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Physical Stimulation Reduces the Brain Temperature of Infant Rats

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Abstract

Previous work indicated that physical stimulation, such as that which mimics the stimulation pups receive from the dam, reduces pup body temperature. The present paper reports that the body and brain temperature of 5-day-old pups covaried under steady-state thermal conditions, cold exposure, and warmth exposure (Expt. 1) suggesting that body thermoregulatory mechanisms may also regulate brain temperature. Indeed, physically stimulating pups decreased brain temperature in the neocortex (Expt. 2) and the olfactory bulb (Expt. 3). The mechanism for this brain temperature decrease appears to be an increase in ventilatory heat exchange, the same mechanism responsible for the decrease in body temperature. Pups increased respiration during stimulation, thereby increasing air flow to the lungs where convective and evaporative heat exchange occurred. Indeed, stimulating pups in a high-humidity environment blocked the decrease in brain temperature (Expt. 4). The ability of physical stimulation to decrease brain temperature appears to be limited to neonatal pups, as 10-, 15-, and 20-day-old pups did not exhibit a brain temperature decrease in response to stimulation (Expt. 5).

Much of the ability to regulate body temperature by pups appears to be mediated by behavioral means (Alberts, 1978a,b; Alberts & Brunjes, 1978). However, physiological thermoregulatory systems are functional enough to provide pups with heat production during cold exposure (Hull, 1973; Hull & Segall, 1965; Knight & Skalla, 1977; Svoboda, Skobisova, & Drahota, 1984; Taylor, 1960) and dissipate heat during heat exposure (Sullivan, Shokrai, & Leon, 1988).

Pups also need to regulate their brain temperature, and may do so independently of body temperature (Aulick, Robinson, & Tzanhoff, 1981; Kiley, Eldridge, & Millhorn, 1984). This may be especially true during periods of thermal instability. Specifically, during periods of cold and heat exposure, when thermoregulatory systems are activated, considerable differences between body and brain temperature may exist, with brain temperature being defended in a more narrowly defined temperature range than body temperature (Cooper & Kenyon, 1957; Delgado & Hanai, 1966; Kiley et al., 1984; Stupfel & Severinghaus, 1956).

Brain temperature is a prominent factor in normal neural functioning (Emirbekov & Meilanov, 1982; Gold, Cahani, Sohmer, Horowitz, & Shahr, 1985; Hussein, Mohamed, Selim, & Din, 1983; Mohamed, Aly, & Selim, 1983; Saad, Blass, Robinson, & Moran, 1984; Thompson, Masukawa, & Prince, 1985). Thus, an understanding of infant brain temperature regulation is likely to provide insight into neonatal neurobehavioral functioning. The purpose of the present report is to begin to assess neonatal rat brain temperature regulation.

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General Methods

Subjects

The subjects were 5- and 6-day-old (Expts. 1-4) and 10-, 15-, and 20-day-old (Expt. 5) male and female rat pups (Hilltop Lab Animals, Scottsdale, PA) born in our animal care facility. The colony room was temperature (21-23°C), and humidity controlled and on a 12: 12 hr light: dark cycle. Females were checked for births at 1700 hrs and litters found at that time were considered 0 days old. At 1 day of age, litters were culled to 8 pups with an even sex distribution. Only one pup of each sex was used in an experimental condition, with equal numbers of males and females in each condition.

Implantation of Brain Thermistor

Pups were anesthetized with either an i.p. injection of a 1: 1 mixture of Ketaset and Rompun (.05 mL/100 g), or with cold anesthesia. Pups were then placed in a standard stereotaxic apparatus and the skull exposed. Two small holes were drilled in the skull, one on each side of the skull lateral to lambda. These holes were used to allow a thin wire (0.05 mm diam) to be attached to the skull, one end hooked in each hole. This wire was used to anchor the head cap to the skull, in a manner similar to that described by Gilbert and Cain (1980). A third hole was placed in the skull over 1) the neocortex, slightly lateral and posterior to bregma or 2) the olfactory bulb (Expt. 3 only). The thermistor was lowered 1.0, 1.3, 1.6, and 2.0 mm, respectively, into the brains of 5-, 10-, 15, and 20-day-old pups and cemented in place with dental acrylic, which surrounded the thermistor assembly and the anchor wire. The thermistor assembly consisted of a thermistor (0.001" diam; Thermonetics, NJ) and 2 male Amphenol pins in an Amphenol connector strip. Following recovery from anesthesia, pups were returned to the litter. The pups seemed to have no difficulty suckling, and after a brief period of increased attention, the mother seemed to treat the pups normally. The body weights of operated and non-operated pups within a litter did not differ.

