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Pharmacology of Spinal Adrenergic Systems Which Modulate Spinal Nociceptive Processing

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YAKSH, T. L. *Pharmacology of spinal adrenergic systems which modulate spinal nociceptive processing.* PHARMACOL BIOCHEM BEHAV 22(5) 845–858, 1985.—Spinopetal pathways may be activated by a variety of brainstem manipulations including microinjections of morphine which are known to modulate spinal nociceptive processing. Based on the ability of these manipulations to release spinal noradrenalin; the ability to reverse the antinociceptive effects by intrathecal adrenergic antagonists and the fact that intrathecal injections of noradrenalin mimic the antinociceptive effect, it appears that the descending modulation may be mediated by descending noradrenergic systems. Examination of the spinal receptor systems with intrathecally administered agents indicates that spinal alpha, but not beta adrenergic receptor agonists produce a powerful analgesia as measured on a variety of reflex and operant measures in mouse, rat, cat, primate and man. On the basis of agonist and antagonist structure-activity relationships it appears that a significant effect can be produced in the absence of any detectable effect on motor function by the occupation of spinal alpha$_2$ receptors. Distinguishable alpha$_1$ receptors also appear "analgetically-coupled," but their effects are uniformly contaminated by signs of cutaneous hyperreflexia at doses required to produce analgesia. The ordering of potency with which intrathecal adrenergic antagonists reverse the effects of intrathecal noradrenalin is indistinguishable from that of the reversal by these intrathecal agents of the antinociceptive effects evoked by brainstem morphine. This suggests that the population of spinal receptors acted upon by exogenously administered adrenergic agonists and endogenously released noradrenalin have indistinguishable characteristics.

Spinopetal pathways Alpha$_1$ receptors Yohimbine Prazosin Analgesia Spinal reflex Pain modulation

IN classic studies by Weber [82] it was demonstrated that the application of adrenalin to the spinal cord would produce an attenuation of the thermally evoked withdrawal response in the cat. In subsequent studies it was shown that a variety of sympathomimetic agents administered systemically in man and animals have antinociceptive activity [12,41]. Later, it was demonstrated that the intravertebral and cisternal injection of adrenalin or noradrenalin would produce a significant modification in the response of the animal to otherwise noxious stimuli [46]. Though not all sympathomimetic agents were able to produce analgesia, it was early recognized that the failure of some of these agents likely resulted from the inability of these drugs to cross the blood-brain barrier. Thus, agents commonly devoid of any antinociceptive effects when administered parenternally (such as oxymetazoline) [62,63], showed significant activity after intracerebral administration. The development of direct acting alpha-sympathomimetic agents which were able to cross the blood-brain barrier (such as clonidine or xylozine) indeed revealed that these drugs when administered systemically would also produce a powerful antinociceptive effect [43, 62, 63]. Though it is clear that many of these systemically administered sympathomimetic agents produce significant sedation (see for example [19,20]), the broad spectrum of tests and the wide variety of species in which these drugs are active, appeared to preclude the likelihood that the observed effects are simply a side effect of a nonspecific depression of behavior [10, 23, 47, 67]. The question may be asked as to first where are the central alpha-adrenergic receptors acted upon by these agents and second, what are the characteristics of these receptors?

SITE OF ACTION OF ALPHA-SYMPATHOMIMETIC AGENTS IN PRODUCING ANTINOCICEPTION

Though the sedative effects clearly supported a supraspinal action of alpha-adrenoceptive agonists, the major advances have been in the area of the spinal adrenoceptor systems; and, this review will focus on the brainstem-spinal axis where the classic studies of Weber [82] had previously shown a powerful antinociceptive action of adrenalin. Takagi [74] had early argued that opiates act to inhibit spinal function by the activation of descending pathway. The observation that altering monoamine tone in spinal transected cats could alter flexor reflex afferent and ventral root reflex function (see below) and the observation of catecholamine containing spinopetal pathways [16,17], led to the speculation that descending pathways might modulate spinal sensory function. Several lines of evidence can be marshalled to support this hypothesis.

First, intracerebral microinjections into the periaqueductal gray or electrical stimulation will produce a powerful modulation of the animal's response to a strong stimulus and importantly, inhibit spinal nociceptive reflex function (see Yaksh and Rudy [93] for review) and these antinociceptive effects are antagonized by the intrathecal administration of alpha-adrenergic antagonists [13, 36, 59, 89].

Second, supraspinal manipulations which altered spinal reflex function, such as the microinjection of morphine or focal brainstem stimulation would produce a significant increase in the release [27] or turnover [15, 65, 75] of spinal noradrenalin stores.

Third and most importantly, if the descending pathways release noradrenalin and presumably activate a local noradrenergic receptor in the spinal cord, then the direct application of noradrenergic agents onto those systems should in fact mimic the effect of these brainstem manipulations. Using intrathecal administration procedures, it has been demonstrated in the unanesthetized animal that indeed, the local activation of spinal adrenergic receptors will produce a powerful analgesia as assayed in mouse [35], rat [44, 53, 54], cat [96] and primate [92]. The characteristics of these effects will be discussed below. In short, a persuasive body of literature suggests that the activation of populations of adrenergic receptors in the spinal cord, secondary to the release of norepinephrine from systems activated by manipulations of supraspinal structures, gives rise to a powerful modulation of the transmission of information relevant to the organization of the response to a strong stimulus.

Examination of the distribution of noradrenergic fiber systems in the spinal cord indicates that these terminals originate from supraspinal structures as there is a virtual abolition of catecholamine levels following spinal transection [16,17]. Combining retrograde transport of HRP and costaining with dopamine-β-hydroxylase immunohistochemistry, it has been demonstrated that the majority of the norepinephrine-containing fibers descend in the lateral funiculi to terminate extensively in the dorsal gray, notably the substantia gelatinosa and in the ventral gray in the vicinity of the motor nuclei [85]. These regions of termination correspond with the intense fluorescence which has been observed in these regions. Importantly, there are significant populations of norepinephrine-containing varicosities which are in the vicinity of the intermediolateral cell column at the thoracic level to provide innervation for the preganglionic/parasympathetic fibers and in the sacral cord to innervate the parasympathetic preganglionic systems. Though it will not be further discussed here, it should be realized that there is increasing evidence that these systems are discretely organized such that for example the fiber systems arising in the A6 (locus coeruleus) appears to project predominantly to the sacral cord; while those originating in the A7 (subcoeruleus/parabrachial nucleus), project primarily to the thoracic cord (see [72,85]). Moreover, it should also be realized that in many of the earlier studies it is difficult to separate epinephrine from norepinephrine containing fibers. In the studies by Westland and colleagues, it was found that the caudal cell groups staining for dopamine-β-hydroxylase (A1/A2), did *not* project to the spinal cord, while Ross and colleagues [55] noted that *adrenalin*-containing neurons in the C1 group, but not noradrenalin cells of the ventrolateral rostral medullary reticular formation did, indeed, project to the thoracic spinal cord.

At the electron micrographic level, Satoh and colleagues [57] observed noradrenalin-containing terminals to be distributed in the dorsal gray to the superficial portions of the gelatinosa (lamina II) and formed axodendritic contacts and to a lesser degree axonic contact on small fibers. Following dorsal rhizotomy, these axo-axonic profiles did not disappear within three days. Thus, the presence of axo-axonic synapses presynaptic to primary afferents appears unlikely, though the possibility that such contacts do lie on small afferents which may disappear at a longer interval following dorsal rhizotomy, cannot be excluded.

Radioligand binding studies have demonstrated the presence of alpha$_1$ [5, 39, 64], alpha$_2$ [32,39] and beta [51] binding sites. Spinal cord hemisection or intrathecal 6-hydroxydopamine in cat failed to reduce the levels of alpha$_2$ binding. Comparable data after 6-hydroxydopamine has been observed by Astrachan *et al.* [5] in rats. Indeed, in both instances after a short interval, increases in binding density were observed, suggesting a possible substrate for the spinal supersensitivity which occurs after denervation [5,31]. These observations clearly argue against the likelihood that alpha$_2$ binding is largely located presynaptically on monoamine terminals. Unilateral sensory ganglionectomy resulted in a 20% decrease in dorsal horn alpha$_2$ binding at 7–21 days. This observation in conjunction with the finding that significant levels of alpha$_2$ binding can be found in dorsal root ganglion cells, suggest the likelihood that a proportion of the alpha$_2$ binding in spinal cord may in fact be found on primary afferent terminals [33].

