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Effects of hyperbaric helium–oxygen on the antipyretic actions of aspirin and acetaminophen in rats

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Hart, J. L. 1978. Effects of hyperbaric helium–oxygen on the antipyretic actions of aspirin and acetaminophen in rats. Undersea Biomed. Res. 5(1): 53–62.—The effects of two antipyretics, aspirin and acetaminophen, were studied under hyperbaric helium–oxygen conditions. Groups of yeast-fevered rats were given three different doses of each antipyretic in 1-ATA air and 31-ATA helium–oxygen. Neither agent was as effective an antipyretic in hyperbaric helium as it was in 1-ATA air. Responses to acetaminophen were reduced an average of 73%, and those to the two lower doses of aspirin by 56%; the highest dose of aspirin (135 mg/kg) caused a significant elevation of temperatures in the hyperbaric environment. A similar increase in temperatures was observed in rats treated with 135 mg/kg of aspirin and exposed to hot (30–31°C) air at 1 ATA. It is concluded that the decreased efficacy of antipyretics in hyperbaric helium environments is caused by the high ambient temperatures maintained in the helium (34–35°C) to compensate for the greater thermal conductivity of helium compared to nitrogen, which may limit the heat-dissipating abilities of rats in the hyperbaric environment.

hyperbaric helium
thermoregulation
antipyretics

The action of common antipyretics under hyperbaric conditions is of interest since these agents are among those that may be used during prolonged stays in underwater high-pressure habitats. The use of thermally active agents in hyperbaric helium environments should be of special concern, for many studies in both man and animals (Raymond 1967; Fischer and Musacchia 1968; Stetzner and Deboer 1972; Timbal, Vieillefond, Guenard, and Varene 1974) have established that thermal balance is significantly modified in more thermally conductive environments. Heat loss is accelerated, and the thermal neutral range is not only elevated but narrowed in helium environments. To compensate for these effects, ambient temperatures must be elevated. However, there is also evidence that thermoregulatory mechanisms may not

be functioning normally in helium, especially hyperbaric helium, environments even if ambient temperature is elevated to prevent excessive heat loss (Brauer 1973).

It has previously been reported (Hart 1974) that the antipyretic effect of sodium salicylate in rats was not altered by hyperbaric air (9 ATA). Further, the hypothermic effects of large doses of sodium salicylate were not modified by helium at 1 ATA or 6 ATA (Hart 1975). In these studies relatively low pressures were used. The ambient chamber temperatures were not controlled; therefore, the hypothermic effects of the environments themselves were a complicating factor. Also, the salicylate was administered intraperitoneally before the actual dive rather than after some time at pressure. Since these earlier studies were done under conditions unlikely to be encountered in actual diving practice, the present experiments were undertaken. In these studies the antipyretic activity of orally administered aspirin and another common over-the-counter antipyretic, acetaminophen, was investigated in hyperbaric (31 ATA) helium–oxygen environments under conditions that more closely parallel those that might occur in actual habitat environments.

METHODS

The hyperbaric chamber

The hyperbaric chamber used in these studies was a steel cylinder 4 ft long by 18 inches in diameter (Bethlehem Corp.), equipped with a sliding platform on which rat restrainers were placed. The oxygen and carbon dioxide concentrations and temperature of the chamber atmosphere were monitored and regulated. A 3-inch electrical fan was used inside the chamber to improve gas mixing. The details of the chamber and environmental control systems used have been described previously (Small 1970). The only difference in the present studies was the method of oxygen analysis. Oxygen was monitored every 15 min by sampling chamber gas with a magnetic resonance oxygen analyzer (Magnetic Oxygen Analyzer, Model 802, Mine Safety Appliances Co.). Oxygen concentration was maintained between 0.20 and 0.25 ATA by adding small amounts of pure oxygen when the Po_2 fell.

Preparation of rats

Female Sprague-Dawley rats [Nmri–0(SE)CV] (190–250 g) were anesthetized on the morning of Day One of the experimental protocol with pentobarbital (V-Pento, A. J. Buck and Son) (40 mg/kg, ip). Short tubes were secured in the cheeks of the rats; 1/8-inch OD nylon tubes were used for the aspirin studies, and PE–240 polyethylene tubes for the acetaminophen studies. These cheek tubes allowed stomach tubes to be inserted for the administration of drugs. The stomach tubes were sized to fit snugly into the cheek tubes, which prevented the rats from pulling out the stomach tubes. After surgery, the rats were returned to housing cages (one per cage) and allowed to recover.

