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Effects of phencyclidine, SKF 10,047 and related psychotomimetic agents on N-methyl-D-aspartate receptor mediated synaptic responses in rat hippocampal slices

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1 The effects of representative drugs from three classes of psychotomimetic compounds (arylcyclohexylamines, benzomorphan opioids and dioxolanes) have been examined on synaptic transmission at an identified monosynaptic pathway in rat hippocampal slices. The compounds tested were phencyclidine (PCP) and ketamine, the racemate and isomers of SKF 10,047 (N-allylnormetazocine), and the isomers of dioxadrol (dexoxadrol and levoxadrol).

2 In the absence of added magnesium ions (Mg) in the perfusion medium low frequency stimulation of the Schaffer collateral-commissural pathway evoked a burst of population spikes in the CA1 cell body region. The secondary components of this response could be abolished by the selective N-methyl-D-aspartate (NMDA) antagonist D-2-amino-5-phosphonovalerate (APV).

3 PCP (1 μM) or ketamine (10 μM) selectively blocked the secondary components of the synaptic response. The effect of PCP was neither mimicked nor prevented by hexamethonium and atropine, phentolamine and propranolol, or clonidine and was therefore unlikely to involve cholinergic or adrenergic neurotransmitter systems.

4 The σ opiate, (±)-SKF 10,047 (10 μM) also abolished selectively the secondary components of the synaptic response. There was no apparent difference between the potency of the stereoisomers of this compound.

5 The action of (±)-SKF 10,047 was not affected by either naloxone or haloperidol, indicating that this effect did not involve opioid receptors or the haloperidol-sensitive σ site.

6 Dexoxadrol (10 μM), but not levoxadrol (10 μM), also selectively blocked the secondary components of the synaptic response.

7 It is concluded that these psychotomimetic agents can block an NMDA receptor-mediated component of synaptic transmission in the hippocampus and that this effect is mediated by a specific PCP/σ site.

Introduction

The dissociative anaesthetic phencyclidine (PCP), although originally developed for use as a general anaesthetic, is now a widely used drug of abuse due to its hallucinogenic properties (Henderson, 1982). PCP has been found to affect many neurotransmitter systems, in particular cholinergic and monoaminergic systems, and a number of theories have been proposed to account for its variety of effects (cf. Kamenka *et al.*, 1983). PCP binds to a specific site in the brain (Zukin & Zukin, 1979; Vincent *et al.*, 1979), and it has been proposed that many of the actions of PCP could be mediated through this receptor. Studies in the rat have shown, using the PCP analogue thienyl-phencyclidine (TCP), that the highest density of PCP binding sites are located in the hippocampus, including the area where the Schaffer collateral-commissural fibres innervate the CA1 region (Contreras *et al.*, 1986; Vignon *et al.*, 1986).

One of the most potent effects of PCP is to block responses to the excitant amino acid N-methyl-D-aspartate (NMDA) (Anis *et al.*, 1983; Lacey & Henderson, 1983; 1986; Duchen *et al.*, 1985) and to suppress NMDA receptor-mediated effects (Snell & Johnson, 1985; Lodge & Johnston, 1985; Aanonsen &

Wilcox, 1986). Other structurally unrelated classes of drugs, such as the benzomorphan opioids (e.g. SKF 10,047 (N-allylnormetazocine)) and the dioxolanes (e.g. dexoxadrol) have been shown to have similar properties to PCP in binding (e.g. Zukin & Zukin, 1981; Hampton *et al.*, 1982), behavioural (e.g. Holtzman, 1980; Shannon, 1983) and electrophysiological (e.g. Berry *et al.*, 1984a,b) studies. Their potency in a number of the binding and behavioural tests correlates closely with their ability to suppress NMDA-induced responses (Berry & Lodge, 1985). There is also a high correlation between the localization of TCP binding and the NMDA receptor in the rat forebrain (Maragos *et al.*, 1986). In addition PCP and selective NMDA antagonists such as D-2-amino-5-phosphonovalerate (APV) have certain properties in common, such as anticonvulsant activity (Chen *et al.*, 1959; Croucher *et al.*, 1982), the ability to induce analgesia (Chen *et al.*, 1959; Cahusac *et al.*, 1984), catalepsy (Koek *et al.*, 1986), and to block long term potentiation (LTP) (Collingridge *et al.*, 1983; Stringer & Guyenet, 1983); a form of synaptic plasticity widely studied as a model of learning and memory (Collingridge & Bliss, 1987).