Recording Brain Temperature

After at least a 24-hr recovery period, pups were connected through a lightweight cable to a Grass polygraph and brain temperature recorded. All recordings took place in a 32°C incubator, with pups in individual glass dishes (9 × 7 × 7 cm). Two pups were always monitored at the same time, in the same incubator; one pup was stimulated, and the other pup was left undisturbed. Following treatment, the thermistor location was verified using standard histological techniques.

Data Analysis

Prior to implantation, each thermistor was calibrated in warm water against a Sensotek thermocouple (Model BAT 12). Specifically, the thermistor was connected to the polygraph lead and placed in water which slowly increased from 32 to 38°C. The corresponding changes in water temperature were noted with the corresponding changes on the polygraph's reading of the thermistor to yield a calibration curve for each thermistor. Thus, following treatment, changes in the polygraph recording from each thermistor could be assigned absolute temperature values.

To determine the effects of treatment on brain temperature, brain temperature changes were calculated by subtracting the post-stimulation temperature from the prestimulation temperature within each animal. The change in temperature in the experimental groups was compared to the change in temperature in the control group (no stimulation). Since one experimental and one control pup were always treated at the same time in the same incubator, a comparison of temperature changes was considered the most reliable index of treatment effects. Statistical

comparisons between groups were done with Student *t*-tests or ANOVAs. Post-hoc Tukey tests were performed when necessary.

Experiment 1

As stated above, adult brain temperature approximates body temperature only under steady-state conditions (Kiley et al., 1984); under situations of varying body temperature, it is maintained within a more restricted range than body temperature (Foster & Ferguson, 1952; Stupfuehl & Severinghaus, 1956; Kiley et al., 1984). The present experiment was designed to determine whether infant rat brain temperature is also maintained within a more restricted thermal range than body temperature. Specifically, we sought to determine whether body and brain temperature covaried in response to various natural temperature fluctuations which would normally be experienced by pups within the nest.

Methods

The subjects were 14 male and 14 female, 5-day-old rat pups from 14 different litters. Only 1 male and 1 female from each litter was used, with equal numbers of males and females in each condition. At 4 days of age, pups were implanted with a brain thermistor in the neocortex and returned to the nest. The following day, pups were connected to the polygraph through light-weight leads and returned to the mother for 1/2 hr before the experiment began. Body and brain temperature were monitored under 3 conditions; 1) steady state—the pup maintained contact with its littermates and mother for 20 min, 2) exposure to cold—the pup was separated from its littermates and mother for 20 min. The ambient temperature during separation was 25°C, and 3) exposure to warmth—the pup was reunited with its littermates and mother for 20 min. Brain temperature was continuously recorded during the entire 60-min experiment. Rectal body temperature (measured as described in Sullivan et al., 1988) was recorded following each 20-min temperature condition interval. Pups were used to record either brain or body temperature, never both, to avoid unduly stressing individual pups.

Results

As is illustrated in Figure 1, pup body and brain temperature appear to respond in a similar manner to all natural temperature fluctuations tested. During steady-state conditions, pup body and brain temperature did not differ significantly from one another. Following exposure to cold, both body ($t = 4.750$; $p < 0.01$) and brain ($t = 7.487$; $p < 0.01$) temperature significantly decreased as compared to the respective steady state temperatures. No statistical difference was found between body and brain temperature under cold exposure. Following exposure to warmth, both body ($t = 5.124$; $p < 0.01$) and brain ($t = 6.990$; $p < 0.01$) temperature significantly increased. No statistical difference was found between body and brain temperature under warmth exposure.