At 1230, one (aspirin studies) or two (acetaminophen studies) days after surgery, fever was induced according to the method of Loux, Depalma, and Yankell (1972). Brewer's yeast (Fisher Scientific Co.) was injected under the skin in the upper back (4 g/kg, 20 ml/kg, aqueous suspension). The rats were then returned to the housing cages and fasted (water was available ad libitum) until the following morning, when they were used for antipyretic testing.

Antipyretic testing procedure

For the aspirin studies, aspirin (acetylsalicylic acid, Aldrich Chemical Co.) was suspended in 0.5% sodium alginate (Fisher Scientific Co.) so that a volume of 8 ml/kg was injected for each dose. Three doses were administered (45, 90, and 135 mg/kg) to groups of eight rats. For the acetaminophen studies, acetaminophen [4-Acetamidophenol (p-hydroxyacetanilides), Aldrich Chemical Co.] was dissolved in 3% ethyl alcohol. Doses of 30, 90, and 135 mg/kg were administered to groups of six rats, also in concentrations so that a volume of 8 ml/kg was received by each rat. These doses are higher than the usual antipyretic doses in humans (10–20 mg/kg); however, they are within the range used for antipyresis in yeast-fevered rats (Loux et al. 1972). For both studies, groups of rats receiving vehicle only were also tested. Injections were delivered through the stomach tubes, which were attached to syringes. The syringes were mounted in a constant-rate infusion pump (Harvard Apparatus Co., Model No. 975), which injected at a rate of 0.4 ml/min. The injection time was, therefore, between 3.8 and 5 min, depending on the size of the rat.

On the day of the antipyretic testing, the fevered rats were put in the restrainers at 0800 (19.5 h post-yeast), and placed on the sliding platform at the mouth of the hyperbaric chamber. Body temperatures were measured using rectal thermistors (Yellow Springs Instrument Co., No. 423) inserted to a depth of 5 cm and secured to the tails with tape. Temperatures were recorded on a Beckman Linear Potentiometer Recorder (No. 619D). Polyethylene tubes were inserted through the cheek tubes so that the distal end was in the stomach. Rats whose temperatures were below 38.50°C at 0900 were not considered adequately fevered and were not used for antipyretic testing. Ten rats were tested on each day, and were randomly chosen to receive one of the drug doses or vehicle only.

Rats to be studied in air were left undisturbed at the mouth of the chamber; their rectal temperatures were recorded at 15-min intervals until 1430. Injections were given at 1030 (22 h post-yeast). Ambient temperatures during these experiments ranged between 20 and 22°C.

Rats exposed to hyperbaric conditions were sealed in the chamber at 0930. The chamber was flushed with a mixture of 79% helium–21% oxygen until gas analysis showed the chamber atmosphere to be free of nitrogen, which took about 10 min. At 0945, compression with pure helium was begun at a rate of 30 psi/min until a pressure of 455 psi (31 ATA) was reached at 1000. After compression, the rats remained undisturbed until 1100, when injections were given. Temperatures were recorded at 15-min intervals until 1500.

For these hyperbaric experiments, chamber temperature was elevated to 31°C just before the beginning of the helium–oxygen flushing, and then maintained between 34 and 35°C while the rats were at the bottom. These elevated ambient temperatures are necessary to compensate for the increased rate of heat loss in the helium environment. The temperatures of rats that were fevered but received no injections did not vary significantly during a 4-h period in this environment.

Groups of six control (0.5% sodium aliginate only) and six aspirin-treated (135 mg/kg) rats were also observed in 1-ATA air at 30–31°C (hot air). These rats were sealed in the hyperbaric chamber at 0930, at which time the chamber temperature was elevated to 30.5°C. Breathing-quality compressed air was used to maintain 2–4 psi of pressure in the chamber so that the gas monitoring instruments and CO_2 scrubber could be operated. Injections in these rats were given at 1100 and temperatures were recorded until 1500.

