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Local anaesthetic actions of cocaine: effects on excitatory and inhibitory synaptic responses in the hippocampus *in vitro*

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1 The basis for the proconvulsant action of cocaine was investigated in the CA1 region of the rat hippocampal slice *in vitro*.

2 Superfusion with 100 μM cocaine depressed inhibitory and excitatory postsynaptic potentials recorded intracellularly from CA1 pyramidal neurones; both types of potentials were inhibited to an equal extent. When inhibition was assessed using extracellular recording of population spike responses before and after conditioning impulses, there did not appear to be any selective effect upon either recurrent or feed-forward γ-aminobutyric acid (GABA)ergic inhibition.

3 Not all responses showed equivalent sensitivity to the local anaesthetic actions of cocaine. In particular, the antidromic population spike evoked by stimulation of the alveus was significantly more sensitive than the presynaptic fibre spike elicited by stimulation of stratum radiatum.

4 The rate of interictal spiking in hippocampus, induced by penicillin and increased potassium in the perfusion medium, was depressed by superfusion with cocaine in the range 5–100 μM.

5 These results suggest that cocaine does not have a selective depressant effect upon inhibitory pathways in the CA1 region of the hippocampus. Although the hippocampus shows epileptiform activity following systemic administration of local anaesthetics such as cocaine in the intact rat, this effect may not reflect a direct hippocampal site of drug action.

Introduction

Cocaine is a euphorigenic drug that is subject to widespread abuse, yet many aspects of its actions on the nervous system at the cellular level remain unclear. The psychopharmacological properties of cocaine are generally thought to be due to one or both of cocaine's primary actions: blockade of monoamine neurotransmitter re-uptake, and local anaesthesia. Blockade of the high affinity uptake mechanisms for monoamines, and dopamine in particular, has been regarded as responsible for cocaine's intense euphorigenic effects; in part, this is because there is a good correlation between the affinity of drugs for the dopamine transporter and their abuse potential (Ritz *et al.*, 1987). However, there may be local anaesthetic involvement as well, since under some circumstances animals will self-administer local anaesthetics that lack the ability to inhibit monoamine uptake (Ford & Balster, 1977).

The toxic and sometimes fatal effects of cocaine are frequently related to central nervous system (CNS) excitation, which is often manifested as seizures. This proconvulsant effect is a property which cocaine shares with virtually all other local anaesthetics, and is thought to be related to the inhibition of the voltage-dependent sodium channel, rather than to some other action of cocaine (DeJong, 1977; Garfield & Gugino, 1987). Although lower doses of some local anaesthetics such as phenytoin or lignocaine are used therapeutically in the management of both seizures and cardiac arrhythmias, in higher

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doses these drugs are epileptogenic (Stripling & Ellinwood, 1977; DeJong, 1977; Munson *et al.*, 1975). Because most previous work has involved systemic administration of local anaesthetics, it is not known whether they act at multiple sites to induce epileptiform activity, or whether there is a primary locus of action that induces aberrant activity in other brain regions via synaptic connections. Although the site(s) at which local anaesthetics act to produce such effects is unclear, the hippocampus plays a major role in the resulting seizures; for example, the only significant increase in cerebral glucose utilization following intravenous administration of lidocaine occurs in the regio superior of the hippocampus (237% increase), whereas glucose utilization in other regions such as the cerebral cortex is significantly decreased (Ingvar & Shapiro, 1981).

The cellular mechanisms underlying local anaesthetic-induced seizures are also unclear. A proposed mechanism by which local anaesthetics might induce CNS excitation and seizure activity is via the inhibition of inhibitory interneurones, or a blockade of conduction in inhibitory fibres (Warnick *et al.*, 1971; Ritchie & Green, 1985). Although there is some evidence to suggest that local anaesthetics can directly interfere with inhibitory synaptic responses in the cerebral cortex (Tanaka & Yamasaki, 1966), the mechanism underlying this effect is unclear.

The present study was conducted to determine (a) whether cocaine has a direct proconvulsant effect in hippocampal brain slices, and (b) whether cocaine selectively affects inhibitory neurotransmission in this brain region, thereby supporting the hypothesis that local anaesthetic-induced CNS excitation results from disinhibition. The hippocampal slice preparation was selected for a test system because epileptiform activity is recorded in hippocampus following local anaesthetic injections *in vivo*, it responds appropriately to a variety of pro- and anticonvulsant drugs (Oliver *et al.*, 1977), and it has well-characterized inhibitory γ-aminobutyric acid (GABA)ergic pathways. Because the hippocampal slice preparation is isolated from the rest of the brain, it is possible to determine whether drug effects result from a direct hippocampal site of action. Both extra- and intracellular recordings were made under normal and epileptogenic conditions in an effort to characterize the cellular actions of cocaine in this isolated tissue.

