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Effects of Sodium Salicylate, Aminopyrine and Chlorpromazine on Behavioral Temperature Regulation[1,2,4]

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POLK, D. L. AND J. M. LIPTON. *Effects of sodium salicylate, aminopyrine and chlorpromazine on behavioral temperature regulation.* PHARMAC. BIOCHEM. BEHAV. 3(2) 167–172, 1975. – To characterize drug actions on thermoregulatory processes it is necessary to know whether compounds which alter body temperature also cause changes in thermoregulatory motivation. In the present experiments the effects of sodium salicylate, aminopyrine and chlorpromazine (CPZ) on rectal temperature (T_{re}) and behavior were measured in rats trained to escape heat and obtain cooling. All three drugs produced hypothermia in a 23°C environment but the effects upon behavior suggest that the compounds have different actions. Sodium salicylate (60–300 mg/kg) increased the amount of time spent responding to escape heat and obtain cooling so that T_{re} was held below control levels. Aminopyrine (12.5–75 mg/kg) did not alter thermoregulatory motivation even though it caused marked hypothermia. The time spent responding decreased after CPZ (2 and 3 mg/kg) so that drug-induced hypothermias were compensated. The results suggest that sodium salicylate influences the central mechanisms of physiological and behavioral temperature control whereas CPZ affects either peripheral thermoeffectors or central effector pathways without disrupting thermoregulatory motivation. Aminopyrine is presumed to act on central temperature controls to lower body temperature and, at the same time, to reduce the significance of the low body temperature to behavior.

Drugs and thermoregulation | Sodium salicylate | Aminopyrine | Chlorpromazine | Rectal temperature
Behavioral thermoregulation | Hypothermia

BODY temperature of homeotherms is controlled through coordinated physiological and behavioral thermoregulatory responses. Certain drugs and chemical substances influence body temperature by causing changes in both physiological heat production/heat loss activity and thermoregulatory behavior. For example, pyrogens cause metabolic heat production to rise, and behavioral responding for exogenous heat to increase [7,41], until body temperature is driven to a higher level. In man, pyrogens cause a shift in the affective value assigned to peripheral thermal stimuli so that higher temperatures are preferred [6]. This change in affective value drives a feverish subject to complement physiological heat production activities with behavioral activity such as moving to a warmer environment, increas-

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ing insulation, etc., until a higher body temperature is reached. Central administration of tetrodotoxin and saxitoxin cause coordinated changes in physiological and behavioral thermoregulatory responses which result in controlled hypothermia [11]. Taken together, the results cited above provide strong evidence that certain chemical substances can cause a complementary shift in the set points for control of physiological and behavioral thermoregulatory activities.

On the other hand, it is clear that the physiological and behavioral thermoregulatory controls are separable in that behavior is often used to compensate for impairment of physiological thermoregulation [27,40]. Injection of dimethylsulfoxide, which causes an impairment of physiological regulation against cold, results in compensatory behavioral responding when rats are allowed to work for heat [32]. Compensatory changes in behavior also occur when body temperature is altered by intracerebral injections of adrenergic and cholinergic agents [1]. The aim of the present experiments was to learn how certain drugs that produce hypothermia influence thermoregulatory motivation. Specifically, the purpose was to characterize the effects of sodium salicylate, aminopyrine and chlorpromazine upon thermoregulatory processes by determining whether the compounds cause changes in behavior which help to maintain low body temperatures or whether they cause behavioral changes that are antagonistic to the hypothermic responses that normally occur when these drugs are given.

METHOD

Animals

The general approach was to inject the drugs and to record changes in body temperature and behavioral responses in rats trained to press a lever to alter the thermal environment. Male albino rats (Holtzman strain, 300–380 g), maintained at 95% of free-feeding body weight by restricting food intake, were used in these experiments. The animals were kept and all experiments were performed in an environment controlled at 23 ± 1°C.

Apparatus

The behavior test chambers have been described in detail previously [27,28]. Each chamber consisted of a Plexiglas cylinder with one open end set in a manifold box. The manifold box was equipped with an exhaust fan such that activation of the fan exhausted air from the box and caused room air to be drawn through the animal's space. In the behavior tests the rat could turn off a heat lamp (250 W) mounted above the chamber, and simultaneously obtain convective cooling from the fan, by pressing a glass lever. The total time spent pressing the lever to escape heat and obtain cooling was recorded automatically. The rats were trained in daily sessions which were gradually extended to one hour. Power dissipation of the heat lamps was adjusted to 160 W so that each animal spent approximately half the time pressing the lever. Each rat was assigned to 1 of 4 chambers for training and testing.

