# *BRAIN NOREPINEPHRINE: EVIDENCE THAT NEURONAL RELEASE IS ESSENTIAL FOR SHAM RAGE BEHAVIOR FOLLOWING BRAINSTEM TRANSECTION IN CAT**

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*Abstract.*—There is a direct relationship between the magnitude of sham rage produced by brainstem transection in cat and the decrease of brainstem norepinephrine. The attacks of rage are augmented by protriptyline and inhibited by haloperidol, drugs respectively facilitating or depressing the action of norepinephrine centrally. Release of norepinephrine by brainstem neurons appears essential for appearance of this behavior.

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Sham rage produced in the cat by electrical stimulation of the brain or by an acute transection of the brainstem is associated with a decrease in the content of brain norepinephrine.[1, 2] The reduction of norepinephrine concentration has been shown by fluorescence histochemistry to occur in most axon terminals of norepinephrine-containing neurons[3, 4] in the brainstem. The lowering of norepinephrine concentration presumably results from augmented activity of these neurons in sham rage behavior with norepinephrine release outstripping the capacity of the brain to resynthesize the amine.[3, 4] It remains to be established, however, if the fall of brain norepinephrine in sham rage is essential for the appearance of the evoked behavior or merely represents an associated phenomenon. If norepinephrine release is necessary it might be expected that when rage is produced acutely by lesion the magnitude of the decline of brain norepinephrine would be, in some manner, proportional to the intensity of the spontaneous outbursts of sham rage. More directly, drugs which facilitate or block the action of norepinephrine centrally, respectively, should augment or reduce the frequency and intensity of the spontaneous, unprovoked attacks of sham rage. In the following study we have therefore investigated the relationship between depletion of norepinephrine and the magnitude of sham rage produced by brainstem transection and the effect of drugs acting to facilitate or inhibit norepinephrine activity centrally on this behavior.

*Method.*—Mature cats of both sexes were studied and prepared as detailed elsewhere.[2] In brief, under ether anesthesia, both carotid arteries were ligated, a tracheal cannula inserted, and the animals placed in a stereotaxic frame and decerebrated by section and suction under direct vision through a parietal skull window. In some animals, blood pressure was recorded through a femoral arterial cannula connected to a Statham transducer and displayed on an ink writer. The general plan of the experiment is shown in Figure 1. Lesions were placed along a plane running from the rostral edge of the superior colliculus to the optic chiasm to produce recurrent spontaneous attacks of sham rage (Fig. 1, high decerebration). After 3 hr, the animals were decapitated, the lower brainstem (consisting of midbrain below the mid-collicular line, pons, and medulla) was removed, homogenized, extracted on alumina columns, and assayed for norepinephrine by the trihydroxyindole method.[5] To control for nonspecific effects of surgical trauma, a

second group of animals was prepared by brainstem transection at the intercollicular level (Fig. 1, low decerebration), a lesion which does not produce spontaneous rage (although attacks may still be provoked by strong noxious stimulation). Norepinephrine was measured in the same block of lower brainstem as in cats with behavioral rage. Concentrations of norepinephrine in the lower brainstem in animals not operated upon or receiving equal amounts of ether anesthesia have been established for this laboratory and recorded elsewhere[2] and do not differ from animals with intercollicular decerebration.

The attacks of rage were quantified by counting the number of spontaneous attacks or fragments of sham rage as characterized by violent alternating limb movements, tail lashing, pilo-erection, extension of claws, hissing, dilation of pupils, retraction of nictitating membrane, for each 10-min period. Experience in this laboratory has shown that a plateau in the frequency of rage attacks is usually reached within 90 min after discontinuation of anesthesia and maintained until the animal is killed 3 hr after the lesion.