Methods

Male Sprague-Dawley rats (150–250 g) were obtained from Sasco, St. Louis, MO, and were housed in groups of 2–5 under a 12 h light/dark cycle. The rats were decapitated and the hippocampus was dissected free from the rest of the brain. Coronal slices of the hippocampus were prepared as described previously (Dunwiddie & Lynch, 1978). Slices were immediately placed in ice-cold artificial cerebral spinal fluid consisting of (mM) NaCl 124, KCl 3.3, KH_2PO_4 1.2, $MgSO_4$ 2.4, $CaCl_2$ 2.5, $NaHCO_3$ 25.7, and glucose 10 which was pregassed with humidified 95% O_2 and 5% CO_2. The slices were transferred within 5 min to the recording chamber, which was maintained at a temperature of 33–34°C. The slices were allowed to equilibrate for a minimum of one hour, during which time the level of medium was maintained at or just below the upper surface of the slices. In some experiments interictal spikes were induced by superfusing slices with a modified medium containing $CaCl_2$ 2.0 mM and $MgSO_4$ 1.3 mM, and adding Na-penicillin G and KCl.

Electrical stimulation and recording

Evoked synaptic responses were elicited by stimulating with a twisted bipolar electrode made of nichrome wire, which was placed in the stratum radiatum near the border of CA1–CA2. Stimulation consisted of monophasic 0.1 ms pulses of 5–50 V delivered to the slice once every 60 s. Extracellular recordings were made with 2–3 megohm glass microelectrodes filled with 3 M NaCl which were placed under visual guidance in the CA1 pyramidal cell layer. Intracellular recordings were made from CA1 pyramidal neurones with electrodes filled with 2.5 M potassium acetate or potassium chloride, and having tip resistances of 50–80 megohms.

The slices were maintained without perfusion until they were to be tested, at which point fresh, oxygenated preheated medium was pumped through the chamber at 2 ml min^{-1}. Drugs were added to the flow of medium with a calibrated Sage Model 355 syringe pump, and in all experiments a stable response was obtained for at least 10 min before adding any drugs. The superfusion with drug was continued until a maximal response was observed. Pharmacological responses were analysed by converting concentration-response data into a Hill plot, which was then used to estimate the IC_{50} (i.e., the concentration of drug required to depress a response by 50%), and the associated 95% confidence limits.

The data from extracellular experiments were entered into a NOVA 3/12 computer in digital form for subsequent analysis. Intracellular records were stored on a multi-channel FM analogue tape recorder and subsequently digitized. Membrane potentials were continuously monitored on a chart recorder, and 10 to 50 responses were averaged and used for comparisons; responses were typically obtained

before, during and after superfusion with cocaine. The data are presented as the mean ± s.e.mean. Significance of the effect of cocaine treatment compared to control values (before cocaine treatment and after washout) was determined by paired 2-tailed Student's t test.

Results

Extracellular recording studies

In initial studies, the effects of cocaine on excitatory synaptic transmission at the Schaffer collateral and commissural synapses in the CA1 region were examined. Cocaine produced a concentration-dependent depression of the amplitude of the presynaptic fibre spike, field excitatory postsynaptic potential (e.p.s.p.) and synaptically evoked population spike. In addition, the latencies of all of these responses were significantly increased. Antidromic population spikes, elicited by stimulation of the alveus and recorded in the CA1 cell layer, were also reduced by cocaine treatment. Figure 1 illustrates the effects of 100 μM cocaine on the orthodromically-evoked population spike, the presynaptic fibre spike and field e.p.s.p., and the antidromically-evoked population spike. The threshold for statistically significant changes was approximately 10–30 μM cocaine, depending upon which response parameter was measured. The concentrations of cocaine required to depress the amplitude of the antidromic population spike, field e.p.s.p., and presynaptic fibre spike by 50% were determined from dose-response curves to be 64 μM, 110 μM and 126 μM, respectively (n = 20, 14 and 17 slices). These effects are all consistent with a local anaesthetic type of effect upon the axons and cell bodies of the CA1 pyramidal neurones and their afferents, and are similar to those obtained previously for olfactory cortex slices by Scholfield & Harvey (1975).

