Activation Level and the Production of Gastric Ulceration in the Rat

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Sensory conditions and frontal cortical ablations thought to increase activation levels were found to produce a significant increase in gastric ulceration as a result of restraint.

SIMPLE RESTRICTION of locomotor activity is one of several techniques used to produce ulcers in experimental animals such as the white rat. This method of ulcer production has been particularly useful as a tool for the investigation of the effect of various factors on ulceration severity. For example, certain drugs, genetic factors, and cyclic activity levels have been shown to influence ulceration rate.[1-3] In addition, Brodie and Hanson[4] have shown that increased duration of restraint, food deprivation, repeated restraint periods, and adrenalectomy each tend to increase the incidence and severity of ulceration in the rat. Furthermore, young rats were found to have more ulcers than older rats stressed under identical conditions.

Through selective breeding, Sines[2] has produced a strain of stress-ulcer-susceptible (SUS) rats and has noted that these animals show a higher level of motor activity,[5] increased reactivity to external stimulation, and more rapid avoidance learning[6] than normal controls. Sines[7] has suggested that these behavioral characteristics may represent an underlying increase in neurological activity, possibly reflecting an elevation of activity in the reticular activating system. Furthermore, he has suggested a possible "causal" relationship between level of neurological activation and ulcer development. If such a relationship does exist, it should be possible to predict the relative rate of ulceration which will occur in a restraint-stressed experimental animal by manipulating those variables which are believed to have the effect of either increasing or decreasing the activity of the reticular formation.

The purpose of the present study was to investigate this proposed relationship between activation level and ulceration rate by varying two factors which are believed to have an effect on the level of neurological activity. The first factor considered was level of illumination. It has been known for some time that the white rat shows considerably less motor activity under conditions of high illumination

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than under lower illumination levels. Sines and others considered gross activity, among other peripheral measures, to be indicative of relative levels of central activation, so that it may be assumed that, in the rat, illumination levels which decrease or increase locomotion have a similar neurological effect in terms of level of activity. The second factor under investigation was the effect on ulceration rate of removing the frontal cortex. It has been shown that ablating frontal cortex in rats increases gross motor activity above normal levels.[9] Isaac and DeVito[10] suggested that the effect of frontal ablation may be to remove the regulatory influence which the area normally has on the reticular formation, thus increasing reticular firing. Stimulation of certain parts of the frontal cortex has indeed been shown to impose an inhibitory effect on the activity of the reticular formation in some animals.[11]

It was proposed, therefore, that increasing the level of neurological activity by restraining subjects in low illumination conditions, or by removing the frontal cortex, would lead to a relative increase in ulceration rate over animals restrained under higher illumination conditions or animals whose frontal cortex had not been removed.

Method

Subjects

The *Ss* were 20 male albino rats of the Holtzman strain ranging from 90 to 110 days of age. All animals were maintained in the colony for at least 1 week prior to operation and were not handled at any time except during operation and when they were placed in the restraining apparatus. Food and water were available at all times in the home cage, and weights were recorded prior to operation and restraint.

Apparatus and Procedure

The restraining apparatus was a cylinder of hardware cloth into which an additional piece of wire was placed so that the restraining area formed a half-circle, the base being 2 in., with a maximum height of 1½ in. Horizontal movement was restricted by inserting a metal bar through the cylinder underneath the animal's tail. The cylinder was secured to the side of a 10- × 18-in. wooden sound-deadened box which had one Plexiglas wall through which light was projected. A Whisper Fan* was located on the opposite wall. This enclosure was placed in a larger sound-treated box with an exhaust blower providing additional ventilation and noise-masking. The light source was a Sylvania Cool-lux 150-w bulb mounted on the outside of the larger enclosure; the bulb provided an illumination of approximately 100 ft-c at the level of the restraining cylinder. Another Whisper Fan was attached to the light mounting to draw off additional heat. Temperature variations between light and dark conditions ranged from 78 to 82° F.

Ss were randomly assigned to one of four groups: frontal-light, frontal-dark, sham-light, or sham-dark. Operation was performed on 1 S per day. The order of operation and restraint conditions were determined by numbers drawn from a 4 × 4 Latin Squares Table. Bilateral ablation of the frontal cortex by aspiration was performed on half the *Ss*, while a small portion of the cortex in the parietal-occipital area was removed in "sham" animals. Operation was performed under sodium pentobarbital (Nembutal†) sedation (0.45 mg./kg.). Four days after operation each S was restrained for approximately 23 hr. under either light or dark sensory conditions. Following the restraint period, *Ss* were immediately sacrificed by injecting 1 cc. of Nembutal into the peritoneal cavity. The stomach was removed and the animal perfused with a 0.9% saline solution, followed by a 10% formalin solution. The stomach was cut open along the center of the rumen portion, and ulcers, defined as an erosion in either the mucosa or the rumen, were counted by the experimenter. An additional ulcer count was made by another individual who had no knowledge of the restraint or surgical conditions. The correlation between these two tabula-

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tions was 0.93 (Spearman Rank Correlation). Following perfusions, all brains were removed and photographed. An opaque projector was used to superimpose the brain photograph on a Lashley diagram and to allow the lesion to be outlined. The extent of the frontal lesion was verified histologically.

Results

A $\sqrt{X} + \sqrt{X+1}$ transformation of raw scores, as suggested by Edwards[12] for frequency data, was carried out. A two-way analysis of variance revealed F values of 9.87 and 15.09 for surgical and illumination conditions, respectively. With df = 1/19, both values were significant at less than the 0.01 level. No significant interaction effects were found. Figure 1 shows the means of the transformed scores for the four groups.

A comparison of the weight of the animals before operation and later prior to restraint showed that the "frontal" subjects had an average weight loss of 51.4 gm. while the sham subjects showed only a 19.6-gm. average loss. This difference was found to be significant beyond the 0.01 level (Mann-Whitney U Test, U = 10). The weight loss between light- and dark-restrained subjects was not significant (U = 31.5).

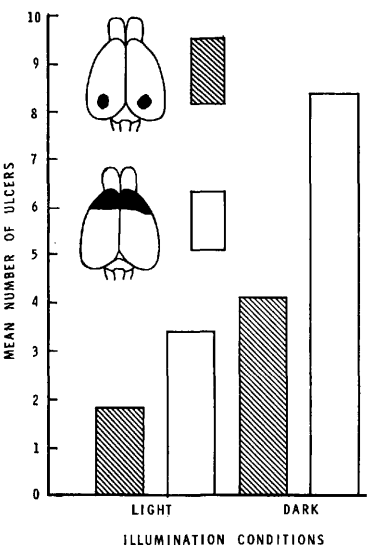

FIG. 1. Ulcer production as related to cortical ablation and sensory stimulation.

Discussion

The results of the present study appear to support the proposed relationship between the level of neurological activity and ulceration rate. Raising the level of activity by restraining animals under low illumination conditions and/or by removing the frontal cortex led to a significant increase in the number of ulcers developed during the 23-hr. restraint period, as compared with the number of ulcers observed in animals restrained under higher illumination conditions or sham-control animals. Although a significant weight loss was observed between subjects whose frontal cortex was ablated and sham-control animals, it is doubtful that this factor accounts for the significant difference in ulceration rate between these groups in view of the fact that Brodie and Hanson[4] found weight not to be an important variable in ulceration incidence in rats restrained for 24-hr. periods. The difference in ulceration rate seen in subjects restrained under low illumination conditions, but between which no significant weight difference was observed, lends further credibility to the proposition that the difference in activation level is the critical factor involved.

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