These results suggest that, within the normal range of ambient temperatures pups experience within the nest, body and brain temperature covary. These results are in contrast to the relationship between body and brain temperatures normally found in adults (Kiley et al., 1984). This suggests that behavioral and physiological thermoregulatory mechanisms responsible for maintaining pup body temperature may also function to maintain pup brain temperature.

Experiment 2

An increase in pup body temperature may be attenuated by activation of a physiological thermoregulatory mechanism involving ventilatory heat loss which is activated by physical stimulation of pups (Sullivan et al., 1988). The fact that body and brain temperature covary under fluctuating thermal conditions suggests that a similar thermoregulatory system may exist

to control brain temperature. The purpose of this experiment was to determine whether, similarly to body temperature, pup brain temperature was decreased by physical stimulation.

To assess the effects of physical stimulation upon pup brain temperature, pups were removed from the natural litter situation. The types of stimulation used in this experiment were chosen because they are thought to approximate the type of stimulation pups receive from the dam (Barnett & Walker, 1974; Butler, Suskind, & Schanberg, 1968; Evoniuk, Kuhn, & Schanberg, 1979; Hofer, 1975, 1983; Kuhn, Butler, & Schanberg, 1978; Pedersen & Blass, 1982; Pedersen et al., 1982; Sullivan, Brake, Hofer, & Williams, 1986a; Sullivan, Hofer, & Brake, 1986b; Wilson, Sullivan, & Leon, 1985). Furthermore, pups were stimulated away from the nest and dam, in a thermally controlled environment. This approach of separating pups from the dam to delineate the effects of maternal stimulation on pup behavior and physiology has been widely used (for review see, Hofer, 1983; Schanberg, Evoniuk, & Kuhn, 1984).

Methods

Ten male and 10 female, 4-day-old pups were cold-anesthetized and implanted with a brain thermistor in the cortex. After recovery from anesthesia, pups were returned to the litter. The following day, pups were placed in a 32°C incubator (an ambient temperature sufficient to maintain pup body temperature at thermoneutral) and the thermistor was attached to leads from the polygraph. Two littermates were always treated at the same time in the same incubator; only one pup received any stimulation. This procedure was done to control for any ambient temperature fluctuations or uncontrolled handling effects which may have contributed to temperature fluctuations. Prior to stimulation, pups were given at least a 10-min adaptation period during which time a 10-min baseline brain temperature was continuously recorded. During the subsequent 10-min stimulation period, pups received one of the following treatments; 1) Stroking—pups were vigorously stroked with a sable-hair brush over all areas of their body. This was done to mimic nonspecific maternal tactile stimulation, such as licking and stepping on pups (Barnett & Walker, 1974; Butler et al., 1968; Evoniuk et al., 1978; Pedersen & Blass, 1982; Pedersen et al., 1982; Sullivan & Hall, 1986; Sullivan & Leon, 1986; Sullivan & Leon, 1987; Sullivan et al., 1986a,b; Wilson et al., 1985; Wilson, Sullivan, & Leon, 1987). 2) Shaking—pups were left in their treatment container while the container was continuously and gently rotated and shook. This treatment was done to mimic nonspecific tactile and vestibular stimulation pups receive when they are jostled by the dam (Hofer, 1975; Wilson, Wilner, Kurz, & Nadel, 1986). 3) No-stimulation control, whose temperature was always used as a reference point for temperature changes which occurred in the stimulated pups.

Results

No difference in prestimulation brain temperature was found among the different treatment conditions (nonsignificant ANOVA) or between stimulated and nonstimulated pups treated together (nonsignificant *t*-tests). The mean brain temperature for the stroked pups and their control was 35.66°C (SE = 0.71) and 35.50°C (SE = 0.65), respectively. The mean brain temperature for shaken pups and their control was 36.00°C (SE = 0.32) and 35.92°C (SE = 0.25), respectively.