A role of NMDA receptors in synaptic transmission in the Schaffer collateral-commissural pathway is well established (see Collingridge *et al.*, 1986). The nature of the response is, however, dependent on the experimental conditions used. Electrophysiological studies *in vitro* are usually performed in the presence of concentrations of magnesium ions (Mg) (1–4 mM) that are believed to occur in the extracellular environment of neurones in the brain. Mg is, however, a potent but voltage-dependent NMDA antagonist (Ault *et al.*, 1980; Crunelli & Mayer, 1984, Nowak *et al.*, 1984). In the presence of millimolar concentrations of Mg therefore, an appreciable synaptic component sensitive to NMDA antagonists is only seen if neurones are depolarized sufficiently to reduce the Mg block. This can be achieved by, for example, high frequency stimulation of the Schaffer collateral-commissural pathway (Herron *et al.*, 1986; Collingridge, Herron & Lester, unpublished observations), or by blockade of synaptic inhibition (Herron *et al.*, 1985; Dingledine *et al.*, 1986). Under these conditions the synaptic component that is sensitive to NMDA antagonists displays the same anomalous, Mg-conferred, voltage-dependence as do the depolarizations of hippocampal neurones induced by the iontophoretic application of NMDA (Dingledine, 1983). A large synaptic component that is sensitive to NMDA antagonists can, however, be evoked by low frequency stimulation, without synaptic inhibition being impaired, by the omission of Mg from the perfusion medium. As would be expected, both this component (Collingridge, Herron & Lester, unpublished observations) and the depolarizations of hippocampal neurones induced by NMDA (Crunelli & Mayer, 1984) display a conventional voltage-dependence. The latter conditions provide a stable and sensitive system with which to investigate the actions of drugs on synaptically activated NMDA receptors and associated events in the hippocampus.

We have found that PCP, ketamine and SKF 10,047 selectively abolish the APV-sensitive component of the synaptic response evoked by low frequency stimulation of the Schaffer collateral-commissural pathway in Mg-free medium (Coan & Collingridge, 1985b; Coan *et al.*, 1985). To investigate the possibility that the effects of these agents may be mediated indirectly via other neuronal systems within the hippocampus, the effects of a variety of cholinoceptor, adrenoceptor and opioid receptor antagonists have been determined both on the synaptic response and on the effects of the psychotomimetic compounds. In addition, in order to identify the type of PCP or σ binding site at which these drugs exert their action on NMDA receptor-mediated responses, the potency of a range of psychotomimetics and their isomers have been investigated and the ability of haloperidol to affect the actions of SKF 10,047 has been determined.

Methods

Experiments were performed on rat transverse hippocampal slices prepared and maintained as described previously (Collingridge *et al.*, 1983). Slices were kept at 30–35°C and perfused with oxygenated (95% O_2, 5% CO_2) medium comprising of (mM): NaCl 124, NaH_2PO_4 1.25, $NaHCO_3$ 26, KCl 5, $CaCl_2$ 2, $MgSO_4$ 1, D-glucose 10. The Schaffer collateral-commissural pathway was stimulated at 0.08 Hz and extracellular recordings were obtained from the CA1 cell body region using microelectrodes containing 4 M NaCl (Figure 1A). Providing maximal stimulation was able to evoke a single population spike with no indication of secondary responses (Figure 1a), the slice was perfused with medium containing no added Mg for at least 1 h to reveal the components of the synaptic response which are sensitive to NMDA antagonists (Coan & Collingridge, 1985a). In the absence of any drug treatment the evoked multiple population spike activity persists for as long as the slices remain viable, typically over 12 h.

When a stable response had been achieved in Mg-free medium, drugs were added via the perfusion medium. In experiments using cholinoceptor, adrenoceptor or opioid receptor antagonists a concentration of drug was selected that would be expected to produce a dose-ratio for antagonism of at least 50. Mixtures of antagonists were used to block both nicotinic and muscarinic receptors and both α- and β-adrenoceptors. Doses of the other compounds were selected on the basis of their potencies in binding

studies. Representative records were stored on disk and subsequently analysed offline using a microcomputer. Results were analysed from 49 slices obtained from 48 adult female rats, of approximately 200 g body weight. The number of slices in which a drug treatment was either effective or ineffective is given in parentheses. In all cases this was the same as the number of slices tested.