In a second set of experiments, the effects of cocaine upon a known GABAergic inhibitory synaptic circuit, the recurrent inhibitory pathway to the CA1 neurones, were examined. Pyramidal neurone axons were antidromically activated by stimulation of the alveus, and the magnitude of recurrent inhibition was characterized by determining the extent to which such stimulation could suppress a synaptic response evoked during the period of recurrent inhibition. Such studies are complicated by the fact that cocaine has direct effects upon both the orthodromic (Figure 1a) as well as antidromic (Figure 1c) population spikes. Therefore, the stimulation voltages were raised during the cocaine superfusion so as to equate the individual responses in the presence of cocaine with those obtained during a control period;

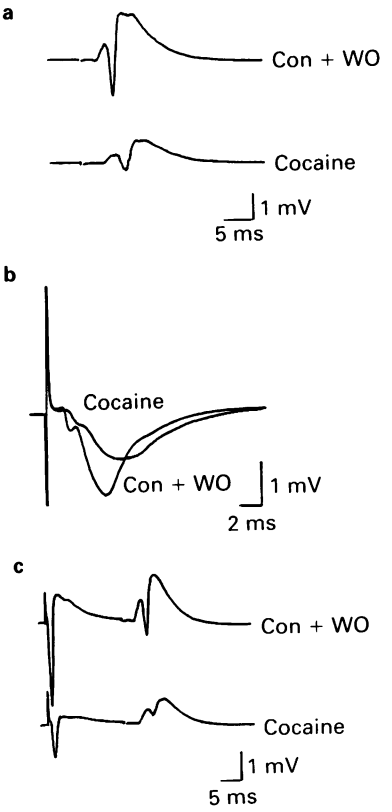

Figure 1 Responses of evoked extracellular field potentials to bath superfusion with 100 μM cocaine. The magnitude of the population spike response (a) was inhibited by perfusion with cocaine, and the latency to the negative peak of the spike was increased as well. Pre-drug control (Con) and post-drug perfusion washout (WO) responses were averaged together. The field excitatory postsynaptic potential (e.p.s.p.) and presynaptic fibre spike (the small inflection on the initial part of the evoked response) were inhibited as well (b). Antidromic population spike responses evoked by alvear stimulation (initial response in c) were also reduced. The recordings in (c) show not only the initial antidromic population spike, but also a synaptically evoked population spike elicited 20 ms following the antidromic stimulus. A similar protocol was used in Figure 2 to measure recurrent inhibition.

stimulation intensities were increased for both the antidromic and orthodromic responses. Examples of two such experiments are illustrated in Figure 2. The degree of inhibition of the test population spike response by a preceding antidromic stimulus was not consistently affected by perfusion with 100 μM cocaine (inhibition of population spike response was 50 ± 6.3%, and 42 ± 15% during perfusion with 100 μM cocaine, n = 5 slices; $P > 0.1$).

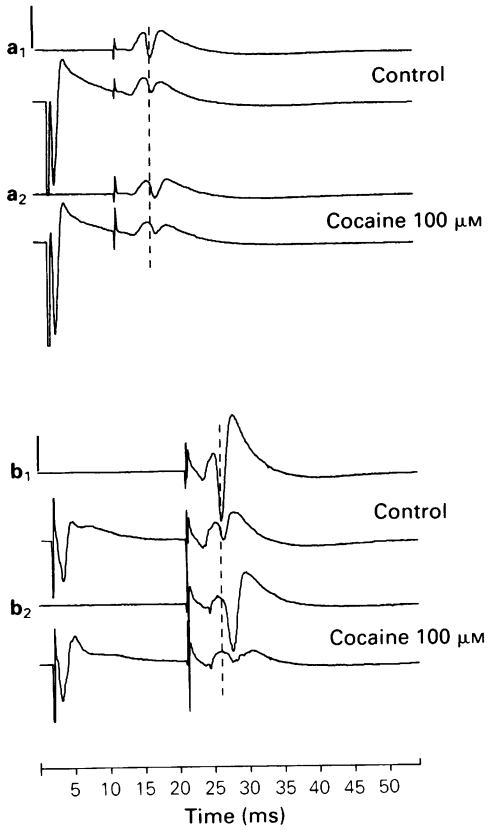

Figure 2 Effect of cocaine upon recurrent inhibition. Slices were stimulated alternately with a stimulus to the stratum radiatum (synaptic response; top record of each pair), and with a synaptic stimulus preceded by alvear stimulation either 10 (a) or 20 (b) ms before the synaptic stimulus. Slices were then exposed to 100 μM cocaine until a maximal depressant effect was achieved, and the stimulation voltages were then increased so as to approximate the pre-drug response amplitudes. Each record illustrates an average of from 13–20 responses evoked under the indicated conditions. The mean $\pm$ s.e.mean % inhibition of the population spike by the alvear stimulation under control conditions and in 100 μM cocaine, respectively, was $50 \pm 1.8\%$, $41.4 \pm 2.5\%$ (a), and $70 \pm 2.4\%$; $77 \pm 3.1\%$ (b). Although the degree of inhibition was not markedly affected by cocaine, the latency to the peak of the population spike was significantly delayed (dashed lines), and the width of the population spike was increased. Voltage calibration bars by traces in (a_1) and (b_1) are 2 mV.