As is illustrated in Figure 2, pups that were stroked ($t = 4.88$; $p < 0.01$) or shaken ($t = 2.98$; $p < 0.05$) showed a decrease in brain temperature from pre-stimulation temperature as compared to the nonstimulated controls present during treatment. As is illustrated in Figure 3, the decrease in brain temperature appears soon after the start of stimulation and continued for the entire 10 min of stimulation. Additionally, brain temperature began to approach the prestimulation baseline soon after the termination of stimulation, with no statistical difference between stimulated and nonstimulated controls within 10 min following stimulation (nonsignificant *t*-test).

Experiment 3

It is possible that the ability of stimulation to decrease brain temperature may be limited to the cortex. Thus, the purpose of the present study was to determine whether a brain temperature decrease occurred in another area of the brain; the olfactory bulb.

Methods

The subjects were 5-day-old pups; 8 male and 8 females from 8 different litters. No more than 1 male or 1 female were used from a given litter. Surgery and recording of brain temperature were done according to the methods of Experiment 2 except the location of the thermistor was in the olfactory bulb and the length of treatment was decreased. Pups were assigned to one of the following 5-min treatment conditions: 1) stroking, and 2) no-stimulation.

Results

The prestimulation olfactory bulb temperatures did not differ between treatment conditions. The mean temperature for stroked and control pups were 35.35°C (SE = 0.22) and 35.40°C (SE = 0.20), respectively. As is illustrated in Figure 4, pups that were stroked exhibited a significant decrease in olfactory bulb temperature as compared to nonstimulated controls ($t = 2.40$; $p < 0.05$). These results indicate that the stimulation induced temperature decrease is not limited to the neocortex.

Experiment 4

Ventilatory heat exchange is a physiological thermoregulatory system which serves to reduce core body temperature or attenuate an increase in core body temperature in infant rats (Sullivan et al., 1988), as well as adults (Grayson & Kuehn, 1979). Specifically, during heat stress, respiratory rate increases and conductive and evaporative heat loss occurs within the respiratory system. The purpose of the present experiment was to determine whether this mechanism of body temperature cooling accounted for the decrease in brain temperature.

Ventilatory heat exchange is dependent upon an increase in respiration and convective and evaporative heat loss (Grayson & Kuehn, 1979). Stimulation produces an increase in respiration (Alberts & May, 1980; Sullivan et al., 1988), and a high-humidity environment, which blocks evaporative heat loss, prevents a decrease in body temperature (Sullivan et al., 1988). Thus, to determine whether evaporative heat loss was also contributing to the decrease in brain temperature, environmental humidity was increased to prevent evaporation during stimulation.

Methods

Ten 5-day-old rat pups from 5 litters were implanted with brain thermistors (neocortex) and returned to the dam following recovery. The following day, pups were placed in a 32°C incubator and the thermistor was attached to the leads from a polygraph. Two littermates were always treated at the same time, in the same incubator; only one pup was stimulated. Pups first received 5 min of stroking at a normal humidity level (74%-77% relative humidity) to ensure the stimulation-induced temperature decrease was reliable in each pup. All stimulated pups exhibited a decrease in brain temperature during stroking. Approximately 1 hr later, the humidity in the incubator was increased (98%-100% relative humidity). The ambient temperature was kept at 32°C. Following a 10-min prestimulation baseline, one pup was given 5 min of stroking; the other pup was left undisturbed. An additional 10 min of post-stimulation brain temperature was then recorded.

Results

No statistical difference in prestimulation brain temperature was noted among the different treatment conditions. Within the normal humidity group, stimulated and nonstimulated pups had a mean brain temperature of 35.20°C (SE = 0.10) and 35.20°C (SE = 0.08), respectively. Within the high humidity group, stimulated and nonstimulated pups had a mean brain temperature of 35.02°C (SE = 0.09) and 35.00°C (SE = 0.06), respectively.

As is illustrated in Figure 5, pups stroked in normal humidity exhibited a brain temperature decrease as compared to nonstimulated controls ($t = 6.734$; $p < 0.01$). Pups stroked in high humidity did not exhibit a brain temperature decrease as compared to nonstimulated controls (nonsignificant t -test). These results suggest that evaporation significantly contributed to heat dissipation within the brain.

