Auditory Stimulation-Induced Analgesia in Rats: Its Irreversibility by Naloxone

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AUDITORY STIMULATION-INDUCED ANALGESIA IN RATS: ITS IRREVERSIBILITY BY NALOXONE

by

Ilsun Miranda White

A Thesis
Submitted to the
Faculty of The Graduate College
in partial fulfillment of the
requirements for the
Degree of Master of Arts
Department of Psychology

Western Michigan University
Kalamazoo, Michigan
August, 1986
AUDITORY STIMULATION-INDUCED ANALGESIA IN RATS:
ITS IRREVERSIBILITY BY NALOXONE

Ilsun Miranda White, M.A.
Western Michigan University, 1986

After receiving intermittent exposure to a tone (3000 Hz, 100 db, SPL), rats were tested on a hot plate for analgesia. Rats that received tone alone showed a higher average paw-lick latency than rats that received either naloxone or saline alone. This result indicates that the auditory stimulus used in this study can be considered a neurogenic stressor and may be added to the list of various noxious stimuli that produce analgesic effects. Naloxone given to tone-treated subjects produced mean paw-lick latencies that were comparable to control group latencies for the first two treatment sessions and to tone group latencies for the last four treatment sessions. However, the difference between the tone group and the naloxone pre-treated tone group was not significant. The failure to find a reversal of the analgesic effect by naloxone supports the position that both opiate (naloxone sensitive) and non-opiate (naloxone insensitive) systems may be involved in the modulation of stress. The results also suggest that the nature of stress and its temporal features may determine which system can be selectively activated by environmental stimuli.
ACKNOWLEDGEMENTS

I would like to thank Dr. David Lyon, Dr. Frederick Gault, Dr. Kay Malott, and Dr. Alan Poling for comments on the manuscript.

I would also like to thank Dr. Alan Poling and Dr. Frederick Gault for equipment and supplies and Jasper Thomas and Mitch Picker for the help in setting up the equipment.

Finally, I would like to thank my husband, Wesley, for assistance at various stages in the research.

Ilsun Miranda White
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CHAPTER I
INTRODUCTION

The endogenous opioid system may have a variety of functions. For example, it may be related to ingestive behavior (Jones & Richter, 1981; Sanger & McCarthy, 1982; Thompson, Welle, Lilavivat, Penicaud, & Campbell, 1982), memory (Gallagher & Kapp, 1978), and learning (Castellano, 1981; Izquierdo, 1980). Its most important function is the analgesic effect (Bolles & Fanselow, 1982). The endogenous opioid system is activated by sudden stress or injury and reduces the animal's sensitivity. It enables the animal to behave adaptively under conditions of stress and so promotes the survival of the organism (Melzack & Wall, 1983). The present study is designed to evaluate the relationship between auditory stimulation and this analgesic effect.

The role of endogenous opioids (or endorphins) in pain-related behavior has been studied since Pert and Snyder (1973) reported that certain areas of the brain are especially sensitive to opiates and opiate antagonists. Shortly after the Pert and Snyder report researchers succeeded in isolating morphine-like substances from bovine pituitary gland (Teschemacher, Opheim, Cox, & Goldstein, 1975), human cerebro-spinal fluid (Terenius & Wahlstrom, 1975), rat brain, and calf brain (Pasternak, Goodman, & Snyder, 1975). Investigators then identified endogenous opioid structures within certain proteins (Hughes et al., 1975; Simantov & Snyder, 1976). Behavioral assays subsequently
demonstrated that endogenous opioids extracted from the brains of
animals (Buscher et al., 1976), as well as similar synthesized pep-
tides (Belluzzi et al., 1976; Malick & Goldstein, 1977), could
actually function as opiate agonists at receptors, and that such
peptides even produced a morphine-like withdrawal syndrome in rats
The brain, then, appears to produce peptides with opioid-like con-
stituents that act as agonists at opiate receptor sites. Recent
experiments have attempted to evaluate the role of endogenous opioids
in the modulation of pain and have concluded that noxious environ-
mental stimuli can cause analgesia, often referred to as stress
analgesia (Baizman, Cox, Osman, & Goldstein, 1979; Bardo, Bhatnagar,
& Gebhart, 1981; Christie, Trisdikoon, & Cheshet, 1982; Madden, Akil,
Patrick, & Barchas, 1977). This conclusion is based on data that
indicate that such stimuli increase the level of endogenous opioids in
the blood and the pituitary. These experiments are not definitive,
because very little is known about the actual relationship between
endorphin activity in the central nervous system and the level of
endorphin in the cerebro-spinal fluid and blood (Terenius & Wahlstrom,
1978).