We also examined the effects of cocaine on feed-forward inhibition, elicited by stimulation of a separate set of afferents to the CA1 pyramidal neurones (Figure 3a). Stimulation of these afferents at a level below the threshold for the population spike (initial response in the lower trace of a_1) resulted in a marked inhibition of the population spike response. Superfusion with 50 μM cocaine inhibited both responses, but when they were returned to approximately control values by increasing the stimulus intensity (a_2), there was if anything a greater degree of post-stimulus inhibition.

In an additional experiment, the effect of cocaine was compared to bicuculline methiodide, which blocks recurrent inhibition by antagonizing $GABA_A$-receptors (Alger & Nicoll, 1982). This often results in multiple population spikes being evoked by a single synaptic stimulus. As can be seen from Figure 3b, cocaine reduced the amplitude of the population spike and increased its latency, whereas the subsequent addition of bicuculline increased spike amplitude, shortened its latency, and elicited the characteristic multiple bursting pattern typically seen with GABA antagonists.

Interictal spikes

Interictal spikes (IIS) were produced by the addition of penicillin (1500 units ml^{-1}) to the perfusion fluid, increasing the total K^+ concentration of the medium to 8 mM, and changing the Ca^{2+} and Mg^{2+} levels to 2.0 and 1.3 mM, respectively. Penicillin interferes with GABA-mediated inhibition, and like other GABA antagonists, can induce repetitive IIS under appropriate conditions (Oliver *et al.*, 1977). As can be seen from Figure 4b, superfusion with 100 μM cocaine had a purely inhibitory effect upon the rate of IIS, with the maximal effect being a complete suppression of the IIS. Cocaine inhibited the IIS rate at all concentrations tested between 5–100 μM (Figure 5), with an IC_{50} value of 19.0 μM (95% confidence limits 13.5–26.9 μM, $n = 13$ slices). At no time either during the onset or termination of perfusion did any concentration of cocaine produce an increase in the rate of IIS, i.e., proconvulsant activity. In contrast, other agents with proconvulsant activity, such as the β-adrenoceptor agonist isoprenaline, increased IIS rates (Figure 4a).

Of the various responses measured, the rate of IIS was significantly more sensitive to the inhibitory actions of cocaine than the presynaptic fibre spike or the antidromically activated population spike response (Figure 6). It was interesting that the antidromic population spike was also significantly more sensitive to the effects of cocaine than the presynaptic fibre spike (IC_{50} values of 64 and 126 μM, respectively, 95% confidence limits 47–86 μM and 106–151 μM), since these measures presumably reflect the sensitivity of the axons of hippocampal CA3 and CA1 pyramidal neurones, respectively.