ELECTROPHYSIOLOGY OF SPINAL ADRENERGIC RECEPTORS

Intravenous administration of L-dopa, a manipulation which is known to increase the synthesis and subsequent release of noradrenalin resulted in an inhibition of the response of dorsal horn neurons to noxious heat. Cells which responded only to innocuous stimuli (hair deflection or light touch) showed a response facilitation. These effects were largely abolished by pretreatment with 6-hydroxydopamine, resulting in a destruction of spinal catecholamine terminals and by inhibition of dopamine-β-hydroxylase using fusaric acid [29]. Takagi and colleagues [73], observed that L-dopa would inhibit the bradykinin induced evoked activity in spinal wide dynamic range neurons in spinal transected cats.

Single unit recording studies reveal that the iontophoretic administration of noradrenalin into the dorsal horn would produce an inhibition of spontaneous firing or the synaptic activity induced by the local administration of DL-homocysteic acid [22]. Later studies confirmed these observations and further indicated that the effects of iontophoretically administered noradrenalin was relatively selective for the activity evoked by noxious (heat), but not non-noxious (hair deflection) activity in dorsal horn wide dynamic range neurons [8,28]. Significantly, the most profound inhibition was observed in the deeply lying wide dynamic range neurons when the noradrenalin was iontophoresed into the gelatinosa, presumably in the vicinity of the terminals of the primary afferents which excited either directly or indirectly the dendritic tree of the underlying neuron. The fact that noradrenalin served to inhibit the effects of excitatory amino acids, however, also suggested that noradrenalin likely possessed a postsynaptic site of action.

The iontophoretic administration of noradrenalin onto spinal motor neurons results in a significant depression of their activity associated with the hyperpolarization [22,84]. Jordan *et al.* [38], observed significant inhibition of interneurons in the vicinity of motor nuclei and suggested that this might explain a hyperpolarizing effect on motor horn

cells. Alternately, it has been demonstrated that while norepinephrine may not uniformly excite motor neurons [49,87], its local application can facilitate the depolarizing effects of excitatory drive or the effects of excitatory neurotransmitters. This effect appears to be mediated by a subthreshold depolarization and an increase in input resistance [80].

Given the likelihood that there are alpha-binding sites on primary afferents, it is reasonable to consider the possibility of a presynaptic action of alpha-adrenergic compounds in the dorsal gray. Using excitability testing procedures, Jeftinija, Semba and Randic [37] observed that the microapplication of norepinephrine into the dorsal gray resulted in dose related increases in the threshold for antidromic activation of C fibers. This effect was antagonized by phentolamine, but not naloxone. Comparable results have been reported by Zimmerman, Carstens, Shreiber and Gilly [100]. In hemisected frog spinal cord, the application of adrenalin or noradrenalin resulted in a significant hyperpolarization of primary afferent terminals. As these effects were reduced by the application of maganese, tetrodotoxin or mephenesin, it appears likely that the effect was mediated by an interneuron. The observed hyperpolarization of the afferent terminals produced by the adrenergic agents were antagonized by yohimbine and piperoxin, but not by either prazosin or the beta-antagonists, sotalol and propranolol. While monoamine oxidase inhibitors had no effect on this phenomenon, it was potentiated by catecholamine uptake blockers [88]. The possibility of a presynaptic action is further suggested by the work of Dunlap and Fischbach [21] in dorsal root ganglion cell culture in which it was observed that norepinephrine resulted in a decrease in the inward calcium current of the soma membrane.

In other *in vitro* studies, Yoshimura and North [99], observed that the superfusion of noradrenalin, resulted in a significant hyperpolarization of gelatinosa neurons in rat spinal cord slices. The effect appeared to occur via the opening of potassium channels and was apparently mediated by a direct action on the membrane as the hyperpolarization continued after application of cobalt, magnesium or low calcium solutions. Importantly, these effects were antagonized by yohimbine and phentolamine, but not by either prazosin or propranolol.

EFFECT OF ALPHA-ADRENERGIC AGONISTS ON SPINAL REFLEX FUNCTION

A large early literature by Swedish investigators not commonly cited, using L-dopa in acutely transected animals, reported complex effects on reflex functions evoked by flexor reflex afferent stimulation. Thus, in acutely spinal transected cat L-dopa: (1) depressed the short latencied dorsal root potential and the ventral root discharge evoked by flexor reflex afferents; (2) resulted in a long latencied dorsal root potential and a facilitation of a late flexor reflex evoked by repetitive stimulation; and (3) evoked a facilitation of monosynaptically activated motor neurons which is accompanied by a concurrent inhibition of the polysynaptic reflexes evoked by cutaneous nerve stimulation [2–4, 6, 48]. Examining the flexion reflex evoked by pinch, Anden and colleagues [1] observed that L-dopa would facilitate the flexion reflex evoked by hindlimb pinch. The complexity reflected by such experiments can be appreciated when one realizes that (1) L-dopa may facilitate neurotransmitter tone in systems not related to noradrenalin; (2) that the systemic administration of the drugs in the spinal transected animal clearly will facilitate activity in all spinal noradrenergic systems; and (3) the released norepinephrine will act on all classes of adrenergic receptors. The combined inhibitory and facilitatory phenomena observed with intravenous L-dopa has been examined in subsequent studies which have attempted to dissect the spinal noradrenergic system functionally and pharmacologically.

Focal administration of norepinephrine by microinjection into the dorsal gray matter of the cat spinal cord was observed to produce a significant depression of C-fiber reflexes evoked by either electrical stimulation of cutaneous nerve or noxious, radiant heat applied to the foot pad [9]. Such microinjections carried out in the ventral horn resulted in a significant facilitation of these C-fiber evoked ventral root reflexes. These observations are consistent with a variety of effects of iontophoretically applied norepinephrine on dorsal and ventral horn cells (see above).

Kawasaki and colleagues [40] demonstrated that clonidine, an alpha-adrenergic agonist, would inhibit the tail flick reflex generated by pinch in spinal transected animals, but only at low doses (0.06 mg/kg), whereas a facilitation of this reflex was observed at a higher dose (0.5 mg/kg). Significantly, the inhibitory effects, but not the excitatory effects were antagonized by yohimbine. These observations are in close agreement with subsequent reports showing differential effects of intrathecally administered $alpha_1$ and $alpha_2$ agonists on motor and nociceptive function (see below). Spaulding and colleagues [68,69] have also observed that clonidine produces a dose-dependent inhibition of the thermally evoked tail flick in the spinal transected rat.

Though difficult to summarize, the following statements appear reasonable based on the above analysis.

1. The local action of noradrenalin in the dorsal gray matter will result in a selective inhibition of A-delta/C fiber evoked activity in wide dynamic range neurons. This effect appears potentially mediated by both a presynaptic action as evidenced by the effect of norepinephrine on primary afferent excitability and postsynaptic as evidenced by the ability to suppress excitatory amino acid evoked discharges. Cells which respond only to innocuous stimuli appear to have their discharges facilitated by norepinephrine. These suppressive effects of norepinephrine in the dorsal horn on neuronal activity appear to be mediated by alpha and not beta receptors and predominantly by $alpha_2$ receptors, though adequate pharmacological studies have not yet been reported.

2. In the ventral horn, norepinephrine can produce a significant hyperpolarization of motor neurons and a suppression of interneurons in the vicinity of the motor neuron pool. Excitation after focal administration has, however, been observed and appears to correlate with the observations that noradrenalin with an action in the ventral horn can produce a facilitation of C-fiber evoked ventral root reflexes. The effect on ventral horn activity has also not been fully characterized with regard to pharmacology, though it appears possible that the suppressive effects are mediated by an $alpha_2$ receptor, whereas those which resulted in facilitation of motor horn outflow either by a direct effect or indirectly through an alteration in ventral horn organization, are $alpha_1$ in character.

