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Comparison of σ- and κ- opiate receptor ligands as excitatory amino acid antagonists

S.C. Berry, S.L. Dawkins & D. Lodge

Department of Physiology, Royal Veterinary College, London NW1 OTU

1 Using the technique of microelectrophoresis in pentobarbitone-anaesthetized cats and rats, the effects of benzomorphans, with known actions at σ- and κ- opioid receptors, were tested on responses of spinal neurones to amino acids and acetylcholine.

2 The racemic mixture and both enantiomers of the sigma opiate receptor agonist, *N*-allylnormetazocine (SKF 10, 047), and the dissociative anaesthetic, ketamine, reduced or abolished excitation evoked by N-methyl-aspartate (NMA) with only small and variable effects on responses to quisqualate or kainate. (+)-SKF 10, 047 was 1.2 ± 0.7 times more potent than the (−) enantiomer in antagonizing NMA.

3 On Renshaw cells, (+)-SKF 10,047 enhanced responses to acetylcholine whereas the (−) enantiomer produced only a small reduction.

4 The κ- opiate receptor agonist, ethylketocyclazocine, had no selective effects on responses to amino acids or to acetylcholine.

5 We conclude that actions at σ- but not κ-, opiate receptors are responsible for the NMA antagonism observed with benzomorphans.

Introduction

Dissociative anaesthetics such as phencyclidine and ketamine, and σ- opioid benzomorphans such as cyclazocine and N-allylnormetazocine (SKF 10,047), have several pharmacological properties in common. For example, both groups of drugs are capable of inducing in man psychotic syndromes characterized by dizziness, catatonia, dysphoria and hallucinations (Martin *et al.*, 1976; Domino & Luby, 1981; Aniline, 1982). Animals cannot discriminate between the subjective effects produced by drugs from these two groups (Herling & Woods, 1981; Shearman & Herz, 1982; Shannon, 1983). In the chronic spinal dog, drugs from both these groups act in a similar way (Jasinski *et al.*, 1981). Furthermore, dissociative anaesthetics and σ- opiate receptor agonists appear to share a common binding site in brain tissue (Zukin & Zukin, 1979; 1981; Quirion *et al.*, 1981).

In tests examining the sensitivity of spinal and other central neurones to putative excitatory amino acid neurotransmitters and their analogues, we have found that phencyclidine and ketamine selectively and stereospecifically block excitation mediated through receptors which are activated by N-methyl-aspartate (NMA; Lodge *et al.*, 1982; Anis *et al.*, 1983a; Berry *et al.*, 1983). Such NMA receptors are thought to play a role in synaptic excitation in several areas of the mammalian central nervous system (Watkins & Evans, 1981). Initial studies have shown that cyclazocine, which has actions at μ- κ- and σ- opiate receptors (Martin *et al.*, 1976; Zukin & Zukin, 1981), also selectively blocked the action of NMA, but the μ- receptor ligands, morphine and naloxone, were without effect (Anis *et al.*, 1983b). In order to elucidate potential correlations between NMA antagonism and the reported behavioural and neurochemical actions common to both dissociative anaesthetics and σ- receptor agonists and in order to eliminate the possibility that κ- receptor agonists also selectively reduce the actions of NMA, it seemed important to compare the effects of such drugs as amino acid antagonists. We therefore set out to test the actions of a classical σ- receptor agonist, SKF 10,047, a classical κ- receptor agonist, ethylketocyclazocine, and the dissociative anaesthetic, ketamine, on the sensitivity of spinal neurones to NMA, quisqualate and kainate. These three excitatory amino acids are used to classify synaptic receptors in the mammalian central nervous system (Watkins & Evans, 1981). Our results, which have been com-

municated in a preliminary form (Allan et al., 1984; Lodge & Berry, 1984), indicate that of the drugs tested only those which are known to act at the σ-receptor selectively antagonize NMA.

Methods

A full description of the methods employed has been published recently (Anis et al., 1983a). In brief, extracellular multibarrelled glass microelectrodes were used to record action potentials of spinal neurones in cats and rats initially anaesthetized with an intraperitoneal injection of pentobarbitone (35 and 50 mg kg^{-1} respectively; supplemented intravenously as necessary). The spontaneous firing rate of single neurones and the responses evoked by microelectrophoretic administration of excitants were monitored continuously. Once submaximal and reproducible responses to NMA, quisqualate, kainate and, in the case of Renshaw cells indentified by venral root (VR) stimulation, acetylcholine had been established, the effects of electrophoretic and occasionally intravenous (i.v.) administration of the test substances were examined. The results are expressed as the % change from values of peak firing rate.