At the end of all experiments, the placement of stomach tubes was verified and the tubes were checked for leaks caused by chewing. The thermistor probe positions were also checked. Data were not used from rats with tubes or probes which were out of position or showed

evidence of leaking. Similarly, data were not used from rats that escaped from the restrainers while in the hyperbaric chamber.

RESULTS

Mean changes (± SE) in temperatures of groups of rats receiving aspirin or vehicle only are graphed as a function of time in panel A of Fig. 1 for 1-ATA air (20–22°C) and in panel B for 31-ATA helium–oxygen (34–35°C). In Fig. 2, results for rats receiving acetaminophen are graphed. Analysis of variance established that the temperatures at the time of injections, both within exposure groups and between exposure groups, were not significantly different.

The temperatures of the control rats in the aspirin studies in 1-ATA air and 31-ATA helium did not vary during the three hours after injections, as determined by analysis of variance. In 1-ATA air, all three of the aspirin doses caused significant decreases in temperatures when compared to the control group (Student's t-test, $P < 0.05$) and these decreases were dose-related. However, in the hyperbaric conditions, the antipyretic effects of the two lower doses of aspirin were greatly diminished, while the highest dose actually caused a significant elevation of temperatures. The magnitudes of the decreases caused by the 45 and 90 mg/kg doses were not different from those of the control group at any time when analyzed by the t-test. However, the sign test (Zar 1974) indicated that both doses caused a significant decrease in temperatures.

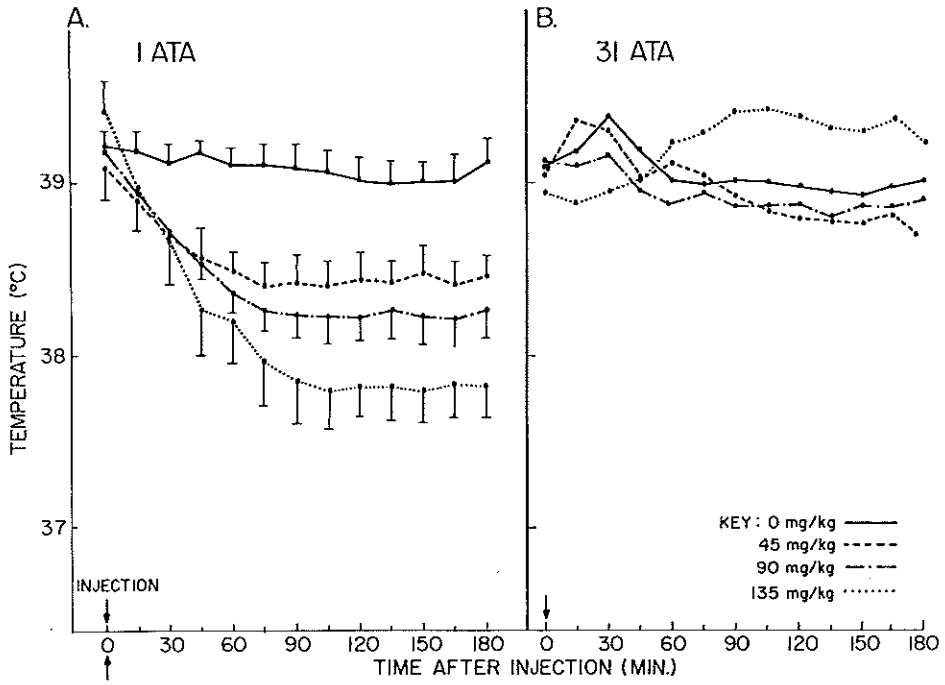

Fig. 1. Temperatures of untreated (0 mg/kg) and aspirin-treated rats in 1-ATA air (20–22°C) (panel A) and 31-ATA helium–oxygen (34–35°C) (panel B). Values are means ± SE of groups of 8 rats; SE have been omitted from the 31-ATA data for clarity. (Data for the helium-exposed control and 135 mg/kg aspirin-treated rats are also plotted, with SE, in Fig. 3.)

