Table 5. Effect of caffeine on plasma corticosterone.

Time (min)	Plasma corticosterone (μg/100 ml)			
	40 days		1 year	
	Control	Treated	Control	Treated
30	15±4	46±8*	10±2	15±1
60	—	23±4	—	55±6*
120	—	15±4	—	33±9*
240	21±5	29±1	19±3	lost
480	—	26±1	—	44±9*

Legend as in Table 4.

explain the data obtained by Peters & Boyd (1967) who found a significantly higher death rate in one-year-old rats than in 1·5–4·5-month-old rats given caffeine chronically at a daily dose of 185 mg kg^{-1}.

This work was partially supported by a grant from Ministero della Sanità, Rome, Italy and by a grant from the International Life Sciences Institute, Washington D.C. U.S.A. We thank Dr. I. Bartosek for the useful suggestions about the liver perfusion experiments.

February 15, 1980

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Increase of cortical excitability induced by pentazocine

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Morphine (2 mg kg^{-1} i.v.) increases significantly the amplitude of the direct cortical response (Jurna et al 1972). This effect, interpreted as an increased excitability of cortical neurons, was recently supported by the results of electrophoretically administered morphine (Davies & Dray 1978).

To help elucidate whether this is an exclusive effect of morphine or a common characteristic of central analgesics, we have examined the action of pentazocine on the direct cortical response. This drug was selected because it is a central analgesic which antagonizes some actions of morphine (Acevedo et al 1967). Since naloxone has been reported as a narcotic antagonist (Martin 1976), its reversing effect on pentazocine actions was also investigated.

Materials and methods. Adult rats (n = 26), 200–250 g, under sodium pentobarbitone anaesthesia (50 mg kg^{-1} i.p.), (+)-tubocurarine and artificial respiration were used. The head was restrained in a Horsley-Clarke type stereotaxic apparatus and one cerebral hemicortex was exposed.

Direct cortical responses were elicited by supramaximal stimulation of the cortex with rectangular electrical pulses of 6 V, 0·01 ms duration and 0·25 Hz frequency applied by means of two silver ball electrodes, both being 2 mm from the recording electrode. The distance between stimulating electrodes was 1 mm.

The evoked potentials were recorded through a silver chloride electrode applied directly to the area SI of the cerebral cortex. The exact location of the electrodes was assessed by latency time analysis and testing fatigability of somatosensory evoked responses elicited by peripheral electrical stimulation. The responses were displayed on a Tektronix 502-A CRO and photographed with a Grass C4 camera. Measurements were made on the photographs.

The control group (n = 5) received 0·3 ml kg^{-1} of the solvent used for pentazocine (lactic acid 1·2% and NaCl 0·28% in distilled water). The experimental group (n = 21) received in 0·3 ml kg^{-1}, pentazocine at 10 mg kg^{-1} and 30 min later 11 animals of this group received in 0·5 ml kg^{-1}, naloxone at 0·5 mg kg^{-1}. Either the drugs or the solvent for pentazocine were administered by injection into the femoral vein. The mean amplitude of direct cortical responses was measured before solvent or drug injection so that each animal served as its own control. The amplitude variations of direct cortical responses obtained after solvent or drug injection were compared: (i) for solvent or pentazocine administration, with respect to the last value of the control period; and (ii) for naloxone

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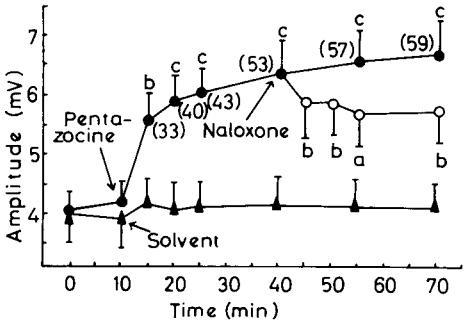

FIG. 1. Changes in the amplitude of the direct cortical response after the i.v. injection of pentazocine. △—△ animals receiving solvent for pentazocine. ●—● animals receiving 10 mg kg^{-1} of pentazocine. ○—○ animals receiving 0·5 mg kg^{-1} of naloxone 30 min after pentazocine. Numbers in parentheses indicate percentage of variation respect to the last value of the control period corresponding to the point 10 min. The mean standard error for each point is represented by the vertical bars. P was calculated according the Student's t-test, in relation to the last point of the control period. a: $P < 0{\cdot}05$; b: $P < 0{\cdot}025$; c: $P < 0{\cdot}005$.

administration, with respect to the last value of the control period and with respect to the value obtained 30 min after pentazocine injection.

Results and discussion. The cortical response in rats to direct cortical electrical stimulation consisted of a large surface negative wave sometimes preceded by a smaller positive wave.

Pentazocine, 10 mg kg^{-1} i.v., significantly increased the amplitude of the direct cortical response whereas its solvent was ineffective. This effect was maintained throughout the experiment (Fig. 1).

The i.v. injection of 0·5 mg kg^{-1} of naloxone after the effect of pentazocine was clearly established (30 min), did not significantly modify the action of pentazocine. However, the amplitude of direct cortical responses after naloxone has a tendency to return to control values (Fig. 1).

These results provide evidence that pentazocine has an influence on the excitability of cortical neurons involved in somatosensory processes. They agree with those obtained by employing other central analgesics. In fact, morphine enhances the direct cortical response (Jurna et al 1972) and excites most single units in the sensory-motor cortex (Davies & Dray 1978). Excitatory effects of methionine- and leucine- enkephalin have been also found in electrophoretic studies on cortical neurons (Davies & Dray 1978).

The level of the cerebral cortex where opiate facilitatory effects could take place and the possible mechanisms involved have been discussed (Martin 1976; Davies & Dray 1978), but still remain unclear.

Recently it has been observed that pentazocine and morphine (Soto-Moyano & Hernandez 1978, 1979), locally applied to the cerebral cortex, strongly facilitates the evoked responses elicited by somatosensory peripheral stimulation. These results agree with the present observations.

It is known that morphine effects on central neurons are reversed by naloxone (Davies & Dray 1978). In our experiments naloxone did not significantly modify the pentazocine actions. This could support Martin's affirmation (1976) that opiate analgesics and pentazocine probably interact with different receptors. However, the effect of pentazocine and morphine on the excitability of the somatosensory cortex is similar.

Therefore, the ability to increase the cortical excitability may be a common characteristic of central analgesics. This excitatory effect could be involved in pharmacological analgesia. In fact, it is known that cortical activation may produce inhibition at the level of the sensory relays of the spinal cord (Hagbarth & Kerr 1954; Lundberg et al 1963; Coulter et al 1974), the reticular formation of the brain stem (Buser et al 1969) and the thalamic nuclei (Ogden 1960; Iwama & Yamamoto 1961; Meulders et al 1963; Burchfiel & Duffy 1974).

Hypoxia is excluded as a cause of this effect since pentazocine does not modify blood Pco_2, Po_2, oxygen saturation and pH (Soto-Moyano et al 1975).

We are grateful to Dr S. Middleton for his help in the preparation of the manuscript. This work was supported by Grant N° B 300–784 from the University of Chile.

February 2, 1980

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