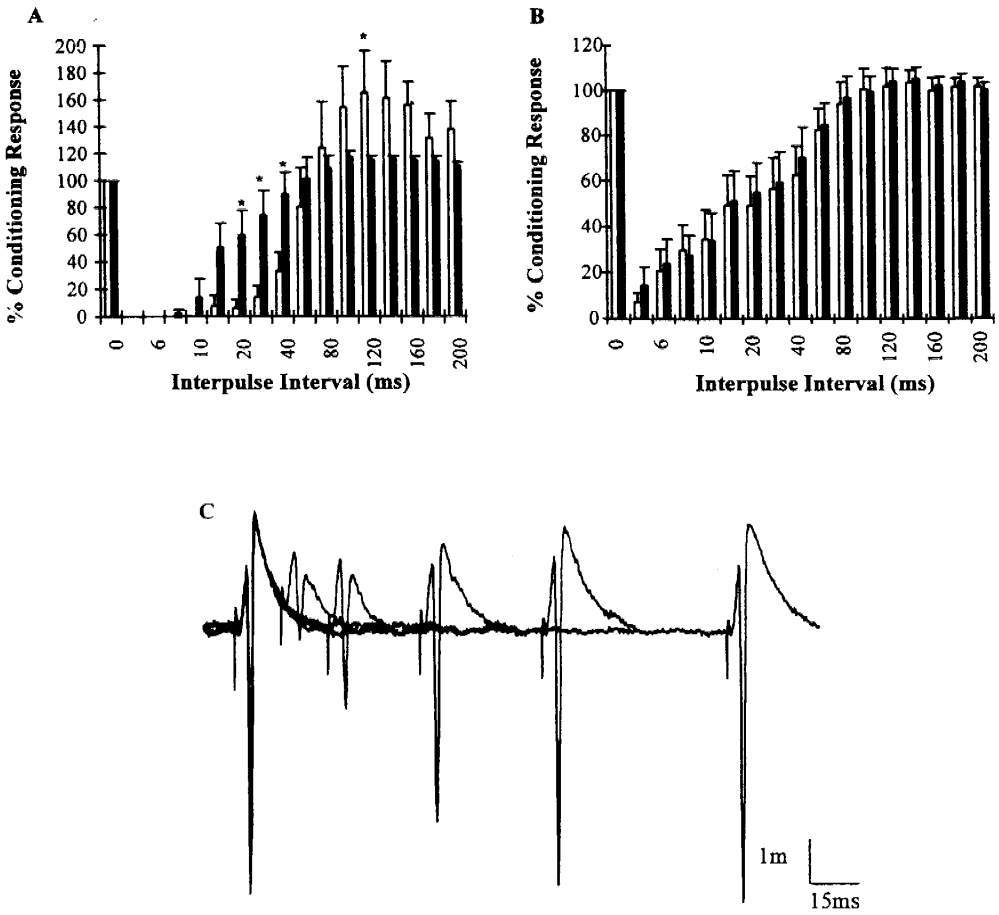

Fig. 1. (A) Effect of stimulus strength on paired pulse depression and facilitation of population spike amplitude recorded from the cell body layer of the CA1 region. Amplitude of population spike evoked by the 2nd (test) pulse is plotted as a percentage of that evoked by the 1st (conditioning) pulse at various interpulse intervals (IPIs) ($n = 6$). Open and closed bars represent experiments performed using a stimulus strength approximately 25 and 75% of that required to elicit a maximal population spike, respectively. Stars indicate low stimulus strength test response is significantly different from high stimulus strength test response at that IPI ($P < 0.05$). (B) Consecutive paired pulse trials performed 20 min apart are not significantly different. In control slices ($n = 12$) no drug was added between the two trials. Open bars represent 1st trial, closed bars represent 2nd trial. (C) Five superimposed records showing synaptic responses recorded from a single slice, at 50% maximum stimulation, using paired pulse stimulation with IPIs of 15, 30, 60, 100 and 160 ms.

20 min had no significant effect on the amplitude of the conditioning response or on the paired pulse depression at any IPI tested (Fig. 3C). Similarly, perfusion of the drug vehicle Tween at the equivalent concentrations ($n = 5$) had no significant effects (data not shown).