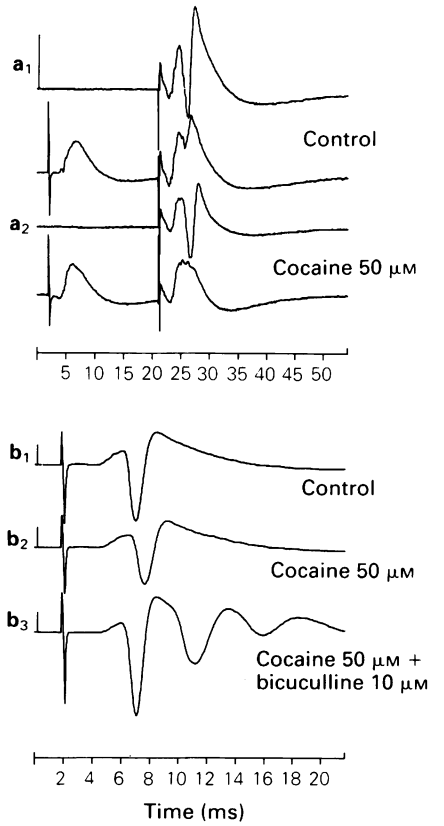

Figure 3 Effect of cocaine upon feed-forward and feed-back inhibition. (a) Slices were stimulated via orthodromically activated fibres in the striatum radiatum (a_1, a_2, upper), or by the same stimulus preceded by a low amplitude stimulus delivered to a separate set of fibres in the stratum radiatum near the border of the subiculum. The feed-forward inhibition elicited by the initial response markedly reduced the amplitude of the test population spike elicited 20 ms later. Cocaine increased the amount of inhibition in this slice ($75 \pm 4\%$ inhibition in the control, $91 \pm 3\%$ inhibition in cocaine), but the overall trend was not statistically significant ($P > 0.1$, $n = 5$ slices). The stimulation voltages required to elicit control response amplitudes in the presence of 50 μM cocaine increased from 13 to 21 volts (orthodromic population spike) and from 15 to 45 volts (antidromic pre-pulse). Calibration bar is 1 mV. (b) Orthodromically evoked population spike responses under control conditions (b_1), in the presence of 50 μM cocaine (b_2), and while superfused with 50 μM cocaine and 10 μM bicuculline (b_3). Bicuculline superfusion resulted in multiple population spikes. Similar responses were observed in another slice treated with the same protocol. Calibration bar is 1 mV.

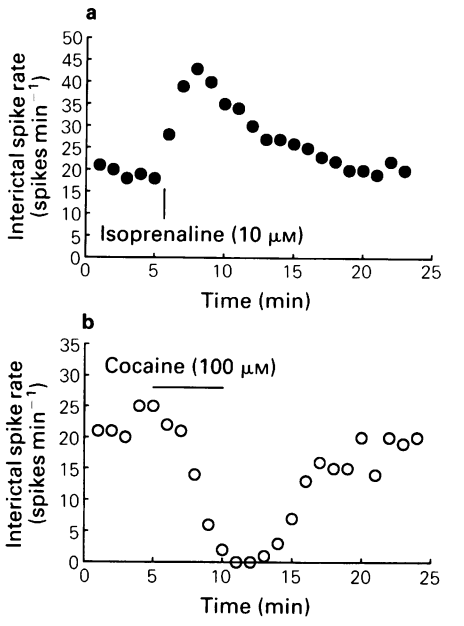

Figure 4 Effects of isoprenaline and cocaine on interictal spike (IIS) rate. Addition of isoprenaline (10 μM) to the recording chamber produces an increase in the IIS rate (a); see also Mueller & Dunwiddie (1983). However, perfusion with 100 μM cocaine (b) completely inhibited IIS. Each part of the figure represents data from 1 slice; each point represents the number of IIS that were recorded during successive 1 min intervals. Isoprenaline was added as a bolus injection to the bath, and washout begun immediately, whereas cocaine was perfused for a 5 min period at the indicated concentration.

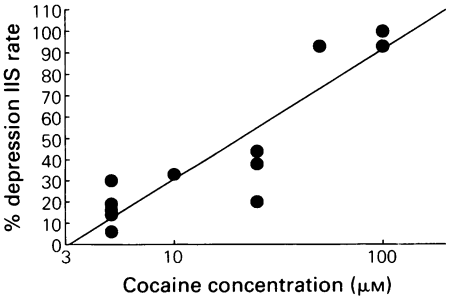

Figure 5 Concentration-response curve for cocaine on interictal spike (IIS) rate. Superfusion of slices with cocaine between 5–100 μM produced concentration-dependent decreases in IIS rate. The concentration of cocaine determined to result in a 50% inhibition of IIS rate was 19 μM (95% confidence limits 13.5–26.9 μM, $n = 13$ slices). The line was fitted using a least-squares criterion to all the data points shown.

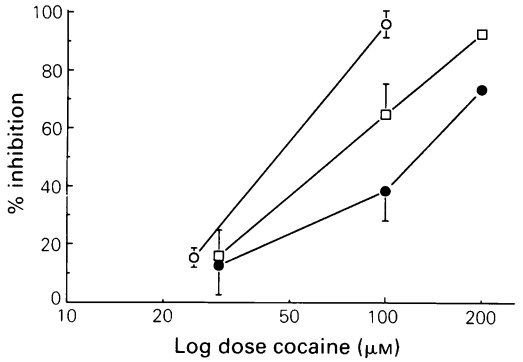

Figure 6 Concentration-response curve comparisons for the effect of cocaine on interictal spike rate (○), antidromic population spike (□), and presynaptic fibre spike (●). IC_{50} values determined from these curves were all significantly different ($P < 0.05$).