Although there is a very large body of literature concerning the
relationship between auditory stimulation and physiological change,
little research has been done describing the relationship between
auditory stimulation and analgesia. In particular, the circumstances,
if any, under which auditory stimulation produces endogenous opioids

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are unknown. This paper will describe one attempt to relate an analgesic effect produced by an auditory stimulus (a tone) to the action of an endogenous opioid system.

A good indirect case can be made for the possibility that endogenous opioids mediate analgesic effects produced by auditory stimulation. One way to make the case is by describing how analgesia has recently been studied using other kinds of aversive stimulation and by describing some of the important physiological features of auditory stimulation.

Analgesia has been defined as the inability to feel pain while conscious. Analgesia has often been studied by examining the sensitivity of an organism after application of intermittent or chronic aversive stimulation. The aversive stimulus which is delivered intermittently or chronically and which engenders analgesia is frequently called the stressor. The effects of the stressor are often assessed by measuring the latency of some adaptive response to acute noxious stimulation before and after stress and is referred to as the test or assay of analgesia. The tail-flick technique is most often used to assay analgesia. The tail-flick test consists of restraining an experimental subject, usually a rat, in a tube, subjecting the subject's tail to focused light from a hot lightbulb, and recording the latency to tail withdrawal (D'Amour & Smith, 1941). In variations of this assay, the latency to flick the tail out of hot water or in response to tail pinching is measured. The hot plate technique consists of placing the subject, again usually a rat, on a hot surface
at some fixed temperature and recording the latency of paw-licking, jumping, or escaping. Analgesia is indicated if, after exposure to stress, there is an increase in the latency to respond on either test. Attempts have also been made to assay analgesia by determining the degree of abdominal constriction produced by stress (Chesher & Chan, 1977). Changes in frequency of grooming (Green, Isaacson, Dunn, & Lanthorn, 1979; Hannigan & Isaacson, 1981) and in locomotor activity (Rodgers & Deacon, 1979) have also been used to infer level of endogenous opioid secretion.

The emergence of analgesia has been associated with the application of various kinds of aversive stimuli or stressors. In studies of analgesia, stimulation has generally been delivered so as to be in-escapable and unavoidable (Drugan, Grau, Maier, Madden, & Barchas, 1981). Researchers have assumed that these features will most effectively trigger the secretion of endogenous opioids. Footshock is often used as a stressor in analgesia studies (Akil, Madden, Patrick, & Barchas, 1976; Chance & Rosecrans, 1979b; Chesher & Chan, 1977; Lewis, Cannon, & Liebeskind, 1980). For example, Akil et al. (1976) reported that intermittent, inescapable footshock produced analgesia in rats. Analgesia was assayed in a tail-flick latency test. Chesher and Chan (1977) used an abdominal constriction test to assess analgesia and reported that even a mild unavoidable footshock engendered analgesia in rats. A defeat-induced analgesic effect was reported by Miczek, Thompson, and Shuster (1982), who suggested that endogenous opioid-mediated analgesic mechanisms are readily activated by
situations involving biologically significant forms of stress, such as defeat. The degree of analgesia induced by attack was assessed in mice by measuring their latency to tail-flick in response to tail-pinchind. Immobilization is a form of nonpainful stimulation (Baizman et al., 1979). Single or repeated immobilizations produced increased latency to escape in rats but had no effect on paw-lick response (Amire & Amit, 1978). Rats exposed to cold water swimming (Bodnar, Kelly, Spiaggia, Paviides, & Giusman, 1978) and to chronic schedules of warm water swimming (Christie et al., 1982) also showed an analgesic response. Analgesia was assayed in these studies with flinch initial jump, and jump threshold tests, and with tail-flick and abdominal constriction assays, respectively.