Experiment 5

Tactile stimulation of pups produces a decrease in body temperature throughout the preweanling period (Sullivan et al., 1988). The ability of stimulation to produce the decrease in body temperature is likely due to the early appearance of ventilatory heat exchange in pups (Sullivan et al., 1988). The ability of stimulation to produce a decrease in brain temperature may, however, change during the developmental period as control of brain temperature matures. The purpose of the present experiment was to determine whether stimulation produces a decrease in brain temperature throughout the preweanling period.

Methods

The subjects were 5-, 10-, 15, and 20-day-old, 10 male and 10 female rat pups from different litters raised as described in Experiment 1. Pups were used at only one age. Brain temperatures were recorded as described in Experiment 2.

Results

Prestimulation brain temperature did not differ among the different treatment conditions at any of the ages tested, nor were statistical differences noted between ages.

Stimulation affected brain temperature differently in the ages studied. As is illustrated in Figure 6, 5-day-old pups exhibited a brain temperature decrease in response to both stroking ($t = 3.97$; $p < 0.05$) and shaking ($t = 2.78$; $p < 0.05$). Stroking and shaking stimulation of 10-, 15, and 20-day-old pups did not result in a reliable brain temperature change. Thus, as is illustrated in Figure 7, stroking and shaking stimulation produces a decrease in body temperature (data from Sullivan et al., 1988) throughout the preweanling period, but its effects on brain temperature are probably limited to the first week of life.

General Discussion

To our knowledge, the present series of studies represents the first assessment of infant mammalian brain thermoregulatory capabilities. The results indicate that, as in birds (Arad, Toledo, & Bernstein, 1984; Bernstein, 1971, 1973; Dawson & Bennett, 1981; Koskimies & Lahti, 1964; Untergasser & Hayward, 1972), infant rats do not appear to possess all the brain thermoregulatory characteristics of the adult. Specifically, under steady-state thermal conditions, pup body and brain temperature did not significantly differ from one another. Indeed, similarly to the adult under steady-state thermal conditions, infant body temperature may be a reliable index of infant brain temperature. However, during times of thermal instability, when differences between adult brain and body temperature emerge (Cooper & Kenyon, 1957; Delgado & Hanai, 1966; Kiley et al., 1984; Stupfel & Severinghaus, 1956), pup

body and brain temperature continue to covary (Expt. 1). Indeed, an increase or decrease of 1.5°C (which is the range of body temperature fluctuations experienced by pups in the present report) in adult rat body temperature, does not produce a significant change in brain temperature (Baker, 1982). This suggests that the independent physiological mechanisms of brain temperature regulation, which exist in adults (Baker, 1982), are not yet functional in neonatal pups. Thus, it is possible that our knowledge of neonatal pup body temperature regulation may be extended to include that of neonatal brain temperature regulation. This conclusion is supported by the results of Experiment 5, which suggests that independent body and brain thermoregulatory capabilities are evident by 10 days of age.

Brain temperature in neonates appears to covary with body temperature even under situations in which body temperature is altered by internal physiological factors (as opposed to a change in ambient temperature). Previous results indicated that physical stimulation of pups produces a decrease in body temperature (Sullivan et al., 1988). The present studies indicate that physical stimulation also produces a decrease in neonatal brain temperature. The present studies used stroking and shaking to physically stimulate pups but other stimuli also appear to reliably produce a decrease in brain temperature; such as, tailpinching, an i.p. or S.C. injection of saline, handling pups, and strong artificial odors (Sullivan, unpublished observations). Thus, the effect of physical stimulation on pup brain temperature does not appear to be due to stimulation of a specific sensory modality; rather, it may be due to a nonspecific response to stimulation in neonates.

The dependence of infantile physiological and behavioral systems on physical stimulation for normal functioning appears to be a fairly typical mechanism for regulating pup behavior and physiology (Hofer, 1983). Specific behaviors of the dam regulate the functioning of many specific behavioral and physiological systems in pups. For instance, periodic milk delivery modulates the sleep-wake cycle of pups (Hofer & Shair, 1982), tactile stimulation, similar to that used in the present study, maintains normal ornithine decarboxylase levels (Butler et al., 1968; Evoniuk et al., 1979; Kuhn et al., 1978), and some unknown nonnutritive aspect of contact with the dam maintains adrenocortical activity at normal levels (Smotherman, 1983; Stanton & Levine, 1984). The results of the present paper indicate that some nonspecific aspect of maternal physical stimulation may also serve to regulate the body and brain temperature of neonatal pups.

