KETAMINE AND E.E.G. SEIZURE WAVES: INTERACTION WITH ANTI-EPILEPTIC DRUGS

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SUMMARY

When unrestrained cats were injected with ketamine 2–6 mg kg\(^{-1}\) i.v., anaesthesia was associated with seizure waves induced in the cortical e.e.g. After cats were pretreated with trimethadione 500 mg kg\(^{-1}\) i.p., ketamine did not induce seizure waves. Pretreatment with diphenylhydantoin 25 or 100 mg kg\(^{-1}\) i.p slightly enhanced seizure waves following ketamine. In both situations the anaesthetic effect of ketamine remained unaffected.

Kayama and Iwama (1972) demonstrated in previous experiments that, when cats were anaesthetized with ketamine, seizure waves appeared in the cortical e.e.g. From the pattern of e.e.g. waves, they found the ketamine-induced seizure waves to be similar to those characteristic of petit mal seizures. We report how anti-epileptic drugs counteracted induction of seizure waves by ketamine.

METHODS

Experiments were performed on five unrestrained cats with chronically implanted electrodes in the sensorimotor and visual cortices and in the optic chiasma. The cortical electrodes were small stainless steel bolts screwed to the skull and the chiasmatic electrodes were a pair of stainless steel wires glued together with tips separated by about 0.5 mm. The cat was placed in a box (60 x 60 x 50 cm) with an observation window through which the effects of ketamine and other drugs were observed. Cables from the input terminals of amplifiers and those from the output terminals of an electronic stimulator (constant voltage type) were led into the observation box and connected to the cortical and chiasmatic electrodes respectively. E.e.g. was recorded on paper and visual cortical evoked potentials, induced by electrical stimulation of the optic chiasma, were displayed on an oscilloscope screen and photographed. The optic chiasma was stimulated every 1.5 s by a square pulse of 0.05 ms duration with a submaximal intensity of less than 40 V.

Ketamine was administered i.v. through a thin polyethylene catheter implanted chronically in the superior vena cava via the jugular vein. In each cat, ketamine was administered in the smallest dose sufficient to cause seizure waves (range 2–6 mg kg\(^{-1}\)). The anti-epileptic drugs used were trimethadione (anti-petit mal agent) and diphenylhydantoin (anti-grand mal agent). Trimethadione was dissolved in distilled water at a concentration of 50–80 mg ml\(^{-1}\) and administered in a dose of 500 mg kg\(^{-1}\) (Everett and Richards, 1944). Diphenylhydantoin, dissolved at a concentration of 50 mg ml\(^{-1}\) in a solvent containing 40% propylene glycol and 10.5% ethanol, was given in a dose of 25 mg kg\(^{-1}\) or 100 mg kg\(^{-1}\) (Everett and Richards, 1944). Both drugs were administered i.p.

The procedure was as follows:
(1) Control observations were made of the effects of ketamine on e.e.g. and behaviour.
(2) Five hours after procedure 1, trimethadione, diphenylhydantoin or the solvent of diphenylhydantoin was administered to observe the effects of these drugs on e.e.g. and behaviour.
(3) One hour after procedure 2, the second administration of ketamine was made in the same dose as in the first procedure. Compared with the findings after the first procedure, those after the third procedure were taken as showing modification, if any, of the effects of ketamine by the drugs used in the second procedure.

At least 6 days was allowed for recovery from the effects of trimethadione or diphenylhydantoin before a cat was used for further experiments.

RESULTS

Changes in behaviour, e.e.g. and cortical evoked potentials after i.v. administration of ketamine were the same as those reported previously (Kayama and Iwama, 1972). Behaviourally, ketamine induced general immobility with occasional twitching move-
ments of the vibrissae or ears. No responses were observed to painful stimuli (strong pinching of the tail or the hairless skin of the paws). The pupils were dilated with a fixed gaze. Cortical e.e.g. during ketamine anaesthesia was characterized by enhanced desynchronized waves in the background and bursts of rhythmic hypersynchronous slow waves or slow waves with sharp spikes which can be interpreted as seizure activity (Kayama and Iwama, 1972) (figs 1B and 2A).