Procedure

Rectal temperature (T_{re}) was measured by inserting a thermistor probe 6 cm past the anus immediately before an injection was made (preinjection), 1 hr later, just before the animal was placed in the behavior chamber (postinjection), and again at the end of the 1 hr behavioral thermoregulation test (posttrial). Because the time course of the drug effects was important to interpretation of the behavioral results, additional experiments were performed in which body temperatures of untrained animals that had received the drugs were simply measured over time, without behavioral tests.

Intraperitoneal injections (0.5 ml) of drugs and saline were administered alternately at intervals of 48 hr. Each drug treatment was thus separated by at least 96 hr to avoid possible cumulative effects. A Latin square design was used to determine the sequence of drug doses for each animal. Nonpyrogenic normal saline was used for control injections and as the vehicle for drug delivery. Care was taken in making up solutions and in making injections to avoid contamination, and only sterile glassware and nonpyrogenic syringes and needles were used. The drugs tested were sodium salicylate (Fisher Scientific Co.), a drug that is antipyretic by virtue of its central action [9, 10, 13], and aminopyrine (4-dimethylaminoantipyrine, Aldrich Chemical Company), a lipid soluble antipyretic and analgesic that causes hypothermia in both febrile and afebrile subjects [3,19]. Chlorpromazine hydrochloride (Smith, Kline and French Laboratories) was tested because it appears to cause hypothermia in thermoneutral environments [12] and thermolability at extreme ambient temperatures [25,36]. The dose levels were selected for their effectiveness in producing hypothermia without blocking behavior as determined in pilot studies.

RESULTS

Body Temperature

All 3 drugs caused hypothermia although the decreases in T_{re} differed in magnitude and in time course.

Sodium salicylate. Sodium salicylate (60–300 mg/kg) produced dose-related decreases in body temperature in naive rats not used in the behavioral experiments (Fig. 1). The greatest hypothermias were recorded 3 hr after the 264 and 300 mg/kg doses were given when mean T_{re} declined 1.7 and 2.1°C, respectively. The 60 and 158 mg/kg doses caused average decreases of 0.5 and 0.9°C, respectively, and body temperature increased toward control levels 2 hr after these doses were administered. The T_{re}s measured 1 hr after the 2 lowest doses of sodium salicylate were given to the rats used in the behavioral experiments (Fig. 2) showed either no change or an increase. In the same rats the highest doses, 264 and 300 mg/kg, caused mean decreases of 0.5 and 0.9°C. Thus, the hypothermogenic effect of sodium salicyclate measured 1 hr after injection in the animals used in the behavioral experiments was considerably less than that observed after a similar postinjection period in naive rats.

Aminopyrine. Aminopyrine produced the greatest decreases in T_{re} observed in these experiments. In naive rats body temperature began to fall within 15 min after injection and reached the lowest level 1–1.25 hr after the drug was given (Fig. 1). The depth of hypothermia was related to the dose. The duration of action of aminopyrine was less than that of sodium salicylate, and T_{re} began to rise within 1–1.5 hr after aminopyrine was injected. The hypothermogenic effect of aminopyrine, like that of sodium salicylate,