For each of the groups of slices reported above, at the end of the two paired pulse trials we attempted to induce LTP by delivering trains of high frequency stimuli (three burst of 100 Hz for 500 ms at test intensity). Controls performed in the presence of Tween alone ($n = 4$) produced a significant potentiation of $123 \pm 5\%$ of the pre-tetanus amplitude when measured 30 min after induction. Likewise induction of LTP in the presence of 5 μM WIN55212-3 ($n = 5$) resulted in potentiation of $132 \pm 15\%$. The presence of 5 μM WIN55212-2 ($n = 6$) however allowed no significant potentiation ($78 \pm 15\%$) (Fig. 4A) and the lower dose of 250 nM WIN55212-2 ($n = 7$) allowed potentiation of $115 \pm 8\%$ although this was not statistically significant. When 5 μM WIN55212-2 was applied in the presence of 5 μM SR141716A ($n = 5$) LTP was significantly increased above control, resulting in potentiation of $166 \pm 36\%$. When LTP was induced in the presence of 5 μM SR141716A alone (in four of the seven slices) it resulted in significant potentiation of $133 \pm 7\%$ (Fig. 4B).

4. Discussion

This study set out to establish whether the blockade of induction of LTP by cannabinoids was a consequence of upregulation of GABA-ergic transmission. To this end, we determined whether the two effects are correlated with regard to the specificity of two stereoisomeric cannabinoids, their concentration depen-

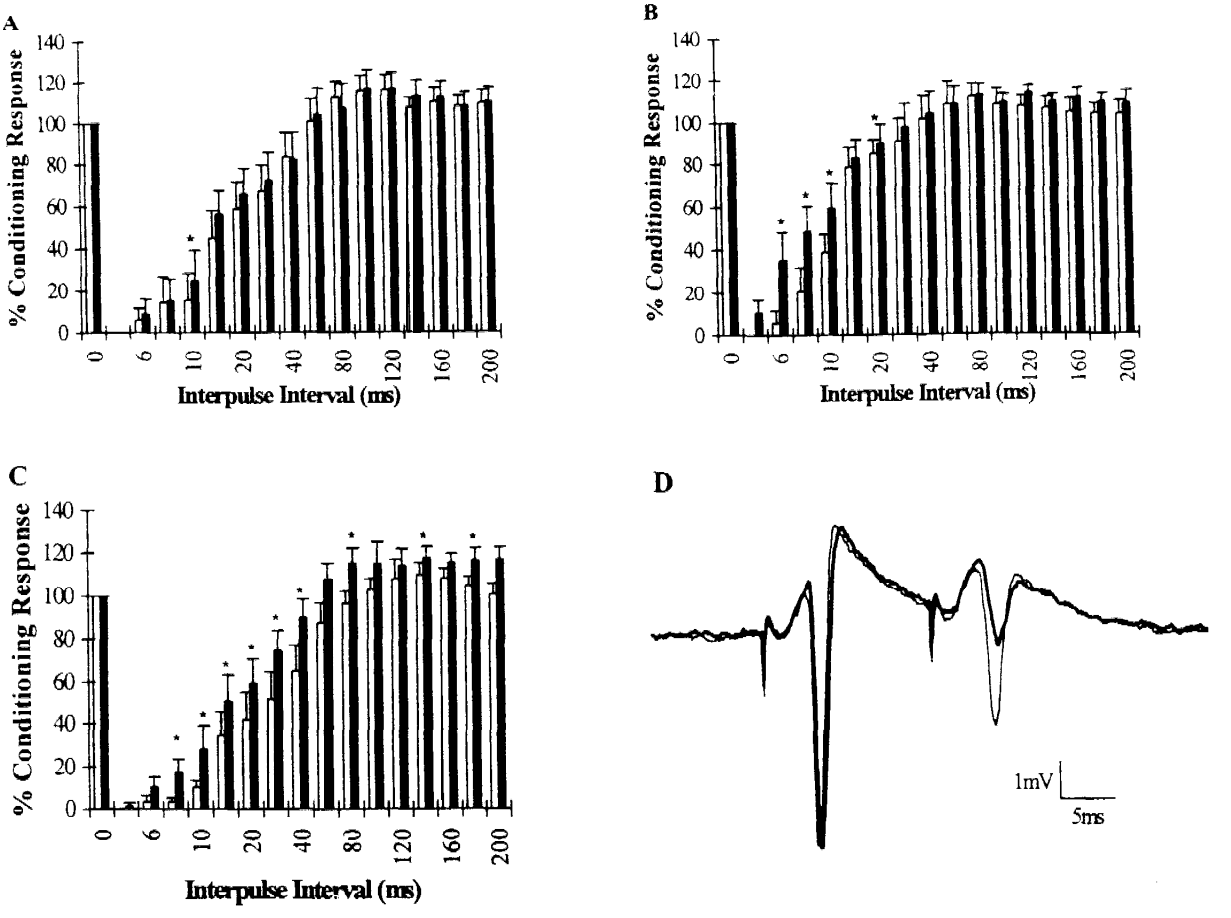

Fig. 2. WIN55212-2 inhibits paired pulse depression in a concentration dependent manner. In each histogram. open bars represent control responses before perfusion of the drug and closed bars represent responses obtained after perfusion of 250 nM(A; $n = 9$), 500 nM(B; $n = 5$) or 5μM(C; $n = 7$) WIN55212-2. Stars indicate the test response after perfusion of the drug is significantly different from control test response at $P < 0.05$. (D) Example of paired pulse responses recorded at 15 ms IPI before (thick trace) and after (thin trace) perfusion of 5μM WIN55212-2.