Intracellular recording studies

Because of the ambiguities in interpreting paired-pulse and antidromic-synaptic field potential responses, intracellular recordings were also used to characterize the synaptically activated inhibitory postsynaptic potentials (i.p.s.p.). The intracellularly recorded e.p.s.p. and membrane potentials were also measured. The i.p.s.p. in hippocampal neurones has been previously characterized as having two hyperpolarizing components (Newberry & Nicoll, 1984; see inset, Figure 7). The initial component, the $GABA_A$ i.p.s.p., is a hyperpolarizing, chloride-dependent, bicuculline-sensitive response to activation of GABAergic interneurones. The second component of the i.p.s.p., or late hyperpolarizing potential, is a bicuculline-insensitive component that reflects an increase in potassium conductance linked to a $GABA_B$-receptor (Dutar & Nicoll, 1988). Intracellular recording experiments revealed no significant changes in either the $GABA_A$ or the $GABA_B$ components of the i.p.s.p. following perfusion with 30 μM cocaine, but both were significantly reduced at 100 μM cocaine (Figure 7). The changes in the magnitude of the intracellularly recorded e.p.s.p. were comparable to the changes in the i.p.s.ps; as expected, the changes in the intracellular e.p.s.p. were very similar to those seen with field e.p.s.p. responses (Figure 7).

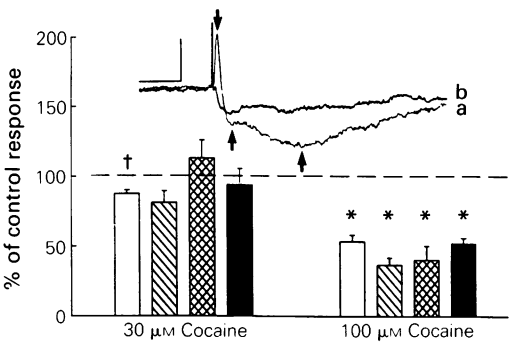

Figure 7 Effects of cocaine on intracellularly recorded excitatory postsynaptic potentials (e.p.s.ps) and inhibitory postsynaptic potentials (i.p.s.ps) of CA1 pyramidal neurones. Extracellular e.p.s.ps, and e.p.s.p./i.p.s.p. sequences recorded intracellularly were elicited by orthodromic synaptic stimulation delivered to the stratum radiatum. Extracellular e.p.s.p. responses (open columns) showed a significant concentration-dependent decrease with cocaine. At a concentration of 30 μM cocaine, there was no significant change in the amplitude of any of the intracellularly recorded parameters, but intracellular e.p.s.ps (diagonally-hatched columns), and both types of i.p.s.p. ($GABA_A$ i.p.s.p., cross-hatched columns; $GABA_B$ i.p.s.p., solid columns) were significantly reduced by 100 μM cocaine. For the intracellular studies, pre-drug and washout responses were averaged, and the mean cocaine response expressed as a % of these control values. Each column for the intracellular measures represents the mean and bars s.e.mean from between 3–7 cells; † indicates $P < 0.05$, $*P < 0.01$ vs controls. The inset shows a recording made from a pyramidal neurone that was superfused with 100 μM cocaine. The pre-drug response (trace a) shows a clearly distinguishable e.p.s.p. (first arrow), initial i.p.s.p. (2nd arrow), and secondary i.p.s.p. (third arrow). In this particular cell the e.p.s.p. was virtually abolished, and i.p.s.ps were inhibited by 27% (initial i.p.s.p.) and 53% (secondary i.p.s.p.) during cocaine superfusion. Calibration bars are 100 ms and 5 mV.

Discussion

Despite a number of investigations, the mechanism underlying the excitatory effects of local anaesthetics upon the central nervous system remains unclear. The most commonly proposed hypothesis is that local anaesthetics can selectively block activity in inhibitory pathways, and the resulting disinhibition underlies the proconvulsant effects that are observed. Several groups (Tanaka & Yamasaki, 1966; Warnick *et al.*, 1971) have demonstrated that local anaesthetics diminish locally and callosally evoked inhibition of cerebral cortical neurone firing, but do not directly interfere with the inhibitory effects of locally applied GABA. These results suggest that local anaesthetics inhibit the firing of inhibitory neurones or their axons, but do not interfere with GABAergic transmission directly. However, the interpretation of these experiments is complicated by the fact that it is difficult to determine whether these are specific

effects upon inhibitory pathways, or simply one manifestation of a generalised depressant action. In addition, some investigators have had difficulties in replicating the initial observations (see Wagman *et al.*, 1967). Furthermore, while these studies provide a basis for excessive neuronal activity in the cortex, the cortex does not seem to be primarily involved in local anaesthetic-induced epileptiform activity (e.g., Wagman *et al.*, 1967). Local applications of anaesthetics to the cortex typically suppress epileptiform activity (Julien, 1973; Garfield & Gugino, 1987).

