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## Effects of some pharmacologic agents on cold tolerance of dogs

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BLATTEIS, CLARK M. *Effects of some pharmacologic agents on cold tolerance of dogs.* Am. J. Physiol. 203(5): 829-833. 1962.— Eight unanesthetized, shaved dogs were studied in 32 experiments for their thermal and metabolic responses to 90 min of exposure to 6 C during peripheral vasoconstriction (metaraminol bitartrate, 0.3 mg/kg), peripheral vasodilatation (trimethaphan camphorsulfonate, 10 mg/kg), and increased heat production [2, 3-dinitrophenol (DNP), 2.5 mg/kg]. Skin and rectal temperatures were measured continuously by means of thermistors and recorded on a Heiland Visicorder. Oxygen consumption was determined by the open method at 15-min intervals. Shivering was monitored visually. In the cold, the temperatures of the metaraminol-vasoconstricted dogs fell more rapidly and lower than temperatures of controls, whereas the temperatures of the trimethaphan-vasodilated dogs decreased more slowly but also fell lower than those of controls; DNP retarded the temperature fall of these hypermetabolic dogs in the cold, but did not affect its degree. The vasodilating drug delayed the onset of shivering, whereas DNP hastened it; shivering in the vasoconstricted dogs began at a time not significantly different from that of controls.

MUCH WORK HAS BEEN DEVOTED in recent years to ways of improving the tolerance of cold. Most efforts in man have been directed toward inducing acclimative changes by prolonged exposure to cold (1) or by prior treatment with various nutritional (2) or hormonal (3) supplements. In animals, treatment with hormones (4, 5), vitamins (6, 7), trial diets (8), and various other materials has been attempted to increase their resistance to low environmental temperatures. Few studies, however, have been made to determine the capability of pharmacologic agents in acutely counteracting the adverse effects of cold ambient temperatures (9-12). Such agents, to be protective against cold, would have to be able to help maintain normothermia either by controlling cutaneous vascular responses to reduce heat loss or by stimulating metabolism to increase heat production, or both.

The present experiments were designed to determine the actions of a vasoconstrictor (metaraminol), a vasodi-

lator (trimethaphan), and a metabolic stimulant (dinitrophenol) on cold-induced metabolic and temperature responses and to test the possible protective powers of these agents in the cold.

### METHODS

Eight healthy, unanesthetized, trained, shaved, post-absorptive, female mongrel dogs (mean body wt. 15.0 kg) were used in 32 experiments. Supine and slightly restrained, the animals lay quietly at room temperature ( $25.4 \pm 1.3$  C, 45% RH) until their rectal temperature was stable. Peripheral vasoconstriction [metaraminol bitartrate (Aramine), 0.3 mg/kg], peripheral vasodilatation [trimethaphan camphorsulfonate (Arfonad), 10 mg/kg], and increased metabolism [2,3-dinitrophenol (DNP) 2.5 mg/kg] were then induced in eight experiments, respectively, by intramuscular administration of these drugs in a single effective dose. Precooling measurements were made for 45 min immediately after the injections. Cooling data were obtained during 90 min of exposure in a refrigerated room ( $6.0 \pm 0.5$  C, 30% RH). Observations made 30 min postcooling at room temperature concluded the experiments. Eight experiments were conducted in the cold without the drugs.

Colonic, ear, chest, upper foreleg, thigh, and hind foot pad temperatures were measured continuously during the experiments by means of appropriate Waters thermistors and a Conrad multichannel thermistor bridge and were recorded on a Heiland 1012 Visicorder. The mean skin and mean body temperatures were calculated according to the formulas of Spurr et al. (13). Oxygen consumption was determined at 15-min intervals throughout the experiments by the Douglas bag technique; the expired air was analyzed by the method of Scholander (14). The dogs were observed visually for signs of muscular tremors.

The data were compared statistically on a paired-sample basis, and the null hypothesis was rejected at the 5% level of confidence.

