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Presynaptic Inhibition in Man during Anesthesia and Sleep

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The slow positive (P_2) wave of the evoked electrospinogram was recorded from the dorsal epidural space in man. The waveform characteristics of the P_2 wave were similar to those of the dorsal cord positive wave (P wave), which is believed to be caused by the primary afferent depolarization (PAD) and to be related to presynaptic inhibitory action in animals. The "second" component of the P_2 wave appeared during excitement or following strong stimulation and disappeared after thiamylal administration and during natural slow-wave sleep. The second component, also demonstrated in the P wave of rabbits during ketamine anesthesia, was abolished by spinal transection. Therefore, these second components in man and rabbits may originate from a feedback loop via supraspinal structures. Thus, supraspinal influences might play an important role in the regulation of presynaptic inhibition in the spinal cord of man during wakefulness and anesthesia. (Key words: Spinal cord, synapses; Anesthetics, intravenous, thiamylal; Sleep, spinal cord activity.)

IT IS NOW generally agreed that the negative dorsal root potential (DRP_V in Lloyd's terminology[1]) and the slow positive wave (P wave) of the dorsal cord are produced by primary afferent depolarization (PAD).[2,3] PAD has been shown to be related to presynaptic inhibition.[4,5] Both the DRP_V and the P wave have been investigated exclusively in decerebrate or spinal animals. More recently, it has been demonstrated in experimental animals that primary afferent terminals are depolarized not only by stimulation of segmental nerves, but also by stimulation of the cerebral cortex[6] and the brain stem.[7] This suggests that supraspinal factors may also be involved in the genesis of presynaptic inhibition as reflected by PAD.[6,8,9] The present investigation demonstrates the existence of a similar mechanism in man and suggests that supraspinal influences might play an important role in the regulation of presynaptic inhibition in the human spinal cord.

Methods

IN MAN

Subjects were five volunteers and 12 patients being prepared for operation. Prior to the study consent was obtained. Safe and simple methods of recording the evoked electrospinogram (EESG) in man have been developed in our laboratory, based on a technique of continuous epidural anesthesia that enables placement of the recording electrodes in the dorsal epidural space.[10] The present experimental procedures resembled previous investigations of the evoked electrospinogram (EESG) in man.[11] Electroencephalograms (EEG's) were recorded monopolarly from the scalp at the vertex with needle electrodes to monitor the states of consciousness and sleep. The H-reflex was also recorded bipolarly from the calf muscle in response to tibial-nerve stimulation at the popliteal space. During the course of the experiment (4–5 hours), the subjects sometimes fell asleep, as indicated by changes in EEG patterns and by unresponsiveness to orders.

The evoked potentials, which were monitored on other channels of the oscilloscope and on an ink-writing polygraph, were fed into a computer for averaging. The computer was triggered by the stimulating pulse. The averaged responses were photographed or plotted by an X-Y plotter. The stimulating pulses were delivered to peripheral nerves

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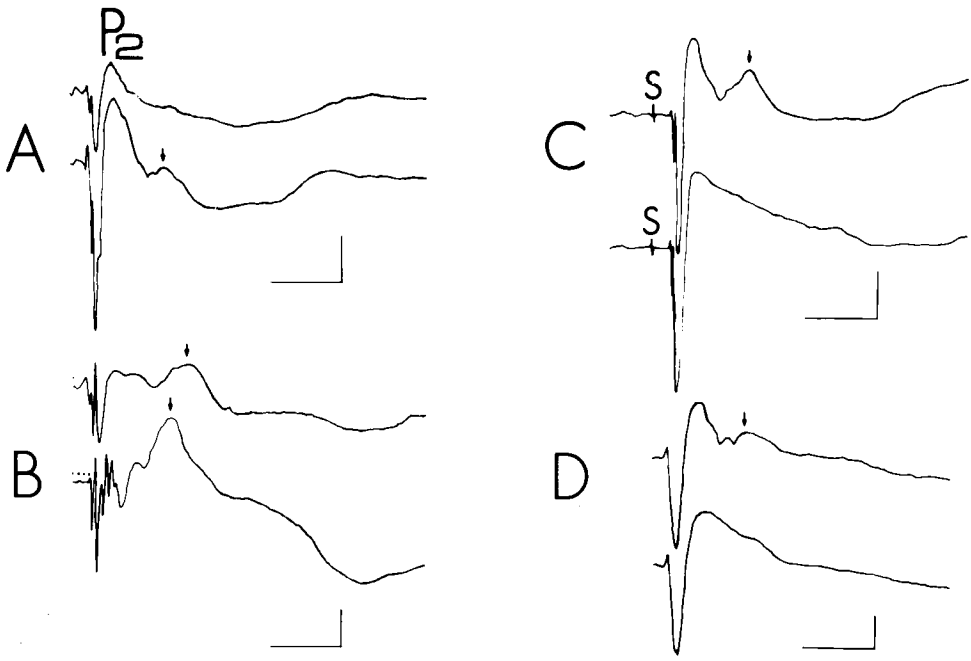

