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Stress Analgesia: Effects of PCPA, Yohimbine, and Naloxone

TERENCE J. CODERRE

Department of Psychology, McGill University, Montreal, Quebec, Canada H3A 1B1

AND

GARY B. ROLLMAN[1]

Department of Psychology, University of Western Ontario, London, Ontario, Canada N6A 5C2

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CODERRE, T. J. AND G. B. ROLLMAN. *Stress analgesia: Effects of PCPA, yohimbine, and naloxone.* PHARMACOL BIOCHEM BEHAV **21**(5) 681–686, 1984.—Evidence suggests that morphine analgesia depends on the integrity of monoaminergic transmitter systems. Some forms of stress analgesia seem to be related to morphine analgesia, while others are not. To assess whether opioid and non-opioid stress analgesia differ in their reliance on monoamine systems, the effects of parachlorophenylalanine (PCPA) and yohimbine on analgesia produced by prolonged intermittent and brief continuous footshock were examined on the hotplate test. The interaction of adrenergic and endorphinergic activity with serotonergic mechanisms following these stressors was also investigated by testing the effects of yohimbine and naloxone on rats with prior PCPA treatment. Yohimbine alone significantly reduced baseline hotplate latencies, while PCPA and naloxone did not. The two stressors differed in the effects produced by both naloxone and PCPA. Naloxone significantly reversed stress analgesia in the prolonged stress condition, but not the brief stress condition. PCPA significantly enhanced the antinociceptive effect of brief continuous shock, while leaving the response to prolonged intermittent shock unaffected. In contrast, yohimbine blocked the analgesic effects of prolonged stress. For the brief stress condition, naloxone reversed the elevated thresholds elicited in PCPA treated rats. Naloxone also reversed stress analgesia for PCPA treated rats exposed to prolonged intermittent stress. Yohimbine lowered the responses of PCPA treated rats subjected to brief continuous shock. These results support an interactive model of stress analgesia dependent upon serotonergic, adrenergic, and endorphinergic transmitter systems.

Analgesia Stress Naloxone PCPA Yohimbine

RECENT studies have shown that various stressful manipulations may elevate nociceptive thresholds. Although the mechanisms of stress induced analgesia are not entirely clear, researchers have distinguished between effects dependent upon opioid and non-opioid pain inhibitory systems. Inclusion in the first category is generally based upon naloxone reversibility or cross-tolerance with morphine. Among the stressors which appear to meet these criteria are exposure to peripheral stimulation of the tail [18], prolonged intermittent footshock [38, 39, 40] shock to the forepaws [62], immobilization [3], food deprivation [43], and intraperitoneal injection of 2-deoxy-D-glucose [54] in laboratory animals, as well as the anticipation of footshock in humans [65]. Non-opioid analgesia (changes in response measures which are not modified by the traditional opiate agonists and antagonists) has been elicited in laboratory animals following brief continuous footshock [38, 39, 40], shock to the hind paws [62], autoanalgesia [22,23], centrifugal rotation [34], cold-water swims [12, 13, 37] and intraperitoneal injections of hypertonic saline [34]. Apparently, some stressors are dependent upon mechanisms which are related to those that subserve morphine analgesia, while others rely upon alternate modulating systems.

Investigators have also attempted to establish the relationship between opiate analgesics and monoaminergic transmitter systems. The evidence strongly suggests that both serotonin and noradrenalin are critically involved in the mechanisms of morphine analgesia (see reviews [6,19]). The role of these monoamines in stress-induced analgesia has only recently received the attention of researchers [10]. Serotonin has been implicated in the mechanisms of opioid stress analgesia since increased nociceptive thresholds induced by shock to the forepaws are attenuated following bilateral lesions of the dorsolateral funiculus (DLF) [63], as well as lesions of the nucleus raphe magnus (NRM) [64]. NRM lesions also disrupt the opioid form of stimulation-produced analgesia elicited from the ventral midbrain [50]. The DLF and NRM are rich in serotonin-containing neurons and are believed to have inhibitory influences on pain transmission. Furthermore, antinociception induced by 2-deoxy-D-glucose injection is abolished following lesions of the periaqueductal gray [17], in both ventral and caudal re-

[1]Requests for reprints should be addressed to Dr. Gary B. Rollman.

gions [10]. In contrast, the serotonin synthesis inhibitor, parachlorophenylalanine (PCPA), has no effects on analgesia following 2-deoxy-D-glucose injection [14], although it does inhibit analgesia caused by immobilization [8].