ANALGESIC EFFECTS MEDIATED BY SPINAL ADRENERGIC RECEPTORS

Though it is clear that alpha-adrenergic receptors in spinal cord produce an alteration in nociceptive processing, an important question is whether or not these spinal effects are relevant to the pain behavior of the intact and unanesthetized animal. As indicated above, the intrathecal administration of

TABLE 1

EXPERIMENTAL PAIN MODELS IN WHICH INTRATHECALLY ADMINISTERED ALPHA-ADRENERGIC AGONISTS HAVE BEEN EXAMINED

Species	References
Mouse	[35]
Tail flick	
Paw lick, response to hypertonic saline	
Intrathecal substance P evoked scratching response	
Rat	[44, 53, 54]*
Hot plate	
Tail flick	
Writhing	
Hind paw pinch	
Tail withdrawal	
Cat	[54]
Skin twitch	
Monkey	[92]
Shock titration	
Man	[14]
Terminal cancer	

*T. L. Yaksh and G. Harty, this paper.

adrenergic agonists, will produce a powerful inhibition of the animal's response in a variety of nociceptive measures. These antinociceptive effects have been observed following spinal administration in mouse, rat, cat and primate. Table 1 lists the tests in which the spinal effects of adrenergic agonists have been so examined. Importantly, the suppressive effects of intrathecally administered norepinephrine on all of these measures demonstrate monotonic dose response curves (see below) in which the maximum inhibition can be achieved in the absence of significant signs of motor dysfunction. It should be stressed that the effects of intrathecally administered alpha agonists have been demonstrated to alter the nociceptive response not only on spinal nociceptive reflexes, but also on tests in which the response substrate involves a supraspinal component. Thus, the primate shock titration, the rat hot plate, the tail shock vocalization and the coordinated paw withdrawal to pinch, are examples of such tests which are altered by intrathecally administered alpha agonists. Recently in man, Coombs and colleagues [14] have observed that intrathecally administered clonidine will produce powerful analgesia as defined by verbal report in terminal cancer patients which have been rendered refractory to spinal morphine by the prior chronic infusion of the opioid. These data offer clear support for the concept that in all species tested, including man, the spinal action of alpha agonists produces a powerful analgesia.

It should be noted that these suppressive effects appear selective. At analgetic doses, there is no change in non-nociceptive reflexes such as placing or stepping [53,54]. The orientation response to light brushing of the flank is unaltered. In systematic studies, Yaksh and Reddy [92] observed that doses of intrathecal clonidine which maximally elevated the shock titration threshold had no effect on the avoidance of ear shock cued by light pressure applied to the analgesic hindpaw.

PHARMACOLOGY OF SPINAL ANTINOCICEPTIVE EFFECTS OF ALPHA-ADRENERGIC AGONISTS

Characterization of the receptor in the spinal cord which mediate the antinociceptive effects of intrathecally administered adrenergic agonists have been carried out by (1) examining the agonist structure-activity relationship; (2) the antagonist structure-activity relationship; (3) the effect of altering spinal norepinephrine disposition (metabolism, uptake and release); and (4) tachyphylaxis.

Agonist Structure-Activity Relationship

In the rat, intrathecal administration of adrenergic agonists produces a dose dependent increase in the response latency on the hot plate and tail flick. Figure 1 displays the time effect curves for intrathecally administered norepinephrine. The duration of the drug effect is proportional to the intrathecal dose. This response suppression is also produced by a variety of intrathecally administered adrenoceptor agents including: L-norepinephrine; DL-epinephrine; DL-alpha-methylnorepinephrine; ST-91; clonidine; L-phenylephrine; 3,4-dihydroxytolazoline; oxymetazoline; methoxamine and cirazoline [30–32, 53, 54]. Beta-agonists such as isoproterenol are without effect at the highest doses [53]. With few exceptions, all agents were observed to produce monotonic increases in the dose response curves [53]. This is illustrated in Fig. 2, in which dose response curves for the hot plate and tail flick after intrathecal administration of norepinephrine, ST-91 (an $alpha_2$ agonist) and methoxamine (an $alpha_1$ agonist) are presented. The failure of $alpha_1$ agonists to produce a maximum effect is related to the fact that these agents also evoke a dose-dependent cutaneous hyperreflexia and a tendency to spontaneous movements of the tail (see below). Based on these systematic studies, the structure-activity series for adrenoceptor agonists in the hot plate and tail flick is: ST-91 = norepinephrine > methoxamine >> isoproterenol = 0. Figure 3 presents the results of recent studies in which the structure-activity relationship of intrathecal adrenoceptors was studied on the acetic acid writhing response. As shown, monotonic dose-response curves were obtained with the relative ordering of activity being ST-91 $\geq$ norepinephrine > methoxamine >> isoproterenol = 0.

In the primate on the shock titration task, though less work has been done, the rank order of drug potency in producing a just maximum increase in the shock titration threshold after intrathecal injection is: clonidine = ST-91 > methoxamine > isoproterenol = 0 ([92]; T. L. Yaksh and G. Harty, unpublished observations). As in the rat, a maximum inhibition could not be achieved with methoxamine due to a dose-dependent motor dysfunction.

Antagonist Structure-Activity Relationship

The ability of intrathecally administered norepinephrine to elevate the nociceptive threshold appears to be uniformly mediated by an alpha-adrenergic receptor. Thus, a dose-dependent inhibition of the effect can be achieved by intrathecally administered phentolamine, but not propranolol [44, 53, 54]. As shown in Fig. 4, the interaction of phentolamine with intrathecal norepinephrine, consistent with classical pharmacology, displays a competitive antagonism of the antinociceptive effects of intrathecal norepinephrine and produced a parallel shift in the norepinephrine dose-response curve [53].

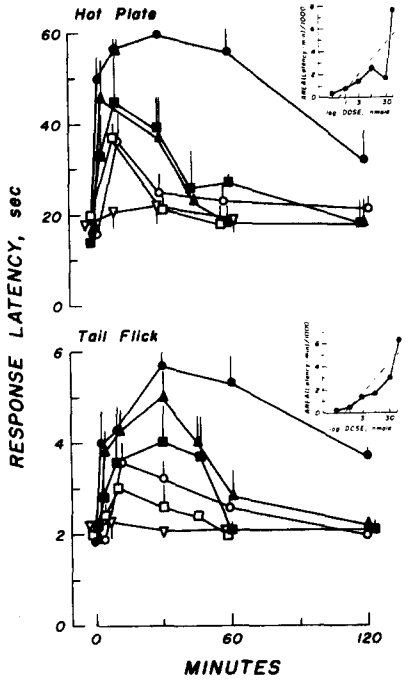

FIG. 1. Analgesia as a function of time after intrathecal administration of norepinephrine; 0.3 nmol (▽); 1 nmol (□); 3 nmol (○); 9 nmol (■); 30 nmol (▲); and 60 nmol (●). Each point represents the mean hot plate or tail-flick latency±S.E.M. of at least four animals. The insert presents the area under the dose-response curve plotted against the log dose NE. The interrupted lines in the inserts are calculated regression lines (Reddy *et al.* [53]).

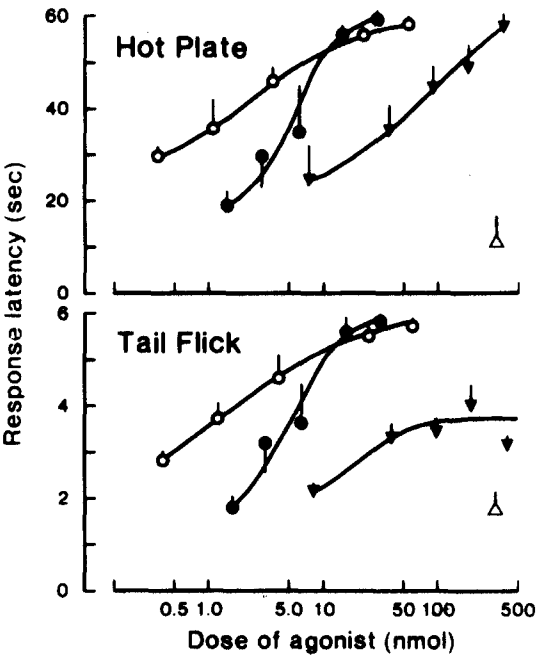

FIG. 2. Mean response latency in seconds, hot plate (top) and tail flick (bottom), 20 min after various IT doses of ST-91 (○), methoxamine (▼), NE (●) or isoproterenol (△). Each point represents mean data obtained from 4 to 12 rats. Bars indicate S.E.M. (modified from Howe *et al.* [30]).