dence, and the effects of the CB1 receptor antagonist SR1417 16A. The two effects did prove to be correlated, however. the direction of the effects on PPD was contrary to expectation.

4.1. Cannabinoid effects on LTP

The stereospecific and concentration-dependent blockade of the induction of LTP by WIN55212-2. but not by its inactive isomer WIN55212-3, is remarkably consistent with that reported by Terranova et al. (1995), and with the effect of another stereospecific cannabinoid HU-210 and it's inactive isomer HU-211 (Collins et al., 1994). WIN55212-2 shows a sevenfold greater affinity for binding at CB2 rather than CB1 receptors (Showalter et al., 1996), however. since it is stereoselective in its action on CB1 receptors. and since there are no CB2 receptors in the CNS (Munro et al., 1993) the results are consistent with the blockade of LTP being mediated by CB1 receptors. This is confirmed by the effects of SR141716A which has been used as a selective antagonist for CB1 receptors (but may in fact be an inverse agonist (Bouaboula et al.. 1997: Landsman et al., 1997) and effectively prevented the action of WIN55212-2. These data are therefore consistent with previous reports that the blockade of LTP in the CA1 region by cannabinoids is mediated by CB1 receptors (Collins et al.. 1994, 1995; Terranova et al.. 1995).

4.2. Cannabinoid effects on PPD

The stimulation conditions (e.g. stimulus strength) were fixed to favour, but not saturate, paired pulse depression over facilitation. PPD is thought to rely partly on recurrent activation of GABA releasing interneurones which activate $GABA_A$ receptors on the pyramidal cell soma and cause a transient inhibition. This is expressed as a reduction in the amplitude of the test response evoked at appropriate ISI's (Schwartzkroin and Knowles, 1983). In these experiments the extent of PPD was therefore used as an index