The role of serotonin in non-opioid stress analgesia is also ambiguous. In one laboratory [20], lesions of the nucleus raphe magnus have been found to reduce analgesia produced by brief footshock and autoanalgesia. Elsewhere, lesions of the dorsolateral funiculus and nucleus raphe magnus failed to attenuate the analgesia produced by brief footshock [35] or hind paw shock [64]. In addition, lesions of the ventral, but not the caudal, regions of the periaqueductal gray attenuate the analgesic effects of cold-water swims [10]. Furthermore, the serotonin agonist, quipazine increases the level of antinociception following brief stress and BC-105, a serotonin antagonist, blocks any increase in tail-flick latency [53]. However, depletion of serotonin by PCPA has no effect on the analgesia produced by cold-water swims or brief footshock [14].

Noradrenalin also appears to be implicated in both opioid and non-opioid stress analgesia. Bilateral lesions of the locus coeruleus, a major adrenergic brain center, have been found to attenuate non-opioid analgesia induced by cold-water swims, as well as the opioid analgesia induced by 2-deoxy-D-glucose injection [16]. In addition, yohimbine, an α-adrenergic receptor antagonist, reverses the non-opioid analgesia elicited by brief continuous footshock and autoanalgesia [24].

The α-receptor agonist clonidine enhances the non-opioid analgesia produced by cold-water swims [15]. This outcome is discrepant from the reported effects of adrenalectomy; the operation abolishes the opioid analgesia produced by prolonged footshock [41] but enhances the non-opioid analgesic effects of cold-water swims [30]. Reserpine, which depletes nonadrenalin and serotonin, has been found to enhance opioid analgesia produced by prolonged footshock [41] while eliminating the non-opioid analgesia elicited by brief footshock [57]. Depression of transmission through both intraspinal and spinal reflex pathways by clonidine is rapidly reversed by yohimbine but not by naloxone; depression produced by morphine is reversed by naloxone but generally uninfluenced by the α-adrenergic receptor antagonist tolazoline [29].

These results, although complex, and often contradictory, suggest that serotonin and noradrenalin may selectively influence both opioid and non-opioid inhibitory systems. The purpose of this study is to further examine the possibility that opioid and non-opioid stress analgesia are differentially reliant on monoaminergic transmitter systems. Stress analgesia produced by prolonged intermittent shock (which is opioid dependent) will be compared with analgesia produced by brief continuous shock (which is non-opioid dependent), with attention to the effects of the serotonin synthesis inhibitor, PCPA and the α-adrenergic antagonist, yohimbine. The effects of these two drug treatments on baseline nonciceptive responses will also be noted. In addition, the combined effects of PCPA with naloxone and yohimbine will be examined in order to identify any interactions of adrenergic and endorphinergic systems with serotonergic ones.

METHOD

Two hundred male Sprague-Dawley rats (Candian Breeding Farms, 200–300 g) were tested for hotplate response latencies. Each rat was placed in an appartus (Technilab Instruments, Model 11) consisting of an electrically heated, thermostatistically controlled metal plate which served as the floor of a Plexiglas chamber (25×27×30 cm high) with a removable lid. The temperature of the floor was kept constant at 53°C. The time was measured until the rat began to lick the underside of a front or hind paw, or until the rat jumped to avoid contact of the paws with the hotplate. To prevent tissue damage, a cut-off time of 45 seconds was employed.

Before testing, the rats were randomly assigned to receive one of six drug treatments: (1) naloxone HCl (Endo Laboratories), 10 mg/kg administered subcutaneously in a volume of 1 ml/kg, (2) yohimbine HCl (Sigma) 4 mg/kg, or (3) PCPA (Sigma) 300 mg/kg administered intraperitoneally in a volume of 2 ml/kg or 4 ml/kg, respectively, (4) normal saline as a vehicle control, with 1 ml/kg given subcutaneously, (5) a combination of PCPA and naloxone, or (6) a combination of PCPA and yohimbine, with dosages and sites of administration for the last two groups as above. Naloxone, yohimbine, and saline injections were given 15 minutes before a hotplate trial; PCPA was administered 48 hours earlier.

In the 15 minutes before the hotplate trial, the rats in groups 1–4 were subjected to one of two stress conditions or a no stress control condition. Of the 40 rats in each drug treatment group, 10 received one stressor, 10 the other stressor, and 20 received no stress. For groups 5 and 6, half of the 20 rats in each group received each stressor.

