"*I would have everie man write what he knowes and no more.*"—MONTAIGNE

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EDITORIAL

Ketamine: its mechanism(s) of action and unusual clinical uses

Since Domino, Chidiff and Corssen[1] reported the first clinical use of ketamine more than 30 yr ago, there have been many clinical and laboratory studies to determine both its mechanism(s) of action and define the most appropriate clinical use of this unusual anaesthetic agent. Although disturbing emergence reactions are associated with its use, ketamine has several clinically useful properties, including analgesia and less cardiorespiratory depressant effects than other anaesthetic agents, in fact it causes some stimulation of the cardiovascular system[1,2]. Clinically, ketamine has been reported to produce not only general but also local anaesthesia[3–5]. It also interacts with *N*-methyl-D-aspartate (NMDA) receptors[6–8], opioid receptors[9,10], monoaminergic receptors[11], muscarinic receptors[10,12,13] and voltage-sensitive Ca^{2+} channels[14,15]. However, unlike other general anaesthetic agents, ketamine does not interact with GABA receptors[16]. Clinically, ketamine is administered as a racemate composed of two optical isomers, S(+) and R(−), and there are some pharmacological differences between these[2] (see below).

In this editorial, in addition to the well established NMDA receptor inhibition, we review other potential pharmacological targets for ketamine and discuss the unusual clinical uses of this agent.

NMDA RECEPTOR ANTAGONISM

The NMDA receptor, a member of the glutamate receptor family, is an example of an ion channel-coupled receptor with excitatory properties[17] which has been implicated in the mechanism of general anaesthesia[16], analgesia[18] and also in neurotoxicity[7]. Ketamine is a non-competitive antagonist of the NMDA receptor Ca^{2+} channel pore[7]. In addition, at clinically relevant concentrations, ketamine interacts with the phencyclidine (PCP) binding site[9] leading to significant inhibition of NMDA receptor activity[8]; this occurs only when the channel has been opened[18]. This interaction with the PCP binding site appears to be stereoselective with affinity (K_i) values of 3.2 μmol litre^{-1} and 1.1 μmol litre^{-1} for S(+) and R(−) ketamine, respectively. An *in vivo* study in the lamprey eel[19] also showed that ketamine inhibits NMDA receptor-mediated neuronal events by 50 % (IC_{50}) at 10–20 μmol litre^{-1}.

ANALGESIA AND INTERACTIONS WITH OPIOID RECEPTORS

Ketamine has been reported to interact with mu (μ), delta (δ) and kappa (κ) opioid receptors[10]. It has been shown *in vivo* that S(+)ketamine is 2–3 times more potent than R(−) ketamine as an analgesic[2]. In agreement with these clinical observations, it has been shown that ketamine produces 2–3 fold stereoselectivity at μ and κ receptors but not at δ receptors[10]. The interaction with opioid receptors is clearly complex and several studies[10,20] have suggested that ketamine may be an antagonist at μ receptors and an agonist at κ receptors. Smith and colleagues[20] found that morphine but not ketamine analgesia was antagonized by microinjection of naloxone into the periaqueductal grey (PAG) region of the rat brain, which contains μ but not κ receptors. Moreover, microinjection of ketamine into the PAG did not produce analgesia but antagonized the effects of morphine. These observations suggest that the analgesic effects of ketamine are not mediated via μ opioid receptors in the CNS. Clearly, further detailed studies with δ and κ agonists are required. While the σ receptor is no longer classified as an opioid receptor, ketamine also interacts with this receptor although the interaction is weak ($\mu > \kappa > \sigma > \delta$) and stereoselectivity is reversed: S(+) < R(−)[10].

ANALGESIA AND MONOAMINERGIC RECEPTORS

Crisp and colleagues found that ketamine (3.0 μmol litre^{-1})-induced spinal analgesia, measured as an increase in tail flick latency in rats, was reversed dose-dependently by administration of s.c. methysergide (serotonin antagonist), phentolamine (α-adrenoceptor antagonist) and naloxone (IC_{50} values 8.0 μg kg^{-1}, 0.88 mg kg^{-1} and 3.0 mg kg^{-1}, respectively)[11]. However, they also found that spinal ketamine did not increase tail-flick latency in rats with bilateral dorsal funiculus lesions (DFL) in a system where morphine was effective. These data suggest that the antinociceptive action of ketamine may involve descending inhibitory monoaminergic pain pathways. One possible flaw in this argument is that ketamine-sensitive opioid receptors on interneurones modulating descending antinociceptive pathways could not be excluded. Specifically, is the naloxone reversible action of ketamine secondary to its ability to interact with interneurones to block amine uptake, that is indirect?