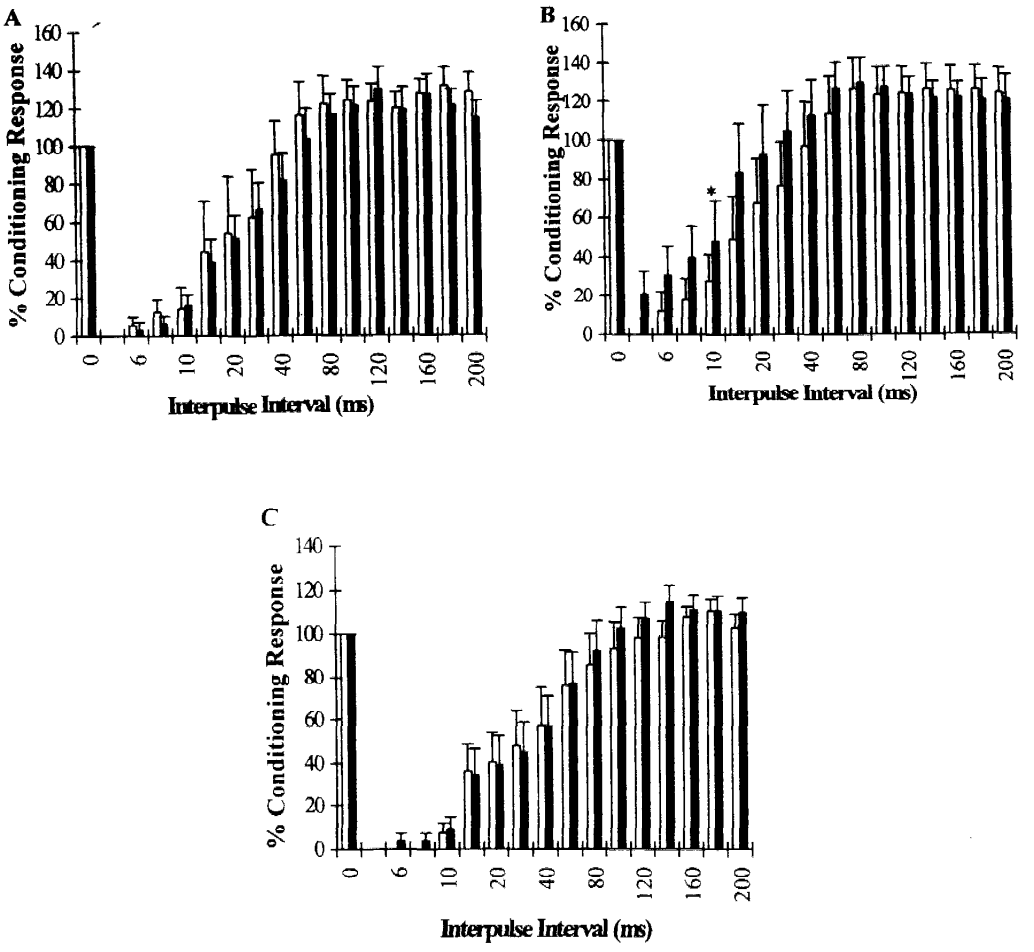

Fig. 3. (A) SR141716A blocks the effect of WIN55212-2 on paired pulse depression. Open bars represent control responses during perfusion of the drug 5 μM SR141716A. 5 μM WIN55212-2 (n = 6) was then added to the SR and perfused for a further 20 min before collection of the data represented by the filled bars. (B) SR141716A alone suppresses paired pulse depression. Closed bars represent responses after perfusion of SR141716.4 for the same period as in 3(A). without the addition of WIN55212-2 ($n = 7$). (C) WIN55212-3 has no effect on paired pulse depression. Open bars represent control data before the application of 5 μM WIN55212-3 ($n = 6$). filled bars represent the data collected after application of the drug.

of the strength of GABA-ergic transmission. WIN55 2 12-2 reduced PPD in a concentration-dependent and stereoselective manner, and this effect was blocked in the presence of SR1417 16A. indicating that the cannabinoid reduced GABA-ergic transmission is via an effect on CB1 receptors. The concentrations of both WIN55212-2 and SR 141716A are relatively high when compared to those used in organ bath preparations however they are comparable to concentrations used in other brain slice preparations (Terranova et al.. 1995). Importantly. the suppression of PPD was not accompanied by any change in amplitude of the conditioning response and so was not a simple consequence of reduced conditioning stimulus response.

These results are contrary to expectations based upon previous reports of the effects of cannabinoids on GABA-ergic transmission. Two previous studies have shown that THC increases PPD in the hippocampus (Vardaris et al.. 1977; Weisz et al.. 1982). however, when dose effect comparisons were made it was found that high doses increased PPD. but lower doses decreased it (Weisz et al.. 1982). It is therefore possible that we are dealing with the lower end of a biphasic dose-response curve.

4.3. Correlation between effects of cannaboinoids on LTP and PPD

Our experiments therefore provide strong evidence that the effects of WIN55212-2 in blocking LTP and in suppressing PPD are both CB1 receptor mediated. At first sight. this correlation might appear to support our hypothesis that the blockade of LTP is via modulation of GABA-ergic transmission. however. the direction of modulation of PPD was exactly opposite to that which would be expected. According to the simplest explanation the suppressed PPD observed in the presence of WIN55212-2 would indicate a reduction in GABA-er-