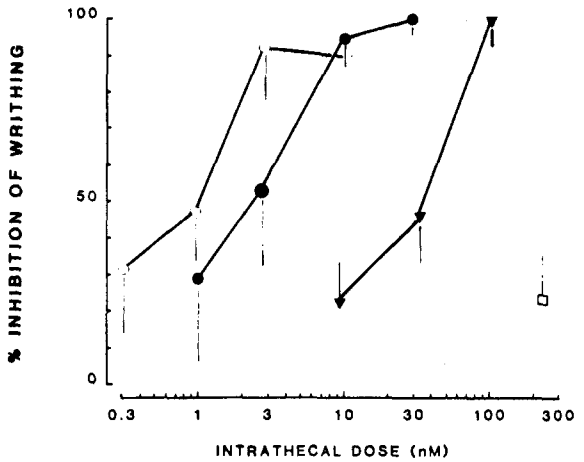

FIG. 3. Inhibition of the writhing response evoked by intraperitoneally 10% acetic acid. Results are expressed as the percent of the writhing response as compared to a concurrent group of rats that received intrathecal saline. Each dose point represents the mean±S.E. of the results obtained in 6 animals. The details of the writhing test are given elsewhere [61]. ○: ST-91; ●: NE; ▼: methoxamine; □: propranolol. The calculated ED_{50} values (and 95% CI) are: ST-91, 0.83 nM (0.3–4.7); NE, 2.3 nM (0.5–19.4); methoxamine, 32 nM (11–98); isoproterenol, >275 nM (Data by G. Harty and T. L. Yaksh).

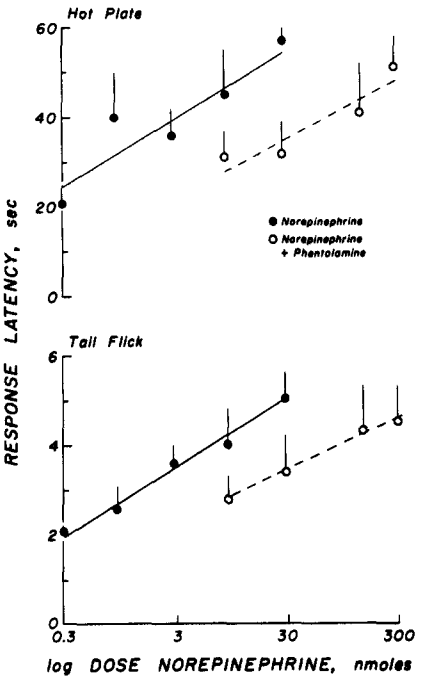

FIG. 4. Dose-response curves of intrathecally administered NE alone (●) and after pretreatment with phentolamine (○) (5 mg/kg IP). Phentolamine was administered 30 min before intrathecal injection of NE. Each point represents the mean hot plate or tail flick latency±S.E.M. of 4 to 10 animals. Calculated regression lines are shown (Reddy *et al.* [53]).

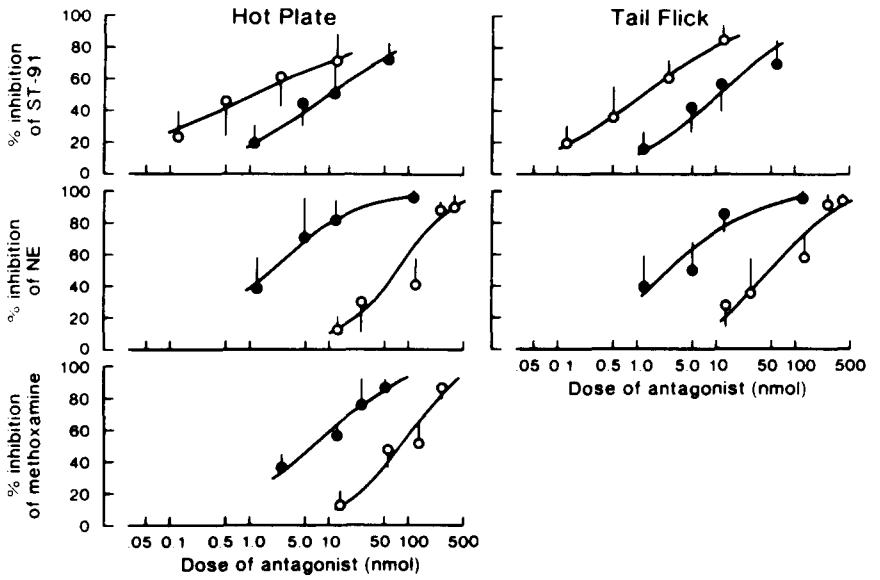

FIG. 5. Mean percentage of inhibition, produced 30 min after IT injection of various doses of prazosin (●) and yohimbine (○), of the elevation of mean response latency, hot plate (left) and tail flick (right), evoked 20 min after the IT injection of ST-91 (top, 15 μg), NE (middle, 10 μg) or methoxamine (bottom, 100 μg). Each point represents mean data obtained from four to nine rats. Bars indicate S.E.M. (Howe *et al.* [30]).

In an effort to assess the relative role of spinal alpha$_1$ versus alpha$_2$ receptors, dose response curves have been carried out examining the ability of alpha$_1$ and alpha$_2$ selective antagonists to alter the antinociceptive effect. Howe and colleagues [30] demonstrated that the alpha$_2$ receptor antagonist yohimbine, can produce a dose dependent suppression of the antinociceptive effects produced on hot plate and tail flick of intrathecally administered ST-91. As shown in Fig. 5, under these conditions, the ID_{50} for yohimbine is approximately 1/10th that of prazosin, an alpha$_1$ selective antagonist. This is consistent with the known alpha$_2$ selectivity of ST-91. In contrast, in the antagonism of the antinociceptive effects of intrathecal norepinephrine and methoxamine, it can be seen that the ordering of activity is reversed such that prazosin is approximately 10 times more effective in antagonizing the effects of intrathecal norepinephrine and methoxamine than yohimbine. This relative potency of yohimbine against intrathecal norepinephrine in the rat had been previously observed [53]. More recently, we have extended these studies to examine the relative potency of the stereoisomers of yohimbine (alpha$_2$), rauwolscine (alpha$_2$) and corynanthine (alpha$_1$) in antagonizing the intrathecal effects of ST-91 and norepinephrine. The results of these experiments are presented in Table 2. As indicated, the relative ordering of activity of intrathecal alpha$_1$ and alpha$_2$ preferring antagonists in reversing the tail flick inhibition produced by intrathecal norepinephrine is: prazosin, phentolamine, rauwolscine, yohimbine, corynanthine, propranolol (=0). The ordering of activity for antagonizing intrathecal ST-91 is: yohimbine, rauwolscine, prazosin, phentolamine, corynanthine, propranolol (=0). Comparable results are observed with the hot plate test.

On the basis of the above information, it appears likely that a spinal receptor population with a pharmacological profile comparable to that of an alpha$_2$ site mediates analgesia as measured by a wide variety of tests in a variety of species. The support for this derives first, from the rank ordering of agonist activity, on the hot plate, tail flick and writhing test in the rat and the shock titration in the primate. Second, the spinal effects of alpha$_2$ agonists on pain evoked behavior is preferentially antagonized by agents with a relative selectivity for the alpha$_2$ receptor. The fact that this ordering of antagonist potency was observed with yohimbine, rauwolscine and corynanthine, three agents which are stereoisomers with identical physicochemical properties offers further validation that the selective inhibition reflects on their selective effects at the spinal alpha$_2$ receptor.