Potency comparisons between NMA antagonists were made by expressing the ratio of the reduction of the response to NMA by equal ejecting currents of the antagonists. Allowance for different dilutions of drugs in the electrode were made as is usual for microelectrophoretic experiments (eg. Krogsgaard-Larsen et al., 1980). Comparisons from individual cells were pooled and the mean and standard deviation presented. Since the data do not meet the criteria for parametric statistical analysis, significance of selectivity of amino acid antagonism was assessed using the Wilcoxon matched pairs signed ranks test, in which differences between reductions of responses to NMA and those to quisqualate or kainate were given a rank and sign.

Each of five outer barrels of the electrode were filled with one of the following solutions:- N-methyl-DL-aspartate Na (NMA; 200 nM, pH 8.1), quisqualate Na (5 mM in 200 mM NaCl, pH 7.8), kainate Na (5 mM in 200 mM NaCl, pH 8.2), quinolinate Na (200 mM, pH 7.5), acetylcholine Cl (ACh; 200 mM, pH 5.5), ketamine HCl (50 mM in 150 mM NaCl, pH 4.8), (±) −, (+) − and (−) −N-allylnormetazocine HCl (SKF 10,047; 25 mM in 175 mM NaCl, pH 3.6) and ethylketocyclazocine methanesulphonate (EKC; 10 mM in 100 mM NaCl, pH 4.0). The sixth outer barrel was used for automatic current balancing.

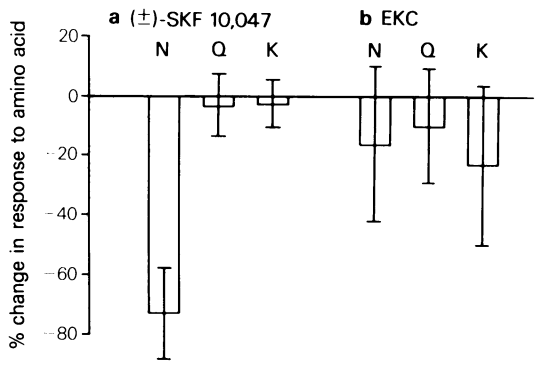

Figure 1 The effects of (±)-SKF 10,047 and ethylketocyclazocine (EKC) on the actions of excitatory amino acids from 46 cat spinal neurones. Each vertical column represents the mean change in response to the agonists N-methyl-DL-aspartate (N) quisqualate (Q), or kainate (K). Vertical lines show s.d. (a) The selective effects of (+)-SKF 10,047 (25 mM in 175 mM NaCl) on N-methyl-aspartate-evoked excitations and (b) the weak non-selective effects of EKC. Ordinate: change in firing rate expressed as a % of control responses.

Results

Comparison of the effects of (±)-SKF 10,047 and EKC

Records showing the effects of (±)-SKF 10,047, EKC and ketamine were obtained from 46 cat and 24 rat spinal neurones, which included 8 cat Renshaw cells. (±)-SKF 10,047, like ketamine, selectively reduced responses of neurones to NMA, and not those to quisqualate, kainate or acetylcholine, whereas EKC showed no such selectivity.

On 36 cat spinal neurones, (±)-SKF 10,047, ejected with currents of 10 ± 5 nA (mean ± s.d.), reduced responses to NMA by 73 ± 15% with almost no effect on those to quisqualate and to kainate. By comparison, EKC (21 ± 13nA) reduced responses to NMA by only 16 ± 26% with responses to quisqualate and kainate being reduced to an equivalent extent. Similarly on 18 rat neurones (±)-SKF 10,047 and EKC reduced responses to NMA by 79 ± 17% and 9 ± 18%, respectively. Data from the cat neurones are presented in Figure 1. The selective reduction of responses to NMA observed with SKF 10,047 was not accompanied by any obvious changes in action potential amplitude or configuration. Recovery from NMA antagonism was usually complete 10–20 min after stopping the ejection of (±)-SKF 10,047. Using the Wilcoxon matched pairs signed ranks test, SKF 10,047 reduced NMA to a greater extent than quisqualate or kainate ($P < 0.01$).