Drugs

Phencyclidine hydrochloride, (+)-N-allylnormetazocine hydrochloride, (−)-N-allylnormetazocine hydrochloride, and (±)-N-allylnormetazocine hydrochloride, were kindly supplied by the National Institute on Drug Abuse (Rockville, Maryland, U.S.A.). Dexoxadrol hydrochloride and levoxadrol hydrochloride were kindly provided by the Upjohn Company (Kalamazoo, Michigan, U.S.A.) and D-2-amino-5-phosphonovalerate was a gift from Dr J.C. Watkins, (University of Bristol). All other drugs were obtained from normal commercial sources.

Results

Synaptic transmission in the absence of Mg

In the absence of Mg, stimulation of the Schaffer collateral-commissural pathway elicits a burst of population spikes (Figure 1b). In slices with intact synaptic inhibition, the selective NMDA antagonist D-2-amino-5-phosphonovalerate (APV) abolishes all the secondary components (Figure 1c) (Coan & Collingridge, 1985a). The involvement of the NMDA receptor in the first component of the synaptic response evoked under these conditions is dependent upon the afferent stimulus intensity (Coan & Collingridge, 1987). At low stimulus intensities APV depresses the

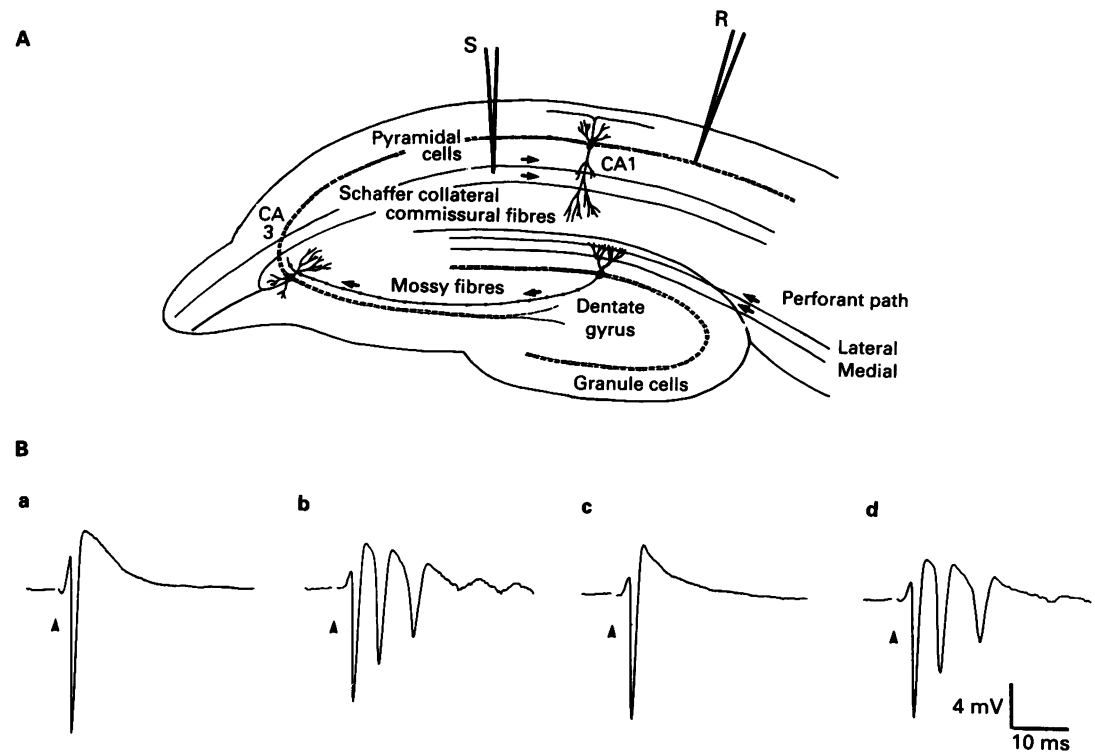

Figure 1 A Schematic diagram of a transverse hippocampal slice, showing main excitatory pathways and position of stimulating (S) and recording (R) electrodes. **B** Typical extracellular responses recorded in the CA1 region in response to Schaffer collateral-commissural stimulation. (a) Maximal response in magnesium (Mg, 1 mM) containing medium, (b) response after 75 min perfusion with Mg-free medium at a reduced stimulus intensity (control), (c) response in Mg-free medium after 10 min perfusion at 10 μM D-2-amino-5-phosphonovalerate, (d) response after 20 min wash with Mg-free medium. In these and subsequent records negativity is down, stimulus artefacts have been blanked for clarity and the time of stimulation is indicated by an arrowhead.

amplitude of the first population spike, whereas at high stimulus intensities APV increases this component of the response. With the stimulus parameters used in the present study, the primary population spike was little affected by APV. Therefore, the effect of the drugs on the subsequent population spikes (i.e. the secondary components) was used as an indication of their ability to antagonize synaptically activated NMDA receptor-mediated responses.