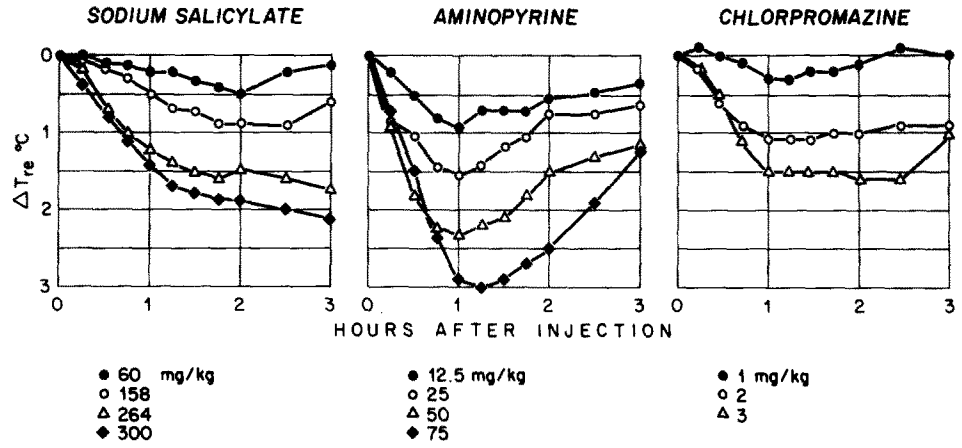

FIG. 1. Changes in T_{re} produced by sodium salicylate, aminopyrine and CPZ over a 3 hr period. Each data point represents the average T_{re} obtained from measures on 6 naive rats.

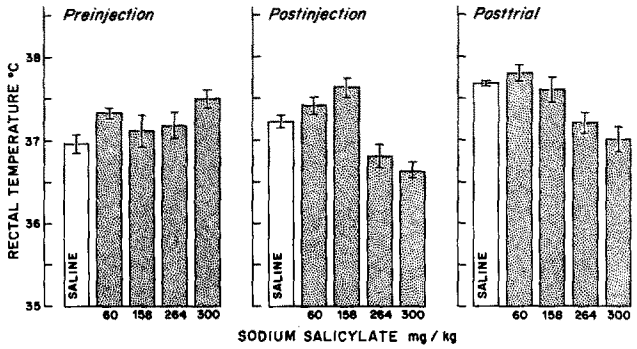

FIG. 2. Rectal temperature measured before injections of sodium salicylate were given (preinjection), one hr post injection (beginning of behavior test), and at the end of the behavior test (posttrial) in 12 rats.

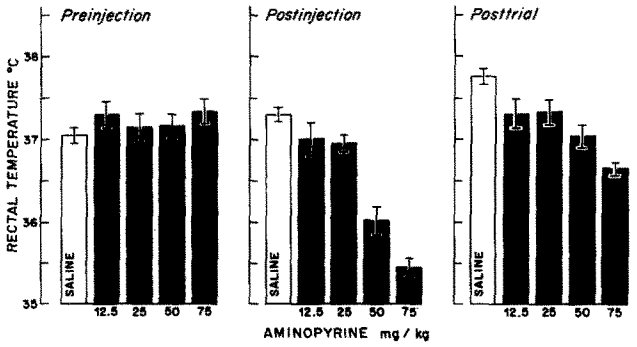

FIG. 3. Effects of aminopyrine on body temperature of animals used in the behavioral tests.

was smaller in the animals used in the behavioral experiments (Fig. 3). In the trained rats only the largest doses (50 and 75 mg/kg) produced clearly significant ($p<0.05$, Wilcoxan signed ranks test) decreases in T_{re} (1.2 and 1.9°C, respectively) by the end of the 1 hr postinjection period.

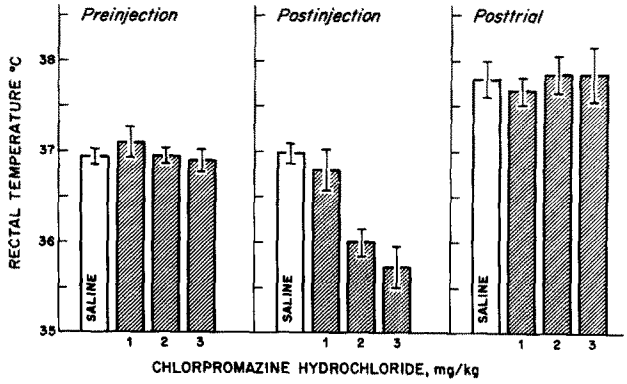

FIG. 4. Effects of CPZ on body temperatures of animals used in the behavioral tests.

CPZ. In naive rats 2 and 3 mg/kg doses of CPZ caused clear hypothermias but 1 mg/kg did not (Fig. 1). With the higher doses the maximum decreases in T_{re}, 1.1°C after the 2 mg/kg dose and 1.6°C after the 3 mg/kg dose, were recorded 1–2 hr after the drug was administered. In the trained rats the 1 mg/kg dose lowered T_{re} in only 4 of 12 cases. The 2 higher doses produced average falls of 0.9° and 1.2°C (Fig. 4), decreases that were slightly less than those seen in the naive rats.

