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NERVOUS CONTROL OF SHIVERING
X. ROLE OF THE FIELDS OF FOREL IN SHIVERING

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ABSTRACT

It is known that neurons in the nucleus of Forel and the central tegmental fasciculus are active during shivering. In this study, bilateral lesions were placed in either of these 2 regions in 35 cats. Their ability to maintain normal rectal temperature in response to external cooling was tested at intervals up to 3 weeks or more. In 10 of these cats, a test was made of the ability to raise rectal temperature from 32° C to normal by shivering before and after the lesions. In six cats, quantitative measures of oxygen consumption rates were made during cold stress before and after the lesions. The results indicate that the lesions did not impair the shivering response, except in cats with postoperative respiratory infections or diminished food intake, and then only after the development of cachexia.

NERVOUS CONTROL OF SHIVERING
X. ROLE OF THE FIELDS OF FOREL IN SHIVERING*

In previous work (Birzis and Hemingway, 1957; Freeman and Hemingway, 1960) on the nervous control of shivering, evidence was found that unit potentials associated with shivering occur in the nucleus of the field of the Forel** and in the central tegmental fasciculus (a mixed collection of long and short fibers passing predominantly longitudinally through the midbrain tegmentum dorsal to the red nucleus). The nerve impulses causing these unit potentials were thought to originate in the large cells of the nucleus of Forel and descend toward the medulla and spinal cord by way of the central tegmental fasciculus. Since the frequency of the unit potentials was correlated with the intensity of shivering, it was hypothesized that the large cells of this nucleus might control the intensity of shivering in conjunction with sensory inputs from the temperature regulating centers in the hypothalamus and from the cerebellum by way of the brachium conjunctivum.

To test this hypothesis, the effect on shivering of lesions in these structures was examined. From previous studies, it is well known that the decerebrate animal, in which the nucleus of Forel has been separated from the lower brain stem, shivers weakly if at all (Bazett, et al., 1933; Bazett and Penfield, 1922). The nucleus of Forel is included in the extensive region of the diencephalon designated as "hypothalamic gray" by Keller and Batsel (1952), who showed that destruction of the "hypothalamic gray" caused loss of shivering in the dog. Birzis and Hemingway (1956) showed that bilateral lesions in the midbrain, that included the central tegmental fasciculus, prevented shivering for at least 6 hours in the anesthetized cat. Because of the importance of these regions in the nervous control of shivering, it was decided to make small bilateral lesions specifically directed at the nucleus of Forel, the central tegmental fasciculus, and adjacent regions to determine if these sites are essential for shivering to occur at its usual intensity.

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**This term was used by Rioch (1929). Another term is "reticular subthalamic nucleus" (Papez, 1929). The term "zona incerta" should be reserved for the nucleus lying laterally in the thalamic fasciculus. The nucleus of Forel is an anterior extension of the mesencephalic reticular formation into the space bounded dorsally by the thalamus, laterally by the cerebral peduncle, and medially by the periventricular gray matter of the dorsal hypothalamus.

METHODS

Care of Animals, Lesions, Postoperative Observations

In order to evaluate the significance of these regions to shivering, it was necessary to minimize the effects of anesthesia and surgical trauma on shivering. Electrolytic lesions were made on adult cats under pentobarbital anesthesia with a monopolar steel electrode through which was passed a direct current (2 ma for 60 to 120 seconds). The lesions were aimed stereotactically at the nucleus of Forel or the central tegmental fasciculus or (as controls) the thalamus or dorsal hypothalamus. Bilateral symmetry of size and placement was sought. Testing was deferred until at least the third postoperative day. The cats were kept in separate cages at 24° C with measurements of weight and rectal temperature being made each day for at least 10 days prior to, as well as after, the operation. Both before and after the operation, they were closely observed for the amount of food and milk intake; for evidence of respiratory, gastrointestinal, or wound infections; for disturbances of posture, gait, or placing, hopping and righting reflexes; for pupillary disorders, paresis, or gross sensory losses; and in some cats, for the ability to acquire conditioned escape and avoidance responses.