Phencyclidine and ketamine

PCP 1 μM selectively abolished the secondary components of the synaptic response ($n = 8$) (Figure 2). The time taken for complete abolition varied between 70–125 min. No reversal of this blockade was seen with up to 165 min of washing. PCP 10 μM had the same effect ($n = 5$), but was fully effective within 30–60 min. PCP 0.1 μM reduced the secondary response but did not completely eliminate it after up to 140 min of perfusion ($n = 2$). In these experiments 20 μM APV abolished the remainder of the secondary population spikes (Figure 2), demonstrating that after this length of time 0.1 μM PCP had only a partial effect on the NMDA receptor-mediated responses.

Mixtures of hexamethonium (250 μM) and atropine (1 μM) ($n = 2$), propranolol (10 μM) and phentolamine (10 μM) ($n = 2$) or clonidine applied alone (0.1 μM) ($n = 2$), when perfused for 30–40 min before and then during application of 1 μM PCP, did not antagonize the depressant action of PCP (Figure 3). In the presence of these drugs the time taken for PCP to have maximum effect varied between 60–125 min. The combination of hexamethonium and atropine appeared to have a very small effect on the secondary components of the synaptic response (Figure 3a), whereas neither phentolamine and propranolol nor clonidine had an effect on any part of the synaptic response (Figure 3 b,c).

Ketamine 10 μM also blocked the secondary responses ($n = 5$) taking 20–45 min to have a maximal effect. The effect of ketamine could be reversed with a 50–60 min wash ($n = 3$) (cf. Coan & Collingridge, 1985b).

SKF 10,047

(±)-SKF 10,047 10 μM had qualitatively the same action as PCP or ketamine, abolishing the secondary components within 40–80 min ($n = 4$). Washing for 60–90 min resulted in at least a partial reversal. Both (+)-SKF 10,047 ($n = 4$) and (−)-SKF 10,047 ($n = 4$) had the ability to antagonize the secondary components of the synaptic response. There was no noticeable potency difference between these stereoisomers (Figure 4). Neither naloxone (10 μM) ($n = 3$) nor

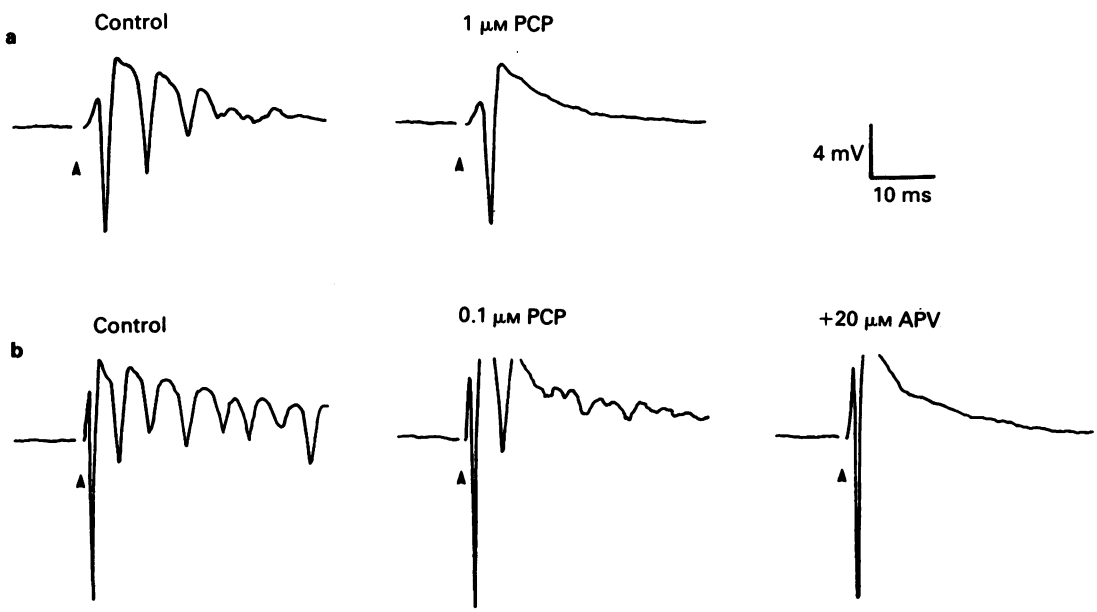

Figure 2 (a) Effect of 1 μM phencyclidine (PCP) (70 min) on the synaptic response recorded in the absence of Mg. (b) Effect of 0.1 μM PCP (135 min) and the addition of 20 μM D-2-amino-5-phosphonovalerate (APV) (10 min) on the synaptic response recorded in a different slice in the absence of Mg.