Behavioral Temperature Regulation

Sodium salicyclate. Intraperitoneal injections of sodium salicylate caused dose-related increases in the amount of time spent escaping heat (Fig. 5). The significant increases ($p<0.05$) in responding to escape heat after the 2 highest doses caused posttrial body temperature to be below saline control levels (Fig. 2).

Aminopyrine. Injections of aminopyrine did not produce significant changes ($p>0.3$ or greater) in heat escape behavior (Fig. 6). However, since the body temperatures were below normal when the behavior tests were begun (Fig. 3), the posttrial temperatures were lower than those seen after saline injection. The magnitude of the difference between posttrial body temperatures after drug and

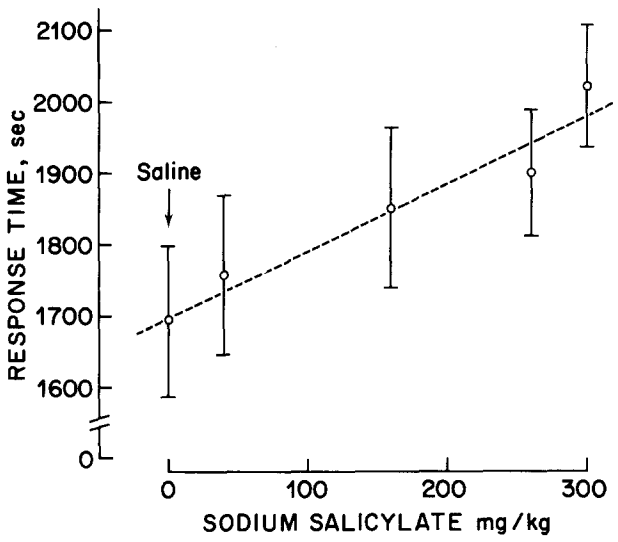

FIG. 5. Time spent responding to escape heat and obtain convective cooling increased after sodium salicylate injections. Scores in this and following graphs are means (± S.E.). Lines were fitted by using the method of least squares.

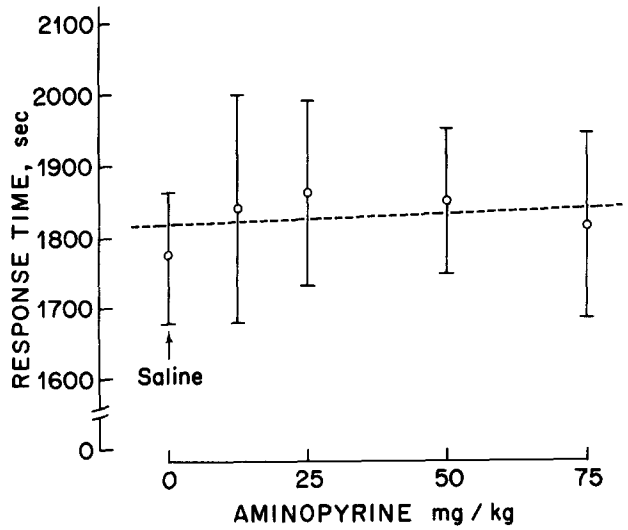

FIG. 6. Aminopyrine did not alter the amount of time spent responding to escape heat.

control injections was related to the dose of aminopyrine administered.

To learn whether this relatively short-acting drug has an effect upon behavior during the period when body temperature is falling most rapidly, separate experiments were performed using 2 new rats. In these animals injections of aminopyrine (50 and 75 mg/kg) given 15–45 min before the behavior test had no effect on thermoregulatory behavior. Posttrial T_{re}s were 1.6–2.2°C below those observed after saline was administered.