Agonists, such as methoxamine and cirazoline with alpha$_1$ receptor selectivity were also observed to produce a suppression of the nociceptive response, but in all measures, these agents were characterized by their lesser activity. In view of the relatively lower activity of these agonists, it is possible that at the higher doses, the effects may be mediated by an action on alpha$_2$ receptors. This appears unlikely as the effects of methoxamine were more potently antagonized by the alpha$_1$ selective (e.g., prazosin) than alpha$_2$ selective antagonist. The possibility that alpha$_1$ receptors are also "analgetically coupled" is further suggested by the observation that norepinephrine can produce a very significant elevation in the nociceptive threshold and this effect is more potently antagonized by prazosin than yohimbine. It should be noted that if both populations of alpha$_1$ and alpha$_2$ receptors do contribute to the antinociceptive effect of spinal noradrenalin then both receptor populations would have to be affected to alter the norepinephrine effect. As intrathecal prazosin *appears* to be equipotent antagonizing agonists which are thought to act at either population of receptors, i.e., alpha$_1$ and alpha$_2$ (see Table 2), it would likely display a similar potency against norepinephrine, as it does. In contrast, the alpha$_2$ antagonist yohimbine against noradrenalin would appear to have the same apparent potency at the receptors for which it is *least* potent. Thus against norepinephrine, yohimbine would appear to have the same potency it would have against alpha$_1$ receptors.

TABLE 2

ID_{50} VALUES (nM)* FOR INTRATHECAL ADRENERGIC ANTAGONISTS ON THE TAIL FLICK (TF) RESPONSES ELEVATED BY PRIOR TREATMENT WITH PERIAQUEDUCTAL GRAY MORPHINE OR INTRATHECAL INJECTION OF NOREPINEPHRINE

	IT: NE§			IT: ST-91§			PAG: Morphine¶		
Drug	N	ID_{50}	(95% CI)	N	ID_{50}	(95% CI)	N	ID_{50}	(95% CI)
Phentolamine	19	26	(18–43)	26	18	(12–31)	12	38	(24–60)
Yohimbine	35	43	(18–100)	35	1.1	(0.8–1.5)	16	4.9	(2.3–10)
Rauwolscine	14	39	(23–58)	30	2.3	(1.0–3.8)	12	14	(8.2–25)
Corynanthine	22	98	(65–154)	18	249	(205–378)	12	140	(58–346)
Prazosin	24	2.4	(0.4–15)	27	10	(3.6–30)	16	5.6	(2–14)
Propranolol	8	>386		8	>386		6	>386	
Vehicle†‡	6	—		—	—		5	—	

*ID_{50} values represent the dose in nM of intrathecally administered antagonists which produced a 50% reduction in the antinociceptive effects of PAG morphine (5 μg/0.5 μl) or intrathecally administered ST-91 or norepinephrine (10 μg/10 μl). In all work, the intrathecal agent was administered 5–15 min after the PAG morphine or 5 min after the intrathecal alpha-agonist. Each entry presents the mean ID_{50} calculated from the regression equation and the 95% dose confidence interval.

†No reversal of the response inhibition was observed.

‡10 μl of 50% DMSO-saline.

§Data derived from [30] and G. Harty and T. L. Yaksh.

¶Data derived from [13] and G. Harty and T. L. Yaksh.

Effects of Altering Spinal Norepinephrine Disposition

The duration of action of intrathecal norepinephrine is relatively short, with the interval of activity being on the order of between 30 and 60 min (see Fig. 1). Co-administration of a monoamine oxidase inhibitor or monoamine uptake blocker, results in a significant facilitation of the intrathecal effect at doses of the drugs which by themselves have no effect [53].

Tachyphylaxis

Reported intrathecal administration at 30 min intervals of norepinephrine at a dose which initially blocked the hot plate and tail flick response, showed a significant reduction after 7–8 injections, a period of approximately 4 hr [54]. Comparable results were also seen with repeated injections of intrathecal ST-91 in which the drug was given on a daily basis for a period of 7 days (T. L. Yaksh, J. Wang and G. Harty, unpublished observations). At this time, the injection of morphine was observed to produce an effect which was indistinguishable from that produced in animals which had received intrathecal injections of saline.

MOTOR EFFECTS OF INTRATHECAL ADRENERGIC AGONISTS

It is stressed that a powerful suppression of the response of the animal otherwise evoked by a high intensity stimulus can be produced by intrathecal adrenoceptor agonists in the absence of any effect on motor function. Thus, in rats at antinociceptive doses of intrathecal norepinephrine or $alpha_2$ agonists, there is no effect on placing, stepping or pinna twitch reflexes [53,54]. In primates, there is no effect on hindlimb withdrawal strength [92]. Nevertheless, alpha-adrenoceptor agonists can and do produce distinguishable motor effects. At doses several times that required to block the hot plate and tail flick response, intrathecal norepinephrine or $alpha_2$ agonists will produce clear signs of hindlimb flaccidity [30,53]. In contrast, $alpha_1$ agonists at doses required to increase the nociceptive threshold in primate on the shock titration will result in hindlimb tremor and an exaggerated reflex withdrawal response to brisk but non-injurious scratching of the foot pad. In rat, the intrathecal injection of $alpha_1$ agonists in doses which appear to elevate the nociceptive threshold will result in dose-dependent cutaneous hyperreflexia, clonic flexion of the hindlimbs, rigidity and serpentine movements of the tail. The different characteristics of the motor effects produced by $alpha_1$ and $alpha_2$ selective agents offers further support for distinguishable spinal adrenergic receptor systems. Moreover, these observations clearly suggest a powerful role of alpha receptors on motor horn function in the intact animal. As noted previously, norepinephrine injected into the ventral horn principally facilitated ventral root reflexes [9]. These effects on motor function observed in $alpha_1$ agonists, are consistent with the effects of high doses of clonidine on tail flexion reflex evoked by pinch [40] and the facilitating effects noted above at intraveous L-dopa. Davis and colleagues [5,18] have observed that intrathecal $alpha_1$, but not $alpha_2$ agonists will produce a powerful dose dependent facilitation of the auditory evoked startle reflex. This group has provided convincing evidence that this phenomenon is mediated by an action on $alpha_1$ receptors. Thus, the effect is selectively antagonized by $alpha_1$ receptor antagonists such as WB40101.

COMPARABILITY OF SPINAL ADRENERGIC RECEPTORS ACTED UPON BY ENDOGENOUS AND EXOGENOUS ADRENERGIC AGONISTS

The data outlined above clearly suggests that the spinal action of alpha adrenergic agonists will produce a significant increase in the nociceptive threshold and an inhibition in activity of dorsal horn neurons. These data are consistent with the observations outlined in the beginning that activa-

