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Yohimbine Potentiates Cold-Water Swim Analgesia: Re-Evaluation of a Noradrenergic Role

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KEPLER, K. L. AND R. J. BODNAR. *Yohimbine potentiates cold-water swim analgesia: Re-evaluation of a noradrenergic role.* PHARMACOL BIOCHEM BEHAV **29**(1) 83–88, 1988.—Continuous cold-water swims (CCWS) elicit a nonopioid and neurohormonal analgesia which displays adaptation. The norepinephrine (NE) system has been implicated since parallel alterations in NE occur following acute and repeated CCWS exposure, and since CCWS analgesia is reduced by locus coeruleus lesions and is potentiated by clonidine and desipramine. The present study evaluated the effects of the alpha-2 NE receptor antagonist, yohimbine upon CCWS (2°C for 3.5 min) analgesia on the jump and tail-flick tests, CCWS hypothermia, and basal nociceptive and thermoregulatory measures in rats. Yohimbine (0.1–2.0 mg/kg, IP) dose-dependently increased basal jump thresholds and potentiated CCWS analgesia: these effects appeared to be additive. Yohimbine potentiated CCWS analgesia on the tail-flick test without altering basal latencies. Yohimbine failed to alter either CCWS hypothermia or basal thermoregulation. Since yohimbine and clonidine, an alpha-2 NE receptor antagonist and agonist respectively, similarly potentiate CCWS analgesia, it appears that NE effects are orthoganol to the intrinsic system mediating CCWS.

Yohimbine Norepinephrine Cold-water swims Nonopiate analgesia Stress Pain Hypothermia

ACUTE exposure to continuous cold-water swims (CCWS) over 3.5 min elicits a nonopioid, neurohormonal analgesic response which is dependent upon the hypothalamo-hypophysial and pituitary-adrenal axes for its full expression (see review: [3]). Chronic exposure to CCWS over 14 daily repeated exposures results in adaptation of the analgesic response [4]. Similarly, acute exposure to CCWS reduces brain norepinephrine levels (e.g., [45–48, 50]), while chronic exposure results in adaptation to this response as well (e.g., [50]). These parallel effects of CCWS led us to examine whether CCWS analgesia was dependent upon noradrenergic systems for its mediation. CCWS analgesia was decreased following lesions placed in the noradrenergic locus coeruleus [8], and increased following pretreatment with either the alpha-2 noradrenergic receptor agonist, clonidine [7] or the noradrenergic reuptake blocker, desipramine [6]. The present study evaluated further the role of noradrenergic influences upon CCWS analgesia by examining the effects of the alpha-2 noradrenergic receptor antagonist, yohimbine [44] upon this analgesic response.

Yohimbine has been shown to affect both basal nociceptive as well as analgesic responses. For instance, a biphasic dose-dependent effect of yohimbine was observed on the tail-shock vocalization test with low (0.35–2.0 mg/kg) doses producing hyperalgesia and high (8–25 mg/kg) doses producing analgesia on this measure [33]. Yohimbine (1 and 4 mg/kg) produced analgesia on the hot-plate and formalin tests, but not on the tail-flick test [19]. Further, yohimbine (4 mg/kg) decreased baseline hot-plate latencies and significantly attenuated both opioid-mediated prolonged intermittent footshock analgesia and nonopioid-mediated brief continuous footshock analgesia [17]. Yohimbine also blocked potentiations of brief continuous footshock analgesia induced by parachlorophenylalanine, a serotonin synthesis inhibitor. Finally, yohimbine blocked the analgesic effects of conditioning to footshock (autoanalgesia: [16]), which has been characterized as nonopioid and neurally-mediated (see review: [12]). Yohimbine also reduced footshock-induced analgesia as well as autonalgesia; in contrast, neither the serotonin receptor antagonist, methysergide, nor the alpha-1 noradrenergic receptor antagonist, phentolamine, blocked these responses [12]. Thus yohimbine produces dose-dependent changes in basal pain thresholds which may contribute to its effects upon analgesic processes. Further, the effects of yohimbine upon basal nociception differ as a function of the pain test employed; the tail-flick test was only used for evaluation of this antagonist upon analgesic effects. Therefore, the effects of yohimbine upon CCWS analgesia were examined using two nociceptive measures, the tail-flick [18] and jump [20] tests, and dose-dependent baseline effects of yohimbine upon each measure were also evaluated. The effects of yohimbine upon basal core temperatures and