CPZ. Injections of CPZ produced decreases in heat escape behavior that were related to the amount of drug given (Fig. 7). The progressive decline in time spent escaping heat offset the low body temperatures observed before

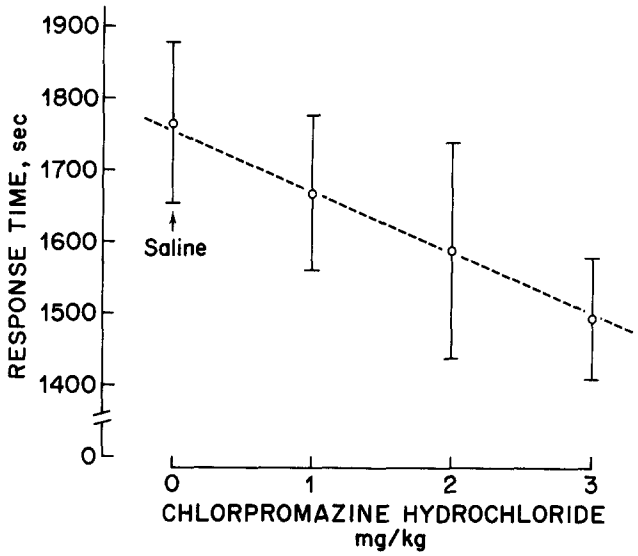

FIG. 7. CPZ injections caused a dose-related decrease in heatescape behavior.

the behavior tests and resulted in posttrial T_{re}s that were not different from those seen after saline injections (Fig. 4).

DISCUSSION

All three compounds used in these experiments caused hypothermia, in both trained and untrained rats, in a neutral environment. However, differences in effects on thermoregulatory behavior suggest that the influences of the drugs on thermoregulatory controls are not the same. The hypothermias produced by sodium salicylate in the 23°C environment were maintained through behavior rather than compensated; i.e., salicylate produced a complementary shift in both physiological and behavioral thermoregulatory processes to maintain body temperature at a lower level. Coordinated changes in physiological and behavioral thermoregulation, attributed to changes in hypothetical set points of control, are also produced by pyrogens [7, 16, 41] and tetrodotoxin [11]. Such a coordinated change would require that salicylate acts upon temperature control mechanisms within the central nervous system. It is clear that salicylates have actions both upon central mechanisms which are not directly associated with the control of body temperature, per se and upon peripheral thermoeffectors. For example, it is well known that salicylate stimulates respiration by acting on control mechanisms in the medulla oblongata [17]. Salicylates have also been reported to produce peripheral vasodilatation [38,39], to decrease the level of plasma free fatty acids [4], and to stimulate sweat glands directly [30]; actions which would tend to reduce body temperature. While it is likely that these effects contribute to the lowering of body temperature observed in the present experiments, it is less likely that they can account for the changes in behavior produced by salicylate. If salicylate acted solely upon effectors or upon effector pathways and not upon central temperature regulation mechanisms, then behavioral compensation for the induced change in body temperature would be expected rather than the coordinated change in

body temperature and thermoregulatory behavior observed. The coordinated response seen in the present experiments together with evidence that peripherally administered salicylate reaches portions of the brain concerned with body temperature control [14] leads us to conclude that salicylate has a direct action upon central temperature control mechanisms. In support of this idea, Wit and Wang [42] observed a slight stimulatory effect of acetylsalicylate upon temperature sensitive neurons in the afebrile cat. According to current theory, thermosensitive cells in the brain are of paramount importance to the determination of normal physiological and behavioral thermoregulatory responses [20,21]. If the effects of salicylate observed in the present experiments are due primarily to a central action then it may be that the drug influences temperature controls outside the PO/AH region (Lipton, 1973). There is evidence that 300 μg of sodium salicylate placed in the PO/AH region does not cause hypothermia [18].

Although it is generally held that most antipyretics have no influence on body temperature except in febrile states, evidence from the present experiments and from previous reports [3, 4, 34] suggests that salicylate alters normal body temperature of rats in neutral and cold environments. In anesthetized cats also, intravenous injections of sodium acetylsalicylate (30 mg/kg) produced decreases in body temperature even when the initial temperature was subnormal [31]. Yokoi [43] observed that acetylsalicylic acid, acetophenitidin, aminopyrine and phenylbutazone at dose levels usually used to produce antipyresis, altered body temperature in afebrile rabbits in hot and cold environments. Jacobson and Bass [23] have also reported that high doses of sodium salicylate potentiate hyperthermia of unacclimatized men working in a hot environment. Thus salicylates can affect the control of body temperature in afebrile states in rats and, under certain conditions, in other species as well. It may be that the effects on temperature in species other than the rat are due to influences on respiration, vasomotor or other effector activities which are normally compensated by the central temperature controls and that the influence of salicylate in these afebrile animals can be clearly observed only when the animals are anesthetized or exposed to thermal stress. In contrast, the salicylate-induced hypothermia observed in rats is believed to result from an influence on the central mechanisms responsible for regulation of body temperature, rather than on effectors or effector pathways alone.