LOCAL ANAESTHETIC ACTION

It is known that ketamine at high doses possesses local anaesthetic properties and these have been compared with lignocaine and procaine[3]. For example, spinal administration of 1.25 % ketamine and lignocaine in dogs produced rapid, reversible and predictable segmental paralysis without any apparent reduction in consciousness[3]. In addition, ketamine and procaine inhibited, with identical IC_{50} values, the compound action potential of the frog sciatic

nerve preparation[3]. In agreement with the mechanism of action of local anaesthetic agents, it has been shown that high-dose ketamine blocks Na^+ channels in frog neurones and in lipid bilayers (containing human Na^+ channels) with IC_{50} values in the mmol litre^{-1} range[21 22]. Moreover, Durrani and colleagues reported that ketamine (>0.3%) produced adequate i.v. regional anaesthesia with complete sympathetic, sensory and motor block[5].

MUSCARINIC RECEPTORS

Ketamine anaesthesia is antagonized by anticholinesterase agents[12] which increase endogenous acetylcholine concentrations and there is evidence for an interaction of ketamine with muscarinic receptors[10 13]. Indeed, ketamine produced stereoselective interaction with muscarinic receptors in guineapig brain membranes in a series of binding experiments (K_i of S(+) and R(−)ketamine: 20 and 37 μmol litre^{-1}, respectively). In addition, Durieux[13] reported that clinically relevant concentrations of ketamine inhibited muscarinic signalling through M1 receptors expressed in *Xenopus* oocytes (IC_{50} 5.7 μmol litre^{-1}), the most prominent subtype in the cortex and hippocampus. Whether ketamine is an agonist or antagonist is unclear. However, as ketamine produces anticholinergic symptoms (postanaesthetic delirium, bronchodilatation and a sympathomimetic action) and ketamine anaesthesia is reversed by anticholinesterases, an antagonist action is likely.

VOLTAGE-SENSITIVE CA^{2+} CHANNELS (VSCC)

Interaction of ketamine with voltage-sensitive Ca^{2+} channels (VSCC) has not been studied extensively. Baum and Tecson[14] reported a small reduction (20%) in the peak current in guineapig myocardium with ketamine 10 and 100 μmol litre^{-1}. In addition, Yamakage, Hirshman and Croxton[15] reported that ketamine (>10 μmol litre^{-1}, IC_{50} 1 mmol litre^{-1}) significantly reduced the peak Ca^{2+} current in porcine tracheal smooth muscle cells. We have demonstrated previously, in cultured neuroblastoma cells, that ketamine produced non-competitive inhibition of K^+-stimulated increased intracellular Ca^{2+} (mediated by L channels), with an IC_{50} of 209 μmol litre^{-1} [23]. The role of VSCC in the action of ketamine remains to be explored fully but non-competitive channel block (similar to the NMDA receptor) is possible.

Clinical use of ketamine

PAIN CONTROL

Systemic administration

Subanaesthetic doses of ketamine have been shown to be either potent analgesics[24] or ineffective[25] in the postoperative period. Recently, Arendt-Nielsen and colleagues[18] reported that a bolus of ketamine 0.5 mg kg^{-1} i.v. followed by continuous infusion at 9 μg kg^{-1} min^{-1} inhibited central temporal summation which is used as an index of dorsal horn responsiveness in humans. These authors demonstrated that ketamine could only inhibit NMDA receptor activity when the receptor-operated ion channel had been opened by nociceptive stimulation, and used this to explain why ketamine only marginally affects acute/phasic pain, and attempts to produce pre-emptive analgesia with ketamine were ineffective. This is clearly a controversial area warranting further study.

Extradural administration

The efficacy of extradural ketamine is also controversial. Naguib and colleagues[26] reported that extradural ketamine 30 mg produced potent postoperative pain relief without respiratory depression or psychic disturbance, while Schneider and Diltoer[27] showed that extradural ketamine (30 mg with 30 mg h^{-1}) provided inadequate analgesia with an associated "unpleasant feeling". Although ketamine has been reported to interact with opioid receptors[9 10], the affinity for opioid receptors may be 10 000 fold weaker than that of morphine[9]. Pharmacokinetic studies of extradural ketamine[28] and morphine[29] in dogs showed that 30 min after extradural injection the concentration ratio of cerebrospinal fluid/plasma was approximately 0.5 and 40, respectively. Therefore, it seems unlikely that extradural ketamine produces analgesia via opioid receptor occupation in the spinal cord and an effective (at the opioid receptor) extradural dose of ketamine is likely to produce not only spinal but also systemic effects, which might include general anaesthesia.