Cold-Exposure Tests

The animals were subjected to the following cold-exposure tests: (1) on the 3rd or 4th postoperative day, (2) on the 7th or 8th postoperative day, (3) during the period between the 14th and 21st postoperative day, and (4) 3 months postoperatively for those who survived. Two types of cold-exposure tests were made which will be designated as Type I and Type II tests. The Type II test is further subdivided into tests IIA, IIB and IIC, to be described below. All of the animals were given the cold-exposure test Type I, and six animals which had survived for more than three postoperative weeks were tested by one (or all) of the procedures IIA, IIB and IIC.

The Type I cold-exposure test consisted of simply placing the animal in a cold room at 4° C for 1 hour and measuring the rectal temperatures at the beginning and end of this 1-hour period. The presence or absence of shivering was determined by visual observation and palpation of skeletal musculature.

The Type II cold-exposure tests were more complex and involved measurements of oxygen consumption rate as well as rectal and tail skin (base of the tail) temperature. This test was divided into parts IIA, IIB and IIC.

Cold test Type IIA. The cat was anesthetized with nitrous oxide. Immediately after anesthetization, a rectal thermocouple was inserted and a skin thermocouple was attached to the base of the tail. The animal was then immersed in cold water until its rectal temperature had reached 32° C. The anesthesia was discontinued, the time duration of anesthesia noted, and the animal dried in a 2-minute period. The cat was placed in a 120-liter sealed metabolism chamber at a warm temperature of 32° C, and its rectal temperature and skin temperature (base of tail) were continuously recorded. Immediately after placing the animal in the metabolism chamber, the rectal temperature continued to fall, reaching a minimum of approximately 29° C. Thereafter, it rose progressively, finally reaching the normal range. During the period of subnormal rectal temperature, shivering was vigorous. When the ascending rectal temperature reached 33° C, a sample of gas was drawn from the gas of the chamber and a second sample was drawn when the rectal temperature had reached 37° C. The time intervals (Anand, et al., 1955) between the time of discontinuation of anesthesia until the rectal temperature reached 33° C and (Bailey and Davis, 1942) between the two gas samples were measured. The gas samples were analyzed for CO_2 and O_2, and the oxygen consumption rate (OCR) was computed. This test was devised to stimulate shivering "centrally", i.e., with a low rectal but elevated environmental (and, hence, skin) temperature.

Cold test Type IIB. The same cat tested in procedure IIA was anesthetized with nitrous oxide and maintained under anesthesia for the same length of time as in procedure IIA. This anesthetization was performed in an environment of from 20° to 25° C. At the end of the period of anesthesia, the cat was taken to the cold room (4° C), immersed once in cold water for a few seconds, and the skin dried in a 2-minute period, as in procedure IIA. The animal was then kept in the cold room for a time interval equal to that in procedure IIA, where the rectal temperature changed from its immediate postanesthesia value (approximately 32° C) until it reached 33° C. The animal was then placed in a metabolism chamber at 4° C, and its OCR measured during an interval equal to that of procedure IIA. In this period during which OCR was measured, the animal shivered virgorously. The stimulus for shivering in this procedure was mainly "peripheral" where the skin temperature was low in the cold environment and rectal temperature changed very little. The time intervals of (1) duration of anesthesia, (2) interval between cessation of anesthesia and OCR measurement, and (3) duration of OCR measurement, were fixed in procedure IIB to be equal to the similar time intervals in procedure IIA, so that the influence of anesthesia and any postanesthesia influences would be the same in the two procedures.