Evoked potentials in the visual cortex induced by single shock stimulation of the optic chiasma (fig. 3) had the same configuration as those described by previous workers (Malis and Kruger, 1956). The first downward deflection is the presynaptic activity, while the other major deflections are produced by activation of postsynaptic structures (Widen and Ajmone Marsan, 1960). Ketamine itself enhanced every component of the evoked potential (fig. 3A, D). It was notable, however, that for a short while after administration of ketamine, the postsynaptic components of the evoked potential were sometimes almost abolished (record at 1 min after ketamine in fig. 3A, D). Hereafter, this phenomenon will be referred to as “blocking of evoked potential”. One interpretation of this phenomenon is that the cortex is already very active, showing seizure waves, and cannot increase or modify its activity in response to stimulation of the optic chiasma (Kayama and Iwama, 1972).

The behavioural and e.e.g. changes caused by ketamine began to appear about 30 s after injection and were maximal between 1 and 3 min. All effects of ketamine disappeared after about 1 h and the second injection of the same dose of ketamine administered after 5 h had the same effects as the first one.

Interaction with trimethadione

Interaction of ketamine with trimethadione was examined six times in four cats. Figure 1 shows typical records from one cat. In A and B, it was confirmed that ketamine 2.7 mg kg⁻¹, which was administered in the resting arousal state (A) slightly increased the amplitude of the desynchronized e.e.g., with occasional bursts of seizure waves (B). After the effects of ketamine disappeared completely, trimethadione was administered. Record C shows

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**Fig. 1.** E.e.g. effects of ketamine modified with trimethadione. All traces were recorded from the visual cortex. A = resting arousal state; B = 2 min after injection of ketamine 2.7 mg kg⁻¹; C = 59 min after injection of trimethadione 500 mg kg⁻¹; D = 2 min after injection of ketamine 2.7 mg kg⁻¹ performed soon after C; E = 2 min after injection of ketamine 5.4 mg kg⁻¹ performed 20 h after injection of trimethadione; F = 2 min after injection of ketamine 5.4 mg kg⁻¹ performed 7 days after injection of trimethadione.

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**Fig. 2.** E.e.g. effects of ketamine modified with diphenylhydantoin. E.e.g. records from the visual cortex recorded before and 3 min after injection of ketamine 3 mg kg⁻¹ are shown. A = before anti-epileptic treatment; B = 60 min after diphenylhydantoin 25 mg kg⁻¹.

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**Fig. 3.** Effects of ketamine on visual cortical evoked potentials induced by single shock stimulation of the optic chiasma. A = before trimethadione; B and C = 1 and 20 h after trimethadione, respectively; D and E = before and 1 h after diphenylhydantoin, respectively. Five to 10 traces were superposed in each record A, B and C were obtained from the same cat as in figure 1. D and E were obtained from the same cat as in figure 2.
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that with this drug no characteristic changes were induced in either the e.e.g. or behaviour. Although the cat sometimes fell into a drowsy state as indicated by spindles in the e.e.g., it was not possible to determine whether these effects could be ascribed to trimethadione. When the same dose of ketamine as in record B was injected 60 min after trimethadione, the desynchronized e.e.g. slightly increased in amplitude but no seizure waves were observed (D). The cat showed typical behavioural signs of ketamine anaesthesia at this time; it became immobile with dilated pupils and was unresponsive to painful stimulation. During this ketamine anaesthesia, enhancement of the evoked potential was observed (fig. 3B). Since in this case ketamine could not induce the seizure waves, the blocking of evoked potential was not encountered (the second record from the top in column B of fig. 3). During recovery from ketamine anaesthesia, ataxia was observed for a longer time than following ketamine alone.

Twenty hours after treatment with trimethadione, a double dose of ketamine (5.4 mg kg$^{-1}$) was tested. E.e.g. traces consisting of low voltage desynchronized waves with occasional slow undulations of the base line were observed (fig. 1B). Since no seizure waves were elicited, it was suggested that the effect of trimethadione had not disappeared. The evoked potentials were enhanced. Because of the absence of the seizure wave, it did not suffer any blocking in the stage of maximal enhancement (fig. 3C). With these electrographic signs, the cat was immobile and unresponsive to painful stimulation and its pupils dilated. Ataxia during recovery lasted more than 6 h. It was 7 days after the trimethadione injection that ketamine 5.4 mg kg$^{-1}$ could induce typical e.e.g. changes (fig. 1F).