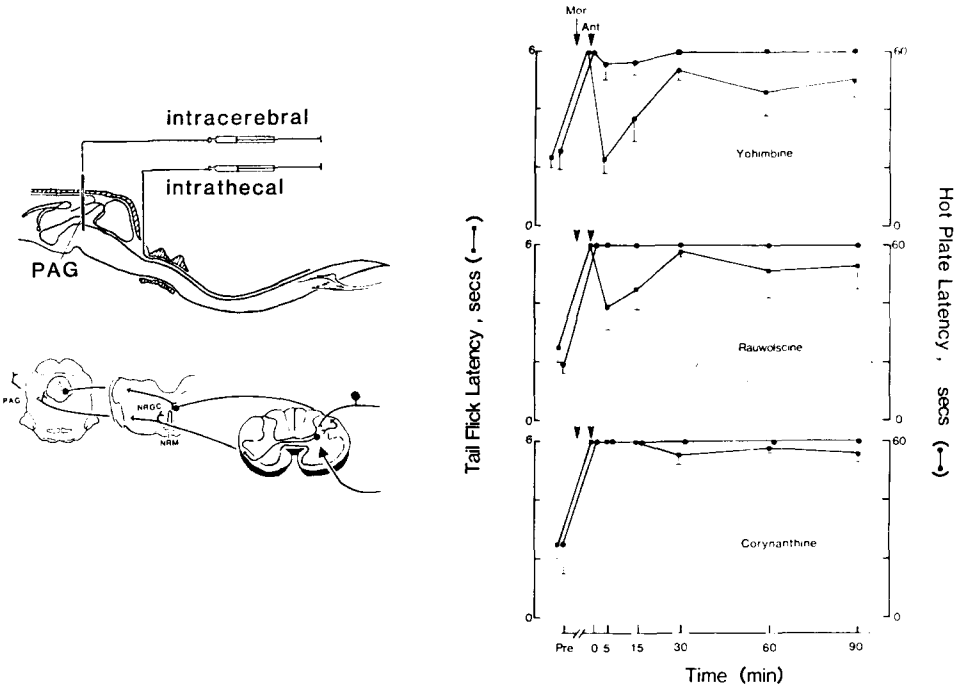

FIG. 6. Graph presents the time course of the effects on the hot plate and tail flick response latencies of morphine (5 μg/0.5 μl) administered intracerebrally at the first arrow followed by the IT injection at the second arrow of yohimbine (top), rauwolscine (middle), or corynanthine (bottom) given in a dose of 30 μg/10 μl. Each graph present the mean±S.E. of the time effect curve measured in 4–6 animals. (modified from Camarata and Yaksh [13]).

tion of spinopetal pathways will produce an increase in the nociceptive threshold. An important question is whether these effects of spinally administered noradrenalin are mediated by a receptor acted upon by *endogenously* released noradrenalin. Several lines of evidence support this hypothesis in the affirmative.

First, the intrathecal administration of tyramine, an agent known to release norepinephrine from rat and cat spinal cord [79,95], will produce an increase in the nociceptive threshold as measured by the hot plate and tail flick in rats, and this effect is antagonized by intrathecally administered phentolamine [53]. Significantly, this effect of intrathecal tyramine is abolished by the prior intrathecal administration of 6-hydroxydopamine, a treatment which is known to significantly deplete spinal norepinephrine stores [31].

Second, if the descending pathways activated by morphine injected at a supraspinal locus exert their effect on spinal receptors which are equivalent to those acted upon by intrathecally administered alpha-adrenergic agents, then the pharmacology of the spinal receptor, as defined by structure-activity profiles for the antagonists, should be the same for the effects produced by brainstem manipulation and intrathecal agents. Previous studies have indicated that the effects on spinal nociceptive reflexes of morphine given into the periaqueductal gray [13, 36, 89], the medial and paramedial medullary reticular formation [36] or glutamate, an excitatory neurotransmitter given into the periaqueductal gray or the medial and paramedial medulla [36] or electrical stimulation of brainstem [27], is significantly antagonized by alpha-adrenergic receptor antagonist. (Significantly, while the effect of brainstem morphine or stimulation on spinal reflex function is readily reversed by intrathecal antagonists, the reversal of the effects on supraspinal measures (hot plate) has not been readily shown. It has been speculated that this reflects the likelihood of a modification of the pain response of the supraspinal level [89].) More recently, selective studies have been carried out to examine the characteristics of the spinal alpha-adrenergic receptor which mediates the spinal antinociceptive effects of periaqueductal gray morphine. Figure 6 shows the rapid and reversible antagonism of the inhibitory effects of periaqueductal gray morphine on the tail flick reflex by yohimbine, and rauwolscine, but not corynanthine. As shown in Fig. 7, the antagonism by these agents is dose-dependent. Table 2 presents the rank order of antagonist potency of a series of intrathecally administered adrenergic antagonists. Significantly, the intrathecal administration of prazosin was observed to produce a significant inhibition of the effects of periaqueductal gray morphine, but its antagonist potency was equal to that of yohimbine. Ligand binding studies and bioassays have shown that prazosin has several orders of magnitude greater affinities for the $alpha_1$ than the $alpha_2$ receptors [70,76]. That it was no more active than yohimbine, argues that prazosin at these concentrations may be acting on a receptor for which it has a relatively low affinity, the $alpha_2$ site. The time of onset for prazosin antagonism was also on the order of 30 to 60 min in contrast to the rapid action of the yohimbine stereoisomers. This delayed onset does not appear to be due to supraspinal redistribution as comparable antagonism was not observed with intracisternal injections. The possibility that the antagonism reflects an action on more deeply lying systems in the spinal gray is a potential alternative. In any case, these lines of data clearly suggest that norepinephrine released from spinal terminals

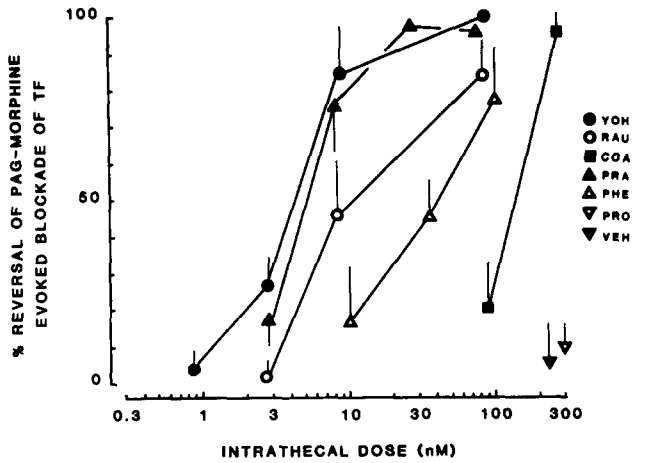

FIG. 7. Log dose response curves plotting the maximum percent inhibition of the periaqueductal gray morphine induced elevation in the tail flick response latency observed within 30 min after the intrathecal drug. Each point presents a mean and standard error of the percent inhibition measured in 4–6 animals. Yoh: yohimbine; Rau: rauwolscine; Coa: corynanthine; Pra: prazosin; Phe: phentolamine; Pro: propranolol; Veh: vehicle (Camarata and Yaksh [13]).

acts to alter nociceptive responses in intact and unanesthetized animals by a receptor which has a profile indistinguishable from that of the receptor activated by exogenously administered norepinephrine. In either case, the pharmacology of the spinal effects appears clearly to possess characteristics of an $alpha_2$ as well as an $alpha_1$ receptor.

MECHANISMS OF ACTIONS OF SPINAL ADRENERGIC AGONISTS IN PRODUCING "ANALGESIA"

As indicated above, there is ample evidence that the release of norepinephrine from spinal terminals and the application of alpha agonists will modify nociceptive transmission and produce "analgesia." An important question is whether this effect is mediated by a direct action on neuronal links in the pathway through which nociceptive information travels or by spinal interneurons which themselves modulate sensory processing. The iontophoretic effects of norepinephrine are not antagonized by naloxone [9,28] and the effects are not mimicked by iontophoretically applied GABA [28]. With regard to intrathecal administration, the effects of norepinephrine on hot plate and tail flick in the rat were not antagonized by methysergide, phentolamine, picrotoxin or strychnine [53]. These data suggest that spinal norepinephrine does not exert its effect through an opioid intermediary, or by the release of two potential inhibitory neurotransmitters in the spinal cord, GABA and glycine or indirectly through a local action on serotonergic terminals.

Given that the adrenergic receptors are known potentially to have significant effects on vascular tone, an important question is whether the effects of agents administered intrathecally onto the pial surface might result in significant changes in vascular reactivity which might produce selective anoxia in systems which are relevant to nociceptive transmission. This question was closely examined in the work of Reddy and colleagues [53], and it was found that the effects of intrathecal norepinephrine were not mimicked by a powerful vasoconstrictor (angiotensin II), nor were the effects of norepinephrine antagonized by vasodilators such as papaverine or bradykinin. These data are consistent with earlier observations which failed to observe any signs of constriction of cerebral pial vessels after the direct application of epinephrine and only slight constriction of large arteries following topical application [24,83]. Indeed, Weber [82] in 1904 presciently considered the importance of this possibility by reporting that adrenalin did not produce "blanching" of the spinal cord after topical application. It should moreover be noted that, with regard to the ability to produce a constriction of cerebral vessels, serotonin is far more powerful than norepinephrine [11,77], yet its antinociceptive potency after intrathecal administration is less than 2% that of intrathecal norepinephrine.