CPZ has been found to produce hypothermia in thermoneutral environments in several species including the rat [22], the mouse [12] and man [2]. Although the effects of CPZ on body temperature have been attributed to specific actions on central temperature control mechanisms [25,36], there is evidence that CPZ placed directly into the PO/AH region causes hyperthermia [24,34], an effect opposite to that found after systemic administration. An alternative explanation for CPZ-induced hypothermia is that it results from increased heat loss through vasodilatation [8] and from the adoption of postures in which more body area is exposed to heat absorbing surfaces in the environment [26]. In line with this idea, the results of the present experiments indicate that CPZ does not alter those central mechanisms responsible for behavioral temperature control. It seems, then, that CPZ promotes heat exchange either through a peripheral action on thermoeffectors or through a central action that causes body temperature to fall without altering the central set point for behavioral thermoregulation.

The behavioral results indicate that chlorpromazine has effects on thermoregulatory processes which are unlike those produced by sodium salicylate but which are similar to the effects of experimental treatments used in previous research. For example, it has been shown that rats tend to compensate for disturbances in physiological temperature control produced by PO/AH lesions [27], high-fat diets [28], severance of salivary ducts [29], central administration of adrenergic and cholinergic drugs [1], and peripheral administration of drugs that increase vulnerability to cold stress [32]. Thus low doses of CPZ, in common with treatments used earlier, disrupt normal physiological thermoregulation but leave behavioral thermoregulation relatively intact. This idea fits with reports of human patients who show marked deviations in body temperature and complain of feeling cold or hot when CPZ treatment is initiated [2].

A third type of effect on thermoregulatory processes was observed after aminopyrine injections. This drug produced marked decreases in T_{re} although it did not alter normal responding to escape heat. The end result of this failure to decrease responding was that uncompensated hypothermias developed in the post-injection period and core temperatures were still below control levels at the end of the behavioral thermoregulation test. The exact nature of the action of aminopyrine which is responsible for the loss of significance of deep body temperature to thermoregulatory behavior is unclear. While the capacity of aminopyrine to decrease responsiveness to thermal stimuli [15,33] may be suspected, interpretation of the present results in terms of selective alteration of sensory information used by temperature control systems would be premature. There is also no previous evidence that aminopyrine has a differential effect upon the appreciation of core temperature as opposed to an effect upon the peripheral temperature sensory information that is required for normal behavioral thermoregulation. On the other hand, it seems reasonable to suspect that aminopyrine causes changes in thermoregulatory processes by acting on the central nervous system. This compound has been found to enter the brain and other body tissues rapidly after oral administration [5]. Ten Cate and Knoppers [37] noted that aminopyrine acts above the level of the cervical spinal cord to produce vasodilatation and marked decreases in body temperature. In related experiments rats with spinal cord transections between C_6 and C_7 still showed some reductions in body temperature, presumably the result of a central action of the drug to reduce heat production. The effect noted in the present experiments, a decrease in body temperature without a change in thermoregulatory behavior, suggests that aminopyrine acts specifically upon temperature control mechanisms in the brain since an action upon effector mechanisms alone should be compensated through behavior, as it was after CPZ. Although interpretations in terms of the specific actions of aminopyrine upon thermoregulatory controls are unwarranted at this time, the data suggest that aminopyrine might be useful in clinical applications when it is desirable to reduce body temperature without discomfort.

In summary, the combination of measures of deep body temperature and of thermoaffective motivation provide a means of further characterization of drugs that influence

thermoregulatory processes. The present findings suggest three types of effects: complementary resetting of physiological and behavioral thermoregulatory set points, behavioral compensation for drug-induced changes in body temperature, and changes in body temperature that are not significant to the animal's motivation. In future experiments it will be possible to characterize the actions of other drugs according to these three types of effects and, using the same techniques, to improve the understanding of the relations between physiological and behavioral thermoregulatory controls.

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