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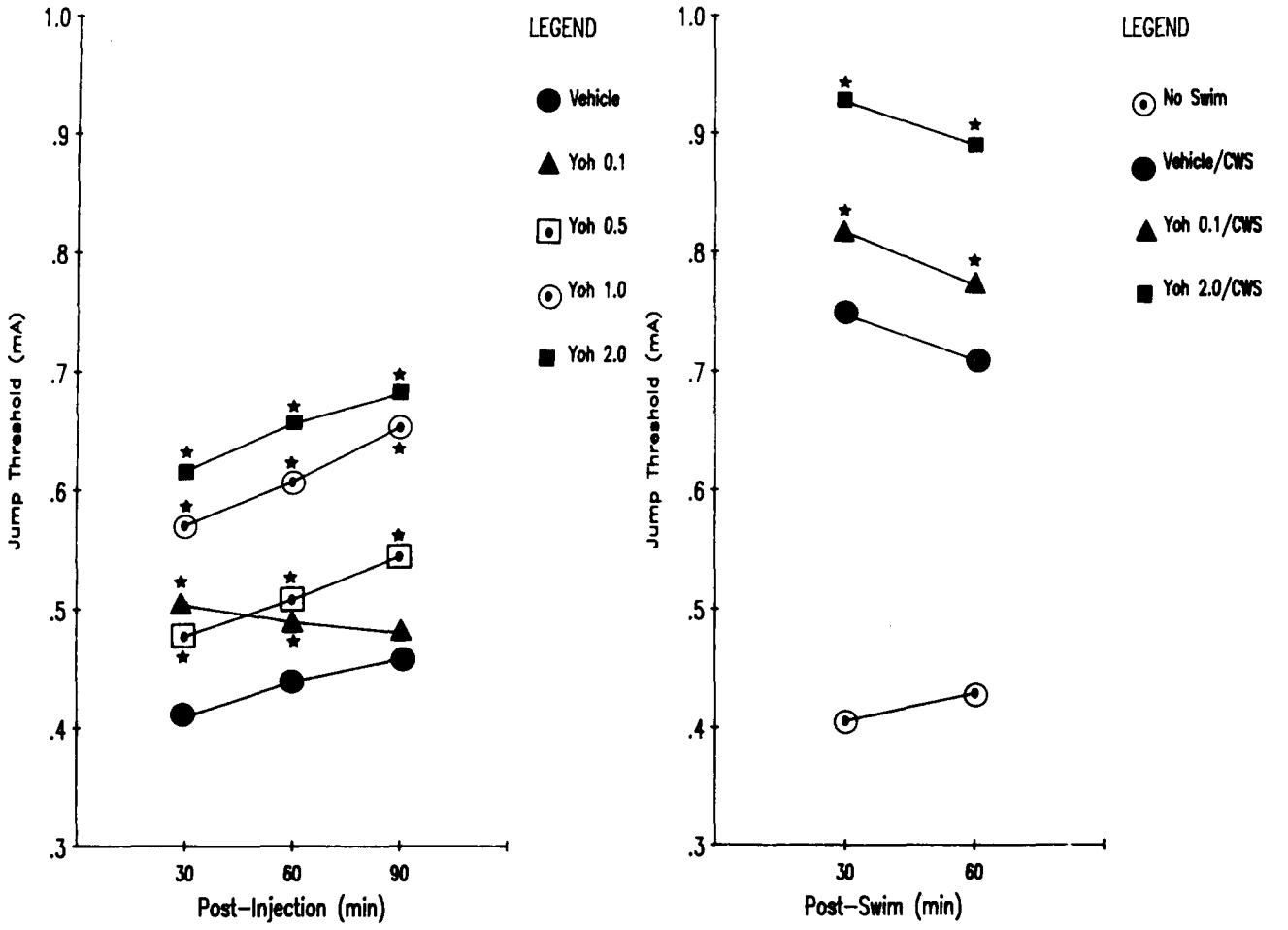