Thus, it appears likely that the effects of norepinephrine applied to the spinal cord are mediated directly on systems in which nociceptive information is processed and not indirectly by conventional neurotransmitter systems known to also powerfully modulate spinal function including opiates, GABA and glycine. The possibility that other endogenous interneuronal systems, such as neurotensin which are known to produce effects following intrathecal administration [94], cannot, however, be excluded.

INTERACTION OF ALPHA ADRENERGIC SYSTEMS WITH OTHER SPINAL MODULATORY SYSTEMS

Early data suggested that alpha agonists, such as clonidine, would potentiate the effects of morphine [66,69]. Recent studies of intrathecally administered $alpha_2$ agonists have indicated that there is a very significant shift in the opioid dose response curve by co-administered $alpha_2$ agonists such as ST-91, clonidine or norepinephrine [35, 81, 92] in mouse, rat and primate, respectively. Though it is possible that the $alpha_2$ agonists produced a significant alteration in the clearance of the opiate drug, this appears unlikely as the clearance of morphine from the intrathecal space is relatively slow and the effects of the alpha agonist are manifested immediately and do not reflect a simple increase in the duration of action. It is therefore speculated that there may be a synergistic interaction between $alpha_2$ receptors and opiates. It is interesting that where examined, opiates and alpha-adrenergic agonists tend to have comparable properties on neural systems; e.g., dorsal root ganglion cells [21]; dorsal horn neurons (see above); primary afferent excitability (see above). Tokymasa, Morita and North [78] observed that opiates and clonidine both prolong the afferent hyperpolarization observed in guinea pig mesenteric plexuses at doses considerably lower than those required to hyperpolarize the resting membrane. Such effects would effectively limit the frequency of activity of discharge in these neurons in the absence of any significant effect on resting potential. Nevertheless, it is clear that $alpha_2$ agonists do not act by an opiate receptor and morphine does not act by a clonidine receptor. Such observations are not supported by efforts to antagonize intrathecal morphine with phentolamine or intrathecal alpha agonists with naloxone [53, 54, 92], or by cross tolerance studies. Thus, Yaksh demonstrated that in primates rendered tolerant to intrathecal morphine there was no loss of response to the intrathecally administered ST-91 (but see [52]). We have thus speculated that this interaction between $alpha_2$ receptors and opiates reflects a synergistic interaction. It is significant that earlier studies directed at investigating the spinal and supraspinal actions of opiates, observed that supraspinal opiates would synergize with the effects of spinal opiates in altering the nociceptive threshold. This speculative hypothesis put forth

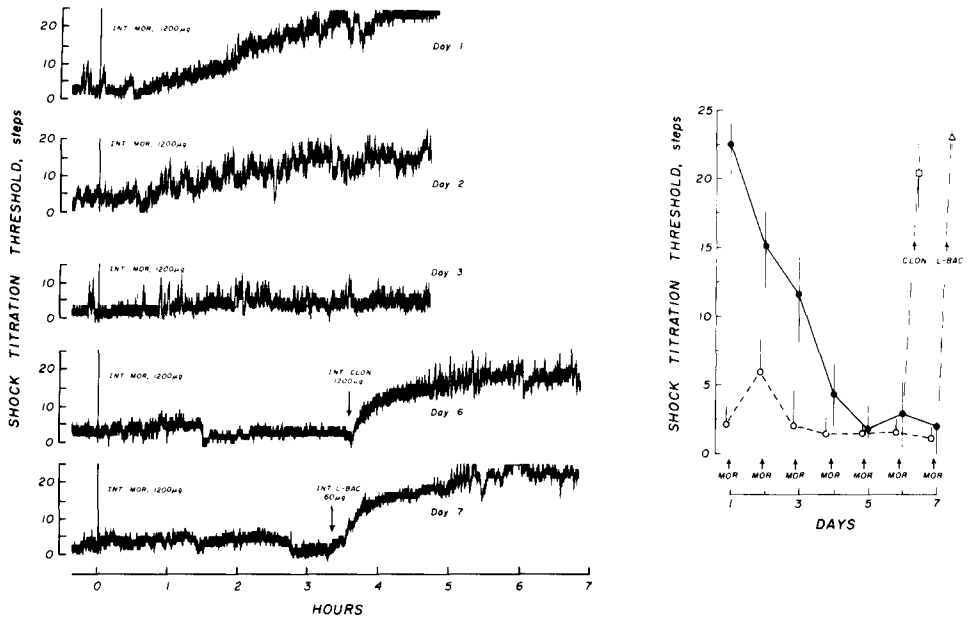

FIG. 8. (Left) Titration threshold records obtained in one animal following the daily intrathecal injection of 1200 μg of morphine sulfate, intrathecally, at the time indicated by the solid line. As described in the text, injections were made daily over a 7-day period; the representative changes in the titration threshold for days 1, 2, 3, 6 and 7 are presented. On day 6 the animals received intrathecal clonidine (2000 μg) and on day 7 intrathecal L-baclofen (60 μg), at the times indicated by the arrows. The animal weighed 5.1 kg. (Right) This shows the mean±SE of the shock titration threshold in three animals following the daily intrathecal injection of morphine sulfate (●=1200 μg) as indicated by the arrow. The open circles (○) indicate the effects produced in the same animals in a pre-experimental run where the animals received equivalent daily intrathecal injections of saline. The arrows on day 6 and 7 indicate the effects of intrathecal administration of clonidine (□=2000 μg) and L-baclofen (△=60 μg) on days 6 and 7, respectively, following the intrathecal administration of 1200 μg of morphine [92].

by Yaksh and Rudy [93] was based on the observation that the effects of systemically administered morphine on hot plate and tail flick tests could be shifted to the right by intrathecally or intracerebrally administered naloxone. Toward the right side of the dose response curves, further shifts could not be produced, suggesting that an action on opiate receptors in either the brain or the spinal cord was adequate at high doses to produce analgesia. Subsequently, it was shown that the dose response isobols for intraventricular and intrathecal morphine were non-linear, suggesting that there was a non-linear interaction between the effects of morphine at supraspinal (after intraventricular injection) and spinal (intrathecal) actions of morphine [97]. Given the literature that some of the effects of brainstem morphine may act on spinal function by the activation of descending noradrenergic pathways, it was a reasonable hypothesis to consider the likelihood that intrathecal alpha-adrenergic agents which mimic the activation of these descending pathways should synergize in a comparable fashion with intrathecally administered morphine. As described above, such synergy has indeed been noted. The important consideration evoking from the apparent synergy is that significant physiological effects (analgesia) can be achieved with doses of either agent which alone produce minimal receptor activation.

A second important consideration which arises from the synergy relates to the development of tolerance. Yaksh and Reddy [92] observed that in contrast to the rapid (3–5 days) loss of analgesia potency observed with intrathecal morphine in primates (see Fig. 8), equiactive dose combinations of morphine and ST-91 showed no apparent loss of activity over a 21-day period (see Fig. 9). They speculated that if the rate of tolerance development were proportional to the degree of receptor activation and if the adrenergic and opiate receptors were independent, then the ability to produce a long term analgesia was consistent with the minimum degree of activation of either receptor required concurrently to produce the maximum physiological effect. In other words, as the level of drug at the receptor is minimized, the rate of tolerance development at the receptor will be less for a given endpoint when the endpoint is achieved by two independent receptor systems being activated concurrently. It is significant that the ability to reverse the effects of combined alpha-adrenergic and opioid activity can be achieved with either naloxone or phentolamine alone ([92] T. L. Yaksh and G. Harty, unpublished observations). This suggests that the effect is indeed dependent upon the coactivation of the two sets of receptors and is not due to an alteration in clearance of one of the other drugs per se. This interesting interaction between these different classes of agents in the spinal cord is a subject of considerable interest and more work is clearly required.

