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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Table 1. Characteristics of patients and subjective ratings of their responses to naloxone. For subjects 1 and 2 we used a single-blind study design; for all other patients we used a double-blind procedure. The sequence of testing was either P/N, placebo followed by naloxone, or N/P, naloxone followed by placebo. The 0 to ++ ratings were the subjective clinical impressions of the investigators: 0, no response; ±, equivocal improvement; +, detectable improvement with decrease in auditory hallucinations; ++, substantial loss of hallucinations.

Subject	Age (years)	Subgroup*	Current neuroleptic treatment	Drug sequence	Clinical impressions of response to naloxone		
					Rating	Duration† (hours)	Report of investigators
				Single-blind study design			
1	33	Pa	No	P/N	++	6	Slightly less anxious, no hallucinations
2	32	Un	No	P/N	++	96	Transiently irritable, then calm, fewer voices
				Double-blind study design			
3	28	Pa	Yes	P/N	++	48	Less rapid thinking, less depressed and anxious, calm
4	41	Pa	Yes	P/N	++	24	Calmer, slept well, less tense
5	26	Pa	No	N/P	0		"Hears" his thoughts. Both infusions "helped"
6	47	Pa	Yes	P/N	±		Became more ill prior to study; naloxone suppressed "voices"
7	45	Pa	No	N/P	0		Very delusional, continued hallucinating
8	26	Un	Yes	N/P	+	6	Briefly irritable, then felt "good"
9	29	Un	No	P/N	+	3	Transiently irritable, then less anxious and relaxed
10	27	Pa	Yes	N/P	+	4	Transiently irritable, then calm and even smiled
11	22	Pa	No	N/P	++	3	Slower thoughts, relaxed and felt "good"

*The abbreviations Pa and Un are for chronic paranoid schizophrenia and chronic undifferentiated schizophrenia. †Duration indicates the patient's report of number of hours after infusion at which auditory hallucinations returned in full.

(*5, 13*), in spite of its short-lived action in antagonizing opiate alkaloids. We used a double-blind cross-over paradigm in which the raters were blind to the study design and the videotaped interviews were scored by standard psychiatric rating scales. With this design we observed the blockade or reduction of auditory hallucinations in a carefully selected subgroup of schizophrenic patients.

The 11 subjects were male volunteers aged 26 to 47 years (*14*). Each patient was thoroughly evaluated both physically and psychiatrically, and was free of any major physical disorder and had no history of drug abuse. All subjects (Table 1) had been given the diagnosis of chronic schizophrenia (paranoid or undifferentiated) according to the Diagnostic and Statistical Manual of the American Psychiatric Association (*15, 16*). The subjects were selected on the basis of the following criteria: they exhibited a stable symptom pattern, had very frequent auditory hallucinations (at least twice per hour including study days), and had an active ratable pathology on the rating scales. Such pathology involved high scores on the anxiety, paranoid, anger, or general agitation ratings on the National Institute of Mental Health (NIMH) scale. It was necessary to screen approximately 1000 general psychiatric patients to locate the 11 used in this study who met all the above criteria.

Five subjects were maintained on their routine dose of antipsychotic medications and six had not received neuroleptics for at least 2 weeks prior to the study (Table 1). Naloxone (10 mg) or a matched volume of the vehicle (both provided by Endo Labs) was administered intravenously. Subjects 3 to 11 were told of the general study plan but not of the theoretical questions. They were seated in a comfortable chair and a line was inserted into one arm for intravenous drug infusion. They were then interviewed and videotaped by two raters using the Brief Psychiatric Rating Scale (BPRS) (*17*) and the NIMH Rating Scale (*18*).

Subjects 1 and 2 were studied on a single day in a single-blind paradigm. Their results are shown in Tables 1 and 2 but are not included in any data analysis. A baseline interview was rated after placebo injection. Forty minutes later, 10 mg of naloxone hydrochloride was administered. The interview was repeated immediately after infusion, and several times within the next few hours. Neither subject knew which infusion contained naloxone, nor the exact nature of the expected effect. Both subjects reported loss of auditory hallucinations lasting several hours (Table 1). Subject 2 became more irritable with paranoid ideation shortly after naloxone administration, returning to his usual mood state in about 45 minutes. With the exception of this transient response, both subjects reported a feeling of well-being and relaxation atypical for them (*19*).

Subjects 3 to 11 were studied in a double-blind, randomized cross-over paradigm, and the data we obtained in this manner formed the basis for the statistical analysis presented below. The usual pattern was to separate the naloxone and placebo infusions by at least 48 hours. Of the nine patients, six reported a clear-cut improvement in hallucinations, one showed borderline improvement, and two did not improve beyond the placebo effect (Tables 1 and 2). The six responders (subjects 3, 4, 8, 9, 10, and 11) reported either a complete loss or a substantial decrease in auditory hallucinations. Subjects 8, 9, and 10 also reported the biphasic mood change seen in subject 2. They became irritable shortly after the administration of naloxone, returning to their usual mood state within 45 minutes, and exhibiting a pleasant, relaxed mood thereafter. All six subjects reported decreased anxiety, an improvement in mood, and better sleep that evening (Table 1).