FIG. 1. Alterations in basal jump thresholds (left panel) and continuous cold-water swim (CCWS: 2°C for 3.5 min) analgesia as measured by the jump test (right panel) following intraperitoneal pretreatment with yohimbine (Yoh). Left panel: Yoh produced a significant (stars: Dunnett comparisons, $p<0.05$) dose-dependent increase in basal jump thresholds. Right panel: CCWS significantly increased jump thresholds above no-swim values in all treatments; Yoh significantly potentiated CCWS analgesia (stars: Dunnett comparisons, $p<0.05$).

CCWS hypothermia were performed because clonidine potentiated both CCWS analgesia and CCWS hypothermia [7].

METHOD

Female albino Sprague-Dawley rats (250–350 g) were housed in pairs in wire mesh cages with Purina rat chow and water available ad lib in the Queeens College Vivarium facility. All animals were maintained on a 12 hr light:12 hr dark cycle at ambient temperatures between 21° and 25°C. For those rats tested on the tail-flick test, the stimulus source (IITC Company) was mounted 8 cm above the dorsum and 3–9 cm proximal to the tip of the tail of a lightly-restrained animal. The intensity of the thermal stimulus was set so as to produce stable baseline tail-flick latencies between 2.5 and 4 sec. Each tail-flick test session consisted of three latency determinations separated by 10-sec intertrial intervals. In order to avoid tissue damage, a trial was automatically terminated if a response did not occur within 10 sec. For those rats tested on the jump test, electric shock was delivered through 16 grids of a 30 cm by 24 cm chamber by a shock generator (BRS/LVE) through a shock scrambler (Campden Instruments). Using an ascending method of limits procedure, the jump threshold was defined in mA as the lowest of two consecutive intensities in which the animal simultaneously removed both hindpaws from the grids. Each trial began with the animal receiving a 300-msec footshock at a current intensity of 0.10 mA. Subsequent shocks were increased in 0.05 mA increments at 10 sec intervals until the jump threshold was determined. After each trial, the current intensity was reset to 0.10 mA and the procedure repeated until six trials were completed. For those rats tested for core body temperatures, a rectal probe of a digital thermometer (Bailey Instruments) was inserted until a stable temperature (0.1°C accuracy) was determined. Baseline tail-flick latencies and jump thresholds were determined for at least four days before experimental testing began.

Protocol 1

Ten rats received six injections in the following order: vehicle, 0.1, 0.5, 1.0 and 2.0 mg/kg of yohimbine (Sigma Chemical Company) and vehicle. All doses were administered intraperitoneally at a concentration of 1 ml normal saline/kg body weight. A one-week interval elapsed between injection conditions to minimize carry-over effects; this was successful because the first and last vehicle conditions failed to differ from each other and were therefore pooled. Jump thresholds were assessed 30, 60 and 90 min after each injection.