These two tests, IIA and IIB, invoked shivering either by a stimulus which was mainly "central" (IIA) or by a stimulus which was mainly "peripheral" (IIB). If "peripheral" shivering was found to be abolished by the brain lesion, whereas the "central" persisted, then it might be concluded that the lesion interfered with sensory impulses traveling to the shivering centers rather than with the motor mechanism of

shivering. However, as will be seen later, shivering stimulated by both procedures was present when the nucleus of Forel was destroyed.

Cold test Type IIC. The same animal tested in either IIA or IIB (or both) was anesthetized for the same length of time at room temperature as in procedure IIA. After discontinuing anesthesia, a time interval was allowed between anesthesia and OCR measurement equal to the similar interval in IIA and IIB. The animal was then placed in the metabolism chamber at room temperature, and OCR was measured during an interval equal to the same OCR measurement interval in tests IIA and IIB. This test provided a control value of the nonshivering oxygen consumption rate (OCR) for a cat subjected to the same anesthesia conditions as those in tests IIA and IIB.

Anatomical Localization of Lesions

Following the sacrifice of the cats, the brains were fixed in situ, sectioned serially, and stained for cells (Nissl). By means of a photographic enlarger, the slides showing the lesions were projected onto drawing paper, and tracings were made of the outlines of the brain stem, the nuclear masses, and the lesions. From slides of intact brains at equivalent levels, tracings were made of the extent of distribution of the structures from which unit potentials had previously been recorded in association with shivering. The outlines were checked by scrutiny of the histological details of the sections with a microscope. The outlines of the lesions and of the distribution of unit potentials were then superimposed on single tracings made at the level of the maximum extent of the lesions.

RESULTS

There were 35 cats with bilateral lesions in the fields of Forel, the central tegmental fasciculus, or neighboring structures. These animals can be divided into four groups according to their postoperative course, their responses to the cold tests, and the extent of involvement by the lesions of the designated regions.

Group I. (Six cats). These animals did not survive the 3-day postoperative period. At autopsy, two revealed massive intracerebral hemorrhage. Two died with acute respiratory infections. Two died with hyperthermia and cerebral edema. In the brief postoperative period in which these cats lived, vigorous spontaneous shivering was observed in four of the six cats.

Group II. (Eight cats). This group included all cats that became hypothermic on one or more cold tests. In these eight cats (Fig. 1, "Deficient") 50 to 100% of the nucleus of Forel, or the central tegmental fasciculus bilaterally, was destroyed resulting in about 75% involvement on the average. Most of this group of cats had, however, an unfavorable postoperative course, which could have contributed to, or could have been responsible for, the hypothermia observed during the cold tests. Three of the cats (No. 179, No. 262, and No. 272) developed respiratory infections which persisted until death, and three (No. 195, No. 267, and No. 274) had diminished food intake with steady weight loss. These six were hypoactive and became cachetic. They shivered adequately during the first or second cold test, but later as they lost muscle mass and subcutaneous fat (insulation), shivering became inadequate to maintain normal rectal temperature. The remaining two cats (No. 207 and No. 218) were healthy until the time of sacrifice. They were hypothermic on the first cold test, but normal on all subsequent tests. Type I cold test was used.