There have been relatively few studies that have characterized effects that can be localised directly in the hippocampus. One study has suggested that systemic administration of procaine can diminish recurrent inhibition in the dentate gyrus of cats (Adamec *et al.*, 1985), but was based upon a paradigm in which it is difficult to attribute changes directly to alterations in inhibition. The present studies clearly do not support the hypothesis that cocaine's proconvulsant effects reflect a selective action upon local inhibitory circuitry, at least within the CA1 region. First, cocaine did not mimic the effects of bicuculline, a drug that is known to interfere with synaptic inhibition. Second, cocaine did not occlude the responses to bicuculline, as would have been expected if they both reduced inhibition. In addition, both the intracellular recordings of i.p.s.ps, and the extracellular investigations of both the feed-forward and feedback inhibitory pathways, suggested that cocaine had depressant effects of similar magnitude upon both excitatory and inhibitory circuitry. The intracellular studies indicated that cocaine reduced both i.p.s.ps and e.p.s.ps with no selectivity for either response. Interpretation of the results of the extracellular studies is less certain, because it was necessary in every case to increase the stimulation intensity during cocaine superfusion in order to maintain constant amplitude test responses. Nevertheless, it was clear that there were no large changes in inhibition such as might have been expected on the basis of previous studies.

To circumvent the difficulties associated with electrical activation of inhibitory circuits, we also examined the effects of cocaine upon interictal spiking; in this model of hippocampal hyperexcitability, only anticonvulsant actions of cocaine were observed. These results are consistent with previous observations of anticonvulsant effects of lidocaine in a penicillin seizure model in the cortex (Julien, 1973), and with the more general observation that anticonvulsant effects of local anaesthetics are observed at low doses, and under conditions where the proconvulsant effects of local anaesthetics are blocked (Sanders, 1967; Garfield & Gugino, 1987). However, they contrast with the findings of Babb *et al.* (1979), that procaine activates hippocampal seizure foci produced by aluminium hydroxide injections in monkeys.

Regardless of the mechanism that underlies the proconvulsant effects of cocaine, the present studies suggest that such effects are not due to any action upon intrinsic hippocampal circuitry. However, it remains possible that cocaine modulates an extrinsic pathway to the hippocampus, such as the noradrenergic input from the locus coeruleus. Activation of β-adrenoceptors has a proconvulsant effect in the hippocampus, and increases the rate of IIS (Mueller & Dunwiddie, 1983; see also Figure 3). Since cocaine can potentiate the effects of bath perfused noradrenaline (Yasuda *et al.*, 1984), a similar action upon synaptically released noradrenaline might lead to proconvulsant effects. Nevertheless, such a mechanism would apply only to cocaine, but not to other local anaesthetics that lack the ability to inhibit the uptake of noradrenaline.

In summary, although systemic administration of cocaine and other local anaesthetics does induce seizure activity in intact animals, it would appear unlikely that this reflects a direct action upon the hippocampus. In addition, the hypothesis that local anaesthetics have a selective inhibitory action upon inhibitory circuitry (Ritchie & Green, 1985) is not consistent with our observations. The finding that the presynaptic fibre spike associated with activation of the Schaffer and commissural afferents was significantly less sensitive to the local anaesthetic effects of cocaine than the antidromic population spike response (Figure 6), suggests that subpopulations of axons in the central nervous system may differ in their sensitivities to local anaesthetics. However, because the fibre spike is essentially a compound action potential, whereas the population spike involves the antidromic invasion of a population of neurones, they may not be directly comparable. If cocaine were more potent in inhibiting the activity of selected subpopulations of axons, then this might result in the suppression of activity in critical inhibitory pathways, which could then lead to the seizure activity that is typical of this as well as other local anaesthetic drugs.

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References

ADAMEC, R.E., STARK-ADAMEC, C., SAINT-HILLAIRE, J.-M. & LIVINGSTON, K.E. (1985). Basic science and clinical aspects of procaine HCl as a limbic system excitant. *Prog. Neuro-Psychopharmacol. Biol. Psychiat.*, **9**, 109–119.

ALGER, B.E. & NICOLL, R.A. (1982). Pharmacological evidence for two kinds of GABA receptor on rat hippocampal pyramidal cells studied *in vitro*. *J. Physiol.*, **328**, 125–141.