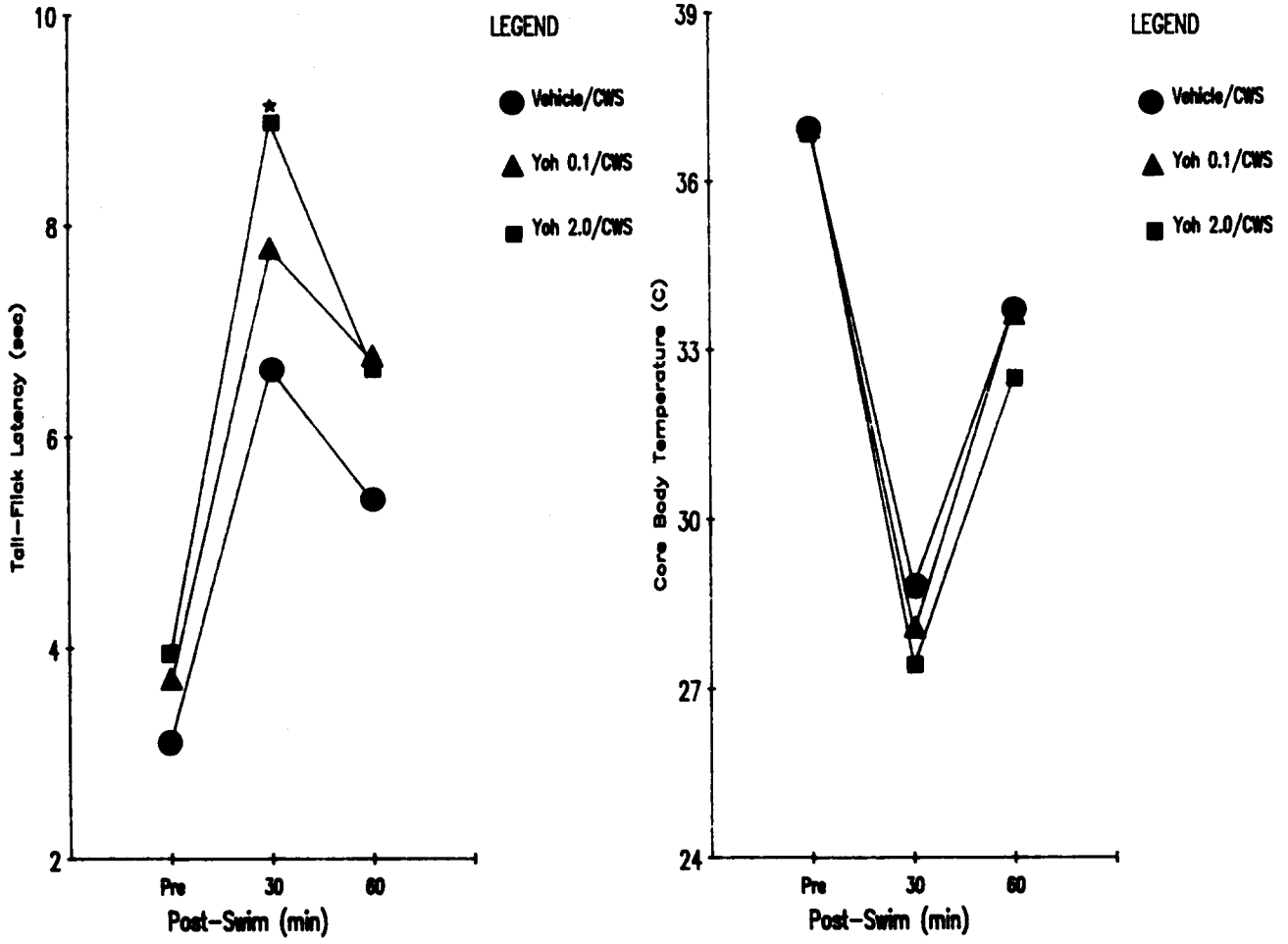

FIG. 2. Alteration in CCWS analgesia on the tail-flick test (left panel) and CCWS hypothermia (right panel) following Yoh. The potentiation in CCWS analgesia on the tail-flick test (star: Dunnett comparisons, $p<0.05$) was not accompanied by corresponding changes in basal tail-flick latencies (data not shown). Yoh failed to alter either CCWS hypothermia or basal thermoregulation (data not shown).

Protocol 2

Ten additional rats received the following four conditions at weekly intervals in counterbalanced order: vehicle/no swim, vehicle/CCWS, yohimbine (0.1 mg/kg)/CCWS and yohimbine (2.0 mg/kg)/CCWS. Each injection occurred 30 min prior to a 3.5 min swim in a 2°C temperature bath. Jump thresholds were determined 30 and 60 min following CCWS.