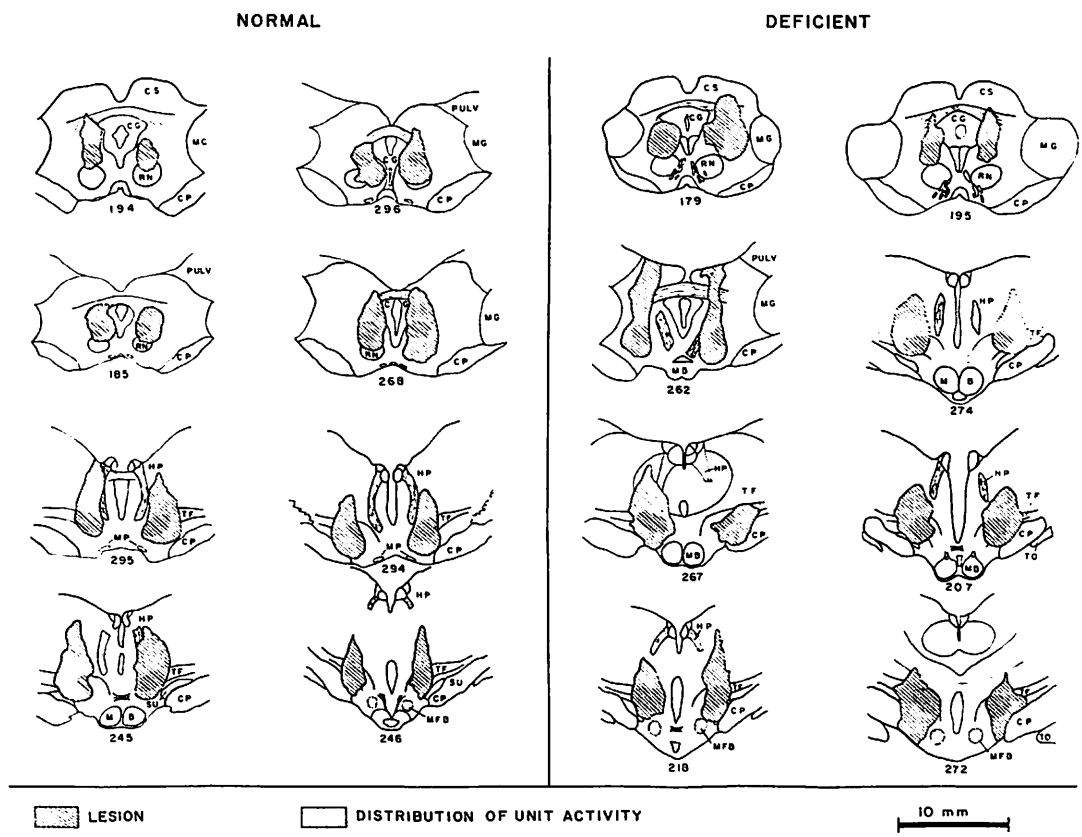

Figure 1.

Group III. (Eight cats). This group was selected because they had lesions of approximately the same extent and placement as did the cats in Group II (Fig. 1, "Normal"). They remained healthy and active postoperatively, did not become hypothermic, and shivered normally on all tests. Three of the cats lived from 104 to 111 days postoperatively, at which time they were sacrificed. Four of them were also tested by the nitrous oxide cooling technique described (Type IIA) and on two (No. 245 and No. 246), measurements of OCR were made during both central cooling (Type IIA) and cutaneous cooling (Type IIB, see Table I). Preoperatively, the metabolic rate increased about 2 1/2 times the corresponding control rate during shivering induced by either technique. The lesions had no effect on either measurement determined 3 weeks postoperatively.

Group IV. (13 cats). This group contains seven cats in which the lesions were erroneously asymmetrically placed with sparing of 50% or more of the designated regions on one or both sides of the brain stem. In three other cats, the lesions were deliberately placed in the thalamus above the fields of Forel, and in three cats they were placed medial to the fields of Forel in the posterior hypothalamus. None of these 13 cats became hypothermic during the cold tests, although 4 became cachectic from failure to re-establish normal feeding postoperatively and 2 had postoperative respiratory infections. Measurements of OCR made on the three cats with hypothalamic lesions were found to be unchanged postoperatively (No. 244, Table I).

