tamine response and suggest that histamine is able to alter the concentration of H_1 receptors.

Mouse neuroblastoma clone N1E-115 cells in culture exhibit many properties of normal nerve cells (*9*). The demonstration that histamine stimulated cyclic GMP formation in this clone by activation of H_1 receptors suggests that histamine also would have this effect on some neuronal cell types in vivo. Although this point remains to be demonstrated, it has been shown that histamine stimulated cyclic GMP formation in bovine superior cervical ganglia (*10*).

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12. Twenty-five microliters each of 3.2*M* $ZnSO_4$ and 3.2*M* Na_2CO_3 were added to the 1.5-ml fraction from the cation exchange column. After sedimentation of the precipitate, the supernatant was quantitatively removed and counted for radioactivity in a liquid scintillation counter (Searle Isocap/300). The efficiency for counting tritium was 35 percent with 10 ml of Quantifluor (Mallinckrodt).
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Enhancement of Conditioned Arterial Pressure Responses in Cats After Brainstem Lesions

Abstract. *Cats were classically conditioned after the baroreceptor reflexes were abolished by bilateral placement of electrolytic lesions in the nucleus tractus solitarii. The conditioned increases in arterial pressure were more than five times larger than the responses obtained in similarly trained controls. This finding suggests that the baroreceptor reflexes actively inhibit conditioned increases of arterial pressure.*

We recently found that, in cats, lesions of the intermediate zone of the nucleus tractus solitarii (NTS) within the medulla oblongata abolish the baroreceptor reflexes (*1*) and produce labile arterial hypertension (*2*). In addition to the lability, the cats exhibit exaggerated arterial pressure responses associated with self-initiated behaviors and, in particular, with behaviors elicited by the incidental presentation of various sensory stimuli. The exaggerated vascular reactivity of these cats to sensory stimulation suggested to us that perhaps even larger and more sustained increases in arterial pressure might be produced if the cats were deprived of normal baroreceptor function by NTS lesions and then classically conditioned (Pavlovian conditioning). These procedures, entailing controlled presentation of sensory stimuli that signal the occurrence of a noxious event, have been used to produce conditioned increases of arterial pressure (*3*).

Twelve adult mongrel cats of both sexes were anesthetized and, under sterile conditions, the right common carotid artery was cannulated for the subsequent recording of arterial pressure and heart rate when the cats were awake and unrestrained (*4*). Another cannula was inserted into the right external jugular for the injection of drugs. Disk electrodes (1 cm in diameter) were implanted subcutaneously over the left flank and the right chest for the passage of electrical shock required by the classical conditioning procedure. All wires and cannulas were led through a cranial plug to a swivel that permitted free movement of the cat within the cage. The arterial cannula was connected to a strain gauge transducer for recording blood pressure and heart rate by standard methods.

After a recovery period of 2 weeks the baroreceptor reflexes were tested in all cats by measuring the reflexively mediated decreases of heart rate in response to administration of pressor doses of norepinephrine (0.5 μg/kg administered intravenously). After completion of these tests and establishment of baseline values of arterial pressure and heart rate, the cats were reanesthetized, and in six of the cats the region of the obex was exposed and electrolytic lesions were made bilaterally in the NTS (*5*). The other six cats, assigned to the control group, were similarly operated except that no current was passed after the electrodes were inserted into the NTS. Two weeks after this operation the tests of the baroreceptor reflexes were repeated and conditioning of the cats began.

Both groups were conditioned by the same procedure. The conditioning procedure was conducted for 30 daily sessions (five to seven per week). Two tones of different frequencies (2222 and 1136 Hz, referenced to a C-weighted scale) were presented randomly during each session, each tone being presented ten times. The high tones terminated with delivery, through the disk electrodes, of an electrical shock, while the low tones were not followed by a shock. The voltage level of the shock (50-Hz square wave, 10 to 36 V for 1 second) was set to elicit an increase in arterial pressure of 40 to 50 mm-Hg. At these voltage levels discomfort to the cats was minimal. The duration of the tones was gradually lengthened as training progressed. In order to expedite the formation of an association between the onset of the tone and delivery of the electrical shock, the duration of the tone was set at 10 seconds for sessions 1 to 10. In order to test the maintenance of the conditioned response, the duration of the tone was lengthened to 30 seconds for sessions 11 to 20 and to 60 seconds for sessions 21 to 30. The intertone interval varied randomly between 60 and 150 seconds.