### RESULTS

The vasoactive drugs used in this study were selected because their site of action is alleged to be in the periph-

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TABLE 1. Effects of metamaminol, trimethaphan, and dinitrophenol on temperatures and respiratory activity at room temperature

Agent	Temperature, C		Resp. Rate per min	Min. Vol., ml/min/kg	O <sub>2</sub> Cons., ml/min/kg	Max. Act., hr
	Rectal	Mean skin				
Control	38.9±0.2	33.0±0.5	28±7	4.7±0.1	12±1	
Metaraminol	+0.5±0.05*	-0.7±0.03†	+56±11†	+2.3±0.05†	+12±2†	1.3
Trimethaphan	-0.8±0.03†	+0.9±0.04†	-8±4	-1.0±0.08*	-7±2*	1.0
DNP	+0.7±0.02†	+0.6±0.05*	+8±5	+1.6±0.03†	+16±2†	1.6

Values are mean maximal changes from control ±SD in 8 dogs supine for 3.5 hr. \*  $P < 0.05$ . †  $P < 0.01$ .

eral vascular beds, where the effects were desired. To assess the effects on body temperature of these drugs and of DNP, preliminary dose-response experiments were conducted at room temperature, and the dose producing optimal thermal effects, without untoward side effects, was determined. The results are presented in Table 1. Metaraminol caused a significant fall in the mean skin temperature and a slight rise in the rectal temperature; it also doubled the oxygen consumption, due to a highly stimulating effect on both respiratory rate and minute volume. Trimethaphan significantly increased the mean skin temperature and decreased the rectal temperature; it halved the oxygen consumption through a depressing effect on minute volume. DNP caused a significant augmentation in the oxygen consumption, through a rise in minute volume only, and consequently increased all the body temperatures. The onset of these effects varied with the drug, the action being usually gradual in developing and reaching maximum at different times, but the experiments in the cold were so timed that the period of effective drug action commenced during the precooling period, was maximal during the cooling period, and was diminishing in the postcooling period.

Figure 1 illustrates the effects of exposure to the cold environment on the rectal, mean skin, and mean body temperatures and on the oxygen consumption of eight unanesthetized, unmedicated, normal dogs. The rectal temperature of these animals was not affected by the cold. Their mean skin temperature fell significantly ( $5.2 \pm 0.1$  C), rapidly at first, then more gradually, reaching a steady level within 45 min after their entry into the cold room. Their calculated mean body temperature decreased correspondingly (mean  $1.7 \pm 0.07$  C). During cooling the oxygen consumption tripled its precooling value, rising to maximum within the first 30 min of the cold exposure. Shivering occurred within  $14.5 \pm 2.7$  min after beginning the exposure to cold, becoming generalized and vigorous almost immediately. All these variables reverted promptly toward precooling levels on return of the animals to room temperature.

The thermal and metabolic responses to cold of the metamaminol-vasoconstricted dogs are shown in Fig. 2.

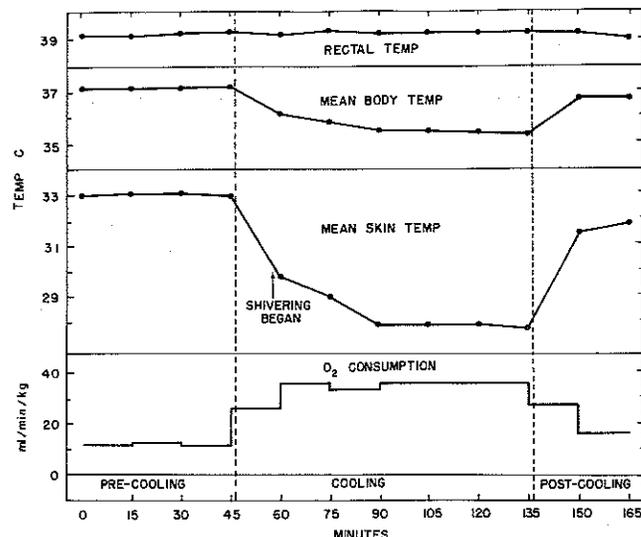


FIG. 1. Response of rectal, mean body, and mean skin temperatures and oxygen consumption of 8 unanesthetized, normal dogs before, during, and after exposure to +6 C.

The effect of the cold exposure on the rectal temperature of these animals was not significantly different from that of the controls. Their mean skin temperature, already falling in the precooling period under the action of the drug, decreased further in the cold at a rate significantly faster than that of the untreated animals; the mean temperature fall from precooling levels ( $6.6 \pm 0.1$  C) was significantly greater in these metamaminol dogs than that in the controls, and the steady level was reached significantly later during the exposure (60 min). The calculated mean body temperature of these dogs fell correspondingly with the decrease in the mean skin temperature and was also significantly greater than that of the untreated dogs. The oxygen consumption of these dogs, already stimulated in the precooling period by metamaminol, increased in the cold more than three and one-half times above its highest precooling value, but the augmentation was gradual, reaching maximum in 60 min of cold exposure, then leveling off concurrently with the mean skin and mean body temperatures for the remainder of the cooling period. The onset of shivering occurred in these metamaminol-vasoconstricted dogs within the first  $14.0 \pm 3.2$  min of the cold exposure (not significantly different from controls). During the postcooling period, these values returned toward their precooling levels in a manner also not significantly different from that of the controls.