Guillemin et al. (1977) broke the tibia and fibula bones in rats and found that this acute form of stress was followed by the release of endogenous opioids. When they analyzed trunk blood periodically taken from subjects between 1 and 30 min after stress, they found that peak secretion of endorphin and ACTH occurred between 5 and 10 min. Akil et al. (1976) and Madden et al. (1977) found that intermittent, inescapable footshock was accompanied by significant increase in the level of endogenous opioids. They also found that tail-flick latency used to assay analgesia behaviorally correlated very well with the level of endogenous opioid measured biochemically. Footshock and immobilization promote an increase in endogenous opioid level in blood plasma and brain. Footshock promoted a five- to six-fold increase in endorphin plasma level (Rossier et al., 1977) and
footshock and immobilization each evoked a 40-50% reduction in stores of endorphin in the pituitary gland (Baizman et al., 1979). A change in a behavioral assay of analgesia and an increase in the utilization of endogenous opioids are not, presumably, accidental concomittants. Even in the absence of direct biochemical evidence, many investigators assume that opioid secretion engendered by stress produces the behavioral changes. If forms of stress so varied as footshock and immobilization produce opioid secretion and behavioral analgesia, then perhaps some form of auditory stimulation also can.

Auditory stimulation has many biological effects apart from causing opioid secretion. Although the acute responses to tone are varied and complex (Geber, 1970), tone stimulation has been considered an outstanding example of neurogenic stress (Szikszay, Benedek, & Hideg, 1985). Data from human and from nonhuman laboratory subjects suggest that tone, either continuous or intermittent, activates subcortical neuronal systems to modify continually the brain's control of cardiovascular, endocrine, metabolic, reproductive, and neurological functions, and so determines the level of many peripheral physiological functions (Buckley & Smookler, 1970; Busnel & Molin, 1978). As one example of the effects stimulation can have through the auditory system, Tamari (1970) reported that intense auditory stimuli (3000-12000 Hz) changed the oestrus and increased the weight of the uterus and ovaries of rats with normal hearing, but had no such effect on deaf rats. Audiogenic stimulation also has been used often to induce audiogenic seizures in susceptible animals (Fink & Iturrian, 1970;
Katz, Roth, Schmaltz, and Sible (1980) examined the effects of noxious but, according to the authors, painless white noise (95 db) exposure upon a conditioned preference response in rats. In a single conditioning session they presented either no noise or 95 db white noise to subjects that had received either control saline or morphine in the nonpreferred compartment of a two way shuttle box. Morphine produced a preference shift toward the conditioned environment, and this preference was further increased by noise stimulation. Katz et al. (1980) supposed that noise stress might have activated some system that could algebraically sum with or act synergistically with the system normally activated by morphine (presumably the endogenous opioid system). There are scattered references to audiogenic analgesia in the literature, but none have demonstrated that tone produces endogenous opioids.

Adrenocorticotropic hormone (ACTH) has been recognized as the primary pituitary hormone secreted in response to acute stress in rats and mice. Research indicates that ACTH and endogenous opioids are closely related. Endogenous opioids can be purified from ACTH powders (Gentleman, Ross, Lowney, Cox, & Goldstein, 1976), and the storage of the two substances seems to be coupled. ACTH and relatives of the endogenous opioids sometimes produce the same behavioral effects. Jacquet and Wolf (1981) reported that rats implanted with bilateral cannulas in the periaqueductal gray exhibited similar hyperactivity (i.e., jumping) following microinjections of either morphine or ACTH.
The adrenal gland may play a major role only in those forms of stress analgesia that are mediated by opioids (Lewis, Tordoff, Sherman, & Liebeskind, 1982). Many stimuli result in the simultaneous release of both ACTH and endogenous opioids. After footshock, plasma and pituitary concentrations of the two substances vary concomittantly and in remarkable parallelism: footshock seems to cause both substances to be secreted simultaneously (Guillemin et al., 1977; Rossier et al., 1977). Tone presentation is also directly related to the secretion of ACTH. Dynamic changes have been observed in ACTH secretion following the application of tone of various intensities (Fortier, 1951; Henkin & Knigge, 1963; Lockett, 1970; Ogle & Lockett, 1966), and within minutes of the onset of tone stimulation (Siegel, Chowers, Conforti, & Feldman, 1980). Given the close relation between ACTH and endorphin and that ACTH is secreted in response to various kinds of auditory stimulation, endogenous opioids may also be commonly secreted in response to noise.