Protocol 3

Nine additional rats received vehicle, 0.1 and 2.0 mg/kg of yohimbine at weekly intervals in counterbalanced order. Tail-flick latenices and core body temperatures were assessed prior to and 30 and 60 min after injection.

Protocol 4

Ten additional rats received the following three conditions at weekly intervals in counterbalanced order: vehicle/CCWS, yohimbine (0.1 mg/kg)/CCWS and yohimbine (2.0 mg/kg)/CCWS. Tail-flick latencies and core body temperatures were determined prior to and following injection, and 30 and 60 min following CCWS.

RESULTS

Baseline Jump Thresholds

Significant differences in jump thresholds were observed among conditions ($F(4,36)=55.52$, $p<0.0001$), across test times ($F(2,18)=35.82$, $p<0.0001$) and for the interaction between conditions and times ($F(8,72)=7.73$, $p<0.0001$). The left panel of Fig. 1 illustrates the significant increase in baseline jump thresholds for up to 60 min following the 0.1 mg/kg dose of yohimbine, and the analgesic effect across the time course for the 0.5, 1.0 and 2.0 mg/kg doses of yohimbine.

CCWS Analgesia (Jump Test)

Significant differences in jump thresholds were observed among conditions ($F(3,36)=211.57$, $p<0.0001$) and between test times ($F(1,36)=5.77$, $p<0.022$). All swim conditions significantly increased jump thresholds above no-swim values. The right panel of Fig. 1 illustrates the significant potentiation of CCWS analgesia following pretreatment with either the 0.1 or 2.0 mg/kg doses of yohimbine.

Baseline Tail-Flick Latencies and Core Body Temperatures

Significant differences in latencies were observed only across test times ($F(2,16)=10.32$, $p<0.002$); neither dose of yohimbine altered baseline tail-flick latencies. Significant effects failed to occur for baseline core body temperatures among doses or test times.

CCWS Analgesia (Tail-Flick Test)

Significant differences in latencies were observed among conditions ($F(2,18)=7.55$, $p<0.004$) and between test times ($F(3,27)=112.41$, $p<0.001$). All swim conditions significantly increased latencies above no-swim values. The left panel of Fig. 2 illustrates the significant potentiation of CCWS analgesia 30 min following pretreatment with the 2.0 mg/kg, but not the 0.1 mg/kg dose of yohimbine.

CCWS Hypothermia

Significant decreases in core body temperature occurred after CCWS ($F(3,27)=188.55$, $p<0.0001$). However, the right panel of Fig. 2 illustrates the failure of either dose of yohimbine to alter CCWS hypothermia.

DISCUSSION

The present study was designed to evaluate further noradrenergic influences upon CCWS analgesia by examining the dose-dependent effects of the alpha-2 noradrenergic receptor antagonist, yohimbine upon CCWS analgesia on the tail-flick and jump tests as well as upon basal nociceptive thresholds and CCWS hypothermia. Previous studies [6–8] suggested that putative changes in noradrenergic availability altered CCWS analgesia. Lesions placed in the locus coeruleus which decrease brain norepinephrine also decrease CCWS analgesia. Pretreatment with the alpha-2 noradrenergic receptor agonist clonidine potentiated CCWS analgesia. Acute pretreatment with the noradrenergic reuptake blocker, desipramine also potentiated CCWS analgesia. The similar pattern of analgesia changes and changes in noradrenergic levels and turnover following acute and chronic CCWS exposure [45–48, 50] also lent support to a direct involvement of noradrenergic systems in the mediation of this analgesic response. These findings would predict that antagonism of the alpha-2 noradrenergic receptor with yohimbine should attenuate CCWS analgesia. Indeed, an opposite pattern of results emerged: yohimbine potentiated CCWS analgesia on the tail-flick and jump tests without affecting the magnitude of CCWS hypothermia. These data are discussed in terms of: a) the relationship of the analgesic alterations relative to basal nociceptive changes; b) comparison of yohimbine effects upon CCWS analgesia relative to other forms of environmental analgesia, and c) examination of these paradoxical effects in terms of noradrenergic effects at different levels of the neuraxis.