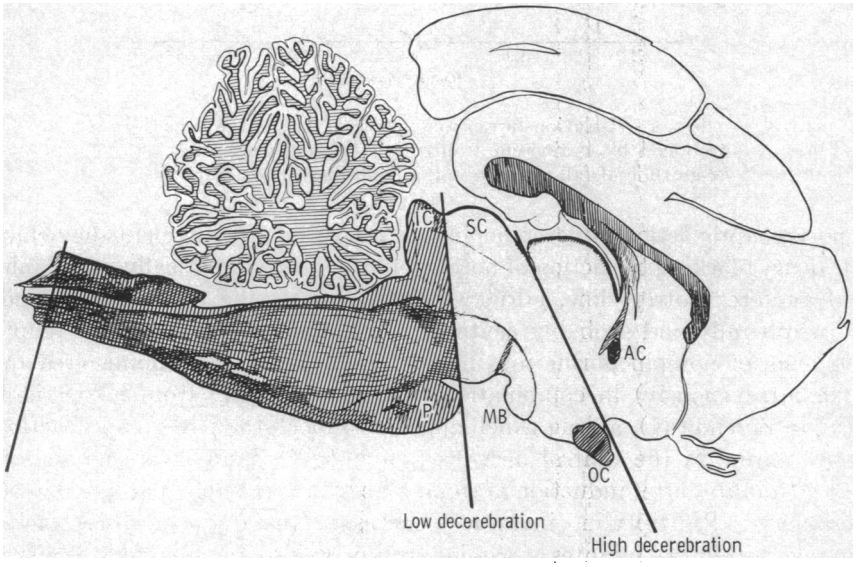


FIG. 1.—Schematic representation of mid-sagittal section of cat brain showing plane of transection producing sham rage (high decerebration) or quiet behavior (low decerebration). The area of brainstem (*cross hatched*) assayed for norepinephrine lies between line to left (at first cervical segment) and plane of low decerebration. Cerebellum and remainder of brain are not assayed. AC, anterior commissure; IC, inferior colliculus; MB, mammillary bodies; OC, optic chiasm; P, pons.

*Results.*—The brainstem concentration of norepinephrine ± standard error in seven cats decerebrated at the intercollicular level and not manifesting spontaneous rage (Fig. 2, control) was 0.230 ± 0.016 μg/gm which does not differ from brainstem norepinephrine concentrations in cats not operated upon or cats simply anesthetized with ether.[2] The norepinephrine concentration in six cats with rage was 0.144 ± 0.012 μg/gm. The difference between the two groups is highly significant ($p < 0.001$) in confirmation of our earlier report.[2] Furthermore, there is an inverse relationship (correlation coefficient −0.71, $p < 0.01$) between the frequency of attacks of rage and the final level of norepinephrine in the brainstem (Fig. 2).

If norepinephrine release is necessary for production of sham rage behavior following brainstem transection it would be expected that agents which facilitate

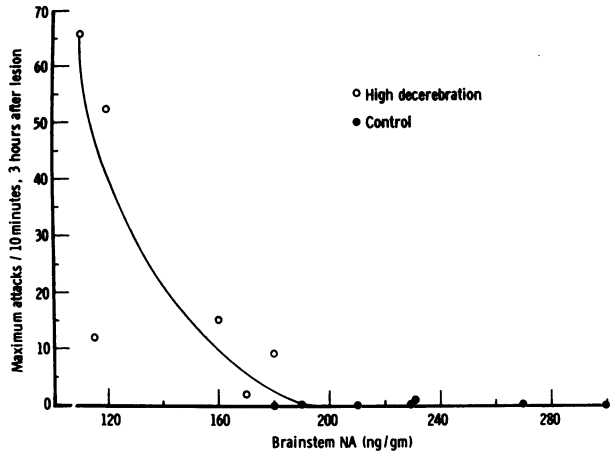


FIG. 2.—Relationship of magnitude of sham rage behavior produced by brainstem transection (high decerebration) to magnitude of fall in brain norepinephrine concentration.