The borderline responder (subject 6, an outpatient), was difficult to evaluate because of an increase in his psychosis coupled with a delayed placebo effect. A public health nurse who knew the subject reported that he had been increasingly sleepless and agitated before the study began and that this was a usual prodrome to an exacerbation of his psychosis. Although this subject did not report any changes in hallucinations within the first few hours after the placebo injection, he reported a decrease in hallucinations 7 hours later and an increase in paranoid delusions over the next few days. On the day of the naloxone in-

fusion, he had higher baseline scores on both global psychosis rating and intensity of hallucinations. Nevertheless, naloxone brought about a decrease in hallucinations lasting for several hours. Two days after infusion this patient required hospitalization.

Of the two nonresponders, in retrospect, subject 7 was too delusional to give reliable reports. However, no changes were observed on any of the scales, including hallucination and mood. Subject 5 had a decrease in hallucinations and anxiety after both placebo and naloxone infusion. This patient's hallucinations had the character of hearing his own cognitions, whereas the other subjects labeled their voices as external.

We performed an analysis of variance on the difference scores between the response to drug and the response to placebo (a response score was the arithmetic difference between that day's baseline and the response to drug or placebo at 1½ to 2 hours after infusion). There was no significant effect of day (or sequence of presentation), $F(1, 7) = 1.55$ (not significant). However, there was a significant effect of drug (naloxone) on hallucinations, $F(1, 7) = 5.62$, $P < .05$. Several subjects appeared less anxious after naloxone, but this trend did not reach statistical significance. The mean on the NIMH anxiety scale on the day that subjects received the placebo was 0.88 ± 0.68 (± standard error of the mean), whereas the mean on the day they received naloxone was 2.12 ± 0.63. None of the nine subjects exhibited any consistent changes in orientation, memory, delusional state or level of consciousness. The means from the BPRS scales for anxiety and hallucinations are in close agreement with those from similar NIMH scales [see bottom of Table 2 and (*18*)].

The duration of the naloxone-induced changes was longer than expected, possibly because of the large dose used. Alternatively, it may be caused by secondary changes in endorphins or other systems brought about by a large dose of antagonist. Of the six responders, the four subjects (Nos. 8, 9, 10, and 11) with the shortest responses (3 to 6 hours) experienced a full return of the hallucinations at the end of that period. The other two subjects (Nos. 3 and 4) reported relief of hallucinations lasting 24 to 48 hours. During that period, these patients reported an improved mood state, and better sleep. Typically, they had less trouble falling asleep or staying asleep. Several patients attributed the changes in sleep pattern to the loss of "voices" which usually disrupted their sleep. As the hallucinations returned, several subjects spontaneously described them as being "very faint" or "in the distance." One subject likened them to a "running blank tape" in that he felt their presence without hearing the sound. These statements are similar to the report by one subject in the study of Gunne *et al.* (*9*).

Table 2. Effects of naloxone (10 mg) on hallucinations in schizophrenic patients. Hallucination ratings (NIMH scale) are given for before infusion of the drug or placebo (baseline) and for 75 to 120 minutes after infusion (the higher the rating the greater the pathology). The difference score is the difference between the baseline rating and the rating after infusion (the higher the number the greater the improvement).

Subject	Placebo			Naloxone		
	Hallucination rating		Difference score*	Hallucination rating		Difference score†
	Before	After		Before	After	
			Single-blind study design			
1				6	0	6
2				3	0	3
			Double-blind study design			
3	3	2	1	4	0	4
4	2	1	1	4	0	4
5	3	3	0	3	4	−1
6	2	2	0‡	6	3	3
7	6	6	0	6	6	0
8	5	3	2	5	1	4
9	6	6	0	6	3	3
10	5	1	4	6	4	2
11	5	5	0	6	0	6

*For subjects 3 to 11 the mean (± standard error) of the difference scores was $0.88 \pm .45$. The sequence of presentation, $F(1, 7) = 1.55$ (not significant). The mean on the BPRS scale was $0.61 \pm .37$. †For subjects 3 to 11 the mean of the difference scores was $2.78 \pm .72$. Drug effect, $F(1, 7) = 5.62$; $P < .05$. ‡Subject lost hallucinations later that day for several days; he became more ill and was hospitalized.

Since naloxone is not known to interact primarily with other neuroregulator systems, our results could implicate the endogenous opiate-like peptides in some schizophrenic symptoms, particularly auditory hallucinations and perhaps anxiety. However, several difficulties intrinsic to the design should be pointed out:

1) Each subject underwent repeated rating and testing. The interaction and sequence effects of such a design may have influenced the results.