FIG. 1. EESG's recorded from the dorsal epidural space in response to peripheral-nerve stimulation in man. *A*, EESG's from the epidural space at the T12 vertebral level, corresponding to the L5 segment of the spinal cord. A weak electrical stimulation (2 × threshold, 2T) of the tibial nerve at the popliteal fossa evoked the P_2 wave with a smooth decay (*upper sweep*): The second component (*arrow*) appeared with an increase in amplitude of other components following a stronger stimulation (7T). *B*, EESG's from the L1 vertebral level, corresponding to S2–S3 levels, in response to single-shock stimulation (5T) of the common peroneal nerve at the popliteal fossa (*upper trace*) and in response to brief trains of repetitive pulses (4 at 300 Hz) (*lower trace*) during excitement. Note the decrease in latency of the second component with the concomitant increase in its amplitude. *C*, EESG's recorded from the dorsal epidural space at the C7 vertebral level, corresponding to the C8 spinal segment, in response to radial-nerve stimulation (5T) at the wrist during wakefulness (*upper trace*) and after intravenous injection of 2.5 mg kg^{-1} thiamylal (*lower trace*). Note the disappearance of the second component and prolongation of the decay. S denotes the stimulus artifact. *D*, EESG's recorded from the dorsal epidural space at the C5 vertebral level, corresponding to the C6 spinal segment, in response to ulnar-nerve stimulation (4T) at the elbow during wakefulness (*upper trace*) and during slow-wave sleep (*lower trace*) as monitored by conventional EEG in four subjects. The start of each trace corresponds to the initiation of the stimulus pulse except in *C*. All traces are averaged responses (N = 30 in *A*, *B*, *C*; N = 20 in *D*). Upward deflection indicates positivity in this and subsequent illustrations. Calibration: 5 μV, 20 msec.

through nonpolarizable needle electrodes 150 μ in diameter inserted adjacent to the nerves. The time constant used for recording the EESG was 1.5 sec. The location of recording electrodes in the epidural space was confirmed by x-ray at the end of recording.

IN RABBITS

Five rabbits (3.0–4.2 kg) were anesthetized with ketamine hydrochloride (10 mg kg^{-1}, iv) and were mechanically ventilated through a tracheal cannula. After laminectomy a ball-tip electrode was placed lightly on the L7 level of the dorsal cord and the indifferent electrode was imbedded in the adjacent musculature. Two chlorided silver needle electrodes were inserted 2 cm apart into the skin of a hind paw for electrical stimulation. Methods of amplification and recording were similar to those in studies of man.

Results

As shown in figure 1, stimulation of a peripheral nerve evoked in the dorsal epidural

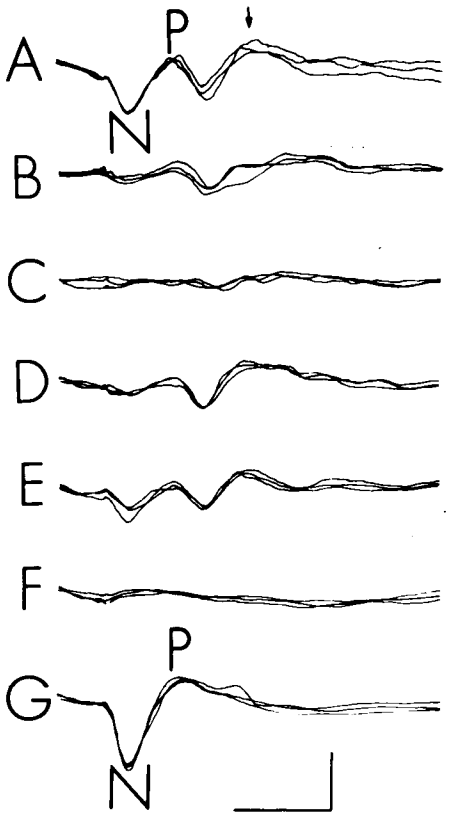

FIG. 2. An example of the EESG recorded from the midline at the L7 level in response to electrical stimulation of a hindpaw in a rabbit. Each trace is an averaged response (N = 15), three of which are superimposed during a given period. *A*, During light ketamine anesthesia (30 min after 10 mg kg^{-1}, iv). Note the second component of the P wave, indicated by an arrow. *B*, *C*, *D*, and *E* are recordings taken 5–10, 20–30, 60–70 and 90–100 min, respectively, after additional iv injection of 10 mg kg^{-1} ketamine. *F*, immediately after transection of the spinal cord at C1 with additional ketamine (2 mg kg^{-1}, iv). The EESG was completely abolished owing to the spinal shock. *G*, After recovery from the spinal shock (30–40 min after transection of the spinal cord). Note the disappearance of the second component. Calibration: 20 μV, 20 msec.

