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PERIPHERAL MECHANISMS OF HUMAN TEMPERATURE SENSITIVITY

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The principal objectives of this research program have been two-fold:

1. to develop apparatus for the investigation of temperature sensitivity, and

2. to incorporate in the stimulator a suitable device for the measurement of vascular activity which may be used to measure changes in vasodilation and constriction during the course of measurements of the thermal threshold. The second objective has been a systematic investigation of factors which provide information about the mechanism whereby changes in the skin temperature are sensed as sensations of warm and cool.

Project titles are summarized below in order to give a brief review of the breadth of the program which has been undertaken during the past three years under this grant.

1. Apparatus development
    - 1.1 Thermal stimulator
    - 1.2 Plethysmograph
2. Systematic investigation of factors which provide information about the mechanism of thermal reception
    - 2.1 Factors which affect the thermal threshold
        - 2.11 Temperature to which the skin is adapted with simultaneous measurements of the cutaneous volume pulse
        - 2.12 Age
        - 2.13 Ovarian cycle
        - 2.14 Sex
    - 2.2 Effects of vasoconstrictor and vasodilator drugs upon the cool threshold
    - 2.3 Summation of thermal stimuli

2.31 Area of stimulation

2.32 Central summation

2.4 Temporal course of adaptation to thermal stimuli

1. Apparatus development

1.1 Thermal stimulator. Peltier refrigerators are almost ideal transducers to provide the precise temperature control necessary for the investigation of thermal sensitivity. The operation of these devices is based on the Peltier effect. When an electric current is passed through the junction of two dissimilar electrical conductors the junction will either warm or cool, depending upon the direction of flow of the current. Recent developments in the field of semiconductors have made it possible to utilize this effect as a heat pump with a commercially feasible figure of merit. A circuit has been developed which allows the precise control of the temperature of one surface of the Peltier refrigerator. This surface of the stimulator, the Peltier refrigerator, may be maintained at any temperature within the physiological limits at ±0.025° C of a predetermined value. Changes in the temperature of the refrigerator can be as little as 0.05° C or as large as 20° C with an error of less than 2%. The rate of temperature change may be controlled at any value up to 2°/sec. Aside from its accuracy, the stimulator has the additional advantage that cues other than the temperature change do not occur since its operation is completely electrical. The stimulator's surface, which has an area of 14.44 cm^2, is held in contact with subject's skin with a pressure of about 12 gm/cm^2 by a counterbalanced lever. The temperature of a copper-Constantan thermocouple, placed between the stimulator and the subject's skin, is displayed on a Hewlitt-Packard digital voltmeter and is recorded by a Brush recorder. This apparatus has been described (Kenshalo, 1963).

1.2 Plethysmograph. Peltier refrigerators have been modified so that a photoelectric plethysmograph is incorporated in the center of the stimulator. The device is essentially similar to that described by Rawson (1959) and Seki, Flath & Hertzman (1962). Its chief virtue is that it records only changes in the cutaneous blood vessel volume. On special order, Peltier refrigerators were manufactured with a 3/8" hole in the middle of them. The remainder of the device was constructed in our laboratory shops. A lucite ring was fitted into the hole and in the center of the lucite ring, but protected from it by a brass cylinder, was a photoconductive cell. Light shining through the lucite ring is diffused by the skin and reflected to the photoelectric cell. Changes in the light dispersion characteristics of the skin, due to changes in the blood volume, are recorded as variations in the electrical resistance of the cell. In this way simultaneous measurements may be obtained of the volume pulse heighth and the thermal threshold. This apparatus will be described in a publication which is currently in preparation (Changes in the cool threshold associated with phases of the ovarian cycle).

2. Systematic investigation of factors which provide information about the mechanism of thermal receptors.

2.1 Factors which affect the thermal threshold.

2.11 The temperature to which the skin is adapted with simultaneous measurement of the cutaneous volume pulse. Investigations of cutaneous temperature sensitivity have been hampered by the lack of an adequate model for the receptor mechanism. The photochemistry of visual pigments, for example, has provided a very useful model for visual sensation in that it provides a basis to account for changes in brightness sensitivity under various conditions of illumination. Such models are useful in that they allow one to infer the characteristics which one system should exhibit based on a knowledge of the other system.