The two stress conditions both consisted of inescapable footshock (60 Hz, 2 mA constant current) delivered through a scrambler to the grid floor of an operant chamber (25×25×27 cm high). In one stress condition, rats were exposed to prolonged intermittent footshock, 1 second of shock every 5 seconds for 15 minutes. In the second, rats were exposed to continuous footshock for 3 minutes following 12 minutes of no shock. These stress conditions were a modification of the methods used by Lewis *et al.* [38].

RESULTS

The mean hotplate response latencies for all drug treatment groups within each stress condition are presented, along with their standard errors, in the bar graphs of Fig. 1. A square-root transformation was performed on the data before analysis since variances were unequal as determined by the Cochran test for homogeneity of variance, $F(16,19)=0.193$, $p<0.01$. Analysis of variance with two between-group independent variables (drug treatment and stress condition) revealed significant main effects for drug treatment, $F(5,184)=15.14$, $p<0.001$, and for stress condition, $F(2,184)=46.20$, $p<0.001$, as well as a significant drug by stress interaction, $F(8,184)=3.16$, $p<0.002$.

In the no-stress condition, Newman-Keuls comparisons revealed that only yohimbine had a significant hyperalgesic effect when compared with saline ($p<0.01$). Naloxone and PCPA-treated rats failed to differ from controls. Post-hoc comparisons (Newman-Keuls) on post-stress response latencies revealed the following effects (all significant at the 0.01 level). Both prolonged intermittent and brief continuous footshock significantly raised response latency of saline treated rats over that of unstressed rats, indicating stress-induced analgesia. As expected, the two stressors differed with regard to the effects of naloxone. In the prolonged intermittent stress condition, naloxone treated rats had significantly lower response latencies than saline treated rats;

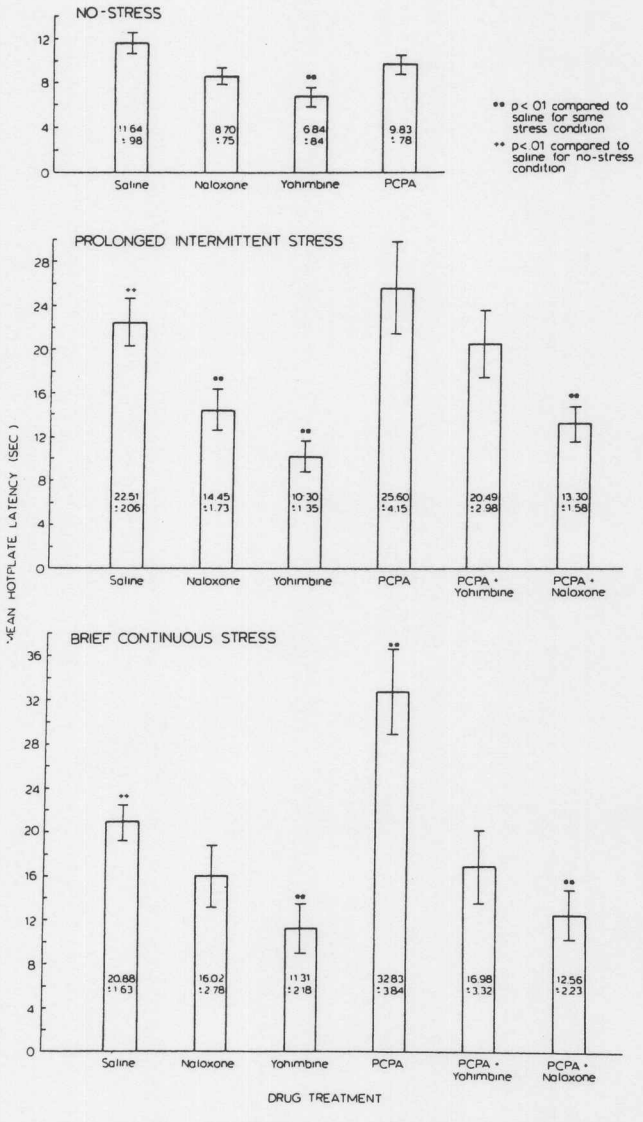

FIG. 1. Mean latency of hotplate paw-lick or jump response as a function of drug treatment for rats receiving no stress (top), prolonged intermittent stress (middle), or brief continuous stress (bottom). The mean latencies and their standard errors are depicted for each group and specified within the bar. Animals receiving saline plus stress are compared to those receiving saline in the no stress condition. All drug groups are compared to rats receiving saline in the identical condition: no stress, prolonged intermittent stress, or brief continuous stress.

naloxone treated rats in the brief-stress condition failed to differ significantly from their saline controls.