If opioid secretion mediates the analgesia produced by auditory stimulation, then a narcotic antagonist would be expected to reduce the analgesia. The standard procedure that has been used to assess the role of endogenous opioids in analgesia is to perform the treatment that causes analgesia and then to administer a narcotic antagonist that blocks opiate receptors (Carlson, 1981; Terenius & Wahlstrom, 1978). If endogenous opioids play a physiological role in an organism's adjustment to a noxious or painful stimulus, the narcotic antagonists should restore pain susceptibility (Rossier et
Naloxone is one of many narcotic antagonists which has been used clinically and experimentally to delineate the physiological roles of endogenous opioids in humans and non-humans (Buchsbaum, Davis, & Bunney, 1977; Goldstein, 1976; Holtzman, 1975; Jones & Richter, 1981). Administration of naloxone has been associated with a variety of physiological and behavioral effects which suggest that naloxone blocks the opioid system (Brown & Holtzman, 1980; Lewis et al., 1980).

Considerable research has shown that stress-induced analgesia can be reduced by the narcotic antagonist naloxone (Amire, 1981; Buchsbaum et al., 1977; Buscher et al., 1976; Chesher & Chan, 1977; Fanselow & Bolles, 1979; Miczek, et al., 1982). Other research has shown that stress-induced analgesia could be partially prevented by naloxone administration (Akil et al., 1976; Belluzzi et al., 1976; Bodnar et al., 1978). However, under certain conditions involving the same kinds of stressors and assays of analgesia, naloxone reversal has not been demonstrated (Amire & Amit, 1978; Chance & Rosecrans, 1979b; Lewis et al., 1980; Malick & Goldstein, 1977). Perhaps procedural differences have concealed the fact that opiate antagonists can reverse the analgesia engendered by all stressors. In this case discrepancies might be traced to experimental variables such as the dosage of narcotic antagonist administered or the temporal relation between the administration of narcotic antagonist and stress application or assay of analgesia. Recent studies offer another explanation, arguing that both opiate and non-opiate systems influence stress...
analgesia and that quantitative characteristics of an organism's response to a given stressor can indicate which system is predominantly engaged (Fanselow, 1979; Lewis, Terman, Watkins, Mayer, & Liebeskind, 1983; Miczek et al., 1982; Watkins, Cobelli, Faris, Aceto, & Mayer, 1982a). In this case only certain forms of stress-induced analgesia will be reversed by naloxone (naloxone sensitive). Such forms will be mediated by peptides which are sufficiently like morphine to occupy opiate receptors and so will be antagonized by naloxone administration. Other forms of stress-induced analgesia will be naloxone irreversible (naloxone insensitive). Such forms of analgesia will be mediated by peptides which are not sufficiently like morphine to occupy opiate receptor sites and so will not be antagonized by narcotic antagonists.

The purpose of this study was twofold: first, to determine whether noxious auditory stimulation could produce analgesia in rats; and second, to determine whether any observed analgesic effect could be reversed by naloxone. If the analgesic effect produced by tone is mediated by endogenous opioids, then the narcotic antagonist, which blocks opiate receptors, will reverse it. If analgesia is not reversed by naloxone, then it is possible that the analgesic effect is related to a non-opiate system.
CHAPTER II

METHOD

Subjects

The subjects were 36 male albino rats from the university colony. The animals were 90 days old and weighed 300-400 gr at the start of the study. They were housed individually under a 12/12 hr light/dark cycle at an environmental temperature of 22° ± 1°C. Food and water were freely available.

Apparatus

The experimental chamber was a small plastic enclosure 28 cm high with a grid floor 26.7 cm square. The chamber was covered with a perforated plastic top that allowed sound to pass into it. A speaker was connected to a tone generator (Audio oscillator; Hewlett Packard 200 ABR) adjusted to produce a tone at 3000 Hz and a sound pressure level of 110 db. The experimental chamber and speaker were enclosed in a wooden sound attenuating box 32.8 cm high with a floor 35.8 cm square.

Session length and tone presentation were controlled automatically with relays and a variable interval tape and tape drive. A hot plate (Chicago Surgical Electrical Co., 26000-4528S), 17 cm x 62.5 cm, enclosed by wooden walls on three sides and on the fourth side by a clear plastic front viewing wall 21.0 cm high, was maintained at
$52^\circ \pm 1^\circ C$ throughout the study. Paw-lick latencies were recorded with a release stop timing device.

Drug

Naloxone (ENDO Co.) was diluted in 0.9% saline and was administered intraperitoneally 3 times throughout the session. All injections were 5 mg/kg for a total of 15 mg/kg per session.