The effects of cold on the temperature and oxygen consumption of the trimethaphan-vasodilated dogs are plotted in Fig. 3. The rectal temperature of these dogs began a gradual fall after 15 min in the cold that had not leveled off by the end of the exposure (mean fall  $1.6 \pm 0.1$  C). Their mean skin temperature, rising in the precooling period under the action of the drug, fell in the cold significantly slower than did that of the controls. However, the mean temperature drop from precooling levels ( $6.1 \pm 0.1$  C) was significantly greater in these dogs than in the control animals, although signifi-

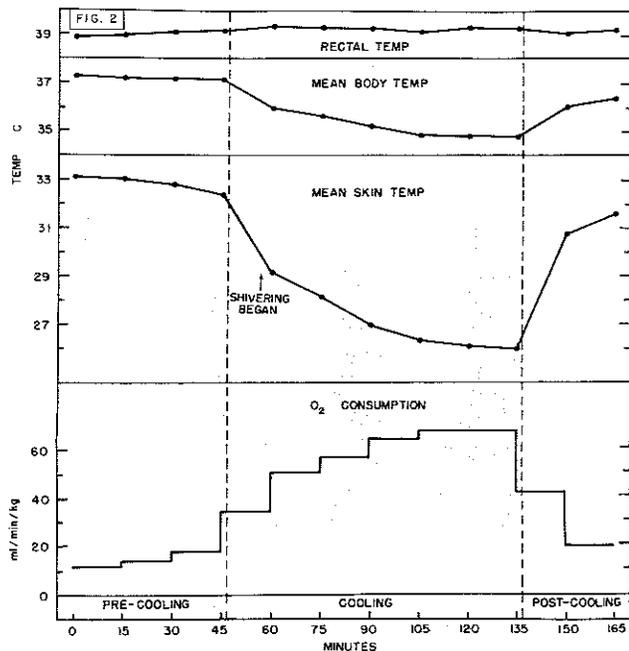


FIG. 2. Response of rectal, mean body, and mean skin temperatures and oxygen consumption of 8 unanesthetized, metaraminol-vasoconstricted dogs before, during, and after exposure to +6 C.

cantly less than in the metaraminol-treated dogs. The steady state was reached in an exposure time equivalent to that of the metaraminol-treated dogs (60 min). The mean body temperature of these dogs decreased significantly more in the cold than did that of the other groups (mean fall  $3.1 \pm 0.06$  C); a steady level was not reached during the cooling period. Their oxygen consumption increased in the cold two and one-half times above their precooling values, rising to maximum within the first 30 min of cold exposure, then leveling off. The maximum oxygen consumption during cold exposure, however, was significantly smaller in these dogs than in the controls. The onset of shivering occurred significantly later in the trimethaphan-treated animals than in the other groups after  $30 \pm 3.7$  min of cold exposure. The return of these variables toward their precooling levels proceeded during the postcooling period in a fashion similar to that of the other groups.

The effects of cold on the temperature and metabolic responses of the DNP-hypermetabolic dogs are illustrated in Fig. 4. Their rectal temperature, rising under the action of DNP during the precooling period, continued to rise slightly more in the first 30 min of the cold exposure, then decreased again, and was not significantly different from the controls during the remainder of the cooling period. The mean skin temperature of these dogs, also rising in the precooling period, decreased in the cold significantly more slowly than that of the untreated animals, reaching a steady level after 60 min of exposure, but neither the minimum temperature reached nor the mean temperature fall was significantly different from that of the controls (mean fall  $5.0 \pm 0.1$  C). The fall in mean body temperature also conformed to this pattern; the mean temperature drop