Intrathecal administration

Ketamine has been administered intrathecally (5–50 mg in 3 ml, approximately 0.2–2% solution) with or without adrenaline 0.1 mg for war casualties with lower limb injuries[4]. Ketamine 50 mg with adrenaline (but not ketamine alone) produced sensory and motor block without respiratory depression or hypotension lasting 45–90 min. Unlike the study of Dowdy, Kaya and Gocho[3] in dogs, central effects such as dizziness and drowsiness were reported in humans[4]. In animal studies[11 30 31], most investigators found that in the absence of adrenaline, ketamine-induced motor block was variable and shortlived[11 31], presumably related to increased systemic absorption. Therefore, intrathecal ketamine should be used in conjunction with adrenaline.

In summary, use of i.v., i.m., extradural or intrathecal ketamine for postoperative pain relief is clearly of limited value.

NEUROPROTECTIVE ACTION

As activation of NMDA receptors is implicated in cerebral ischaemic damage, NMDA receptor antagonists, including ketamine, have neuroprotective potential. In a study using MK-801 (an NMDA antagonist) and ketamine, Church, Zerman and Lodge reported neuroprotection after transient cerebral ischaemia in rats[32]. However, they also observed that high doses of ketamine and MK-801 produced behavioural disturbances. Hoffman and colleagues[33] showed that ketamine improved neuronal outcome from incomplete cerebral ischaemia in rats by a mechanism related to a decrease in plasma catecholamine concentrations. In contrast, Jensen and Auer[34] failed to demonstrate any protection against ischaemic damage in rats using ketamine. It is difficult to explain the discrepancy in these two studies[32 34] (both in rats), especially as the mechanisms for producing ischaemia, ischaemic time and the ketamine administration regimen were very similar. Further mechanistic studies are required to determine any neuroprotective efficacy.

CRITICAL ILL PATIENTS

Septic shock

Ketamine has been shown to reduce the need for inotropic support in septic patients[35], an effect that may be related to inhibition of catecholamine uptake[36]. In addition, infusion of ketamine resulted in better sedation, increased arterial pressure and diminution of bronchospasm in a patient with acute lymphatic leukaemia who developed bilateral fulminating pneumonia with marked agitation, hypotension and bronchospasm[37]. In this patient infusion of midazolam failed to provide adequate sedation. Several animal studies also indicated that ketamine anaesthesia may reduce pulmonary injury via a reduction in endotoxin-induced pulmonary hypertension and extravasation[38] and produce haemodynamic stability (presumably via reduction in catecholamine reuptake[36]) in a model of endotoxic shock[39]. In a recent study, Schmidt and colleagues showed that ketamine reduced endotoxin-mediated leucocyte adhesion to vessel walls[40].

Haemorrhagic shock

The sympathomimetic effects of ketamine[1] may be advantageous in patients with haemorrhagic shock compared with other conventional anaesthetics. Several clinical reports indicated that induction of anaesthesia with ketamine produced either no change or a slight increase in arterial pressure and heart rate[2]. However, ketamine should be used cautiously for shock patients as severe hypotension may occur on induction of anaesthesia. Ketamine-induced hypotension in shock may result from loss of sympathoadrenal activity that accompanies loss of consciousness[33].

Asthma

Ketamine has been used successfully in the treatment of status asthmaticus[41]. Laboratory studies indicated that the spasmolytic[42,43] and anti-inflammatory actions[38,40,44] of ketamine may contribute to its efficacy in asthma. The mechanism by which ketamine produces airway relaxation is still unclear although several mechanisms[15,42,43] have been suggested, including increased catecholamine concentrations, inhibition of catecholamine uptake, voltage-sensitive Ca^{2+} channel block and inhibition of postsynaptic nicotinic or muscarinic receptors.

In this editorial we have described the pharmacology of ketamine and discussed its clinical use. However, our knowledge of the mechanism(s) of action of ketamine is still far from complete and we hope further research with this interesting compound may provide clues to the mechanism(s) of ketamine anaesthesia and analgesia.

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