An inventory of other types of neurological deficit resulting from the lesions was kept on each animal, with the expectation that some characteristic syndrome might appear. None did, but two types of deficit were observed. As mentioned, there were 12 cats (6 in Group II and 6 in Group IV) which manifested decreased food intake, hypoactivity, and eventual cachexia. In five of these there were superimposed respiratory infections which could have accounted for these signs at least in part, but in the other seven the deficits appeared to have resulted from the lesions. Most of these cats also showed diminished responsiveness to nociceptive stimulation, such as brief electrical shocks to the paws. From the nature of the deficits, it is not possible to state whether they were primarily sensory or motor in nature. Because of the proximity of the lesions to the mesencephalic reticular formation, particularly at its cephalic end, it seems reasonable to explain the observed deficits as due to an interruption of both ascending and descending connections of the mesencephalic reticular formation with higher centers (Magoun, 1958), but there is no direct proof of this.

The second group of neurological disorders consisted of abnormal gait (a high-stepping, slapping nature characteristic of cerebellar dyskinesia), mild to moderate rigidity and hyperreflexia, forced circling or asymmetric posture (especially in cats with asymmetric lesions), loss or impairment of placing and hopping reactions, anisocoria and diminished pupillary reactivity to light. Tremor at rest was not observed. The disorders were most prominent during the first 3 postoperative days and tended to

TABLE I

THE SHIVERING AND NONSHIVERING OXYGEN CONSUMPTION RATES (OCR in ml O_2 STPD/min/kg) BEFORE AND AFTER LESIONS IN THE FIELDS OF FOREL

	OCR (Pre-Lesion)			OCR (Post-Lesion)		
Cat No.	Test IIA	Test IIB	Test IIC	Test IIA	Test IIB	Test IIC
244	26.2	22.7	9.3	22.7	27.0	11.7
245	23.1	22.3	11.3	22.3	32.5	8.6
246	23.5	26.5	11.1	26.5	28.1	10.9
Mean	24.3	23.8	10.6	23.8	29.2	10.4

Test IIA - Low rectal temperature; environmental temperature 32° C; shivering.
Test IIB - Normal rectal temperature; low environmental temperature; shivering.
Test IIC - Normal rectal and environmental temperatures; nonshivering.

RATIO OF $\frac{\text{SHIVERING OCR}}{\text{NONSHIVERING OCR}}$ BEFORE AND AFTER LESIONS IN FIELDS OF FOREL

	Ratio Pre-Lesion		Ratio Post-Lesion	
Cat No.	IIA/IIC	IIB/IIC	IIA/IIC	IIB/IIC
244	2.8	3.0	1.9	2.3
245	2.0	2.3	2.6	3.8
246	2.1	2.5	2.4	2.6
Mean	2.3	2.6	2.3	2.9

disappear during the next 3 weeks. Beyond 3 weeks, there persisted only a slight anisocoria and an occasional awkwardness not characteristic of normal cats. These defects were found alike in Groups II, III, and IV. They were without significant correlation with any shivering deficit, although it should be pointed out that there are as yet inadequate criteria for distinguishing inefficient or "poorly coordinated" shivering from "well coordinated" shivering.

DISCUSSION

In a previous study (Birzis and Hemingway, 1956), evidence was found that moderately large bilateral lesions in the brain stem of the anesthetized cat prevented shivering for at least 6 hours after the lesions were made. Comparison of the histological location of these lesions then showed that the one part of the mesencephalon these lesions included in common bilaterally was the region dorsal and lateral to the red nucleus. Recordings from microelectrodes in the brain stem of anesthetized cats demonstrated the existence of unit potentials associated with shivering in the central tegmental fasciculus and the nucleus of Forel (Freeman and Hemingway, 1960). The characteristics of these unit potentials and of the microscopic anatomy of the structures in which they were recorded indicated that long fibers from the field of Forel to the medulla became active during shivering. Therefore, would bilateral lesions restricted to this nucleus, or its descending efferent fibers, have a detectable effect on shivering?

