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Effects of Third Cerebral Ventricular Injections of Cyclic Guanosine Nucleotides on Body Temperature of Cats (40267)

WESLEY G. CLARK

Department of Pharmacology, Southwestern Medical School, The University of Texas Health Science Center at Dallas, Dallas, Texas 75235

It has been suggested on the basis of several systems in which adenosine 3′,5′-monophosphate (cyclic AMP) and guanosine 3′,5′-monophosphate (cyclic GMP) apparently exert antagonistic influences that a balance between these nucleotides may regulate the activity of many tissues (1). In a number of recent studies, the effects of central administration of the dibutyryl derivative of cyclic AMP on body temperature have been examined. The most consistent responses have been primarily hyperthermia in the rabbit (2–4) and hyperthermia often preceded by hypothermia in the cat (5–7). In the present study the effects on body temperature of intraventricular injections of cyclic GMP and its dibutyryl derivative were determined for comparison with results obtained previously with dibutyryl cyclic AMP (6). Rather than being opposite, the responses to the cyclic guanosine nucleotides were very much like responses to dibutyryl cyclic AMP in the cat.

Materials and methods. Cannulas were implanted into the third cerebral ventricle (8) and thermocouples into the retroperitoneal space (9) of twenty-two adult cats. Procedures for their care and feeding, for automatically recording retroperitoneal temperature from these unrestrained, conscious animals and for avoiding pyrogenic contamination have been described previously (9). Environmental temperature was 22 ± 1°. Each animal received a single intraventricular injection of a cyclic nucleotide and a control injection of saline solution on separate occasions. These were given in randomly determined order so that half of the cats received the vehicle before the nucleotide and half received the nucleotide first. The order of administration had no apparent effect on the results. Injections were given at 10:00 AM (±5 min), and the average of temperature readings at 9:30, 9:45 and 10:00 AM was used as the baseline from which changes were measured. The mean baseline temperature ± SE before injections of nucleotides was 38.3 ± 0.1° and before control injections of vehicle was 38.5 ± 0.1°. Deviations of body temperature from the baseline were tabulated at 15 min intervals. Changes in temperature were calculated as a 'thermal response index' (TRI), one unit of which is equivalent to a 1° change lasting for 1 hr (10). TRIs for the hypothermic response of each cat to the nucleotide were determined from the time of injection until body temperature had risen to intersect the control value after injection of vehicle. TRIs for the subsequent hyperthermic response were determined from the beginning of hyperthermia until the response had decreased to again intersect the control curve or until 20 hr after injection if full recovery had not yet occurred. TRIs after saline injections were determined for these same two time periods with each cat. The paired *t* test was used for statistical analysis.

Monosodium salts of cyclic GMP and dibutyryl cyclic GMP (Boehringer Mannheim) were stored at −9°. Doses refer to these salts. They were weighed and dissolved in commercial, nonpyrogenic 0.9% NaCl solution immediately before intraventricular injection in a volume of 0.05 ml.

Results. Injections of 2 mg dibutyryl cyclic GMP produced an initial hypothermia in all animals (Fig. 1). The fall in temperature was accompanied by tachypnea, and the animal whose temperature decreased the most (2.2°) panted for several minutes. All of the animals defecated within 12 min, and three vocalized loudly for several minutes. One cat vomited three times from 5 to 17 min after injection. After recovery from the hypothermia which lasted approximately 2 hr, hyperthermia developed with a return to control levels about 12 hr later. A dose of 1 mg (Fig. 1) lowered body temperature in only three of the cats but caused hyperthermia in five. Table I sum-

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marizes the results. No appreciable change in temperature was produced by 0.5 mg dibutyryl cyclic GMP in four cats. Intraventricular administration of 5 mg cyclic GMP (Table I) produced initial hypothermia in four animals and relatively high hyperthermias in all six. Four of these cats vomited from 5 to 10 min after injection with additional episodes up to 22 min later. The only other consistent activity was lying down with gentle rocking of the body or shaking of the head from side to side. Two cats vocalized and one defecated.

Discussion. The effects of third ventricular administration of dibutyryl cyclic GMP in the cat were very similar to those after dibutyryl cyclic AMP in an earlier study in which injections were made into the lateral ventricle (6). In terms of concentration, dibutyryl cyclic GMP was less potent than dibutyryl cyclic AMP. With either nucleotide hyperthermia was the most consistent thermoregulatory change. If cyclic nucleotides are of physiologic significance in thermoregulation, the present study with exogenous cyclic guanosine nucleotides suggests that cyclic GMP and cyclic AMP would be more likely to produce similar thermoregulatory changes rather than to provide regulation by a balance between opposing actions. However, such a conclusion may be premature. Goldberg *et al.* (11) have pointed out that high concentrations of exogenous cyclic GMP can mimic cyclic AMP in several systems and may not necessarily mimic the effects of elevated levels of endogenous cyclic GMP.