Yohimbine, CCWS Analgesia and Basal Thresholds

In addition to the potentiation of CCWS analgesia on the tail-flick and jump tests by yohimbine, this antagonist also produced differential effects upon basal nociceptive thresholds. The present study found that baseline jump thresholds, but not baseline tail-flick latencies were significantly increased by yohimbine in a dose-dependent manner. The increases in jump thresholds by yohimbine at doses as low as 0.1–2.0 mg/kg contrasts with the increased shock-induced vocalization thresholds following 8–25 mg/kg doses of yohimbine [33]. Indeed, the 0.1–2.0 mg/kg range which produced analgesia on the jump test in the present study elicited hyperalgesia on the shock-induced vocalization test [33]. It should be noted that these results are not inconsistent because jump thresholds and vocalization thresholds following brief exposure to shock are different quantitatively in terms of necessary intensities required for elicitation, and qualitatively in terms of different levels of the neuraxis mediating the sensory-discriminative aspects of jump thresholds and the motivational-affective aspects of vocalization (e.g., [11]). That yohimbine failed to alter baseline tail-flick latencies is consistent with previous findings [16,19]. This may reflect the use in all studies of high-intensity heat which elicits short latencies, and thereby produces a 'floor' effect in which hyperalgesia is not readily observed. In addition, yohimbine has alternately failed to affect [19] or decreased [17] hot-plate latencies. That yohimbine can increase pain thresholds is somewhat paradoxical given the observed analgesic effects of the alpha-2 noradrenergic agonist, clonidine [7, 19, 31, 32, 34, 36].

The present study found that yohimbine increased jump thresholds and increased CCWS analgesia on the jump test. Perusal of these data strongly indicate that the nature of the latter increase is a function of additivity between the CCWS effect following vehicle treatment and the intrinsic analgesic activity of the particular yohimbine dose. The total increase in CCWS analgesia 30 min after the swim paired with the 2 mg/kg dose of yohimbine (0.52 mA) is an additive function of CCWS itself (0.34 mA) and the analgesic effect of this yohimbine dose (0.22 mA). Similarly, the total increase in CCWS analgesia 30 min after the swim paired with the 0.1 mg/kg dose of yohimbine (0.41 mA) is an additive function of CCWS itself (0.34 mA) and the analgesic effect of this yohimbine dose (0.10 mA). In contrast, yohimbine increased CCWS analgesia on the tail-flick test without significantly altering baseline tail-flick latencies. In this latter case, the potentiation in CCWS analgesia by yohimbine was not the result of mere additivity, but rather a facilitation of the analgesic effect. It should be noted however, that in terms of magnitude of effect, yohimbine potentiated CCWS analgesia more on the jump test than on the tail-flick test. The above data are quite similar to the potentiations of CCWS analgesia on the jump and tail-flick tests by clonidine [7]. The potentiation of CCWS analgesia by clonidine on the jump test was in most part the result of additivity between CCWS and clonidine analgesia. In contrast, since clonidine did not display increases in baseline tail-flick latencies yet increased CCWS analgesia on the tail-flick test at the doses employed, it appeared that this latter effect was due to a true facilitation. The clonidine and yohimbine effects upon CCWS did differ in terms of hypothermia in that the former, but not the latter manipulation potentiated CCWS hypothermia. Thus, administration of either an alpha-2 noradrenergic agonist or antagonist produces identical effects upon CCWS analgesia. The alpha-2 noradrenergic receptor has recently been implicated directly in responsiveness to cold. Cold-restraint stress significantly decreased the density of 3H-rauwolscine binding to alpha-2 adrenoreceptors in hippocampus and amygdala, but increased binding density in the midbrain. This stressor increased binding affinity in the amygdala, decreased binding affinity in the midbrain and had no effect upon affinity in the hippocampus [30]. How the paradoxical effects of alpha-2 adrenoreceptor agonists and antagonists upon CCWS analgesia relate to these binding characteristics is not clear, but the data appear to suggest that any changes

in CCWS analgesia by noradrenergic manipulations are due to orthogonal processes rather than direct manipulation of the intrinsic pain-inhibitory system activated by CCWS.