BABB, T.L., PERRYMAN, K.M., LIEB, J.P., FINCH, D.M. & CRANDALL, P.H. (1979). Procaine-induced seizures in epileptic monkeys with bilateral hippocampal foci. *Electroencephalog. Clin. Neurophysiol.*, **47**, 725–737.

DE JONG, R.H. (1977). Central nervous system effects. In *Local Anesthetics*, 2nd edn. pp. 84–114. Springfield, Ill.: Thomas.

DUNWIDDIE, T.V. & LYNCH, G.S. (1978). Long-term potentiation and depression of synaptic responses in the rat hippocampus: Localization and frequency dependency. *J. Physiol.*, **276**, 363–367.

DUTAR, P. & NICOLL, R.A. (1988). A physiological role for $GABA_B$ receptors in the central nervous system. *Nature*, **332**, 156–158.

FORD, R.D. & BALSTER, R.L. (1977). Reinforcing properties of intravenous procaine in rhesus monkeys. *Pharmacol. Biochem. Behav.*, **6**, 289–296.

GARFIELD, J.M. & GUGINO, L. (1987). Central effects of local anesthetics. In *Local Anesthetics*, ed. Strichartz, G. pp. 253–284, Berlin: Springer-Verlag.

INGVAR, M. & SHAPIRO, H.M. (1981). Selective metabolic activation of the hippocampus during lidocaine induced pre-seizure activity. *Anesthesiology*, **54**, 33–37.

JULIEN, R.M. (1973). Lidocaine in experimental epilepsy: correlation of anticonvulsant effect with blood concentrations. *Electroenceph. Cline Neurophysiol.*, **34**, 639–645.

MUELLER, A.L. & DUNWIDDIE, T.V. (1983). Anticonvulsant and proconvulsant actions of alpha- and beta-noradrenergic agonists on epileptiform activity in rat hippocampus *in vitro*. *Epilepsia*, **24**, 57–64.

MUNSON, E.S., TUCKER, W., AUSINSCH, B. & MALAGODI, M. (1975). Etidocaine, bupivacaine, lidocaine seizures thresholds in monkeys. *Anesthesiology*, **42**, 471–478.

NEWBERRY, N.R. & NICOLL, R.A. (1984). A bicuculline-resistant inhibitory post-synaptic potential in rat hippocampal pyramidal cells *in vitro*. *J. Physiol.*, **348**, 239–254.

OLIVER, A.P., HOFFER, B.J. & WYATT, R.J. (1977). The hippocampal slice: a system for studying the pharmacology of seizures and for screening anticonvulsant drugs. *Epilepsia*, **18**, 543–548.

RITCHIE, J.M. & GREEN, N.M. (1985). Local anesthetics. In *The Pharmacological Basis of Therapeutics*, ed. Gilman, A.G., Goodman, L.S., Rall, T.W. & Murad, F. pp. 302–321, New York: MacMillan.

RITZ, M.C., LAMB, R.J., GOLDBERG, S.R. & KUHAR, M.J. (1987). Cocaine receptors on dopamine transporters are related to self-administration of cocaine. *Science*, **237**, 1219–1223.

SANDERS, H.D. (1967). A comparison of the convulsant activity of procaine and pentylene tetrazol. *Arch. Int. Pharmacodyn. Ther.*, **170**, 165–177.

SCHOLFIELD, C.N. & HARVEY, J.A. (1975). Local anesthetics and barbiturates: effects on evoked potentials in isolated mammalian cortex. *J. Pharmacol. Exp. Ther.*, **195**, 522–531.

STRIPLING, J.S. & ELLINWOOD, E.H. (1977). Potentiation with behavioural and convulsant effects of cocaine by chronic administration in rats. *Pharmacol. Biochem. Behav.*, **6**, 571–579.

TANAKA, K. & YAMASAKI, M. (1966). Blocking of cortical inhibitory synapses by intravenous lidocaine. *Nature*, **209**, 207–208.

WAGMAN, I.H., DE JONG, R.H. & PRINCE, D.A. (1967). Effects of lidocaine on the central nervous system. *Anesthesiol.*, **28**, 155–168.

WARNICK, J.E., KEE, R.D. & YIM, G.K.W. (1971). The effects of lidocaine on inhibition in the cerebral cortex. *Anesthesiol.*, **34**, 327–332.

YASUDA, R.P., ZAHNISER, N.R. & DUNWIDDIE, T.V. (1984). Electrophysiological effects of cocaine in the rat hippocampus *in vitro*. *Neurosci. Letts*, **45**, 199–204.

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