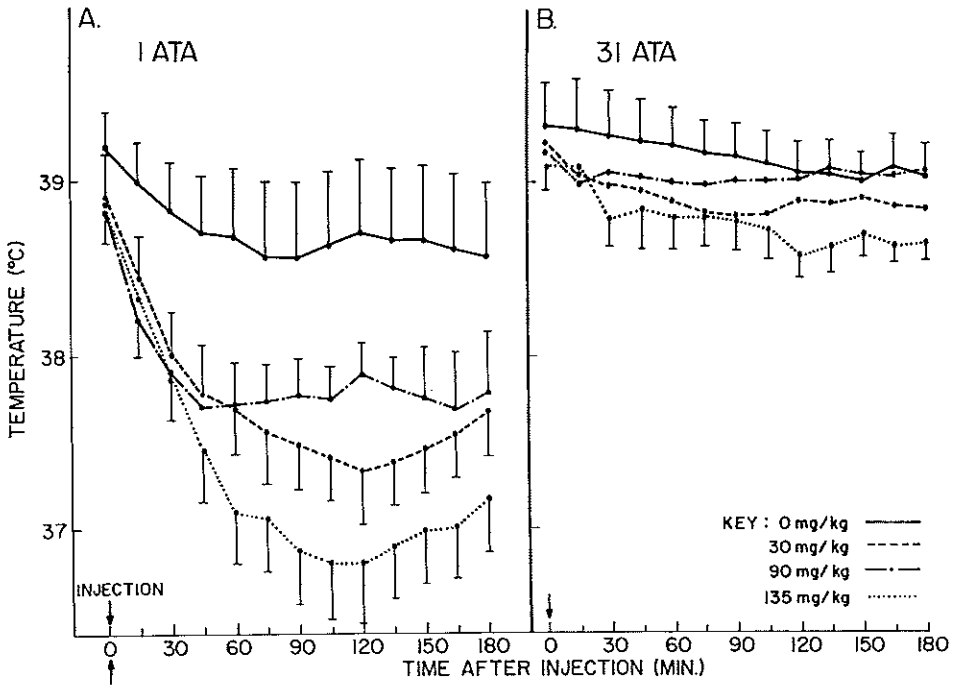

Fig. 2. Temperatures of untreated (0 mg/kg) and acetaminophen-treated rats in 1-ATA air (20–22°C) (panel A) and 31-ATA helium–oxygen (34–35°C) (panel B). Values are means ± SE of groups of 6 rats; SE have been omitted from some of the 31-ATA data for clarity.

The temperature of the control rats in 1-ATA air in the acetaminophen experiments, those receiving the 3% ethyl alcohol only, did show significant decreases in temperature (as determined by analysis of variance) during the three hours after injections. This temperature-lowering effect of alcohol is well known and has been attributed to its vasodilating effect, especially in cutaneous blood vessels (Hirvonen 1975). A gradual decline of temperatures of control rats in the hyperbaric conditions was also apparent (Fig. 2, panel B); however, these changes were not significant. All three doses of acetaminophen caused decreases in temperatures below those of controls in 1-ATA air. The acetaminophen antipyresis was diminished in the hyperbaric conditions. Using the *t*-test, only the 135 mg/kg dose caused a significant decrease, although the sign test indicated that all three doses caused a significant time-dependent depression in temperatures below those of the control group.

The data in Figs. 1 and 2 are presented as means of temperatures taken at the same times after injections; however, all of the rats receiving a given dose did not achieve maximum temperature changes at the same time after injection. For this reason, the means of the maximum change in temperatures, either increase or decrease, for each rat were determined for each dose. These data are presented in Table 1.

A two-factor analysis of variance of these maximum deviation data for the aspirin-treated rats indicated that there were significant dose and condition effects, and interaction of dose and condition ($P < 0.005$). For the acetaminophen-treated rats there were also significant dose and condition effects ($P < 0.005$), but no significant interaction of dose and condition ($P > 0.05$).

To determine where, within each condition, differences existed between means, the Student-Newman-Keuls (SNK) multiple range test was performed (Zar 1974). Results of this test are indicated in Table I by the double horizontal lines drawn under the means. No

TABLE 1

EFFECTS OF ASPIRIN AND ACETAMINOPHEN ON TEMPERATURES OF RATS IN 1-ATA AIR AND 31-ATA HELIUM–OXYGEN

Condition	Dose, mg/kg 0	45	90	135
		Aspirin		
1 ATA	− 0.34 ± 0.19	− 0.87 ± 0.12	− 1.14 ± 0.13	− 1.80 ± 0.17
31 ATA	− 0.10 ± 0.16	− 0.44 ± 0.10	− 0.43 ± 0.10	+ 0.63 ± 0.20
Condition	0	30	90	135
		Acetaminophen		
1 ATA	− 0.55 ± 0.32	− 1.68 ± 0.30	− 1.43 ± 0.24	− 2.17 ± 0.17
31 ATA	− 0.35 ± 0.13	− 0.50 ± 0.10	− 0.30 ± 0.21	− 0.68 ± 0.10