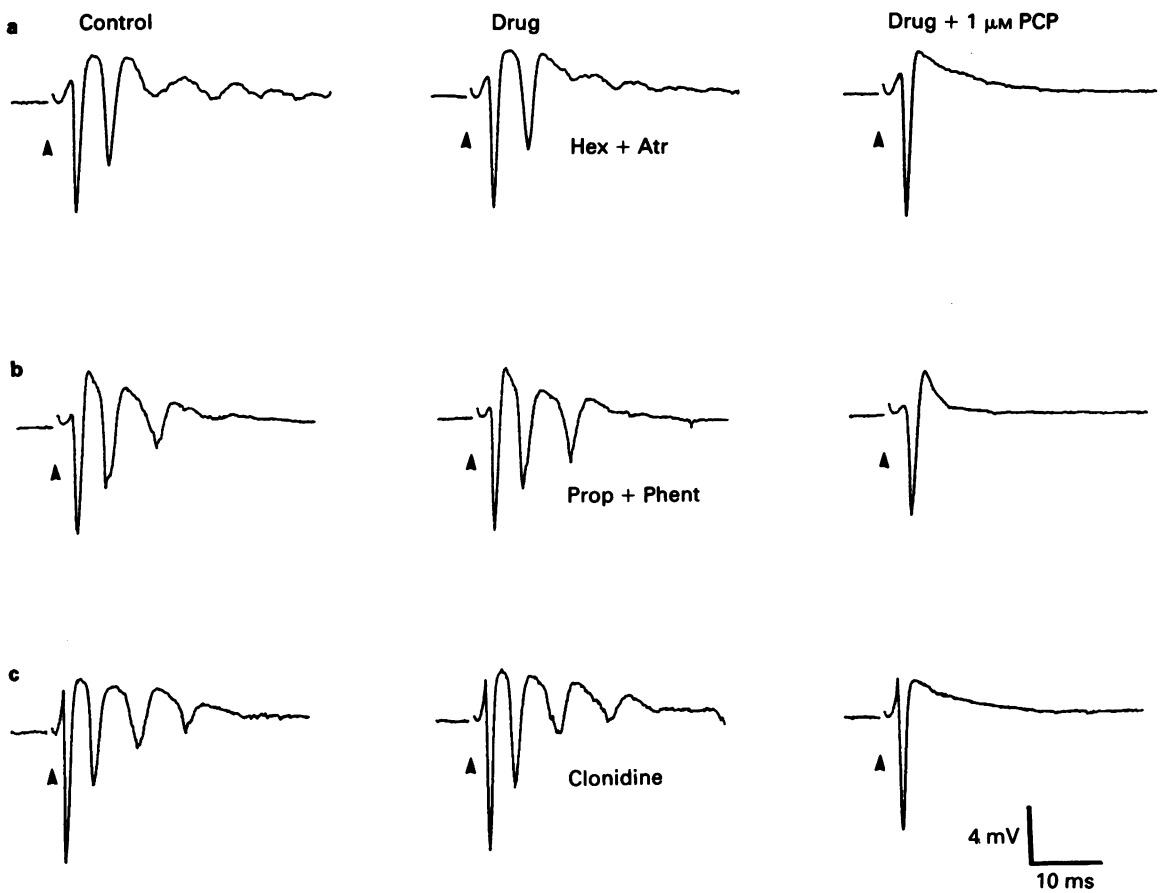

Figure 3 Effect of 1 μM phencyclidine (PCP) on the synaptic response in the absence of Mg and the presence of (a) 250 μM hexamethonium (Hex) and 1 μM atropine (Atr) (PCP perfused for 125 min), (b) 10 μM propranolol (Prop) and 10 μM phentolamine (Phent) (PCP perfused for 90 min), (c) 0.1 μM clonidine (PCP perfused for 110 min). Each experiment was performed using a different slice and in each case the antagonist was perfused for 30–35 min before and then during administration of PCP.

haloperidol (10 μM) ($n = 3$) (Figure 5) altered the depressant effect of SKF 10,047. The maximum effect was achieved within 40–80 min in the presence of either of these antagonists. These drugs were also without effect on the synaptic response (Figure 5).