On the other hand, ejection of EKC often caused a reduction in action potential amplitude. It was there-

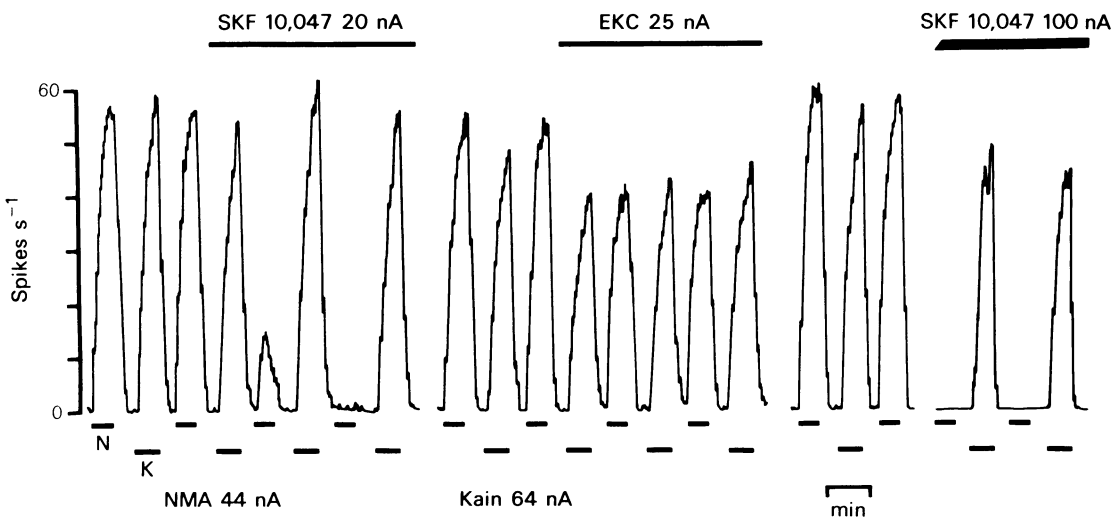

Figure 2 Effect of (±)-SKF 10,047 and ethylketocyclazocine (EKC) on responses of a cat spinal neurone to excitatory amino acids. The record shows the increase in firing rate in response to the ejection of N-methyl-DL-aspartate (NMA), 44nA (N) and of kainate (Kain), 64nA (K). Ejection of (±)-SKF 10,047, 20nA for 5 min resulted in abolition of the response to NMA. Full recovery had occurred 8 min after terminating the ejection of (±)-SKF 10,047. The ejection of EKC, 25nA for 5 min resulted in a small non-selective reduction in responses to both NMA and kainate, recovery being observed some 4 min later. Increasing the (±)-SKF 10,047 ejecting current to 100nA caused a 20% reduction in the response to kainate with complete abolition of the action of NMA. Ordinate scale: firing rate in spikes s^{-1}. Abscissa scale: time. Calibration bar = 1 min.

fore necessary to take particular care in monitoring the accuracy of the electronic counting procedure during the ejection of EKC. However, with doses of EKC ranging from those having no effect to those producing considerable reduction of action potential amplitude, no consistent selective effect between amino acid responses was observed (Wilcoxon test: $P > 0.1$). Recovery from both the action potential-reducing effect and the non-selective suppression of responses to the amino acids was usually complete within one or two minutes of stopping its ejection.

Direct comparisons of the effects of (±)-SKF 10,047 and EKC were made on 23 and 13 of these cat and rat neurones, respectively. Whereas (±)-SKF 10,047 invariably produced a selective reduction of NMA-induced excitations, EKC did so only on two occasions. An example of the effects of (±)-SKF 10,047 and EKC on responses of a cat neurone to NMA and kainate is presented in Figure 2; this shows selective and non-selective effects of the σ- and κ-receptor ligands, respectively, on responses to excitatory amino acids. In a previous test on this neurone, 10 nA of (±)-SKF 10,047 was just sufficient to abolish completely the action of NMA and, in Figure 2, it can be seen that a 10 times greater ejecting current was still selective.