Procedure

The hot plate was used to test for analgesia. During these tests a rat was placed on the hot plate, and the time from contact to a lick of the hindpaw (if any occurred) was recorded. Subjects were kept on the hot plate for 20 sec regardless of their behavior. Subjects were returned to their home cages shortly after a test. Paw-lick latency tests were identical throughout the study.

The study consisted of two phases. During the first phase subjects were adapted to the hot plate, and a baseline paw-lick latency was determined. Each subject was placed on the hot plate every other day and its paw-lick latency was recorded. The mean latency for all 36 subjects was calculated along with a standard deviation at the end of each test day. When there were no apparent systematic changes in these measures for six consecutive sessions, phase two began. The first phase was in effect for twelve test days.

Before the first session of the second phase, subjects were randomly divided into four groups of 9 subjects each. These four
groups will be called the tone (T) group, the naloxone (N) group, the naloxone and tone (NT) group, and the saline (S) group. Members of each group were placed in the experimental chamber for 30 min every other day for six sessions. Depending on the group to which it was assigned a subject received one of four treatments during its sessions in the experimental chamber. All subjects were given a paw-lick latency test, as described above, immediately after the session.

During treatment sessions the tone (T) group was exposed to a 3000 Hz tone amplified at a level of 110 db. The tone was presented on a variable time (VT) 90-sec schedule. Each presentation was 1 min in duration. The tone was presented 12 times.

The naloxone (N) group was injected intraperitoneally with 5 mg/kg of naloxone three times: immediately before the session, in the middle of the session, and immediately before the paw-lick latency test. No tone was presented.

The naloxone + tone (NT) group was given both naloxone and tone during its session. The tone was presented to this group in the same way that it was presented to the T group. Naloxone (5 mg/kg) was administered to this group in the same way that it was administered to the N group.

The saline (S) group was given an equivalent volume of isotonic saline in the same way in which the N group was administered naloxone. Neither tone nor naloxone was given to this group.
CHAPTER III

RESULTS

Figure 1 shows the mean paw-lick latencies for the four treatment groups during the six experimental sessions. The mean paw-lick latency for each group during the last six baseline days is also presented in Figure 1. The tone group showed the longest paw-lick latencies among the four groups, and the saline and naloxone groups showed the shortest paw-lick latencies. The naloxone + tone group showed mean latencies which were comparable to control group latencies for the first two sessions and latencies that were comparable to the tone group latencies for the rest of the sessions. Figure 1 shows that the mean response latencies for the T, N, and NT groups decrease from session 1 to session 6, although an analysis of variance reveals no significant changes in response latencies for any group across sessions (T group: F(5,48) = .277, p > .05; NT group: F(5,48) = .7169, p > .05; N group: F(5,48) = .047, p > .05; S group: F(5,48) = .5884, p > .05).

An analysis of variance based on paw-lick latencies collected over all six treatment sessions showed a significant difference among the four groups (F(3,212) = 6.51, p < .01) (Table 1). The Tukey method (Hopkins & Glass, 1978) was used to test differences between pairs of means for the four groups. The results of this test are shown in Table 2. Significant differences were obtained between the tone and
**Figure 1.** Mean Paw-lick Latency in Sec for Tone, Naloxone+Tone, Naloxone, and Saline Groups during Baseline and Treatment Sessions.

Baseline points are average latencies for each group during the six baseline sessions preceding treatment. The final set of points are average latencies for each group during the six treatment sessions. Bars represent one standard deviation above and below the mean.
saline groups ($F(4,212) = 3.99, p < .05$) and between the tone and naloxone groups ($F(4,212) = 3.48, p < .05$). These results show that auditory stimulation (tone) caused a significant increase in paw-lick latency.

Table 1

Analysis of Variance Based on All Treatment Data for Tone, Naloxone+Tone, Naloxone, and Saline Groups

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<td>Between</td>
<td>552.7</td>
<td>3</td>
<td>184.2</td>
<td>6.51 **</td>
</tr>
<tr>
<td>Within</td>
<td>6003.8</td>
<td>212</td>
<td>23.8</td>
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</tr>
<tr>
<td>Total</td>
<td>6556.5</td>
<td>215</td>
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** Significant at the $p < .01$ level.