Data are means ± SE of maximum deviation in temperature (°C) from that at time of injection for rats in each group. Double horizontal lines connect means within a condition between which no significant differences ($P > 0.05$) could be detected with the SNK multiple range test (*see* text). Means individually underlined are different from all other means in that group; vertical lines connect means between conditions which are not significantly different ($P > 0.05$) as determined by Student's t-test.

difference could be detected ($P > 0.05$) between means connected by these lines. Individually double-underlined means are significantly different from all other means in that group.

In addition, for both drugs, the mean maximum temperature changes at each dose were compared between 1 ATA and 31 ATA by Student's t-test. The vertical lines in Table I indicate means which were not significantly different. Note that for both aspirin and acetaminophen, the temperature changes of control rats were not different in the hyperbaric helium conditions from those in 1-ATA air. However, for all groups of acetaminophen-treated rats, there was a significant reduction in antipyretic effects under hyperbaric conditions. These reductions were 70% for 30 mg/kg, 81% for 90 mg/kg, and 69% for 135 mg/kg. Rats receiving the two lower doses of aspirin also showed reductions in responses: 50% for 45 mg/kg and 62% for 90 mg/kg. The group treated with the highest dose (135 mg/kg) of aspirin showed an increase in temperature in the hyperbaric conditions.

Results of rats studied in hot air (30–31°C) are graphed in panel A of Fig. 3. Mean maximum deviation of the control group was +0.01 ± 0.32°C, while that for the aspirin-treated (135 mg/kg) group was +0.85 ± 0.27°C, which was a significant elevation as determined by the t-test. For comparison, the results of control and aspirin-treated rats in 31-ATA helium–oxygen are graphed in panel B of Fig. 3. The maximum deviation in temperatures for these rats (see Table I) was +0.63 ± 0.20°C, which was not significantly different from the mean response of rats receiving the same dose of aspirin in the hot 1-ATA air.

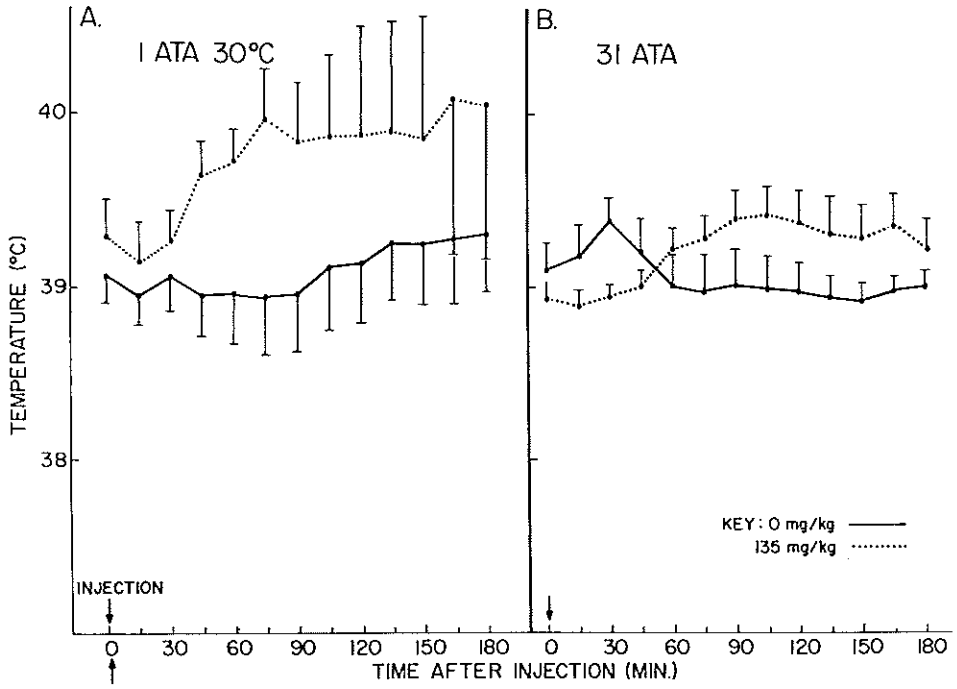

Fig. 3. Temperatures of untreated (0 mg/kg) and aspirin-treated (135 mg/kg) rats in 1-ATA hot air (30–31°C) (panel A) and 31-ATA helium–oxygen (34–35°C) (panel B). Values in panel A are means ± SE of groups of 6 rats, while those in panel B are of groups of 8 rats.