In no surviving cat was shivering absent. A deficit in shivering (hypothermia on exposure to cold) occurred only under certain conditions. (1) In 2 of the 29 cats surviving there was hypothermia during the first postoperative cold-test, but not during later tests. (2) In three of five cats that developed respiratory infections, there was development of hypothermia only during later cold tests. (3) In three of seven cats with postoperative loss of appetite and cachexia, there was hypothermia only during later cold tests. Since there was little difference in size and location between the lesions in these eight cats and the lesions in another group of eight healthy cats with normal shivering responses, it is concluded that the operation was without specific effect on the shivering response. Hence, the nucleus of Forel and the central tegmental fasciculus are not essential for adequate shivering, even though the neurons in them are active during shivering in the intact cat.

The explanation for these findings appears to be that following the lesions there are reorganizations of adjacent neuron systems, which in large part compensate for the loss (Brouwer, 1950; Monakow, 1914). These reorganizations require alternate neurons so that the failure of the occurrence of shivering in animals with massive

lesions of the brain stem appears to result from the loss of such alternate neurons. The process of "recovery" is clear evidence for such reorganization; alternate neurons appear to be available particularly in the lateral hypothalamus and midbrain reticular formation, which are very similar in histological structure to the nucleus of Forel and are in anatomical contiguity with it.

As a corollary to this explanation, one would expect that neurons in the nucleus of Forel could compensate to some extent for bilateral loss of adjacent structures, so that bilateral lesions in the subthalamic region would not result in discrete motor or behavioral deficits. Rather, there would occur a series of compensated deficits of many activities, with increasing deficit and decreasing compensation as the size of the lesions was increased, until following a large lesion a catastrophic breakdown would occur with severe loss of many functions. The exact size and location of a lesion that causes breakdown appear to be a matter of individual variation, but in general this result has been observed repeatedly in this laboratory. Shivering is not impaired unless there is gross impairment of other highly organized activities (e.g., walking, feeding, control of rage, care of fur) such as occurs after decerebration, during anesthesia, in severe infections, or during early recovery from cerebral trauma. Cats that have "recovered" from an operation sufficiently to walk to a feeding tray and lap have no difficulty in shivering. Similar deficits in reactivity ("somnolence," (Harrison, 1940; Kelly, et al., 1946; Lindsley, et al., 1950; and Ranson, 1939)), hypokenesia (Bailey and Davis, 1942; Hinsey and Ranson, 1928; and Mettler, 1945), and impaired feeding responses (Anand, et al., 1955; Kelly, et al., 1946) have been reported to occur following bilateral lesions of varying extent in the mesencephalic reticular formation, the hypothalamus, the periaqueductal gray and the fields of Forel. It is well known that stimulation of the former structures results in widespread potentiation of reflex and electrical responses (Magoun, 1958; Murphy and Gellhorn, 1945; and Rhines and Magoun, 1946).

The technique of recording spontaneous electrical activity during the shivering response has already shown that: (1) detectable activity in this pathway is not necessary for the initiation of shivering; (2) the amount of electrical activity is related to the intensity of shivering; and (3) the electrical activity stops abruptly when the clonic contractions of shivering are superceded by a generalized contraction induced by a nociceptive stimulus. It has also been noted that anatomically the nucleus of Forel receives afferents predominantly from the cerebellum, the hypothalamus, and the globus pallidus. It is therefore strategically located for combining proprioceptive, thermal and exteroceptive information, and it can transmit the resultant directly to the medullary reticular formation (perhaps also into the spinal cord). The large neurons of the nucleus of Forel may, from this evidence, be said to facilitate shivering already in

progress in the normal cat, to an extent determined by temperature receptors in the hypothalamus and by the scale of needs for motor activity of all types organized in higher centers.

The study of the effects of ablation suggests that a more precise delineation of the function of the nucleus of Forel will not be feasible until it has been determined whether these same neurons become active during other types of motor response. If such neuronal activity occurs, some common denominator of function might be discerned which can be used (1) to define groups of motor responses in which the neuronal activity is present or absent, or (2) to distinguish the common characteristics of such responses (e. g., intensity of shivering) for which the neuronal activity is responsible.

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