E.E.G. AND MULTIPLE UNIT ACTIVITY DURING KETAMINE AND BARBITURATE ANAESTHESIA

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SUMMARY

Cortical e.e.g. and multiple unit activity (m.u.a.) of the mesencephalic reticular formation, the anterior hypothalamic area, the basal nuclear group of the amygdala and the dorsal hippocampus were studied before and following i.p. injection of different doses of ketamine hydrochloride and a barbiturate in cats with chronically implanted electrodes. Barbiturate administration resulted in a rapid decrease in m.u.a. in the mesencephalic reticular formation which was accompanied by a significant decrease of activity in the limbic structures. No m.u.a. response was observed to visual, acoustic or somatosensory stimulation or to pain. The m.u.a. of the mesencephalic reticular formation and limbic structures increased gradually following ketamine injection. Intermittent or continuous hypersynchronous activity was characteristic in the cortical e.e.g. During the hypersynchronous activity the responsiveness of m.u.a. in the mesencephalic reticular formation, to visual and acoustic stimuli, was blocked. Somatosensory and painful stimulation, however, resulted in a significant increase in the activity both of the mesencephalic reticular formation and of the limbic neuronal pools.

Since the publications of Winters, Mori and Wallach (1969), Winters, Ferrer-Allado and Guzmán-Flores (1972), Guzmán-Flores and Alcaraz (1970), Guzmán-Flores and colleagues (1971), Guzmán-Flores, Garcia-Castells and Buchwald (1972) and Mori and colleagues (1972), it has been well established and generally accepted that the continuous monitoring of m.u.a. in the brain-stem reticular formation and other brain areas is a very sensitive and valuable method in the assessment of levels of c.n.s. activity. Such studies can be applied to the evaluation of the mode of actions of different drugs, such as tranquillizers, anaesthetics or central nervous system excitants, which influence neuronal behaviour.

Ketamine hydrochloride is a unique non-barbiturate general anaesthetic. Speculation on its mode of action on the central nervous system as reflected by the literature is controversial. On the one hand, excellent anaesthesia following its use in man has been reported, but, on the other hand, during the period of recovery from anaesthesia, adverse reactions such as vivid dreaming, psychomotor activities and evasive behaviour have been described also (Domino, Chodoff and Corssen, 1965; Corssen, 1970; Mori et al., 1971; Collier, 1972; Cronin et al., 1972; Hervey and Hustead, 1972).

The aim of the present work was to compare the actions of ketamine (Ketalar) and pentobarbitone (Nembutal) on the level of c.n.s. activity and on the responsiveness to different sensory stimuli.

METHODS

The experiments were performed on six cats of both sexes (weight 2.5–4.0 kg). Standard stereotaxic procedure was used to implant cortical stainless steel screw electrodes and subcortical semi-microelectrodes (nickel wire, diameter 0.25 μm, insulated with enamel at the factory, and cut to give an uninsulated tip. The electrodes were directed to the following structures: mesencephalic reticular formation (MRF), anterior hypothalamic area (AH), the basal nuclear group of the amygdala (AMY) and the dorsal hippocampus (HIPP).

The method for recording m.u.a. was based on that of Guzmán-Flores and Alcaraz (1970). This technique records the activity of small neuronal pools. The analyser device, built from operational amplifier circuits, analysed simultaneously m.u.a. from four subcortical structures. The neuronal spikes of a given height were chosen by means of a voltage gate. The output of the spike discriminator was fed
to a staircase generator and multivibrator system which drove the pen of the driver amplifier of the e.e.g. apparatus (EMG-Orion type EEG 4) and reset to zero every 16 pulses. This produced a saw-tooth line on the e.e.g. channel (fig. 1).

During the experiments cats were placed in an electrically shielded, sound-attenuated, dimly illuminated chamber with a glass front which allowed observation of the animal. The chamber was equipped with a loudspeaker which emitted the sound for auditory stimulation. Continuous m.u.a. recording was made for 2 hr before, and for 4 hr following, administration of the anaesthetic agents. Ketamine was injected i.p. in doses of 20 mg/kg, 40 mg/kg and 60 mg/kg (12 experiments on six cats). Pentobarbitone was injected i.p. in doses of 20 mg/kg and 40 mg/kg (four experiments on four cats). At least 7 days elapsed between the periods in which an animal received ketamine or pentobarbitone.