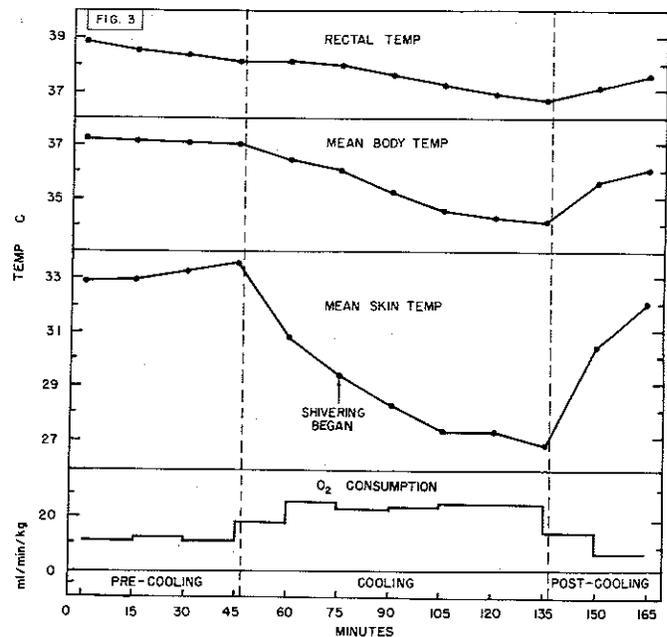


FIG. 3. Response of rectal, mean body, and mean skin temperatures and oxygen consumption of 8 unanesthetized, trimethaphan-vasodilated dogs before, during, and after exposure to +6 C.

and the minimum temperature reached were not significantly different from those of the controls. The precooling DNP-induced hypermetabolism nearly doubled again in value within the first 30 min of the cooling period. However, the maximum oxygen consumption of these dogs in the cold did not significantly differ from that of the control dogs. Shivering began in the DNP-treated dogs significantly earlier than in the other groups, after only  $9.0 \pm 1.5$  min of cold exposure. On re-entering room temperature, all the values returned promptly toward precooling levels in a manner similar to that of the controls.

#### DISCUSSION

The purpose of this experiment was to determine whether certain vasoactive and metabolic agents were protective during acute exposure to low environmental temperatures. Protection may be inferred when the administered agent opposes the actions of the environmental factors in such a manner that the homeokinetic upset caused by the environment is obviated by the administration of the drug. In the sense of this definition, none of the drugs used in the present experiments was protective; all failed to assist the animals in maintaining normothermia in the cold. Indeed, any attempt to pharmacologically regulate the cutaneous heat-loss mechanisms in the cold by prior treatment with vasoactive drugs seemed, under the conditions of the present experiments, to aggravate rather than improve the total heat loss in the cold. Thus, augmentation of the insulation of the skin with metaraminol caused, in the cold, a fall in the mean skin temperature in these dogs to levels even lower than in the untreated animals. Their

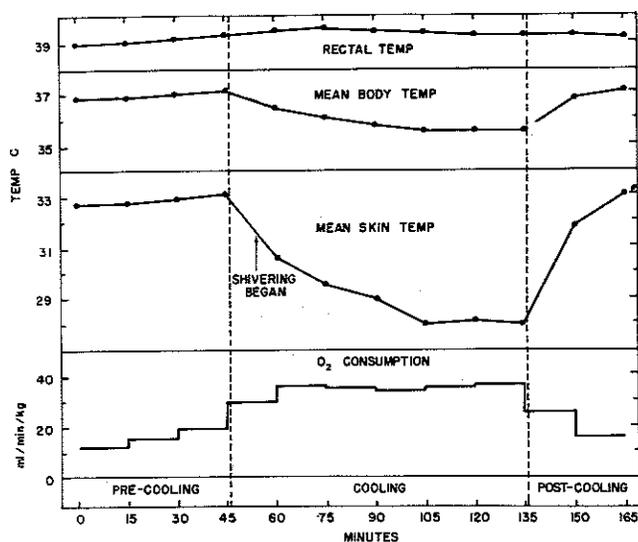


FIG. 4. Response of rectal, mean body, and mean skin temperatures and oxygen consumption of 8 unanesthetized DNP-hypermetabolic dogs before, during, and after exposure to +6 C.

rectal temperatures, however, were not affected differently from that of the controls, despite the oxygen consumption of these dogs being nearly two times above that of the untreated dogs in the cold and two and one-half times above the drug-induced hypermetabolic level at room temperature. It is not made clear from the present data whether the peripheral vasoconstriction (possibly not maximal at this dosage of metaraminol at room temperature) was thus augmented by the added stimulus of cold, independently of any effect on the rectal temperature or whether the only transient and relatively weak action of a single dose (as administered in these experiments) was simply inadequate to raise the rectal temperature in the cold. It is interesting to note (Fig. 5) that the metabolic effect of this agent was quantitatively the same in both the control and the cold environments, being, however, slightly calorogenic in the former environment. It is suggested that, under the conditions of the present experiments, the hypermetabolism in the cold environment served to maintain rectal temperature, while that of metaraminol was lost in the expired air in consequence of the hyperpneic effect of this drug (Table 1), and that this excessive ventilatory heat loss was perhaps additive with the cutaneous heat loss to cause the greater fall in surface temperatures seen in these dogs in the cold. Thus, the present technique of artificially increasing the "shell" was of no benefit when the animals were cooled, for despite a greater heat production it also caused a larger heat loss. There are no comparable data with metaraminol, but these results confirm, in the main, the observations of previous workers on the effects of epinephrine on the body heat balance in the cold of mice (9) and rats (15, 16), but disagree with the findings of Good and Sellers (10) in dogs.