The choice of systems within the skin which might serve as a model for temperature receptors is limited. These are the terminations of nerve which end free of any systematic encapsulation among the cells of the dermis and perhaps the lower layers of the epidermis, and the tissue of non-nervous origin. Of the non-nervous tissue in which cutaneous nerves terminate, only the smooth muscle of the cutaneous vascular system is known to respond directly to changes in temperature. Hence, the choice of a model is limited either to nerve terminals, themselves, or to smooth muscle of the cutaneous vascular system in which some of these nerves terminate. The question is, which system demonstrates characteristics in common with thermal sensitivity?

Since it is easier to measure changes in the cutaneous vascular system than in the sensitivity of bare nerve terminals, the initial attempt was made in this direction. Concurrent measures of the cool threshold and volume pulse amplitude were made, as a function of the temperature to which the skin was adapted. Both measurements involved the same area of tissue on S's forearm. In the range of adapting temperatures from 30° - 34° C, the cool threshold remains relatively constant at a temperature reduction of about 0.15° C. The cool threshold increases markedly as higher adapting temperatures are employed. The amplitude of the volume pulse, as used here, is an index of the degree of vasodilation of the cutaneous arterioles. An increase in the amplitude of the volume pulse represents an increase in the degree of vasodilation. There is good agreement between the measurements of the cool threshold and the volume pulse amplitude.

It has yet to be shown that changes in the volume pulse amplitude, e.g., as changed by drugs, will result in an altered cool threshold. However, the data presented here strengthen the case for considering the cutaneous vascular system as a model for cutaneous temperature receptors (Kenshalo & Nafe, 1963).

2.12 Age. Cool threshold measurements, as a function of the temperature to which the skin is adapted, have been completed on two males and two females, age 21 - 26, and on one male and one female, age 73-75. Additional data have been collected on one female, age 76, and one male, age 74. However, during the course of collection it was found that both of these subjects were taking daily medication of vasodilator drugs, hence their data are discarded for purposes of comparisons of thermal thresholds as a function of age. Until additional subjects in the older age group, who are not on medication, are tested, no publication is anticipated. Considerable difficulty is being experienced in finding healthy subjects in this range who are not taking medication of some sort. In general, the results indicate that there is no marked change in sensitivity to either warm or cool stimuli with advancing age. There is a marked change, however, in the variability of the reports obtained from aged subjects, as compared to those of the young group.

2.13 The ovarian cycle. When the cool threshold is measured after the skin has been adapted to 40° C for 20 minutes, on a daily basis in female subjects, it is found that during the period from the onset of menses until the time of ovulation, the threshold is large. After ovulation, however, there is a two-fold increase in sensitivity. On the average, female subjects show a thermal threshold, when adapted to 40° skin temperature, of 1.2°. After ovulation, the threshold decreases to about 0.7°. When the cool threshold, during the pre- and postovulatory periods, is plotted, as a function of the temperature to which the skin is adapted, it is found that within the range of 30 to 34° there is no difference between the pre- and the postovulatory cool threshold. However, above 34° there is a widening of the difference until at a skin adapting temperature of 40°, there is almost a two-fold difference between the pre- and the postovulatory thresholds, the preovulatory threshold being the larger. It was determined that changes in the cool threshold are associated with the estrogen-progesterone level in the subjects. During two cycles in two subjects oral contraceptives were administered on the 5th through the 25th day of the cycle. Within 24 hours of the initiation of progesterone, the cool threshold changed from its preovulatory level to a level which was comparable to the regular postovulatory level during both cycles. A third cycle was run under normal conditions and the threshold again shifted on the 14th day as it had before progesterone therapy had commenced. There is, therefore, a clear link between the change in the threshold and a change in the hormone balance of the female. In addition, we have successfully demonstrated on two of our subjects that accompanying this change in the cool threshold are changes in the size of the volume pulse as measured by photoelectric plethysmography. During the postovulatory period, when the cool threshold is small (subject more sensitive to cool stimuli) there is a relatively greater degree of vasodilation at all skin temperatures than during the preovulatory period when the cool threshold is normally quite large. Similar observations were made immediately after the onset of progesterone medication. A report of these data is currently in preparation (Changes in the cool threshold associated with phases of the ovarian cycle).