To test neuronal responsiveness in the cats, visual (flicker 1 Hz), acoustic (1000 Hz), somatosensory and painful stimuli were presented, each lasting for 10 sec.

Changes of m.u.a. were calculated as percentage values of the average activity recorded during the animal’s quiet wakefulness in the control period.

At the end of the experiments the animals were sacrificed with an overdose of pentobarbitone. The electrode locations were checked according to the method described by Guzman-Flores, Alcaraz and Fernandez-Guardiola (1958).

RESULTS
Ketamine 20 mg/kg i.p. initially produced ataxia and increased motor activity. Cataleptoid behaviour occurred within 8–10 min, lasting for 40–50 min during which continuous movements of head and limbs, bizarre postures, so-called pseudo-attentive behaviour, mydriasis as well as vertical nystagmus could be observed. Anaesthesia did not occur. The stereotyped motor activity still persisted 3 hr after ketamine administration. During recovery, the cats showed slightly increased locomotor activity, aversive reactions, escape or attack behaviour and vocalization.

Intraperitoneal administration of ketamine 40 or 60 mg/kg resulted in opisthotonus after a short period of ataxia, slow movements of the head, stretching of the forelimbs, hyperextension of the body, and increased muscular tone within 4–6 min. Ketamine induced a state of anaesthesia and intermittent hypersynchrony (2.5–3.5 Hz) including desynchronization in the cortical e.e.g. occurring 10–15 min after the injection (fig. 1). The hypersynchronous wave patterns were superimposed on spikes or spike and wave complexes.

M.u.a. in the mesencephalic reticular formation increased to a high level and remained increased over 3–5 hr. The rate of increase ranged from 180% to 250% of the control value of activity recorded during quiet wakefulness. The increase of activity in the mesencephalic reticular formation was accompanied by a significant increase of m.u.a. in the anterior hypothalamic area (170–190%), amygdala (128–160%) and hippocampus (130–200%). Moreover, the firing
FIG. 3. Average m.u.a. base levels and responsiveness in the mesencephalic reticular formation (MRF) during ketamine and barbiturate anaesthesia. The horizontal lines represent the control level of m.u.a. recorded during quiet wakefulness. Stippled columns: m.u.a. base level during anaesthesia. White columns: responsiveness; A: acoustic; V: visual; S: somatosensory; P: painful stimulation. Both ketamine and barbiturate were injected in doses of 40 mg/kg.

Pentobarbitone injection in a dose of 20 mg/kg i.p. did not induce anaesthesia in the cat. The m.u.a. of all subcortical structures was decreased and significant depression of activity was found in the MRF. Pentobarbitone administration in a dose of 40 mg/kg i.p. produced typical “barbiturate spindles” in the e.e.g. within 3–5 min. Ten minutes after injection MRF m.u.a. decreased to a very low, stable level, the firing frequency varying by about 2–3% of the activity recorded in the control period. A sharp decrease of m.u.a. was found also in the anterior hypothalamic area, amygdala and hippocampus and the activity declined to 20–30% of the control values.

No m.u.a. response to acoustic, visual, somatosensory or painful stimulation during this stage of barbiturate anaesthesia was observed (fig. 2). Between 60 and 80 min after induction of barbiturate anaesthesia the MRF m.u.a. began to increase slightly. However, it remained markedly depressed throughout the experiment. The first movement of the head occurred after 130–150 min, and this was followed by uncoordinated motor activity. Even at 3 hr after the barbiturate injection, MRF m.u.a. did not reach 50% of control activity.

DISCUSSION

Barbiturate anaesthesia resulted in a sharp decrease of multiple unig activity in the mesencephalic
reticular formation accompanied by a significant decrease of activity in the anterior hypothalamic area, amygdala and hippocampus.