space of the same or an adjacent segment a potential change that closely resembled the potential produced in the dorsal cord of animals. The initial spike potentials (P_1) and subsequent large negative wave (N_1 wave) were followed by the slow positive wave (P_2 wave) (fig. 1). The central latency to the peak of the P_2 wave, measured from the initial positive dip of the spikes (P_1), was 12–16 msec in these 17 subjects, similar to that observed in the spinal cat.[1,2] The time course of decay of the P_2 wave in man, however, was somewhat different from that reported to occur in spinal or decerebrate animals. With weak stimulation, a smooth exponential decay of the P_2 wave was observed during the resting state, the half-decay time of which was 6–10 msec in nine subjects. With stronger stimulation a second component of the P_2 wave preceded by a negative dip became manifest (fig. 1, *A*). The second component was large in subjects (fig. 1, *B*) who were considerably excited during the measurement, as monitored by the low-amplitude high-frequency waves of the EEG, increases in the H-reflex, and tachycardia. This excitement was particularly observed during the early stage of the experiment (within 30 min after the start of recording). The central latency to the peak of the second component was variable from 30 to 60 msec, and became shorter with greater stimulus intensity or with brief trains of pulses (fig. 1, *B*). Intravenous injection of a small dose of thiamylal sodium, 2.5 mg kg^{-1}, promptly (within 2 min) abolished the second component, making smooth and prolonging the decay of the P_2 wave (fig. 1,*C*). The second component also disappeared when the subjects fell into natural (slow-wave) sleep (fig. 1, *D*).

Stimulation of a hind-paw in rabbits consistently evoked the P wave, which during ketamine anesthesia consisted of two distinct components (fig. 2, *A*) similar in configuration to those recorded in normal man. Additional doses of ketamine inhibited all components of the dorsal cord potential (fig. 2, *B*, *C*, *D*, and *E*). Transection of the spinal cord at C1 led to disappearance of the second component after recovery from spinal shock (fig. 2, *F* and *G*). We therefore conclude that the second component of the P wave in the rabbit is produced by a long feedback loop via supraspinal structures.

Discussion

The present observation demonstrates that the P_2 wave recorded from the dorsal epidural space in man is similar in central latency and in response to thiamylal to the P wave

recorded directly from the dorsal surface of the spinal cord in decerebrate animals.[1,2] Therefore, the P_2 wave reflects PAD in man as the P wave does in animals. The results in rabbits suggest that the second component of the P_2 wave is produced by a long feedback loop that involves the supraspinal structures. The "secondary" component of the DRP_V has been observed by Tang[9] in cats anesthetized with α-chloralose and by Benoist *et al.*[12] in cats that received bicuculline. They suggested that this secondary component of the DRP_V in the cat might originate from supraspinal structures. It is postulated that the second component of the P_2 wave in man has the same origin as the secondary component of the DRP_V in the cat observed by Tang[9] and Benoist *et al.*[12]

Eccles *et al.*[13] demonstrated that both pentobarbital and thiamylal in moderate doses prolonged and increased the DRP_V and P wave in decerebrate cats. The prolongation of the decay of the P_2 wave with a small dose of thiamylal in the present study coincides with the results of this animal study. However, it remains to be determined whether the main site of action of thiamylal on the P_2 wave is spinal or supraspinal. Concomitant disappearance of the second component of the P_2 wave affected by the drug suggests that the prolongation of the P_2 wave is also influenced by the supraspinal structures. Shimoji *et al.*[14] found that the peak latency of the P_2 wave was prolonged by a moderate dose of thiamylal, but these authors could not measure the time course due to technical difficulties. Kano and Shimoji[15] observed that ketamine depressed the amplitude of the P_2 wave, with enhancement of the H-reflex. The blocking effect of ketamine on the P_2 wave is similar to that on the P wave in the rabbits. The second component of the P wave, however, is hardly affected by ketamine in rabbits (fig. 2). From these data it might be concluded that the PAD in man arises from two distinct origins, "segmental" and "supraspinal," and that the segmental PAD is suppressed by ketamine and enhanced by thiamylal, while the supraspinal PAD, which might be caused by a feedback loop involving supraspinal structures, is susceptible to thiamylal and natural sleep but hardly affected by ketamine.

In summary, it is postulated that presynaptic inhibition in the spinal cord of man is influenced by impulses from supraspinal structures. This fact might be of importance in explaining the presynaptic inhibition in the spinal cord of man associated with anesthetics and analgesics.

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