the postsynaptic action of norepinephrine would similarly augment the behavior while drugs blocking the action of norepinephrine post synaptically would inhibit it. Therefore, protriptyline, a drug which potentiates the action of norepinephrine peripherally and probably centrally, presumably by blocking the reuptake mechanism of norepinephrine into nerve terminals,[6-9] was administered (5–10 mg/kg intravenously) in combination with or separately from haloperidol (5 mg/kg intravenously), a drug which appears to block the postsynaptic action of norepinephrine in the central nervous system.[10-14] Drugs were administered about 90 minutes after induction of sham rage by a supracollicular lesion in eight experiments. Protriptyline invariably increased the frequency of attacks of sham rage within two minutes of administration, and this augmented activity was sustained for over an hour or until the animal was killed. A representative experiment is shown in Figure 3. Haloperidol invariably abolished or markedly reduced the frequency of the attacks of sham rage within five minutes after intravenous administration, whether the attacks were spontaneous or facilitated by prior administration of protriptyline. Neither protriptyline nor haloperidol in the same dose produced any behavioral effects on animals with intercollicular lesions which did not manifest spontaneous attacks of sham rage.

*Discussion.*—These findings, therefore, indicate that the magnitude of the fall of norepinephrine in brainstem with sham rage produced by lesions is related to the intensity of the induced behavioral response. Furthermore, the pharmacological evidence strongly suggests that the release of norepinephrine is essential for the occurrence of sham rage. Since both protriptyline and haloperidol act at the adrenergic synapse, it appears that the activity of neurons which are postsynaptic to the norepinephrine neurons is a necessary event leading to the manifestations of rage as produced in this study.

It is of considerable interest that in the medulla, the bulk of norepinephrine terminals are concentrated in the nucleus tractus solitarii, dorsal motor nucleus of

the vagus, and the nuclei of the raphe in rat and cat,[4, 15] and that depletion of norepinephrine occurs in these terminals when sham rage is produced by a lesion.[2] While recurrent rises in blood pressure and increased heart rate characterize individual outbursts of sham rage[2, 16] and persist even when body movements are blocked by curare (Reis, unpublished data), these medullary regions in which the norepinephrine terminals are found are those in which electrical stimulation produces a fall of blood pressure, slowing of the heart rate, EEG signs of sleep, inhibition of motor activity, and even inhibition of sham rage.[17-20] They also are, in part, the site of termination of afferent fibers from the carotid sinus and aortic baroreceptors which, on activation, will reflexly inhibit sham rage.[21-24] Thus, norepinephrine release is maximal in medullary regions which appear to be inhibitory to some or all of the autonomic and somatic components of the behavior. One possible hypothesis to explain this paradox is that norepinephrine neurons may act by inhibiting some brainstem nuclei which are inhibitory for all or fragments of the integrated autonomic and somatic components of sham rage behavior. Consistent with the hypothesis is the fact that norepinephrine most often inhibits both spontaneous and evoked discharge of neurons in the brain when applied iontophoretically.[25-29] Whether sham rage behavior may in part be the result of neural disinhibition, however, remains to be determined by further experimentation.

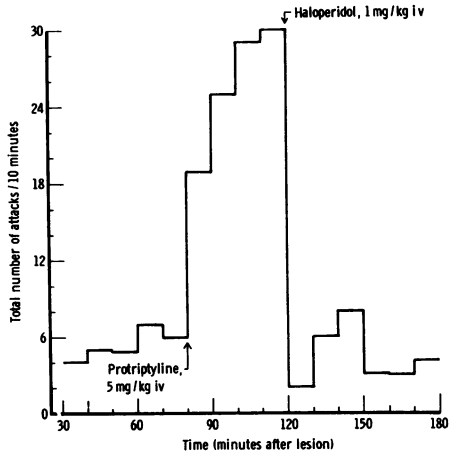


FIG. 3.—Effect of protriptyline and haloperidol on frequency of spontaneous attacks of sham rage in cat following brainstem transection. Note immediate facilitation of behavior by protriptyline and inhibition by haloperidol.

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