Dexoxadrol and levoxadrol

Dexoxadrol, the (+)-isomer of the dioxolane dioxadrol, also suppressed the secondary population spikes although it did not seem as potent as PCP. Dexoxadrol 10 μM reduced or abolished the secondary responses after 75–110 min ($n = 6$) (Figure 6). In contrast 10 μM levoxadrol, the (−)-isomer of dioxadrol, had very little effect on any part of the synaptic response when perfused for up to 200 min (n = 3).

NMDA antagonists, since 10–20 μM APV eliminated the secondary component of the response on each occasion (Figure 6).

Discussion

We have shown that three different classes of drug, arylcyclohexylamines (PCP and ketamine), benzomorphan opioids (SKF 10,047) and dioxolanes (dexoxadrol), are potent and selective depressants of a component of synaptic transmission in the hippocampus that can be recorded in Mg-free medium. This secondary component of the synaptic response is believed to be mediated by NMDA receptors since it can be blocked by micromolar concentrations of Mg

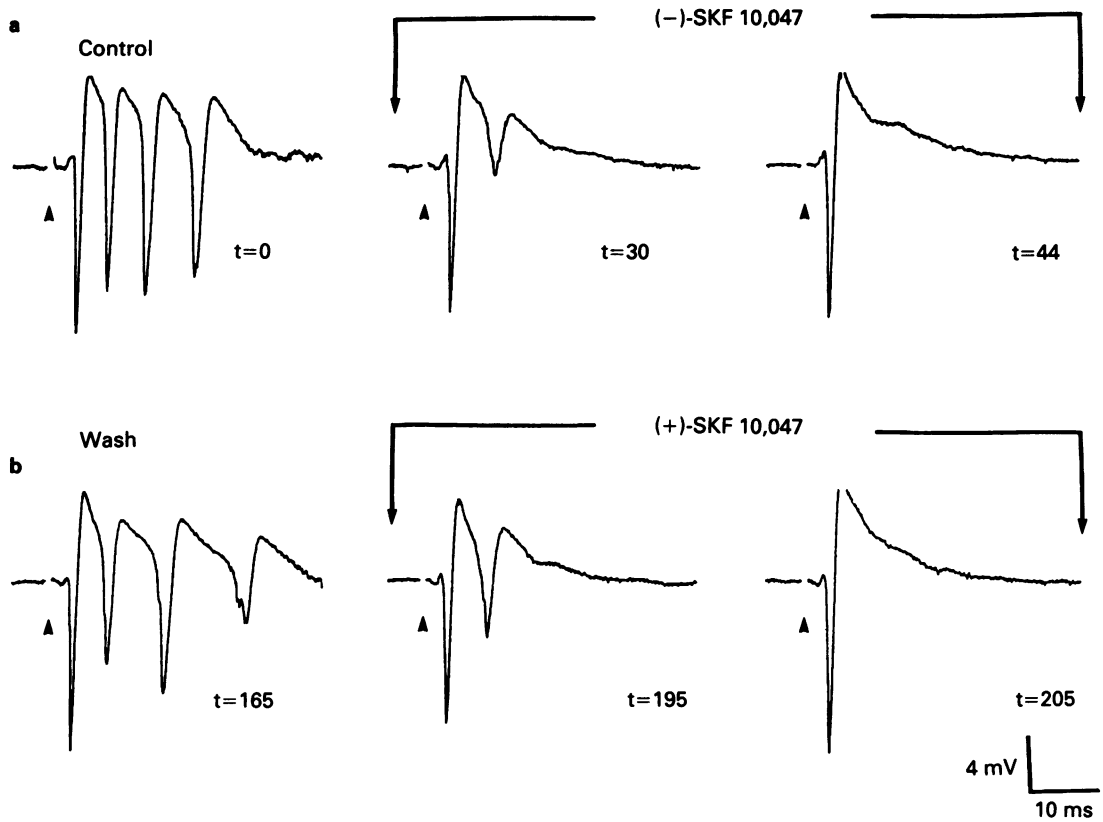

Figure 4 Comparison of the effect of (a) 10 μM (−)-SKF 10,047 and (b) 10 μM (+)-SKF 10,047 on the synaptic response recorded from the same slice in the absence of Mg. (−)-SKF 10,047 was perfused at t = 0 for 30 min and took 44 min to achieve its maximum effect. The slice was then washed with Mg-free medium for 135 min. (+)-SKF 10,047 was perfused at t = 165 for 30 min and took 40 min to achieve its maximum effect.