On 4 neurones we also examined the possibility that EKC might interfere with the ability of (±)-SKF 10,047 to produce NMA antagonism. Even if ejection of EKC was commenced before or during that of (±)-SKF 10,047, this latter benzomorphan still produced a selective antagonism of NMA. No evidence for any interaction between EKC and (±)-SKF 10,047 was obtained.

The effects of ketamine, examined on 15 of the above cat cells, were found to be similar to those found previously for ketamine (Anis *et al.*, 1983a) and to those of (±)-SKF 10,047 described above, both in terms of specificity and duration of action. With 10 cells on which (±)-SKF 10,047 and ketamine were ejected with equal currents, (±)-SKF 10,047 was calculated to be 2.6 ± 1.9 times more potent than ketamine as an NMA antagonist.

On Renshaw cells, (±)-SKF 10,047 and EKC exhibited similar selectivity as amino acid antagonists to that described above. Excitation evoked by acetylcholine was largely unaffected by either benzomorphan. The mean effects on acetylcholine responses were an increase of 4 ± 15% during the ejection of (±)-SKF 10,047 and a decrease of 4 ± 8% during that of EKC.

Systemically administered (±)-SKF 10,047 also resulted in a selective reduction of NMA-induced excitation on both cells on which this was tested. Slow intravenous injection of 2 mg kg^{-1} resulted in a halving of the NMA responses with only minor and

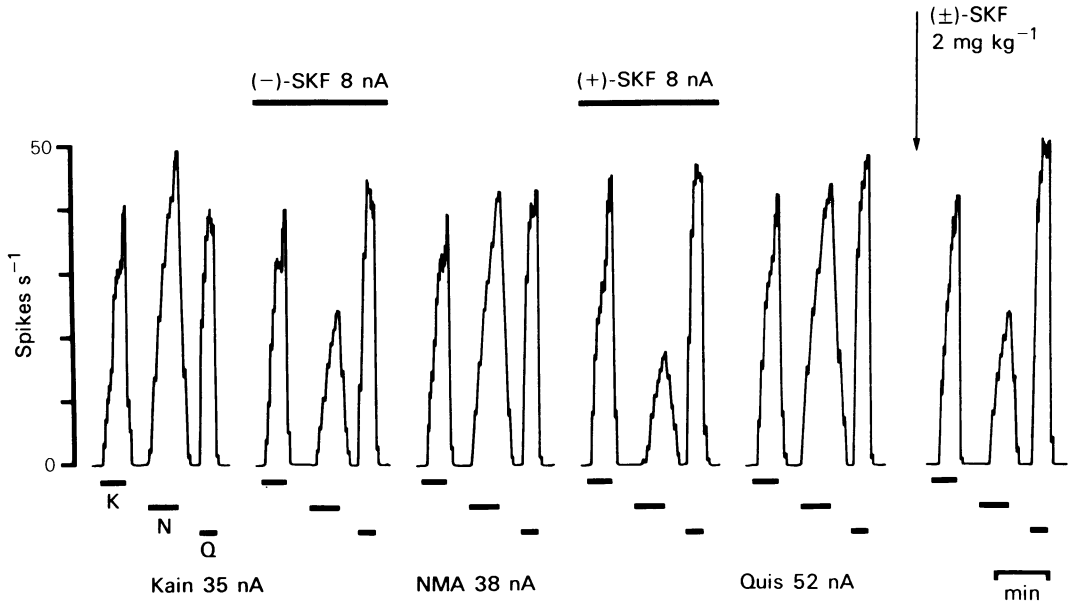

Figure 3 Effects of electrophoretically administered (+)- and (−)-SKF 10,047 and intravenous (±)-SKF 10,047 on the response of a cat spinal neurone to excitatory amino acids. The record shows increases in firing rate produced by the ejection of kainate (Kain) 35nA (K), N-methyl-DL-aspartate (NMA) 38nA (N) and quisqualate (Quis) 52nA (Q). From left to right the six traces show control responses, responses during the ejection of (−)-SKF 10,047, 8nA for 6 min, responses 7 min after stopping the ejection of (−)-SKF 10,047, responses during the ejection of (+)-SKF 10,047, 8nA for 6 min, responses 15 min after stopping the ejection of (+)-SKF 10,047 and responses 4 min after giving (±)-SKF 10,047 2 mg kg^{-1} i.v. A further 3 mg kg^{-1} of (±)-SKF 10,047 resulted in an 80% reduction in the NMA responses and recovery to about half control values was observed over the subsequent 70 min. Ordinate scale: firing rate in spikes s^{-1}. Abscissa scale: time. Calibration bar = 1 min.