ACTIVATION OF THE SPINAL ADRENERGIC SYSTEMS

Stimulation of brainstem sites which alter spinal function will facilitate the release of noradrenalin from spinal cord [27]. What naturally activates these spinopetal systems? Using the release of norepinephrine as an index of activity in

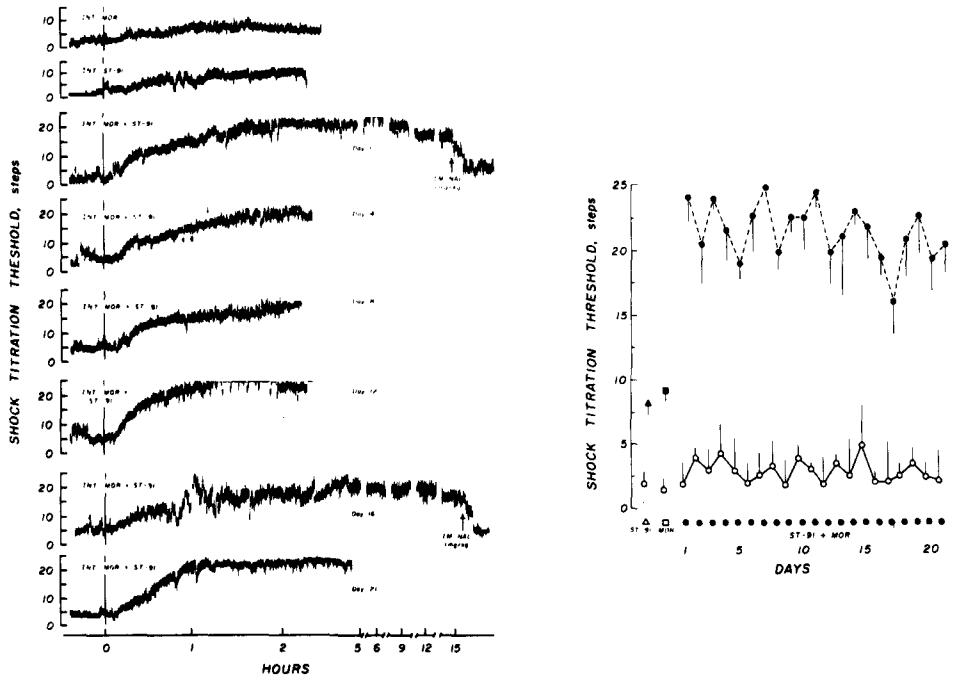

FIG. 9. (Left) Shock titration records obtained in one animal following the intrathecal injection of: morphine, 400 μg (record 1); ST-91, 1000 μg (record 2). Records 3–8 present the effects of the intrathecal administration of morphine (400 μg) concurrently with the intrathecal administration of ST-91 (1000 μg). These injections were made once daily for 21 days. Records 3–8 are representative results observed on days 1, 4, 8, 12, 16 and 21, respectively. In records 3 and 7, phentolamine (16 mg/kg) and naloxone (1 mg/kg), respectively, were administered intramuscularly at the times indicated by the arrows. The animal weighed 6.2 kg. (Right) This graph presents the effects of ST-91 (1000 μg=▲) or morphine (400 μg=■) administered intrathecally. Black circles (●) indicate the effects on the shock titration threshold of the concurrent administration of 400 μg of morphine and 1000 μg of ST-91 given repeatedly on days 1–21. The open circles (○) represent the effects of daily intrathecal administration of saline in a similar volume. Each curve represents the mean±SE of such an experimental series carried out in three separate animals [92].

adrenalin containing spinopetal systems, it has been demonstrated that stimulation of A-delta/C fiber volleys in the sciatic nerve will markedly increase the release of noradrenalin in cat spinal superfusates. This release possessed two interesting characteristics: (1) the spinal release evoked by sciatic nerve stimulation was attenuated by cervical cold block; and, (2) the spinal release could be evoked by stimulation of the infraorbital branch of the trigeminal nerve [79]. These observations point to the likelihood that small fiber input from the entire body surface can drive activity in spinofugal noradrenergic systems. These observations, however, are limited by our inability to determine from which spinopetal adrenergic terminal systems the release originated. As noted, spinopetal adrenergic systems can be distinguished not only in terms of location of cells of origin, but in terms of terminal regions as well. These observations, however, suggest a substrate for the observations of McCreary and Bloedel [50] that pinching the ear will inhibit spinothalamic neurons in the cat.

Vaginal probing has been shown to produce a significant increase in the nociceptive threshold of estrogenized rats [42]. Intrathecal alpha-adrenergic antagonists can significantly antagonize this effect [71]. Importantly, such studies have also indicated the probing gives rise to a significant elevation in spinal norepinephrine release.

In short, it appears on the basis of (1) the ability of intrathecal NA antagonists to block the antinociceptive effects of physiological stimuli which alter the nociceptive threshold; (2) the ability to activate NA release by these same manipulations; and (3) the comparable effects and pharmacology of intrathecally administered alpha agonists, that one possible function of the spinopetal noradrenergic systems is to modulate spinal sensory processing related to high intensity stimulation. Significantly, these descending systems appear activated by small fiber input. This led to the suggestion that these spinopetal systems are reflexly activated and serve to modulate the "gain" of the transmission system through which such information travels [79,91].

Several points, however, should be made. The above comments do not imply that this is the only role of the descending noradrenergic systems (see below) nor does it mean that these spinal noradrenergic terminals constitute an "antinociceptive system." As we have argued elsewhere [91], the selective inhibition of A-delta/C fiber stimulation in fact converts a polymodal wide dynamic range neuron (responding to A-beta/A-delta and C fibers) into a modality selective neuron responding only to A-beta input. Thus, these systems likely play a natural role in the coding of dorsal horn sensory processing allowing for the large number of polymodal neurons to be specifically coded for different mo-

dalities depending upon circumstances, in a way similar to a "user defined" computer keyboard.

It should be noted that while a significant proportion of the previous discussion has been directed at the topic of modulation of sensory transmission, notably that related to pain processing. The descending noradrenergic pathways play a significant role in modulating a variety of other functions. Based on anatomical distribution of descending catecholamine systems and the physiological effects on these systems when these receptors are functionally studied in these *in vitro* and *in vivo* preparations, it is clear that these systems exert significant modulatory effects on sympathetic preganglionic outflow and sacral parasympathetic outflow [86]. In addition, the significant terminations in the ventral horn and the powerful effects on motor horn activity demonstrated by intrathecal administration of alpha$_1$ agonists and the iontophoretic studies of norepinephrine on motor horn cells and motor horn nuclei interneuron systems, indicate that these systems no doubt play a powerful role in modulating motor horn function. The gross level of analysis thus far simply reflects powerful actions on motor horn excitability. Nevertheless, the likelihood that these systems modulate subtle controlling influences on organized motor horn function and synergy is an area of great interest [25].

It should be stressed that the diversity of spinal substrates which possess alpha-adrenergic receptors, precludes simple interpretations of function. These observations should also make us wary of interpreting a reflex function as being reflective of changes in sensory processing. It is never adequate to assess changes in nociceptive transmission simply on the basis of an observed inhibition of a spinal reflex such as the tail flick or the skin twitch. It should be stressed that the spinal reflex could be inhibited (1) by the blockade of sensory input, or (2) equally well by a direct effect on motor horn cells. Moreover, such a direct effect on motor horn cells need not be one of an inhibitory character. Thus, excitation of extensors or alteration of the synergy between motor neuron pools would result in an impairment of motor function and a subsequent increase in reflex latency which would be interpreted functionally as an "inhibition" of the tail flick reflex. There are, however, numerous published studies purportedly studying pain transmission in which the only end point examined is a spinal reflex (usually the tail flick).

In short, it appears however that alpha$_2$ agonists given intrathecally, can produce a powerful analgesia in the absence of any distinct effect on motor functions. The specific pharmacology of this effect and the clear evidence of functional interaction with other modulatory systems appear to suggest a promising future and potential role in clinical pain therapy.

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