Infant rats thermoregulate primarily by behavioral means by changing their distance and position with their heat source, the dam and littermates (Alberts, 1978a, 1978b; Alberts & Brunjes, 1978). However, they do possess some physiological thermoregulatory capabilities. Additional heat may be provided by activation of brown fat metabolism (Hull, 1973; Hull & Segal, 1965). The present series of experiments suggests that a physiological system of heat dissipation may also exist in the neonate. Similarly to the adult (Grayson & Kuehn, 1979), pups may dissipate both body and brain heat by ventilatory heat exchange. Indeed, this system may be of considerable significance to pups since it may provide pups with a mechanism to dissipate heat without leaving the huddle and dam (pups' sole source of nutrition and protection). For instance, during the early stages of a nursing bout, pups may dissipate heat during periods of stimulation from the dam. Ultimately, however, the pups may be unable to dissipate enough heat to maintain thermal homeostasis and may need to remove themselves from the litter. However, the ability to defend body and brain temperature would enable pups to extend the length of time they spend in close contact with the dam and other pups. Thus, physiological thermoregulatory mechanisms may be used in conjunction with behavioral thermoregulatory mechanisms to maintain pup body and brain temperature within the thermoneutral range. This hypothesis is currently being tested in our laboratory.

The ability of stimulation to modify pup temperature may have an indirect influence on additional pup physiological systems. For instance, an attenuated increase in pup body temperature during contact with the dam may allow prolonged contact bouts. The dam terminates a contact bout when her temperature rises and cannot be defended (Croskerry, Smith, & Leon, 1978; Jans & Leon, 1983; Leon, Croskerry, & Smith, 1978). Thus, an attenuated increase in pup temperature may attenuate the temperature increase of the dam, permitting her to increase the length of contact bouts. The longer pups remain with the dam, the more milk and maternal care they are likely to receive.

In summary, neonatal rat pups do not appear to defend their brain temperature independently of body temperature; pup brain temperature is similar to body temperature under a variety of thermal conditions. Furthermore, neonatal pups appear to be capable of defending their body and brain temperature against hyperthermia, given that they receive appropriate stimulation. By 10 days of age, however, physical stimulation only produces a decrease in body temperature; brain temperature appears to be defended against this temperature decrease.

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Fig 1.

Mean brain (closed bars) and body (open bars) temperature ($\pm$ SE) recorded under three different naturally occurring thermal conditions; 1) steady-state conditions during normal mother-infant interactions. 2) cold exposure during separation of the pup from the dam and littermates. and 3) warmth exposure during reunion of the pup with the dam and littermates.

Fig 2. Mean change in neocortical brain temperature ($\pm$ SE) of; 1) stroked pups and their nonstimulated controls present during treatment, and 2) pups that were shaken and their nonstimulated controls present during treatment.

Fig 3. Temporal aspects of mean brain temperature of stroked (closed circles) and nonstimulated controls (open circles) during 5 min prestimulation, 10 min during stimulation, and 5 min post-stimulation.

Fig 4. Mean change ($\pm$ SE) in olfactory bulb temperature of stroked pups and their nonstimulated controls present during treatment.

Fig 5. Mean change ($\pm$ SE) in pup brain temperature in stroked and nonstimulated control pups in normal humidity and high-humidity environment.

Fig 6.

Mean change ($\pm$ SE) in pup brain temperature in 1) stroked and nonstimulated control pups and 2) shaken and nonstimulated control pups at a) 5, b) 10, c) 15, and d) 20 days of age.

Fig 7. Comparison of change ($\pm$ SE) in pup brain (closed circles) and body (open circles) temperatures at 5, 10, 15, and 20 days of age for shake (A) and stroke (B) pups. Data points were calculated by subtracting the change in temperature of a given control pup from that of its companion stimulated pup.