The conditioned cardiovascular responses recorded from each cat were sampled at a rate of 50 Hz for processing by a digital computer. In order to adjust for baseline variations, each conditioned response was computed as the change relative to the average response level recorded for the 10 seconds just prior to presentation of the tone. The number of data samples was reduced to 60 values by dividing the tone period into 1-second intervals and computing the average cardiovascular response that occurred during each interval. The same procedure was followed for the 10-second period following termination of the tone. Each conditioned response for purposes of statistical comparison was reduced to the maximum response increase during the tone, the response during the 20th second of the tone, and the average re-

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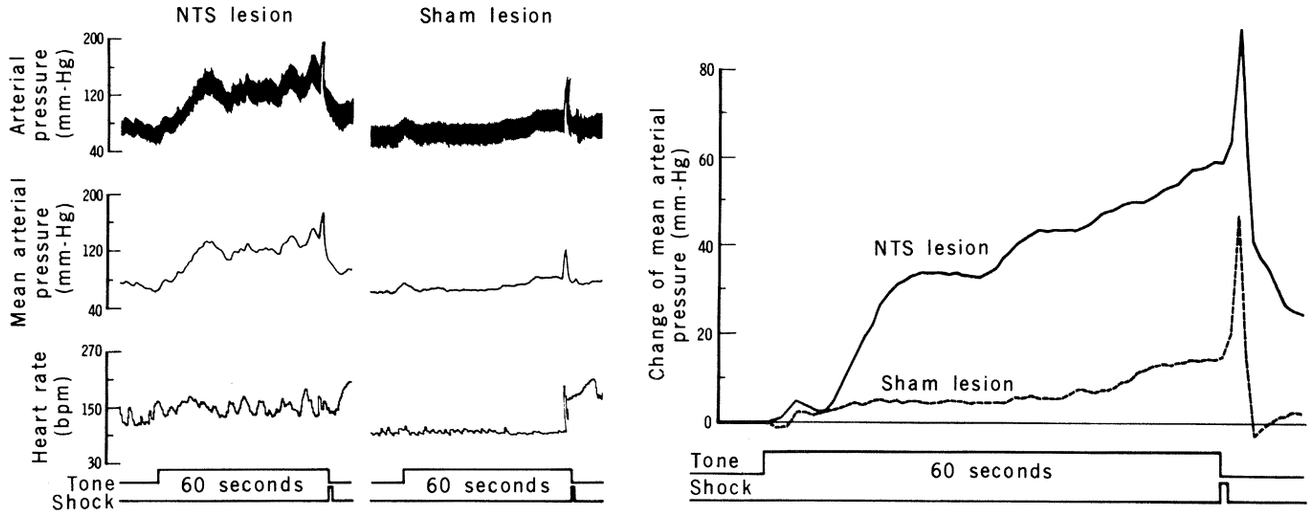

Fig. 1 (left). Conditioned cardiovascular responses of a cat with NTS lesions and a cat with sham lesions. Deflection of the signal pen at the bottom of the figure indicates the onset, duration, and termination of the tones and electrical shock. Abbreviation: *bpm*, beats per minute. Fig. 2 (right). Conditioned increases of mean arterial pressure in the NTS lesion group and the sham lesion group during session 30. Signal pen indications as in Fig. 1.

sponse increase that occurred during the entire duration of the tone. The maximum response increase was the largest of the 60 values that had been calculated as described above. Attention was given to the response at the end of 20 seconds, because the greatest increase in arterial pressure of the cats in the lesion group occurred during this time period. The average response increase was calculated as the mean of the 60 values. For purposes of graphical presentation of the response to the tone and to the electrical shock, the corresponding interval values from each cat were pooled according to group, and the average interval value was computed. This procedure was repeated for each 1-second period of measurement. Statistical comparisons between the lesion group and the control groups were made with a t-test for independent samples. The computer-generated graphs and statistical analyses were based on data from four cats in each group. Data from the other four cats were destroyed during a malfunction of the computer-system, bulk-storage device.