Interaction with diphenylhydantoin

Interaction of ketamine with diphenylhydantoin 25 mg kg$^{-1}$ was examined in three cats. Essentially the same results were obtained. Records from one cat are shown in figure 2. After ketamine 3 mg kg$^{-1}$ was found to anaesthetize the cat with induction of e.e.g. seizure waves (fig. 2A), diphenylhydantoin was injected. This treatment did not cause any marked behavioural and e.e.g. changes except for a slight increase in the amplitude of the desynchronized waves. Sixty minutes thereafter, the same dose of ketamine was injected (fig. 2B); seizure waves appeared in bursts at shorter intervals and desynchronized waves in the inter-burst intervals had greater amplitudes than in the control ketamine anaesthesia. Although in the ordinary condition the ketamine-induced seizure waves could not be found beyond 6 min after injection, this time was increased up to 9 min following pretreatment with diphenylhydantoin.

The facilitation of evoked potential following ketamine also took place in the diphenylhydantoin-treated condition (fig. 3E). The second record from the top of figure 3E shows that in the diphenylhydantoin-treated condition, the blocking of evoked potential sometimes took place in an early period after ketamine in the same way as in the untreated condition. This was because the seizure wave inducing effect of ketamine could not be antagonized by diphenylhydantoin.

Behaviourally, ketamine anaesthesia in the diphenylhydantoin-treated cats was not essentially different from that in the untreated cats.

While studying the blocking effect of diphenylhydantoin upon electrically induced generalized convolution in rat, Everett and Richards (1944) noted that it became more obvious when the dose administered i.p. was increased from 25 to 135 mg kg$^{-1}$. It was suspected therefore that, if administered in a considerably larger dose, diphenylhydantoin might antagonize the seizure-inducing effect of ketamine. Two cats received diphenylhydantoin 100 mg kg$^{-1}$ followed by ketamine 5 mg kg$^{-1}$; the e.e.g. after ketamine showed alternation of the strongly enhanced desynchronization and the spike and wave complex followed by electrical silence of 1-3 s duration. Thus, even diphenylhydantoin 100 mg kg$^{-1}$ failed to antagonize the seizure wave inducing effect of ketamine.

The solvent for diphenylhydantoin did not exert any marked effects on the ketamine-induced seizure activity.

DISCUSSION

In a previous study using unrestrained cats, Kayama and Iwama (1972) found that, during ketamine anaesthesia, bursts of hypersynchronous slow waves were induced in the e.e.g. These slow waves were identified as seizure activity: (1) they were very rhythmic and appeared in various sites synchronously, (2) they were frequently accompanied by spikes, forming the spike and wave complex, and (3) there were many neurones the discharges of which were modified during the slow wave bursts in the same way as observed in experimental seizures (Kayama and Iwama, 1972). This finding has been confirmed by other workers who studied the effects
ity, the animals were immobile, showing only occasional myoclonic jerks. The encephalin-induced e.e.g. seizure was suppressed by anti-petit mal drugs, not by anti-grand mal drugs (Snead and Bearden, 1980), which indicates that the seizure activity induced by ketamine and that by encephalin are similar. In addition, both ketamine and encephalin have strong analgesic effects. Since ketamine and encephalin have common effects upon the central nervous system, it is possible that at least part of the effect of ketamine on the central nervous system is exerted in close relation to the opiate receptor.

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KETAMIN UND PAROXYSMALE EEG-TATIGKEIT: INTERAKTION MIT ANTIEPILEPTIKA

ZUSAMMENFASSUNG

Nicht in ihrer Bewegungsfreiheit eingeschränkte Katzen, die 2 bis 6 mg kg\(^{-1}\) Ketamin erhalten hatten, zeigten bei der Narkose paroxysmale Tätigkeiten im kortexalen EEG. Bei mit 500 mg kg\(^{-1}\)Trimethadion vorbehandelten Katzen rief Ketamin keine Anfallstätigkeiten im EEG hervor. Vorbehandlung mit 25 oder 100 mg kg\(^{-1}\)Diphenylhydantoin intraperitoneal hemmte leicht die auf Ketamin folgende Anfallstätigkeit. In beiden Fällen blieb die anästhetische Wirkung von Ketanest unbeeinflußt.