Yohimbine treatment affected the two stressors similarly. In both the prolonged and brief-stress conditions, yohimbine significantly lowered the response latencies compared to saline. The effects of PCPA, however, varied across the two stressors. After brief stress, PCPA-treated rats had significantly higher response latencies than saline control rats. In the prolonged-stress condition, the effects of PCPA were not significant. As noted earlier, PCPA given without stress had no effect.

For both prolonged and brief stress conditions, naloxone reversed the hotplate responses of PCPA treated rats to a level significantly below the latencies of saline-treated control rats ($p<0.01$, Newman-Keuls comparison). For brief stress, yohimbine lowered the response latencies of PCPA-treated rats. Yohimbine given in combination with PCPA did not affect the rats exposed to prolonged stress. Their response latencies failed to differ from those receiving only PCPA or from the saline controls. Since the response latencies of yohimbine-treated rats are significantly lower than those of saline-treated rats in the no stress condition, it is difficult to determine whether yohimbine's effects in the two stress conditions are due to a reversal of stress analgesia or a baseline shift. Single degree of freedom contrast of difference scores reveal that the mean difference between the saline and yohimbine groups is significantly greater in the prolonged intermittent stress condition than in the no stress condition, $F(1,184)=5.51$, $p<0.05$. This difference is not greater in the brief continuous condition than it is in the no stress condition, $F(1,184)=2.45$, $p<0.05$. In addition, the mean difference between PCPA and PCPA plus yohimbine in the brief stress condition is significantly greater than the mean difference between saline and yohimbine in the no stress conditions, $F(1,184)=7.25$, $p<0.01$.

DISCUSSION

In the present experiment, hotplate response latencies for unstressed rats were significantly reduced by yohimbine, but not by naloxone or PCPA. Naloxone significantly reversed the analgesic effects produced by prolonged intermittent, but not brief continous footshock. Yohimbine reversed the analgesia produced by prolonged intermittent stress; PCPA significantly increased analgesia in rats exposed to brief continuous footshock but not prolonged intermittent stress. Yohimbine also reversed the enhanced analgesia in PCPA treated rats that received brief stress; there was no effect on prolonged stress combined with PCPA. Naloxone reversed the analgesic effects of both stressors in PCPA treated rats.

It seems that it is possible to use footshock to elicit both opioid and non-opioid stress analgesia. Lewis *et al.* [38] demonstrated that analgesia elicited by prolonged intermittent shock was naloxone sensitive, while analgesia produced by brief continuous shock was naloxone insensitive. In further experiments, Lewis *et al.* [39] demonstrated that prolonged intermittent, but not brief continuous stress, developed cross-tolerance with morphine. The naloxone sensitivity results were replicated here, despite reductions in shock intensity and duration and the use of a hotplate test rather than a tail-flick test as a nociceptive measure [27]. It has been suggested that opioid and non-opioid analgesic effects are differentially activated depending upon the temporal parameters of shock [38], the total amount of shock [32], or the relative amounts of contact of the front and hind paws [62]. Whatever the distinguishing characteristics, it seems apparent that prolonged intermittent shock depends on opioid analgesic mechanisms, while brief continuous shock depends on non-opioid ones [40].

Yohimbine's hyperalgesic effects on both baseline pain response and analgesia produced by prolonged intermittent stress are consistent with the results of Chance and Schecter [24]. They reported that yohimbine blocked antinociception elicited by conditioned fear, as well as lowering baseline tail-flick latencies. The present replication of these findings adds further support to the proposal by Shiomi and Takagi

[52] that incoming pain signals are influenced by an α-adrenergic descending inhibitory system. The present findings suggest that system is both tonically active and acutely sensitive to stressful stimuli. Furthermore, activation of this inhibitory system seems independent of the opioid or non-opioid mechanisms of stress analgesia.

The sizeable facilitation of continuous stress analgesia by prior injection of PCPA is both noteworthy and possibly unexpected. PCPA's reported influence on baseline responses is a reduction in jump-flinch thresholds [14,36] but an increase in tail-flick latency [14]. Others [2] have found no effect on baseline tail-flick latency. According to the present results, hotplate latencies are unaffected by the drug.