2.14 Sex. Cool threshold measurements on 21 - 26 year old male and female subjects indicated that the males are less sensitive to cooling temperature changes than the females when the skin is held at temperatures above approximately 35° C. Furthermore, females adapt completel (complete disappearance of thermal sensation) to higher skin temperatures than males. This is probably related to the thermal comfort index. Based on this assumption, it is predicted that females would be more comfortable in higher environmental temperatures than males. However, this appears to have little, if anything, to do with their tolerance of, and ability to perform work in extremely high environmental temperatures. The sensitivity of humans to cool stimuli appears to be unique among the senses in that it shows a sex difference. Other sense departments, e.g., vision and audition, seem to be remarkably sexless.

2.2 Effects of vasoconstrictive and vasodilator drugs upon the cool threshold. Measurements of the cool threshold and the volume pulse have been conducted both before and immediately after adrenaline has been forced into the skin by iontophoresis. Both the general appearance of the skin and the measurements of the cutaneous volume pulse leave little doubt that adrenaline was successful in producing vasoconstriction in the area of stimulation. The result of such treatment upon the cool threshold was to depress it when the skin had been adapted to temperatures above about 35° C. Comparisons of the elderly subjects who were taking vasodilator drugs indicated an increased sensitivity to cool stimuli when the skin had been adapted to temperatures above 35°. Results of this line of investigation are preliminary at this stage. Considerable difficulty has been encountered in the use of iontophoresis as a method of inducing vasoconstriction or vasodilation. There is a persisting tingling sensation which interferes with the measurement of the threshold for some time following iontophoresis. Therefore, the study will be undertaken in which a general state of vasodilation and constriction will be induced by daily medication. During this period measurements of volume pulse will be made, along with measurements of the thermal threshold. These measurements will then be compared with measurements of the same subject under normal conditions taken at a subsequent time. No publication of these data is anticipated at this time.

2.3 Summation of thermal stimuli.

2.31 Area of stimulation. Measurements of the intensity of radiant energy necessary to produce a threshold warm sensation were made as a function of the size of area of the skin exposed. The areas ranged in size from 1 to 14 cm^2 on the forehead, forearm and back. Equations fitted to the curve thus derived have the general form of $\log I + K \log A =$ a constant, where I is intensity, A is area, and K is a constant. It is interesting to note the similarity between the form of this equation for areal summation and the Weber-Fechner equation describing changes in sensation as a function of increased intensity of stimulation. Measurements of the intensity of radiation applied to the skin at various areas were converted to elevation in the skin temperature by the formula proposed by Lipkin & Hardy (1954). Comparisons were made between the warm threshold obtained by the method of radiant energy and that obtained by conducted stimuli having areas of 6 and 14.4 cm^2. The agreement between the thresholds thus obtained is good and are within the range of variability experienced in both methods of measurement.

2.32 Central summation. One may think of the summation, described above, as being a function of the peripheral receptor, perhaps even as an indication of the size of the receptive field described by a single fiber responding to warming. On the other hand, a second kind of summation has been described by Hardy & Oppel (1938). This involves the simultaneous application of radiant energy to the backs of the two hands. When this was done, it was found that the threshold was 40%

lower than it was when the threshold is measured on only one hand. The authors suggest that this may be a central type of summation. Mr. Don Scott, in our laboratory, has tried to replicate these measures, comparing the summation found when the backs of the hands are stimulated simultaneously, as compared to stimulation of the back of the hand and the forehead. There seems to be some tendency for summation effects to occur here. However, they are neither as dramatic nor as reliable as one would be led to believe by the report of Hardy & Oppel (1938).

2.4 Temporal course of adaptation to thermal stimuli.

The term "physiological zero" refers to the temperature of the skin when there is no detectable sensation of warmth or cold. The temperature of the skin at physiological zero may vary considerably with changes in the physiological state of the organism but is usually thought of as being about 32° C.

The concept of physiological zero may be extended to include a range of skin temperatures which are not accompanied by sustained sensations of warm or cold. For example, if one gets into bath water at 35° C, it will feel warm at first, but after a time, if one sits quietly, it becomes thermally neutral. Has the water cooled or has one become adapted to its temperature? The answer is both. One may convince oneself of this by immersing a part of the body, which has not previously been immersed, in the water. That part feels warm. Two physiological zeros exist simultaneously at different parts of the body. By immersion in water at 35° C the physiological zero has been shifted to a higher skin temperature. In this way, a study of the temperature range through which complete (and by "complete" it is meant that sensations of warmth and cool cannot be detected) thermal adaptation occurs can be thought of as a study of the range through which physiological zero may be changed.