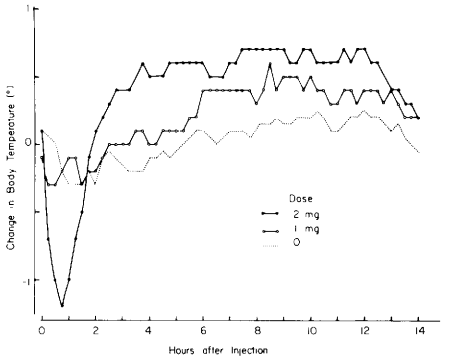

FIG. 1. Mean responses to third cerebral ventricular injection of dibutyryl cyclic GMP. Six cats were given each dose. The control responses of both groups to saline vehicle have been combined for clarity.

Since intraventricular injections of cholera toxin, which activates adenylate cyclase (12, 13), produced only hyperthermia in the cat (6), the predominant effect of endogenously synthesized cyclic AMP on body temperature is probably hyperthermia, and the less consistent hypothermic response to injection of dibutyryl derivatives may be attributable to the dibutyryl moiety. If so, cyclic GMP would be expected to produce little or no initial hypothermia. This possibility was at least partially borne out. Even though cyclic GMP caused greater hyperthermic responses than dibutyryl cyclic GMP, the dose of cyclic GMP caused a considerably smaller mean hypothermic response, and only four of the animals responded. Thus cyclic GMP can cause hypothermia, but this ability compared to its ability to cause hyperthermia is less than that of its dibutyryl derivative.

At present there is no consensus regarding a role of cyclic nucleotides in thermoregulatory responses. Injections of dibutyryl cyclic AMP into the hypothalamus of the cat (7) produced responses similar to those after intraventricular administration: namely, hypothermia followed by hyperthermia. Control injections of vehicle often also caused delayed

TABLE I. CHANGES IN BODY TEMPERATURE AFTER INJECTIONS OF CYCLIC GUANOSINE NUCLEOTIDES INTO THE THIRD CEREBRAL VENTRICLE. SIX PREVIOUSLY UNTESTED CATS WERE GIVEN EACH DOSE. RESULTS ARE EXPRESSED AS MEAN VALUES ± SE.

		Hypothermia		Hyperthermia	
Nucleotide	Dose (mg)	Maximum decrease (°)	TRI[a] (Δ° × hr)	Maximum increase (°)	TRI[a] (Δ° × hr)
Dibutyryl Cyclic GMP	2	1.2 ± 0.3*	−1.6 ± 0.7*	0.9 ± 0.2**	7.3 ± 3.7*
	0	0.3 ± 0.1	−0.3 ± 0.3	0.5 ± 0.1	1.5 ± 1.9
	1	0.5 ± 0.3	−0.6 ± 0.4	0.9 ± 0.2**	6.0 ± 2.3**
	0	0.1 ± 0.1	0.1 ± 0.1	0.3 ± 0.1	0.0 ± 1.4
Cyclic GMP	5	0.6 ± 0.2	−1.1± 0.6	1.4 ± 0.2***	14.0 ± 3.0***
	0	0.2 ± 0.1	−0.2 ± 0.1	0.7 ± 0.2	2.4 ± 1.5

[a] TRI = Thermal response index; see Methods section.
* $P < 0.05$ vs. control. ** $P < 0.025$. *** $P < 0.01$.

hyperthermic responses, and the authors concluded that the nucleotide caused primarily hypothermia. However, control intraventricular injections of vehicle in the rabbit (3) and cat (6, this study) did not cause hyperthermic responses like those after administration of cyclic nucleotides or cholera toxin so these latter responses were not due to the injection procedure. Futhermore, it has been shown that the response to cholera toxin was not due to pyrogenic contamination since the activity of the toxin was readily destroyed by heating conditions which did not alter the activity of a bacterial endotoxin (6). Evidence that cyclic nucleotides might be involved in development of fever includes the indication provided by cholera toxin that endogenous synthesis of cyclic AMP can cause hyperthermia (6) and reports that concentrations of cyclic AMP in cerebrospinal fluid increase during febrile states (14–16), that an inhibitor of adenylate cyclase can reduce the febrile effect of bacterial endotoxin (17) and that phosphodiesterase inhibitors enhance pyrogenic responses (2).

Summary. Third cerebral ventricular administration of dibutyryl cyclic GMP and cyclic GMP caused changes in body temperature similar to those after dibutyryl cyclic AMP; namely delayed hyperthermic responses preceded less consistently by tachypnea and hypothermia. These results do not support a regulatory role in thermoregulation provided by a balance between opposing actions of cyclic AMP and cyclic GMP.

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