

# BRIEF COMMUNICATION

## Observations on the Hypothermic Effect of Metrazol in the Conscious Cat<sup>1</sup>

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BELESLIN, D. B. AND R. D. MYERS. *Observations on the hypothermic effect of metrazol in the conscious cat.* PHARMAC. BIOCHEM. BEHAV. 1(6) 727-729, 1973--In the unanesthetized cat maintained at an ambient temperature of 22-24°C, metrazol injected intraperitoneally in doses from 60-90 mg/kg first caused restlessness followed by autonomic changes and tonic-clonic convulsions. During these convulsions a simultaneous rise in temperature of 0.3-0.5°C occurred that lasted for about 90 min. Thereafter, a long-lasting hypothermia of about 6 hr duration developed. Within 24 hr the temperature returned to its normal level. Pretreatment with an intraperitoneal injection of phenobarbital sodium (50.0-150.0 mg/kg) 30 min prior to metrazol prevented the long-lasting fall in temperature, as well as the autonomic phenomena and tonic-clonic convulsions. The initial transient hyperthermia was not observed when the temperature was lowered by prior treatment with phenobarbital. The hypothermic effect of metrazol is probably the consequence of its direct action on thermoregulatory centers in the hypothalamus.

Temperature and convulsions    Metrazol and phenobarbital    Hypothalamus    Inhibition of thermoregulation

CONSIDERABLE evidence now exists for the hypothermic effect of metrazol in dogs, rabbits, rats and mice [9]. The cat, however, has received little attention with regard to the thermoregulatory action of metrazol, although it has been shown that when the cerebral ventricles of cats anesthetized with chloralose are perfused with this agent, shivering followed by a rise in colonic temperature occurred [5]. The present experiments were undertaken to determine the effect on the body temperature of the cat of the intraperitoneal injection of metrazol. Furthermore, it was of interest to study the effect of phenobarbital on the thermoregulatory response elicited by this substance.

### METHOD

The experiments were performed on 11 adult cats of either sex, weighing between 2.4-4.0 kg. Metrazol was injected intraperitoneally in doses of 60.0-90.0 mg/kg. Each cat was held in a plastic restraining chamber with the head outside the box. The body temperature, plotted continuously on a potentiometric recorder, was monitored by a thermistor probe (Yellow Springs Instrument) inserted about 10 cm into the rectum and held in position by adhesive tape wrapped gently around the base of the tail. The animals were kept at an ambient temperature of 22-24°C

and the injections were given only after the base line temperature had stabilized for at least 1 hr.

### RESULTS AND DISCUSSION

In the unanesthetized cat, a number of behavioral and autonomic effects were obtained following an intraperitoneal injection of metrazol. Restlessness appeared first, then tonic-clonic convulsions which were followed by deep hypothermia.

Within 2-3 min after an intraperitoneal injection of 60-90 mg/kg metrazol, the tonic-clonic convulsions began. These convulsive episodes continued from 20-70 sec, the frequency and intensity depending on the dose of metrazol. Even in a dose of 60 mg/kg, metrazol was sometimes lethal to the unanesthetized cat. The temperature during the convulsion rose from 0.3-0.5°C and remained elevated for about 90 min, after which a long-lasting hypothermia of about 6 hr duration occurred. Within 24 hr the temperature returned to its normal level. When the animal was pretreated with an intraperitoneal injection of phenobarbital sodium (50.0-150.0 mg/kg) 30 min prior to an injection of metrazol, the colonic temperature reached its normal level after 6 hr. The results of such an experiment are shown in Fig. 1.