2) Hallucinations are highly variable phenomena and are subject to changes induced by levels of activity of the subject, social interactions, stress, or anxiety. Thus the possibility that the effects we have observed are due to an effect of naloxone on responsiveness to stress is a very real one.

3) Naloxone is short-acting, even if effects can be seen hours after administration. This prevents the study of the consistency or reliability of any of its effects, especially on an intrinsically subjective and variable behavior. The use of a longer-acting antagonist, such as naltrexone, might prove helpful in overcoming this problem.

Our results are suggestive of an involvement of endogenous opioids in some schizophrenic symptomatology. Whether the effects are direct or indirect remain to be established. It should be pointed out, however, that the endogenous opioids are strategically localized for a function in modulating sensory-emotional events (such as pain) in limbic structures (*2*). Further, their potential interactions with other neuroregulators such as monoamines (*2*), substance P (*20*), and adrenocorticotropic hormone (*21*) are becoming increasingly apparent. In general, the existence of multiple endogenous opiate-like peptides and multiple opiate receptors (*22*) suggests a set of widespread systems with complex functions, sharing some pharmacological susceptibilities. Any or all of these systems could underlie some of the symptoms of schizophrenia and be responsible for the effects of naloxone we report.

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Induction of *Zugunruhe* by Photostimulation of Encephalic Receptors in White-Crowned Sparrows

Abstract. *Daily 20-hour encephalic photophases (DEPP), transmitted (hours 0 to 20) via chronically implanted light-conducting fibers to selected sites in the basal hypothalamus of male white-crowned sparrows, were superimposed on daily 8-hour (hours 0 to 8) external ambient photophases (DAPP). Initially the birds displayed motor activity only during the 8-hour DAPP. After a delay of at least 2 weeks, some of the birds became intensively active during hours 8 to 20. We postulate that this period of "nocturnal" activity is equivalent to the nocturnal* Zugunruhe *shown by caged individuals of many nocturnally migratory species subjected to long days; such activity is generally regarded as the expression of migratory behavior.*

It is well known that day length is the primary environmental information in the control of the annual cycles of many species of birds (*1*). Experiments with bilaterally enucleated birds have demonstrated that eyes are not necessary for the perception of light in the photoperiodic induction of gonadal development in several species (*2*). In *Passer domesticus* (house sparrow) extraretinal photoreception is also involved in the entrainment of circadian locomotor rhythms (*3*). The extraretinal photoreceptors in the photoperiodic gonadal response in the domestic mallard (*4*), Japanese quail (*5*), and house sparrow (*6*) are localized in the brain, and in the first two, specifically in the hypothalamus. In the house sparrow the extraretinal photoreceptors that entrain circadian rhythms are also encephalic (*7*).

To locate the extraretinal photoreceptors involved in the photoperiodically induced testicular growth of the highly photoperiodic, migratory white-crowned sparrow, *Zonotrichia leucophrys gambelii*, we devised a scheme (*8*) for introducing a minute light source into selected encephalic sites in the brains of relatively unrestrained birds by the use of light-conducting fibers. Two light-conducting fibers are used. The first is plastic (Crofon, Du Pont) and is about 0.25 mm in diameter and 20 cm long. This fiber is coiled to permit movement by the bird; it conducts light from an incandescent lamp to a second fiber of rigid glass (Corning) that is about 0.05 mm in diameter and 7 to 13 mm in length and is ensheathed with stainless steel tubing so that light leaves only from its very distal end. This second fiber conducts light from the plastic fiber to the selected encephalic site. The rate of emission of light from the end of the glass fiber into the brain tissue is of the order of 10^{-4} μW for the range λ = 400 to 700 nm.

We have found that the direct illumination of the ventromedial and tuberal hypothalamic regions for 20 hours per day induces testicular growth in both intact and bilaterally enucleated white-crowned sparrows; this growth may be as rapid as that induced by an ambient daily photophase of the same duration (*8*). We describe here the effect of 20-hour daily photophases (DEPP) delivered directly to hypothalamic and adjacent areas, and superimposed on an 8-hour daily ambient photophase (DAPP), on the temporal pattern of perch-hopping in white-crowned sparrows.

Male white-crowned sparrows were placed individually in cages (22 by 13 by 22 cm) with a perch that activated a recording microswitch so that motor activity could be monitored. Ambient illumination (DAPP) was provided with two 50-W incandescent lamps housed in reflectors to provide an intensity of 3 to 10 lux at perch level. The birds were neither visually nor acoustically isolated from each other. Light-conducting fibers were inserted stereotaxically into selected sites in the brains of males that had been held on a short-day regime [8 hours of light and 16 hours of darkness (8L:16D)] for 8 months, and were, therefore, highly

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