DISCUSSION

These results clearly show that under the conditions of these experiments, neither aspirin nor acetaminophen is as effective an antipyretic in hyperbaric helium as in 1-ATA air. The acetaminophen responses were reduced by an average of 73% in hyperbaric helium. The response to the two lower doses of aspirin were 56% less than that in 1-ATA air, while the highest dose actually raised temperatures in the hyperbaric conditions.

There are a number of possible causes for the reduced antipyretic action of these agents under hyperbaric helium conditions. The absorption, distribution, or excretion of the drugs may be altered. However, the acute oral toxicity of aspirin in mice has been shown not to be altered in helium at 20 ATA (Small 1970), suggesting that the pharmacodynamics of at least high doses of aspirin are not modified by hyperbaric helium.

Another possible factor involved in the reduced action of the antipyretics is that the high hydrostatic pressure, the helium, or a combination of both may be acting as antagonists to these agents at their sites of action. Both aspirin and acetaminophen are postulated to exert their antipyretic action on central nervous system sites (Milton 1976), probably on the temperature control centers of the hypothalamus. However, the majority of studies on therapeutic drugs indicates that hyperbaric helium has little effect on their activity (Small and Friess 1975).

It appears more likely that the unusual thermal properties of hyperbaric helium and the resulting modifications of thermal balance and perhaps thermoregulatory mechanisms account for the reduced antipyresis observed. It is well established that the high heat capacity of hyperbaric environments and the high thermal conductivity of helium compared to nitrogen

make hyperbaric helium environments even at normal ambient temperatures environments in which animals lose heat much more rapidly than in 1-ATA air (Raymond 1967). Clarkson, Schatte, and Jordan (1972) reported that the thermal neutral temperature of rats in 1-ATA helium–oxygen was elevated to 31–33°C compared to a range of 26–28°C in 1-ATA air. Also, Stetzner and Deboer (1972) studied thermal balance in rats in hyperbaric helium–oxygen and found that it was necessary to maintain ambient temperatures at 94°F (34.4°C) to "maintain core temperatures" at 41 ATA. To avoid a drop in core temperature and the metabolic stimulation of a "cold" helium environment, it is therefore common practice to elevate the ambient temperature of such environments. This was done in the present experiments; ambient temperature in hyperbaric helium was maintained between 34–35°C. That this was a thermal neutral temperature for rats at 31 ATA is supported by the observation that rats receiving no antipyretics did not show significant changes in temperatures during a 4-h observation period.

If the chamber temperatures were actually warmer than the thermal neutral range, one would expect that some of the heat-dissipating capacity needed during antipyresis would already be in use to maintain core temperature. The capacity for further heat dissipation would therefore be limited. Heat dissipation in rats is reported to occur primarily via peripheral vasodilation, with panting and sweating playing a minor, if any, role (Rommelspacher, Schulze, and Bolt 1975). Further, cutaneous vasodilation is known to play an important role in the temperature-lowering actions of both aspirin and acetaminophen (Milton 1976).

Other differences in the environments of the controls and helium-exposed rats may have influenced their relative heat-dissipating capacities, since the control animals were not confined in the chamber but only placed at the entrance to the chamber. For instance, it is assumed, although no actual measurements were made, that the relative humidity in the closed chamber was higher than that in the room, making heat elimination somewhat more difficult in the chamber.