Reduction of the cutaneous insulation with trimethaphan was also not protective in the cold. Although the vasodilatory action of this drug allowed in the cold a

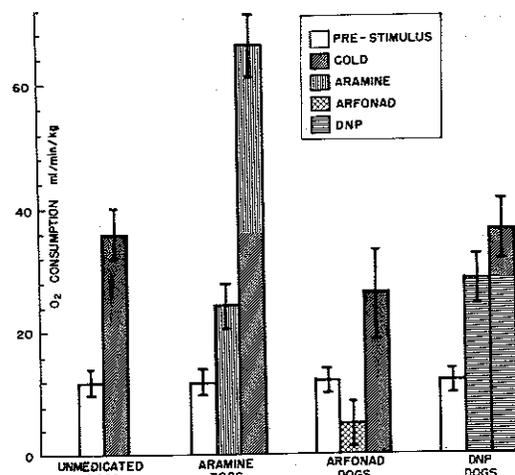


FIG. 5. Oxygen consumption of 8 dogs in 4 types of experiments (unmedicated, metaraminol-vasoconstricted, trimethaphan-vasodilated, and DNP-hypermetabolic) at room temperature and in the cold.

slower fall of the peripheral temperatures and significantly retarded the development of shivering, it also thereby increased the body-to-environment temperature gradient and promoted a greater cutaneous heat loss, causing the final temperatures of these dogs to fall lower than those of the control animals. This was further aggravated by the reduced oxygen consumption in the cold after this drug (35% less than unmedicated dogs in the cold), possibly either due to a direct depressing effect on respiration or in consequence of the hypotensive action of trimethaphan interfering, reflexly or otherwise, with pulmonary circulation and gaseous exchange (Dawes and Mestyan, personal communication) (Table 1). Thus, while possibly adding temporarily to the animal's comfort, i.e., its perceptive tolerance of the cold (11), keeping the body surface warm by drug action in the cold is eventually physiologically detrimental from the point of view of the body's total heat economy. These findings agree in substance with those of Honda (15) in rats, Schaumann (9) in mice, and Webb (12) in man, who all used various other, but analogous, vasodilating agents. Opposite results were obtained with Ilidar (10) in dogs, and with Dibenamine and megaphen (9) in mice.

Enhancing the heat production with dinitrophenol likewise did not help to maintain normothermia in the cold, although the pyrexia so induced at room temperature was maintained for a time in the cold and caused a slower rate of cooling in these dogs, without affecting their final degree of cooling. Thus, artificially produced fever may possibly be a beneficial guard against acute exposure to cold. An interesting result was the behavior of the oxygen consumption of these animals (Fig. 5): DNP apparently replaced a part of the metabolic stimulation produced by the cold environment. Only that portion of cold-induced metabolism necessary to contravene the environmental conditions was added to the stimulation of dinitrophenol. This latter finding did not

agree with earlier reports (16-18) that the thermogenic action of DNP is abolished in the cold. On the contrary, the present data suggested that it was the ambient cold that failed to exert its full metabolic stimulation in the DNP-treated dogs, since the maximum effects of both the drug and the cold were evidently not additive in the animals. In closer agreement with the present observations are the results of Magne et al. (19), Fuhrman et al. (20, 21), Hall et al. (22, 23), and Hollinger (24), who found that, allowances being made for the metabolic cost of shivering, the calorogenic effect of DNP could still be demonstrated.

There was an apparent correlation between the onset

of shivering and the mean skin temperatures of the unmedicated, metaraminol-treated and trimethaphan-treated dogs ( $29.6 \pm 0.2$  C). The correlation failed, however, in the case of the DNP-treated dogs (31.4 C). There was no relation between onset of shivering, duration of cold exposure, rectal temperature, and deep body-to-surface temperature gradients; however, the DNP-treated dogs, who shivered earliest, had the highest rectal temperature and the smallest core-to-shell temperature gradient at the onset of shivering.

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