The NT group had relatively short mean latencies during the first two treatment sessions and longer mean latencies during the remaining sessions. Though the data are suggestive, there is no significant difference between the NT and T groups ($F(4,212) = 1.48, p > .05$) regardless of the way in which session data are combined for analysis. In fact, when data are collected across all six sessions, the difference between the NT and S groups approaches significance.
Thus, naloxone administration (total of 15 mg/kg) did not reduce the paw-lick latencies of tone-treated rats.

Table 2
The Difference Between Pairs of Means by Tukey HSD Method

<table>
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<td>T</td>
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* Significant at the p < .05 level.
CHAPTER IV

DISCUSSION

The tone (T) group in this study had a significantly longer mean paw-lick latency than the saline (S) and naloxone (N) groups. Analgesia has been operationally defined as an increase in the latency to lick the hindpaw in response to heat as a result of exposure to intermittent auditory stimulation. By this definition the T group in this study developed analgesia in response to the tone, and thus provides evidence that an auditory stimulus should be included in the list of various noxious stimuli that produce analgesic responses (Akil et al., 1976; Chance & Rosecrans, 1979b; Christie et al., 1982; Drugan et al., 1981; Jensen & Smith, 1981; Lewis et al., 1980; Szikszay et al., 1985).

Not all attempts to produce stress analgesia have been successful. Amire and Amit (1978) reported that immobilization resulted in increased latency to escape but had no effect on paw-lick latency. However, the majority of reported efforts to produce stress induced analgesia have succeeded. The mean paw-lick latency for the group of subjects given naloxone in addition to tone (NT group) is not significantly different from the means of the S and N groups. Administration of naloxone before and during tone seems to have had some effect. However, the difference between the group means for the T and NT groups is not significant and so the results are ambiguous.
Clearly, naloxone administration has not completely reversed the analgesic effects of tone. Because the difference between the mean of the NT and S groups approaches significance, one must suppose, in the absence of more substantial statistical evidence, that naloxone had no effect on tone-induced analgesia.

There are a number of reasons why naloxone may not have reversed the analgesia produced by tone. The most obvious possibility is that too little naloxone was administered to antagonize any endogenous opioid effect. Millan et al. (1981) found that 10 mg/kg of naloxone administered prior to 5 min of footshock slightly reduced analgesia but that 1 mg/kg did not. When rats were given 0.3, 1.0, 3.0, and 10.0 mg/kg/ip of naloxone, Miczek et al. (1982) observed a dose related decrease in the level of defeat induced analgesia in a tail-flick latency assay. Insufficient dosage is an unlikely account for all reported failures to reverse analgesia produced by different stressors and assayed by different means. Either these studies suffer from other methodological problems or the analgesia produced in these studies is naloxone insensitive. A total of 15 mg/kg of naloxone was given to rats in this study, and it seems unlikely that such a large dosage could have failed to reduce any analgesic effect mediated by endogenous opioids. Perhaps the type of analgesia produced by tone is not mediated by a naloxone sensitive opiate system.

Another possibility is that naloxone sensitive endogenous opioids mediated the analgesia produced by tone but that analgesia was assayed either before or after naloxone had acted. In either case analgesia
would appear naloxone insensitive even though it was, in fact, opioid mediated. According to Akil et al. (1976) and Madden et al. (1977), naloxone given immediately before shock sessions did not completely reverse analgesia in rats during the early portion of sessions but significantly reversed analgesia later in sessions. Millan et al. (1981) found that naloxone injected immediately before shock sessions in which analgesia was repeatedly assayed was ineffective, but that naloxone administered 10 min prior to stress reversed analgesia. The timing of naloxone administration can control the expression of stress-induced analgesia. Naloxone's refractory period may even account for the observations that brief, continuous footshock for 3 min produced analgesia which was naloxone irreversible, whereas prolonged intermittent footshock for 30 min produced analgesia which was naloxone reversible (Lewis et al., 1980). On the other hand, naloxone is known to act at receptors for a relatively short time (Terenius & Wahlström, 1978) and opioid peptides are also rapidly inactivated by enzymatic degradation (Lord, Waterfield, Hughes, & Kosterlitz, 1977). If the time between naloxone administration and the assay of analgesia is too great, naloxone will have dissipated before its effect can be detected. In other words, timing of administration may have been inappropriate to antagonize endogenous opioids. In this study, multiple injections of naloxone were given to minimize temporal confounds. In addition, no significant difference in paw-lick latency between N and S groups was observed in this study.
When the paw-lick latency in this study increased following tone presentation this observation was interpreted by analogy to other research. Auditory stimulation (tone), like footshock stress, increases the latency of an adaptive response. If the change produced by shock is an instance of analgesia then so is the change produced by tone. The analogy may not be appropriate. Analgesia is plausible in the case of shock because it can be so readily reversed. When shocked rats are given naloxone they are as sensitive to acute stress as they were in the absence of shock. This study fails to demonstrate that some treatment can make subjects as sensitive to acute stress following tone as they were before tone. Perhaps the paw-lick latency observed in this study was not the result of an analgesic response, but the result of some other unconditioned effect of the stressor. Rats may have been as sensitive after tone as they were before it but unable to make the adaptive response as rapidly. If this is the case, then perhaps the behavioral definition of analgesia common in the literature will have to be reevaluated. Alternatively, tone might not have incapacitated rats but might have made them, either directly or indirectly, hyperactive. Jacquet and Wolf (1981) suggested that morphine produces not only an inhibitory effect (analgesia) but also an excitatory action that results in hyperactivity. A subject exposed to tone and, as a result, manifesting such a syndrome, might take longer to make an adaptive response than a subject not exposed to tone. This alternative is not a plausible explanation of the results obtained here because casual observation...
suggested that rats exposed to tone were less active on the hot plate than rats not exposed to tone.