Yohimbine and Stress-Induced Analgesia

Previous studies have shown that yohimbine reduces prolonged intermittent footshock analgesia, brief continuous footshock analgesia and autoanalgesia [12, 16, 17]. Prolonged intermittent footshock analgesia is reduced by opiate receptor antagonist treatment, morphine tolerance, hypophysectomy and adrenalectomy [26–29] and has been characterized by the Watkins and Mayer schema [49] as neurohormonal-opioid. Both brief continuous footshock analgesia and autoanalgesia are unaffected by opiate receptor antagonism, are not cross-tolerant with morphine analgesia and are unaffected by pituitary-adrenal manipulations [13–15, 26–29]. Hence they have been characterized as neural-nonopioid in nature. CCWS analgesia displays a different pattern of results: it is unaffected by naloxone or morphine tolerance, yet is reduced by hypophysectomy and medial-hypothalamic damage, and is potentiated by adrenalectomy, but not adrenal demedullation (see review: [3]). Thus, CCWS analgesia has been characterized as neurohormonal-nonopioid. That CCWS and opioid forms of stress-induced analgesia show opposite results as in the present study is not surprising given that decreases in opiate function by naloxazone treatment increases CCWS analgesia while increases in opiate function by D-phenylalanine treatment decreases CCWS analgesia [5,24]. The decreases in opioid forms of footshock analgesia and the increase in CCWS analgesia by yohimbine is consistent with such differentiations.

Possible Differential Sites Along the Neuraxis

The question still remains why CCWS analgesia and certain basal pain thresholds are similarly affected by systemic administration of either an agonist or an antagonist of the alpha-2 noradrenergic receptor. Some answer may derive from recent central analyses of the role of noradrenergic influences in nociceptive and analgesic processes. Opiate-mediated analgesia in the spinal cord appears to be dependent in part upon alpha-noradrenergic receptors: alpha-noradrenergic receptor agonists produced analgesia following intrathecal administration, and intrathecal administration of alpha-noradrenergic receptor antagonists blocked the analgesic effects of intrathecally-applied opiate or alpha-noradrenergic agonists [23, 25, 36, 37]. Intrathecal administration of alpha-noradrenergic receptor antagonists were then shown to produce hyperalgesia [35,39]. In contrast administration of alpha-noradrenergic antagonists into the nucleus raphe magnus, a medullary locus of opiate analgesia (e.g., [1,2]), induces analgesia [21,40]. This latter form of analgesia is blocked by intrathecal administration of either serotonergic antagonists [22] or alpha-noradrenergic antagonists [38,42]. It appears that the analgesic effect of alpha-noradrenergic antagonist treatment in the nucleus raphe magnus is mediated by noradrenergic fibers in the medullary A5 catecholamine nucleus [41]. Indeed, the spinal noradrenergic system mediates other forms of analgesia other than opiates and norepinephrine: the cholinergic agonist, carbachol produces analgesia following administration into the nucleus raphe magnus [9] which is enhanced by intrathecal pretreatment with alpha-1 noradrenrgic receptor antagonists and decreased by intrathecal pretreatment with alpha-2 noradrenergic antagonists [10]. Additional differentiations can be observed for clonidine analgesia: lesions placed in the dorsal noradrenergic bundle transiently decreased clonidine analgesia [43]. Yet, lesions placed in the locus coeruleus or administration of alpha-methyl-para-tyrosine failed to affect clonidine analgesia, and intraspinal administration of 6-hydroxydopamine potentiated this analgesic effect. These differential effects of noradrenergic agonists and antagonists are in line with the postulation [33] that these apparent paradoxical effects of systemically-administerd alpha-2 noradrenergic agonists and antagonists may represent differential functioning at different levels of the neuraxis. Future studies for the role of these agonists and antagonists in stress-induced analgesia must analyze such differential effects as a function of the level(s) of the neuraxis at which they are presumably acting.

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