In agreement with our earlier findings (*2*), cats with NTS lesions no longer had baroreceptor reflexes, exhibited the usual increase in lability of arterial pressure, and were mildly hypertensive. By session 30, all six cats with the lesions showed substantially larger conditioned pressure responses than the cats with sham lesions, trained under the same conditions. A representative example of the difference in conditioned arterial pressure response between a cat with lesions and a control cat is illustrated in Fig. 1. During presentation of the tone, the systolic pressure of the cat with the lesions rose to nearly 180 mm-Hg and the diastolic pressure reached 140 mm-Hg. In contrast, the maximum systolic pressure of the control was only 100 mm-Hg and the highest diastolic pressure was 70 mm-Hg. In both cats, as in each group, the heart rate was unaffected by presentation of the tone.

Comparisons of the group responses demonstrate additional differences (Fig. 2). The comparisons were made by using the change in mean arterial pressure relative to baseline, because the baseline pressures varied over a wide range (54 to 106 mm-Hg). There were, however, no differences in the mean baseline levels (t = 1.18, d.f. = 6, P <.30) between the lesion group (80 mm-Hg) and the control group (77 mm-Hg), nor did the magnitude of change in the mean arterial pressure correlate with the baseline level in either group. The response increase to the electrical shock was higher in the lesion group than in the control group, but the response increases were nearly identical when measured relative to the pressure level recorded at the end of the tone. The latency of the increase of arterial pressure from the onset of the tone in both groups was similar (2 to 3 seconds). However, the rate of increase of arterial pressure in the NTS lesion group was more rapid and generally more sustained. In the lesion group the steepest rise occurred during the first 20 seconds of tone presentation. By the 20th second the increase in pressure had reached 34 mm-Hg, while during the same time period an increase of only 5 mm-Hg was observed in the control group (t = 3.98, d.f. = 6, P <.01). After the first 20 seconds the arterial pressure of the lesion group continued to rise, although not so steeply, and it reached a maximum of 59 mm-Hg 1 second before termination of the tone. In contrast, the response of the control group increased more gradually and reached a maximum of only 15 mm-Hg at the end of the tone (t = 5.93, d.f. = 6, P <.01). The most striking difference between the two groups was found when the average increase of pressure during the tone was examined. The NTS lesion group showed an average increase of 35 mm-Hg, a value more than five times larger than the average increase of 7 mm-Hg recorded from the control group (t = 7.94, d.f. = 6, P <.001).

The conditioned pressure responses obtained in cats with NTS lesions are substantially larger than those previously reported from classically conditioned animals and, with the exception of a few investigations, the responses exceed those in which operant conditioning procedures were used (*3*). The procedures of operant and classical conditioning are quite different and thus the results obtained by these two procedures are difficult to compare except perhaps on the basis of total time of conditioning required to produce comparable increases of arterial pressure. The studies utilizing operant conditioning, in which increases comparable to ours were obtained, involved training animals to either press a lever or, in response to a signal, to raise their arterial pressures to avoid electrical shocks. However, in such studies the conditioning extended over a period of 4 to 6 months (*3*), whereas in our study the animals were condi-

tioned for 4 to 6 weeks. Therefore, abolition of the baroreceptors by lesions of the NTS seems to increase the efficacy of conditioning unusually large pressure responses and suggests that baroreceptor activity vigorously opposes the conditioned increases of arterial pressure.

The demonstration that abolition of the baroreceptor reflexes by lesions of the NTS potentiate conditioned pressure responses does not rule out the possibility that the lesions may additionally destroy pathways other than those carrying baroreceptor activity. Pathways exerting an inhibitory influence on sympathetic vasomotor activity have been reported (*6*), and destruction of these pathways by the lesions may have contributed to the potentiated conditioned pressure responses we observed.