Unlike the other senses, very little quantitative work has been done on the temporal course of adaptation to thermal stimuli. This can be accounted for, in part, by the lack of adequate control of thermal stimuli and, in part, by the tediousness of the methods employed. The usual technique has been to expose an area of skin to the particular temperature and ask the subject to report when it no longer feels warm or cool. An example of the results is shown in the work of Hensel (1950). He reports that his subjects showed "complete" thermal adaptation after about twenty minutes to temperatures as low as 23° C and as high as 40° C. Our investigators have reported even wider ranges of temperature and longer times. It is difficult for a subject to attend to a sensation for even one minute, let alone for twenty or thirty minutes. Another method which insures the subject's constant attention is desirable.

The psychophysical method of average error, in which the subject constantly adjusts the temperature of the stimulator to maintain a particular level of sensation, was employed in order to follow the temporal course of adaptation to thermal stimuli. Four thoroughly trained subjects were instructed to maintain the stimulator at a temperature which felt just warm or just cool. The apparatus had been modified so that the subject could control the temperature of the stimulator by moving a key in either direction. At five minute intervals the experimenter changed the temperature of the stimulator by 1° and the subject was instructed to readjust the stimulator temperature to the criterion level.

The results of this investigation indicate that physiological zero may be shifted within a range of about 29° to 37.5° C. In practically all instances adaptation was complete within twenty minutes and, in some instances, within ten minutes, as indicated by the fact that the temperature of the stimulator was not changed by the subject regardless of how long it remained on the arm beyond this period. No relationship was apparent between the initial skin temperature and the range through which physiological zero could be changed.

Interest in this problem has both a theoretical and a practical side. The theoretical side has to do with the aspect of the stimulus which produces a characteristic thermal sensation and with the temporal course of thermal adaptation. Kenshalo, Nafe & Brooks (1961) presented some data which showed changes in the warm and cool threshold as a function of the temperature to which the skin was adapted. Within a restricted range of adapting temperatures, measurements of the warm and cool thresholds were fairly straight forward. The direction of the temperature change seemed to determine the thermal sensation which resulted, that is, a rise in temperature felt warm while a decrease in temperature felt cool. Outside of this range, however, complications arose. The subjects began to report a complex array of thermal sensations. When measurements of the warm threshold were being made at low adapting temperatures, a warm stimulus first produced a sensation of "less cool" followed by neutrality and finally a warm sensation. In the measurement of the cool threshold at high adapting temperatures, much the same events occurred. A cool stimulus was felt first as "less warm", then neutral and finally cool.

The data presented here may account for this complex array of sensations experienced in the measurement of the thermal threshold at extreme adapting temperatures. The subjects failed to adapt completely and hence, had either residual warm or cool sensations which must first be overcome before cool or warm sensations accompanying a threshold stimulus could be felt.

These data, taken together, also suggest that within the limits through which physiological zero may be shifted, the direction of the temperature change is of importance in determining whether a thermal sensation will be warm or cool. This is the theory which Weber proposed in determining characteristics of thermal stimuli. However, outside of the range of temperatures through which physiological zero may be shifted, the theory does not hold, for here a temperature increase from an existing low temperature, e.g., from

25 to 27° C, does not result in a warm sensation but one of "less cool". Observations of this kind led Hering to propose a theory of temperature stimulation, similar to his color vision theory, which involves two temperature dependent processes. Unfortunately, sufficient data do not exist at the present time to allow reasonable speculation about the correctness of either theory.

The second point of theoretical interest is now that the course and limits of thermal adaptation have been determined, another datum has been added to those already present which must be taken into account in assigning a function of thermal reception to some structure of the skin.

On the practical side, the data presented here have a strong resemblance to the measurements of the "comfort zone" made by heating and air conditioning engineers. They suggest that thermal comfort is dependent upon skin temperature. So long as skin temperature remains within the range of physiological zero, and the ambient temperature changes sufficiently slowly, subjects will be comfortable.

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