variable effects on responses to other excitants. Recovery was slow, requiring about 3 h. By contrast, EKC, administered in increasing doses up to 2 mg kg^{-1} intravenously showed no tendency to reduce responses to NMA. The effects of intravenous (±)-SKF 10,047 on responses of a cat spinal neurone to amino acids are shown in Figure 3. The selective reduction of NMA action observed on this neurone following systemic administration of the racemic mixture is similar to that seen during the local ejection of the separated enantiomers of this σ-receptor agonist.

Comparison of enantiomers of SKF 10,047

The actions of (+) and (−) isomers of SKF 10,047 were compared on 12 cat spinal neurones which included 6 Renshaw cells. Both enantiomers selectively reduced responses to NMA and had little or no effect on responses to quisqualate. Compared on individual cells using the same ejecting currents, the (+) enantiomer was 1.2 ± 0.72 times more potent than the (−) enantiomer as an NMA antagonist. Figure 3 illustrates the comparative effects of the enantiomers of SKF 10,047 on amino acid-evoked excitations of a cat dorsal horn neurone. Such effects of (+)-and (−)-SKF 10,047 are presented as histograms in Figure 4. With 3 of these cells we also examined the actions of (+)- and (−)-SKF 10,047 on excitations evoked by quinolinate, a selective NMA agonist (Perkins & Stone 1983). We found that such excitations were reduced by 60–90% whereas excitations evoked by quisqualate were almost unaffected. On these cells (+)-SKF 10,047 was 1.5–3 times more potent than the (−) enantiomer as a quinolinate antagonist.

With the Renshaw cells, the two enantiomers had similar selective effects on amino acid evoked excitations, but their effects on responses of these neurones to acetylcholine were quite different. (+)-SKF 10,047 reversibly enhanced the action of acetylcholine by about 50% on 5 of the 6 Renshaw cells tested whereas responses to acetylcholine were largely unaffected by the (−) enantiomer. These effects on responses to acetycholine are shown in Figure 4. Records showing the stereoselective effects of SKF 10,047 on acetylcholine-evoked excitations have been illustrated previously (Lodge & Berry, 1984).

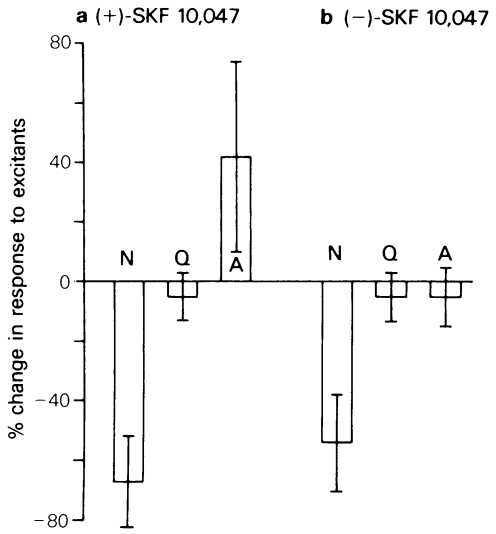

Figure 4 The effects of (+)- and (−)-SKF 10,047 on the actions of excitatory amino acids and acetylcholine from 12 cat spinal reurones. (a) Shows that (+)-SKF 10,047 (10±6nA) reduced responses to N-methyl-aspartate (N), had little effect on responses to quisqualate (Q) and enhanced responses to acetylcholine (A), whereas (b) shows that (−)-SKF 10,047 (12±7nA) resulted in a selective reduction of responses to NMA with only small effects on responses to quisqualate and acetylcholine.