(Herron *et al.*, 1986) and by selective, competitive NMDA antagonists (Coan & Collingridge, 1985a). It seems unlikely that the secondary components of the synaptic response are mediated by or dependent upon, activation of cholinoceptor, monoamine or opioid receptor systems since they were unaffected by the antagonists of these neurotransmitter systems used in the present study. By the same reasoning, it is unlikely that the actions of the psychotomimetic drugs on this synaptic component, recorded under the present conditions, involved any of these neurotransmitter systems. Thus, with the doses of antagonist used substantial blockade would have been achieved by hexamethonium and atropine of, respectively, nicotinic and muscarinic receptors, by phentolamine and propranolol of, respectively, α- and β-adrenoceptors, by haloperidol of dopamine receptors, and by naloxone or μ-, δ- and κ-opioid receptors. Furthermore, 5-hydroxytryptamine$_1$ (5-HT$_1$) receptors would have been blocked by propranolol (Middlemiss, 1984; Engel *et al.*, 1986) and 5-HT$_2$ receptors by propranolol and haloperidol (Peroutka & Snyder, 1979; Middlemiss, 1984; Engel *et al.*, 1986).

Clonidine, a specific and potent α_2-adrenoceptor agonist has been shown to disrupt certain PCP-induced behavioural effects (Tang & Franklin, 1983). It did not, however, affect the actions of PCP in the present study, suggesting that α_2-adrenoceptors are not involved in this synaptic effect of PCP.

There is increasing evidence that the arylcyclohexylamines, benzomorphans and dioxolanes interact with two pharmacologically distinct binding sites; a σ site and a common PCP/σ site (e.g. Su, 1982; Tam, 1983; 1985; Martin *et al.*, 1984; Gundlach *et al.*, 1985; Itzhak *et al.*, 1985; Sircar *et al.*, 1986). Although the physiological significance of these sites has not yet

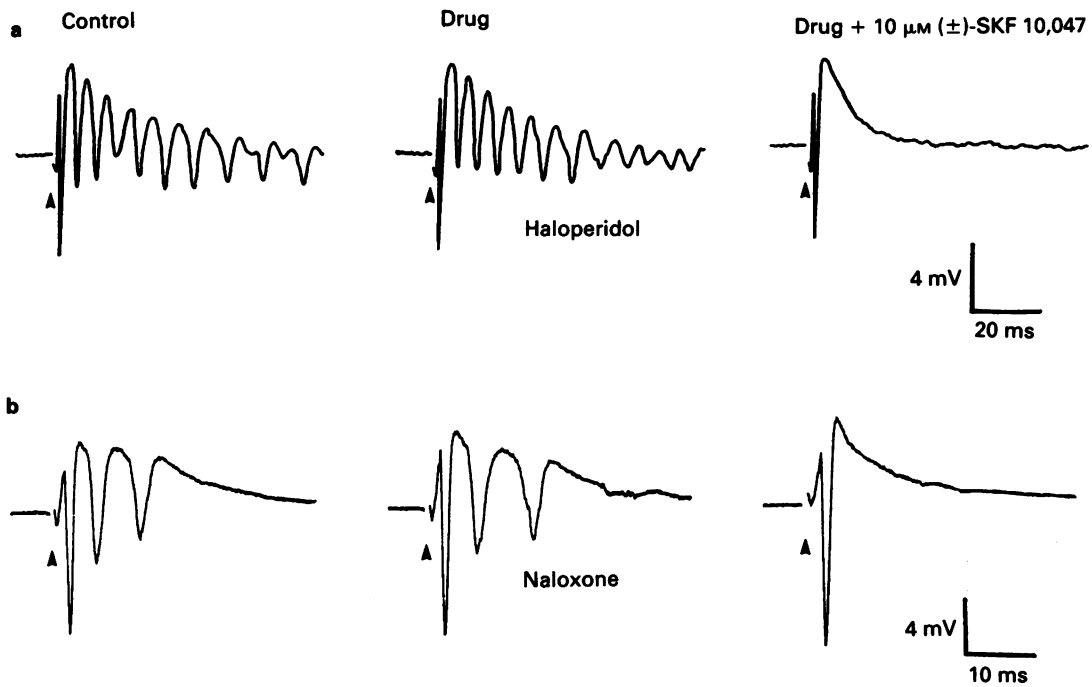

Figure 5 Effect of 10 μM SKF 10,047 on the synaptic response in the absence of Mg and the presence of (a) 10 μM haloperidol (SKF 10,047 perfused for 45 min), (b) 10 μM naloxone (SKF 10,047 perfused for 50 min). Each experiment was performed using a different slice and in each case the antagonist was perfused for 30–40 min before and then during administration of SKF 10,047.