PCPA is a specific depletor of brain serotonin [36,61], particularly in raphe terminals [1]. Among its behavioral effects are an increased response to electrical shock in rats [28,55] and an antagonism of analgesia produced by morphine [31, 56, 60], amphetamine [31], stimulation of the ventral central gray near the dorsal raphe magnus [2], and acupuncture [44]. As well, PCPA has been reported to partially block high-frequency electroacupuncture without affecting naloxone-reversible low-frequency analgesia [25,26]. Bhattachurya *et al.* [8] indicated that PCPA reversed the antinociceptive responses on a tail-flick test induced by four hours of immobilization. Bodnar *et al.* [14] found that PCPA had no effects on the analgesia produced by cold-water swims and 2-deoxy-D-glucose injection as measured on a jump-flinch test or the elevated tail-flick latencies following brief footshock stress. These findings indicate opioid stress analgesia can be reversed [8], or unaffected [14] by PCPA, while non-opioid stress analgesia is unaffected [14] by the drug.

Consequently, it may appear surprising to find an enhancement of stress-induced analgesia due to PCPA in this study. However, there are some previous findings which show related outcomes. Akil & Mayer [2] noted that stimulus produced analgesia for electrodes falling in the dorsal central gray and the subjacent tegmentum was generally increased by PCPA, Saarnivaara [51] reported that PCPA enhanced the analgesic effects of morphine in the rabbit. Recently, Tricklebank *et al.* [58] presented data which were similar to those described here; brief continuous footshock induced tail-flick and paw-lick analgesia that was greatly potentiated by PCPA pretreatment but unaffected by naloxone. Their dose of PCPA, which was half of that used in this study, decreased brain 5-HT by 81%. Although there are suggestions that serotonergic mechanisms play a significant role in the mediation of both opiate [5,6] and non-opiate [48] analgesia, the degree to which these pathways contribute to stress analgesia is evidently still ambiguous.

The demonstration that yohimbine abolishes the enhanced antinociceptive effects of brief continuous stress in PCPA-treated rats suggests an interaction of serotonergic and α-adrenergic inhibitory mechanisms. If these two adjacent systems have inhibitory influences on each other, yohimbine may produce direct α-adrenergic blockage and post-synaptic antagonism of serotonergic neurons [24]. Likewise, inactivation of the bulbospinal mechanisms through serotonin depletion by PCPA may disinhibit the activity of the α-adrenergic system. The resulting increased inhibition of spinal pain-transmission mechanisms could then counteract the effects of serotonin depletion and strongly potentiate the analgesia arising from continuous shock. The different stressor types may vary in the degree to which they activate the serotonergic system, with opioid stressors having the greater effect [45]. Autoradiographic study of the nucleus raphe magnus and the dorsolateral funiculus following tritiated leucine enkephalin injections suggests that endogenous opioid peptides play a role in the inhibitory mechanisms of the bulbospinal serotonergic system [5,6]. Consequently, stressors which are reversed by naloxone or are cross-tolerant with morphine, may be so because of a greater reliance on this serotonergic inhibitory system. Also, since opiate drugs and opioid peptides have been found to hyperpolarize the noradrenergic locus coeruleus neurons in vitro [49], it is highly likely that the serotonergic system, through its interaction with opioid peptides, would have an inhibitory influence on an α-adrenergic inhibitory system.

The observation that naloxone significantly reduces stress analgesia in PCPA-treated rats suggests that endorphinergic influences other than those implicated in the bulbospinal serotonergic pathway contribute to stress analgesia. Since stress is known to activate the pituitary-adrenal cortical axis [42], and since pituitary β-endorphin has been found to be released in response to stress [33], it is possible that pituitary β-endorphin acts as a third inhibitory influence in stress analgesia. Support for this view comes from the findings that hypophysectomies antagonize the antinociceptive effects of cold-water swims [9], immobilization [4], intraperitoneal injection of insulin [4], tail shock [59], and intermittent footshock [47]. The fact that hypophysectomy does not reverse analgesia produced by 2-deoxy-D-glucose injection [11], autoanalgesia [21], and brief footshock [21] need not rule out pituitary β-endorphin as a factor in stress analgesia; rather, it suggests it is not the only factor involved. Furthermore, since it has been found that serotonin precursors tryptophan and 5-HTP inhibit, while PCPA enhances pituitary-adrenal system functioning [7], it is probable that serotonin has an inhibitory role over β-endorphinergic inhibitory mechanisms. As well, given that lesions of the ventral noradrenergic bundle produce increases in the level of plasma β-endorphin following stress [46], it seems likely that noradrenalin may also inhibit the release of pituitary β-endorphin. Thus, both serotonin and noradrenalin may have modulatory roles over β-endorphinergic activity.

In conclusion, stress analgesia seems to depend on the interactive effects of serotonergic, α-adrenergic and endorphinergic transmitter systems. It is expected that bulbospinal serotonergic and α-adrenergic inhibitory systems interact together with pituitary β-endorphin to modulate incoming pain signals.

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