Discussion

Our results clearly show that racemic SKF 10,047, but not EKC, is a potent and selective NMA antagonist. Although (±)-SKF 10,047 may have some effects at κ-opiate receptors beside the predominant action at σ-receptors, it seems that EKC is devoid of σ-receptor agonist (or phencyclidine-like) actions (Martin *et al.*, 1976; Jasinski *et al.*, 1981). It would therefore appear that the antagonism of NMA by SKF 10,047 as described here, as well as that by cyclazocine (Anis *et al.*, 1983b), are related to actions at the σ-opiate receptor as defined by Martin *et al.*, (1976). Furthermore the intravenous dose of (±)-SKF 10,047 required for antagonism of NMA is similar to that used in other whole animal studies (e.g. Martin *et al.*, 1976; Shannon, 1983) and the relative potencies of the drugs tested as NMA antagonists parallel their potency in both discrimination (Herling & Woods, 1981; Shearman & Herz, 1982 Shannon, 1983) and binding studies (Zukin & Zukin, 1979; 1981; Quirion *et al.*, 1981).

The somewhat greater potency of (+)- relative to (−)-SKF 10,047 as an NMA antagonist is also similar to that described in σ-receptor binding (Hampton *et al.*, 1982), behavioural (Shearman & Herz, 1982; Shannon, 1983) and neurophysiological (Vaupel, 1982) studies. Furthermore the finding that (−)-, but not (+)-, SKF 10,047 has some κ- receptor agonist activity (Herling & Shannon, 1982), and yet this former enantiomer is weaker as an NMA antagonist, supports the view that actions at κ- receptors are unrelated to NMA antagonism.

The present observation that (±)- SKF 10,047 did not reduce the actions of acetylcholine differs from the acetylcholine antagonist effects of ketamine and phencyclidine (see Anis *et al.*, 1983a), although all three of these are NMA antagonists and share some behavioural properties. Similarly the enantiomers of SKF 10,047 whilst having equivalent effects in discrimination studies (Sherman & Herz, 1982; Shannon, 1983), have disparate effects on Renshaw cells, the (+) enantiomer enhancing, and the (−) enantiomer reducing, responses to acetylcholine. These effects may in part be explained by the differential effects of the two enantiomers on cholinergic systems *in vitro*, (+)-SKF 10,047 being more potent than (−)-SKF 10,047 as an inhibitor of acetylcholinesterase, and (−)-SKF 10,047 more potent than (+)-SKF 10,047 as a muscarinic antagonist (Johnson & Hillman, 1982). Thus since σ-receptor agonists can reduce, enhance or have no effect on the sensitivity of central neurones to acetylcholine, it seems unlikely that actions on cholinergic systems are causally related to the behavioural effects common to such drugs (see also Lodge *et al.*, 1981; Berry *et al.*, 1983).

Our results are consistent with the hypothesis that σ-receptor agonists and dissociative anaesthetics share a common binding site (Zukin & Zukin, 1979; 1981; Quirion *et al.*, 1981), and further suggest that this site is related to the NMA receptor-ionophore complex. However, it seems unlikely that these NMA antagonists bind to the NMA recognition site, as amino acids including NMA receptor agonists, do not displace phencyclidine binding (Zukin & Zukin, 1979; Quirion *et al.*, 1981; and personal communications from these authors), ketamine does not displace binding of the competitive NMA antagonist, 2-aminophosphonovalerate (Watkins, personal communication) and NMA antagonism by ketamine on the frog spinal cord *in vitro* (Martin & Lodge, unpublished observations) and on acetylcholine release from rat cerebral cortex *in vitro* (Johnston & Lodge, 1984) appears to be non-competitive. It is therefore probable that the site of action of dissociative anaesthetics and benzomorphans with actions at σ-receptors is not the NMA recognition site but rather a subsequent step in the process which leads to the change in membrane excitability.

The good correlation between drugs having phencyclidine-like behavioural effects and NMA antagonism may suggest a causal relationship. That

NMA receptors mediate some synaptic excitations appears to be well established (Watkins & Evans, 1981); furthermore such receptors seem to be important in some of the pathways that transfer information into, within and out of the cerebral cortices (e.g. Stone, 1979; Martin, 1980; Kemp & Sillito, 1982; Hicks & Guedes, 1983). It seems likely then that drugs which interfere with information transfer at such sites will produce abnormalities of perception and behaviour, a prediction consistent with the psychotomimetic effects produced in man by both dissociative anaesthetics and benzomorphans with actions at σ-receptors (see Introduction).

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