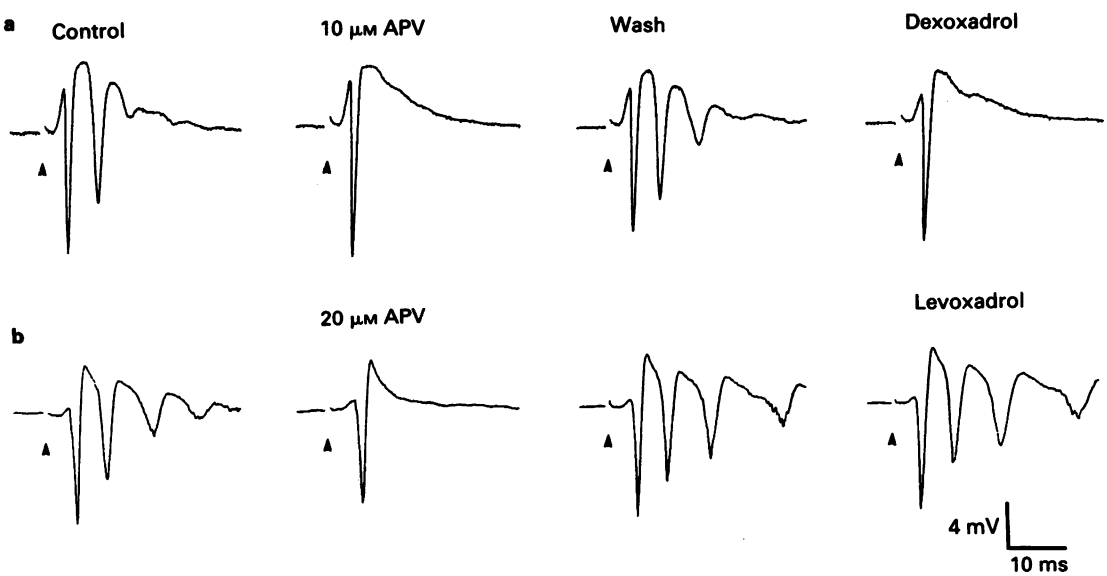

Figure 6 Comparison of the effect of (a) 10 μM dexoxadrol and (b) 10 μM levoxadrol on the synaptic response in the absence of Mg. Each drug was perfused for 90 min. Each experiment was performed on a separate slice. In (a) 10 μM D-2-amino-5-phosphonovalerate (APV) and in (b) 20 μM APV abolished all secondary responses.

been established, it is generally considered that the PCP/σ site mediates at least some of the psychotomimetic effects of these compounds. However, the importance of the σ site is still an open question. Although there is considerable overlap in the affinities of various ligands for these sites they may be distinguished by the following criteria. Firstly, the neuroleptic drug haloperidol is a potent inhibitor of binding to σ sites (Su, 1982; Tam, 1983). Secondly, (+)-SKF 10,047 has a higher affinity than (−)-SKF 10,047 for binding at the σ site, but has a similar affinity at the PCP/σ site (Gundlach *et al.*, 1985). Thirdly, dexoxadrol has a higher affinity than levoxadrol for binding to the PCP/σ site, but a similar affinity at the σ site (Hampton *et al.*, 1982; Largent *et al.*, 1984). On the basis of these three criteria the effects we observed in the present study would appear to be mediated via the PCP/σ site.

It appears that, at least in certain region of the CNS, the PCP/σ site is directly associated with the NMDA receptor-channel complex. In the cortex and spinal cord antagonism by PCP or ketamine of an NMDA-induced response has been shown to be non-competitive and distinct from the site of action of APV and Mg (Harrison & Simmonds, 1985; Martin & Lodge, 1985). It has been proposed that these drugs exert their action either by blocking the channel associated with the NMDA receptor (Honey *et al.*, 1985), or by interacting with an allosterically linked site (Loo *et al.*, 1986). The mechanism by which these drugs exert their effects in the hippocampus and the behavioural consequences of such actions remain to be determined. The ability, however, of these psychotomimetics to block NMDA receptor-mediated synaptic transmission in the Schaffer collateral-commissural pathway offers an explanation for how these drugs prevent LTP in this pathway (Stringer & Guyenet, 1983; Stringer *et al.*, 1983), since the induction of LTP is dependent upon NMDA receptor activation (Collingridge *et al.*, 1983).

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