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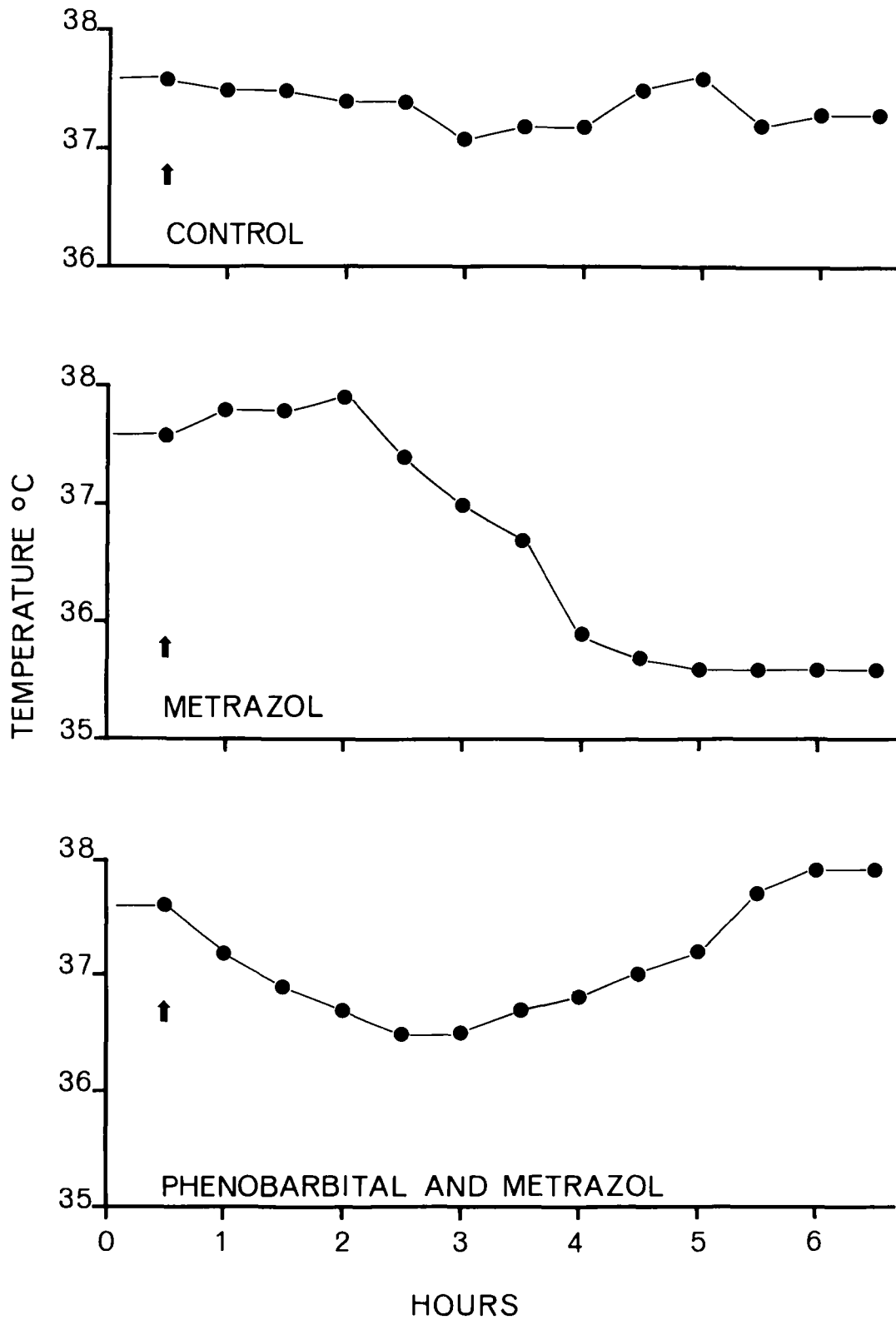


FIG. 1. Temperature response of an unanesthetized cat after intraperitoneal injections of metrazol (middle record) and phenobarbital and metrazol (lower record). The arrows indicate intraperitoneal injections in a dose of 60 mg/kg. At zero hour, phenobarbital sodium was injected intraperitoneally in a dose of 150.0 mg/kg.

Apart from tonic-clonic convulsions and the fall in temperature, metrazol produced the typical autonomic responses including retraction of the nictitating membrane, maximal mydriasis, hippus, nystagmus, exophthalmus, lacrimation, piloerection, salivation, micturition and defecation.

In examining the effect of a convulsant dose of metrazol on autonomic phenomena with special reference to the temperature of the conscious cat, we have found that a long-lasting hypothermia occurs. In contrast, metrazol perfused through the cerebral ventricles of the cat anesthetized with chloralose evokes a rise in body temperature [5]. Acting on the structures lining the cerebral ventricles, metrazol first produces shivering which leads to a rise in body temperature. However, when epinephrine is added to the perfusate, shivering is greatly reduced and the elevated temperature soon begins to fall [5]. Furthermore, when the hypothermia in cats anesthetized with pentobarbitone sodium subsides and the temperature rises, chloralose perfused through the cerebral ventricles suppresses shivering and the temperature again begins to fall [8]. Thus, the hyperthermic effect of metrazol in the anesthetized cat may not necessarily be due to a direct action on thermosensitive elements in the anterior hypothalamus, but rather

seems to be initiated and maintained by shivering.

Metrazol enhances the release of acetylcholine [1] but does not alter the content of norepinephrine and 5-hydroxytryptamine in tissue extracts [3,13] or their release in the brain [2]. When these substances are microinjected into the hypothalamus or injected into the cerebral ventricles, hyper- or hypothermia develops, depending on the species used [4, 6, 7, 11]. However, metrazol uniformly produces hypothermia in all species examined. Thus, the hypothermic effect of metrazol could probably be the result of a direct effect of the drug on the thermoregulatory mechanism in the hypothalamus, and not necessarily mediated by a release of a neurohumoral substance from the hypothalamus.

Phenobarbital pretreatment abolishes the hypothermic effect of metrazol in that the convulsant maintains the cat's body temperature at a normal level. This finding is in agreement with those of previous workers [9, 10, 12]. Hypothermia was not observed, probably because the return of the body temperature to normal is the consequence of a restoration of the normal function of the central nervous system in the anesthetized animal, which is somehow coupled with the action of metrazol [10].

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