Ketamine produced a striking increase of m.u.a. both in the brain-stem and limbic structures. Intermittent hypersynchrony, including desynchronization superimposed by spikes or spike and wave complexes, dominated the cortical e.e.g. Several investigators (Kayama and Iwama, 1972; Manohar, Maxwell and Winters, 1972; Winters, 1972) have considered the ketamine-induced e.e.g. activity as typical of the patterns seen in seizures. Ferrer-Allado and colleagues (1973) performed experiments in man with depth electrodes implanted in the limbic and thalamic regions, and observed that different doses of ketamine induced seizure activity in both brain areas. Our cortical e.e.g. findings and the markedly increased m.u.a. in the brain-stem and limbic structures together with the characteristic burst patterns of amplitude-discriminated cell discharges occurring in the MRF and hippocampus after ketamine confirm these earlier observations.

Neuronal responsiveness to different types of stimulation, including pain, was completely abolished by barbiturate anaesthesia. Ketamine also induced interruption of acoustic and visual responsiveness, whereas somatosensory and painful stimulation resulted in a sharp increase of m.u.a. in each brain area.

It is accepted that the criteria for general anaesthesia are a low level of multiple unit activity in the brain-stem reticular system, the complete loss of arousal, and modulation of sensory inputs (Winters et al., 1967). The barbiturate-induced anaesthesia meets these criteria; however, the present paper would suggest reconsideration of the analgesic effect of ketamine.

REFERENCES


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**ELECTROENCEPHALOGRAMME ET ACTIVITE DES UNITES MULTIPLES Pendant L'ANESTHESIE PAR LA KETAMINE ET LES BARBITURIQUES**

**RESUME**

L'électroencéphalogramme cortical et l'activité des unités multiples (m.u.a) de la formation mésencéphalique réticulaire, de la zone hypothalamique antérieure, du groupe nucléaire de base des amygdales et de l'hippocampe dorsal étaient observés avant et après une injection intrapéritonéale de différentes doses de chlorhydrate de ketamine et d'un barbiturique, sur des chats ayant des électrodes implantées chroniquement. L'administration de barbiturique a eu pour résultat de réduire rapidement l'activité des unités multiples de la formation mésencéphalique réticulaire qui a été accompagnée d'une baisse significative de l'activité des structures limbiques. On n'a observé aucune réponse de l'activité des unités multiples à la stimulation visuelle, acoustique somatosensorielle, ou à la douleur. L'activité des unités multiples de la formation mésencéphalique réticulaire...
et des structures limbiques a augmenté graduellement à la suite d’une injection de ketamine. L’activité hypersynchrone, intermittente ou continue, a été caractéristique dans l’électroencéphalogramme cortical. Pendant l’activité hypersynchrone on a mesuré la réponse de l’activité des unités multiples dans la formation mésencéphalique réticulaire aux stimulations visuelles et acoustiques. La stimulation somatosensorielle et douloureuse a toutefois entraîné une augmentation significative de l’activité de la formation mésencéphalique réticulaire et des masses neuronales limbiques.

EEG UND MEHRFACHSYSTEM-AKTIVITÄT WÄHREND KETAMIN- UND BARBITURAT-ANÄSTHESIE

ZUSammenfassung


ACTIVIDAD DE UNIDAD MULTIPLE Y EEG DURANTE LA ANESTESIA DE QUETAMINA Y BARBITÚRICO

SUMARIO

Se estudiaron la actividad de unidad múltiple (m.u.a.) y la electroencefalografía (EEG) cortical de la formación reticular mesencefálica, la zona hipotalámica anterior, el grupo nuclear basal de la amígdala y el hipocampo dorsal, antes y después de una inyección i.p. de diferentes dosis de hidrocloruro de quetamina y un barbitúrico, en gatos con electrodos implantados crónicamente. La administración de barbitúrico resultó en un rápido descenso en m.u.a. en la formación reticular mesencefálica acompañada de un descenso significativo de la actividad de las estructuras limbicas. No se observó respuesta alguna m.u.a. a la estimulación visual, acústica y somatosensorial o al dolor. El m.u.a. de la formación reticular mesencefálica y las estructuras limbicas aumentaron gradualmente después de la inyección de quetamina. Fué característica en el c.e.g. cortical una actividad hipersínchrona continua o intermitente. Durante la actividad hipersínchrona la correspondencia de m.u.a. en la formación reticular mesencefálica a los estímulos acústicos y visuales fue bloqueada. La estimulación dolorosa y somatosensorial, sin embargo, resultó en un aumento significativo en la actividad tanto de la formación reticular mesencefálica como de las rebalsas neuronales limbicas.