Finally, the naloxone insensitive analgesia observed here may have been mediated by a type of endogenous opioid that is not readily antagonized by naloxone. Several endogenous opioid peptides have been discovered, as well as a variety of opiate receptors. The affinity of particular opioid peptides for different receptors varies (Belluzzi et al., 1976; Goldstein, 1976; Lord et al., 1976, 1977; Malick & Goldstein, 1977). For example, Lord et al. (1976, 1977) found that the receptor populations in two in vitro models were not identical. In the guinea pig ileum, opioid peptides interact mainly with the mu-receptors, which mediate the action of the classical morphine-like compounds. In the mouse vas deferens, however, the opioid peptides interact mainly with delta-receptors, for which leucine-enkephalin, another endogenous opioid peptide, has a high affinity. Other research suggests that there are probably two classes of receptors for leu-enkephalin, one of which is not blocked by opiate antagonists like naloxone (Devries, Chance, Payne, & Rosecrans, 1979). The supposition that only naloxone sensitive opioid receptors mediate analgesia is probably misleading. A number of researchers have failed to reverse stress-induced analgesia with naloxone (Bodnar et al., 1978; Chance & Rosecrans, 1979b; Chesher & Chan, 1977; Jensen & Smith, 1982; Millan et al., 1981). This failure has led a number of people to propose that both opiate, or naloxone sensitive, and non-opiate, or naloxone insensitive, systems.
may be involved in the modulation of stress and that the nature of the stress or its temporal features determine which system can be selectively activated by environmental stimuli (Chance & Rosecrans, 1979a; Lewis et al., 1980, 1983; Miczek et al., 1980; Watkins et al., 1982a; Watkins, Cobelli, & Mayer, 1982b). Chance and Rosecrans (1979b), for example, found that even administration of 20 mg/kg of naloxone failed to reverse an analgesic effect produced by footshock and assessed with a tail-flick test, and argued for the existence of opiate and non-opiate systems to account for the result. Lewis et al. (1980) found that long intermittent footshock produced analgesia which was naloxone reversible but that short continuous shock produced naloxone irreversible analgesia. Some researchers (Watkins et al., 1982a) have found that hindpaw shock produces non-opiate analgesia whereas frontpaw shock produces opiate analgesia, suggesting that one critical factor determining the involvement of endogenous opioids is the body region shocked. However, Terman, Shavit, Lewis, Cannon, & Liebeskind (1984) found that lower shock intensities caused opioid analgesia and higher shock intensities caused nonopioid analgesia whether the front paws or the hind paws were shocked. Lewis et al. (1980, 1983) and Lewis, Terman, Shavit, Nelson, and Liebeskind (1984) accounted for these observations by arguing that both opioid and non-opioid systems mediated analgesia and that the temporal parameters (pattern and duration) or intensive properties of stress determine which system will be predominantly engaged. In spite of recent theorizing, the characteristics of such a non-opioid pathway
are unknown.


seizure in mice. In Welch, B. L., & Welch, A. S. (Eds.), *Physiological effects of noise* (pp. 185-201). New York: Plenum Press.