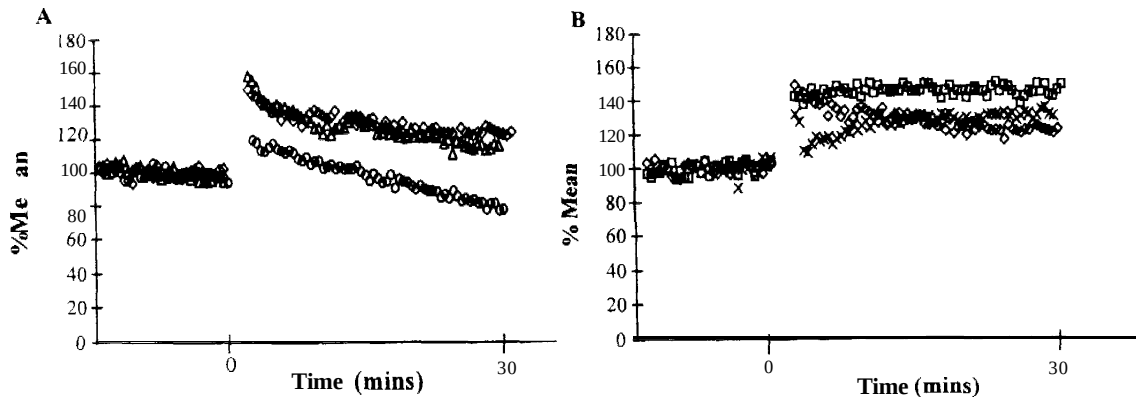

Fig. 4. (A) WIN55212-2 blocks the induction of LTP in a concentration dependent manner. Amplitude of population spike is plotted against time. three high frequency trains (100 Hz for 500 ms at test intensity) were delivered at time 0. Symbols represent pooled data from slices **treated** with 5 μM Tween (diamonds: $n = 4$). 250 nM WIN55212-2 (triangles; $n = 7$) and 5 μM WIN55212-2 (circles; $n = 6$). (B) SR141716A prevents blockade of LTP by WIN55212-2. Symbols represent pooled data from slices treated with 5 μM Tween (diamonds; $n = 4$) (same data as above). 5 μM WIN55212-2 in the presence of 5 μM SR141716A (squares: $n = 5$) and 5 μM SR141716A alone (crosses: $n = 4$).

gic transmission such as a reduction in GABA release, an increase in GABA uptake. or some postsynaptic antagonistic effect on GABA receptors.

Current evidence does not suggest that cannabinoids exert **such** effects on GABA-ergic transmission. Several groups have shown that cannabinoids decrease GABA uptake (Maneuf et al., 1996; Glass et al.. 1997) hence potentiating GABA mediated responses (Coull et al,, 1997). However, this would be expected to increase PPD, the opposite of what we found.

One of the more robust effects of the cannabinoids is the inhibition of voltage dependent Ca^{2+} currents (Mackie and Hillie. 1992) which, assuming the same effect occurs in presynaptic terminals, may be functionally expressed as a reduction in transmitter release. It has been suggested that cannabinoids may attenuate GABA release in the substantia nigra pars reticulata (Anderson et al., 1995), however, GABA release in the globus pallidus is unaffected by cannabinoids (Maneuf et al., 1996: Shen et al., 1996). Most relevantly however, in the hippocampus WIN55 2 12-2 appears to inhibit glutamate release. but not GABA release (Shen et al., 1996). It is therefore unlikely that. in this region, a reduction in GABA release could explain the reduction in GABA-ergic feedback inhibition and hence a reduction in paired pulse depression.

4.4. *A speculative hypothesis*

Since cannabinoids do not apparently inhibit GABA release in the hippocampus (Shen et al., 1996), or postsynaptic responses to GABA (Coull et al., 1997) an alternative hypothesis is that they inhibit the excitatory drive of the interneurones. However, a striking observation is that WIN55212-2 suppressed PPD without reducing the conditioning response amplitude which would require that cannabinoids selectively inhibited the excitatory drive of interneurones, but not of CA1 pyramidal neurones. This profile of action is remarkably similar to the effects of metabotropic glutamate receptor agonists on synaptic transmission in the CA1 region (Bordi et al.. 1997). In this area the mGlu receptor agonist 1S,3R-ACPD produces a very similar effect to WIN55 2 12-2 (Brown and Reymann, 1995) and there is now direct and convincing evidence that activation of group III mGlu receptors by L-AP4 selectively inhibits the release of glutamate onto interneurones and not onto CA1 pyramidal cells (Scanziani et al._ 1997).

We therefore speculate that cannabinoids suppress PPD by acting on presynaptic receptors located selectively on the terminals of glutamatergic neurons which synapse onto inhibitory interneurones and therefore reduce excitatory drive of these cells. Whether this effect is via mGlu receptors, or the second messenger systems which CB1 and some mGlu receptors share, e.g. inhibition of cAMP accumulation (Bidaut-Russell et al., 1990: Pin and Duvoisin, 1995). remains to be determined. It does appear however that the cannabinoids are suppressing PPD via the alteration of presynaptic glutamate release probabilities rather than affecting GABA-ergic transmission directly. This is supported by other studies which suggest that changes in presynaptic release probability and intracellular Ca^{2+} accumulation is responsible for PPD (Katz and Miledi, 1969; Debanne et al., 1996). It would also explain why less PPD is seen at high stimulus strengths= when one would expect a greater degree of GABA-ergic activation.

4.5. *Relationship to LTP*

The original aim of these studies was to test the hypothesis that upregulation of GABA-ergic inhibitory

transmission was the mechanism by which cannabinoids inhibit the induction of LTP. Our results show that although both modulation of GABA-ergic transmission and blockade of LTP are likely to be receptor mediated, feedback GABA-ergic inhibiton was actually reduced by WIN55 212-2. This is therefore highly unlikely to be a causal step in the blockade of LTP. The possibility remains however, that some interaction with mGlu receptors or their second messengers may underlie both the reduction in PPD and the blockade of LTP.

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