Our observation that abolishment of the baroreceptor reflexes by a central lesion promotes the establishment of large conditioned pressure responses is important because of its relevance to the many recent attempts to use conditioning procedures as a means of producing an animal model of neurogenic hypertension (*3*). The extended periods of time required to produce conditioned elevations of arterial pressure suggest that events, other than the conditioning process itself, must occur before the pressure rises. Among these events may be an adaptation or resetting of the baroreceptor reflexes, which then permits the arterial pressure to increase to hypertensive levels. Placement of lesions in the NTS, thereby removing the inhibitory influence of the baroreceptors, may be a means to condition more rapidly sustained increases of pressure and thus shorten the time required to produce an animal model of neurogenic hypertension.

The need for an expedient way of producing such an animal model has increased in recent years because of gathering evidence that heightened sympathetic activity, possibly governed by the central nervous system, may contribute importantly to the mediation and perhaps the initiation of essential hypertension in man (*7*). Thus an animal model of neurogenic hypertension would greatly aid in the understanding of the mechanisms and treatment of this form of hypertension.

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Effects of Naloxone on Schizophrenia: Reduction in Hallucinations in a Subpopulation of Subjects

Abstract. *Endogenous opiate-like peptides (endorphins) are putative neuroregulators located throughout the mammalian brainstem. There is some evidence for their role in pain, stress, and affect. We report that the opiate antagonist, naloxone, alters some schizophrenic symptoms. In a double-blind, cross-over study, naloxone produced decreases in auditory hallucinations in some schizophrenic patients. This finding supports the hypothesis that the endorphins may play a roll in modulating hallucinations in a highly selected subgroup of chronically hallucinating schizophrenic patients.*

The central nervous system of mammals, including man, contains a family of opiate-like peptides (endorphins) and specific receptors for these endogenous substances (*1*). These peptides are thought to be stored in neurons, and they appear to be widely distributed throughout the nervous system, especially in areas associated with sensory integration and the control of affect (*2*). The endorphins have a number of pharmacological actions, including analgesia, and can produce tolerance and dependence (*3*). Further, there is evidence that the endogenous opiate-like peptide systems are engaged by painful and stressful stimuli (*4*, *5*).

Several investigators have suggested a role for the endorphins in psychiatric disorders (*6*). Aside from the known mood-altering properties of opiates such as heroin, it is well established that a subgroup of opiate alkaloids can produce naloxone-reversible dysphoric feelings and auditory hallucinations in man (*7*). Terenius *et al.* (*8*) presented the first biochemical evidence in support of a relation between endorphins and psychosis. They reported increased amounts of endorphins in the cerebrospinal fluid of acutely disturbed schizophrenic and manic patients. Some of these subjects showed decreased amounts of endorphins during the remission of their psychosis. Gunne *et al.* (*9*) reasoned that if increased amounts of endorphins were correlated with psychosis, then the administration of the opiate antagonist naloxone might alter psychotic symptoms. They reported in a single-blind study the reversal by naloxone (0.4 mg) of auditory hallucinations in four out of six chronic paranoid schizophrenics. However, that study had some methodological limitations, particularly its single-blind nature and its focus on auditory hallucinations in the absence of standard psychiatric rating scales. The three studies (*10*) which attempted to replicate the findings of Gunne *et al.* (*9*) rectified some of these limitations and all produced negative results. However, in all three studies, the investigators infused intravenously doses of naloxone that were between 0.4 to 1.2 mg (very few subjects received higher doses). Further, Davis and co-workers and Janowsky and co-workers (*10*) evaluated their subjects for only a brief period of time after infusion (15 minutes to 1 hour).

In the study described here, we used high doses of naloxone (10 mg), because this antagonist may be less effective in reversing the action of endogenous opioids than in blocking some opiate alkaloids (*11*). Further, certain agonist-antagonist opiates, such as cyclazocine and nalorphine, which produce hallucinations in man, can require up to 20 to 60 times more naloxone for reversal than does morphine (*12*). We also observed our patients for several hours after drug injection because there are reports of the effects of naloxone lasting several hours

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