In addition, both Clarkson and his group (1972) and Stetzner and Deboer (1972) observed that the surface temperatures of rats in thermal neutral helium environments were elevated above surface temperatures of rats in thermal neutral air. This suggests that significant cutaneous vasodilation may be the usual condition of rats in thermal neutral helium environments, while this is not the case in thermal neutral air environments, hypotheses which are supported by results with the 135 mg/kg dose of aspirin. This dose was strongly antipyretic in rats in a 20–22°C 1-ATA air environment (Fig. 1). However, in hot air (30–31°C) it caused a significant elevation in body temperatures (Fig. 3). Temperature elevation is a well-established effect of high doses of aspirin, and has been attributed to its ability to uncouple oxidative phosphorylation (Smith and Smith 1966). The actual dose at which this temperature-elevating effect overcomes the antipyretic effect has been reported to be dependent on the environmental temperature (Yokoi 1969; Hart 1975). As environmental temperature is increased, heat dissipation mechanisms are employed to maintain core temperature and are therefore not available for further heat dissipation imposed by an uncoupling dose of aspirin; this results in an elevation of core temperature in hot environments with doses that cause decreases in temperatures in a cooler environment.

A similar response, temperature elevation, was observed in rats in the hyperbaric helium environment after the 135 mg/kg dose of aspirin (Fig. 3). This could indicate that the thermoregulatory mechanisms of these helium-exposed rats were comparable to those of rats in the hot air environment. No such hyperthermic effects of acetaminophen have been reported, nor were there any elevations in temperatures of rats treated with acetaminophen and exposed to the hyperbaric helium, although there were significant reductions in the antipyretic effects.

For these reasons, acetaminophen-treated rats were not studied in the hot air environment.

It is possible, therefore, that the reduced effectiveness of antipyretics in thermal neutral hyperbaric helium is entirely due to the state of the heat-dissipating mechanisms, which appear to be similar to those in hot 1-ATA air. The possibility that peripheral vasodilation in helium is due to a specific physical or pharmacologic effect of helium or of high hydrostatic pressure has not been ruled out, however.

Brauer (1973) has suggested that simply elevating ambient temperature does not solve all of the thermal problems of high pressure helium environments. This procedure prevents excessive heat loss and provides for "thermal comfort," but appears to modify thermoregulatory processes in other as yet unexplained ways. He points out that "paradoxic temperature regulation," i.e., simultaneous shivering and sweating, is not an uncommon experience in persons sojourning in high pressure helium environments. Results of the present studies further indicate that thermoregulation in hyperbaric helium is not the same as in air, and suggest that caution should be used in employing thermally active agents in hyperbaric helium environments.

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Naval Medical Research and Development Command, Research Task No. MPN 10.02–5012. The opinions and assertions contained herein are the private ones of the author and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large. The experiments reported herein were conducted according to the principles set forth in the "Guide for the Care and Use of Laboratory Animal Resources," National Research Council, DHEW, Pub. No. (NIH) 74–23.—*Manuscript received for publication July 1977; revision received September 1977.*

Hart, J. L. 1978. L'influence d'un mélange hélium-oxygène hyperbare sur l'activité antipyrétique de l'aspirine et de l'acétaminophène chez le rat. Undersea Biomed. Res. 5(1): 53–62.—Les activités de deux antipyrétiques, l'aspirine et l'acétaminophène, ont été étudiées en milieu hyperbare. Une fièvre a été produite chez les rats par des levures, et les animaux ont été séparés en groupes pour recevoir trois doses différentes de chaque antipyrétique, en air (1 ATA) ou en hélium–oxygène (31 ATA). Ni l'un ni l'autre des deux médicaments n'est aussi efficace contre la fièvre en hélium hyperbare qu'il ne l'était en air à 1 ATA. Les réponses à l'acétaminophène étaient réduites par 73% en moyen, et les réponses aux doses plus basses de l'aspirine par 56%. La dose maximale d'aspirine (135 mg/kg) a abouti à une élévation significative de la température corporelle en milieu hyperbare. Une hausse semblable de la temperature a été constatée chez des rats traités avec 135 mg/kg d'aspirine et exposés à l'air chaud (30–31°C) à 1 ATA. Nous concluons que la température ambiante élevée maintenue en milieu hélium (34–35°C) ait pour résultat éventuel la réduction de l'efficacité des antipyrétiques. Cette température, maintenue pour compenser la plus grande conductivité thermiuqe de l'hélium realtif à l'azote, limiterait la thermorégulation corporelle des rats en milieu hyperbare.

hélium hyperbare
thermorégulation
antipyrétiques

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