ANTI-NOCICEPTIVE EFFECT OF TRICYCLIC ANTI-DEPRESSANTS FOLLOWING INTRATHECAL ADMINISTRATION

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SUMMARY

The anti-nociceptive effects of three tricyclic anti-depressants (desipramine, protriptyline, fluoxetine) were evaluated in mice following intrathecal administration. Nociceptive behavior was produced by intrathecal administration of Substance P and measured for 60 seconds following subcutaneous and intrathecal administration of vehicle and increasing doses of the drugs being tested. Systemically administered protriptyline produced dose related antinociception in this paradigm. A similar effect was seen following systemic desipramine; while fluoxetine was inactive systemically. Both protriptyline and desipramine given intrathecally were antinociceptive while fluoxetine had a biphasic effect, being analgesic only at low doses. These results indicate that tricyclic antidepressants may produce analgesia at the spinal level in rodents. This action may be related to the therapeutic success of tricyclic antidepressants in chronic pain syndromes.

The clinical use of tricyclic antidepressants in the treatment of chronic facial pain syndromes has been correlated with pain relief. This study evaluated the ability of tricyclic antidepressants to produce analgesia at the spinal and trigeminal nerve levels by blocking reuptake of norepinephrine and serotonin into nerve terminals of the ascending pain pathways. By studying the hypothesized analgesic effect of tricyclic antidepressants in the spinal cord, which is more easily accessible than the trigeminal system, one should be able to draw some inferences concerning their effects on the trigeminal system.

Pain and somesthetic sensation are subserved by peripheral somatic sensory nerves which terminate in the trigeminal nucleus and the dorsal horn of the spinal cord. The trigeminal nerve provides somatic sensory innervation to the head in the same way that the other peripheral nerves provide innervation to the spinal cord via the dorsal roots.[13] In effect they are homologs.[2]

It has been theorized that analgesia is produced at the spinal level via a descending system of pathways involving at least two neurotransmitters. One pathway travels from the periaqueductal gray (PAG) of the caudal midbrain, involving the nucleus raphe magnus (NRM), and descends via the dorsolateral funiculus to terminate in the dorsal horn. The neurotransmitter thought to mediate this transmission is serotonin (5-HT).[2,11,15] Similarly, when the locus coeruleus, located in the rostral pons, is stimulated, norepinephrine (NE) is released to the spinal dorsal horn with a resultant spinal analgesic effect. This descending pathway seems to be important in opiate-induced analgesia.[2,9]

Since depression often accompanies chronic facial pain, antidepressants have been used therapeutically in the clinical setting at times. Surprisingly, some patients report pain relief.[4] It has also been demonstrated in laboratory animals that certain tricyclic antidepressants (TCA's) enhance narcotic-induced analgesia.[1,10] The potential advantage of using antidepressants in place of opiates is that antidepressants lack the undesirable (opiate) side effects of tolerance and physical dependence. While the TCA's do have other undesirable side effects including blurred vision, dry mouth, constipation, and urinary retention, newer compounds are being introduced to minimize some of these effects. The demethylated analogs (e.g. amitriptyline, desipramine, protriptyline) are more potent in blocking NE reuptake while the methylated analogs (e.g. fluoxetine) are more potent 5-HT reuptake blockers.[5]

Clinically, severe facial pain often results from injury to the trigeminal nerve since it provides the main sensory innervation to the head.[12] The pain of trigeminal neuralgia and herpes zoster of the trigeminal ganglion, for example, is communicated via the trigeminal nerve. Also, it has been suggested there is a large representation of the tooth pulp in the more rostral parts of the trigeminal complex (main sensory and oralis nuclei).[3] Furthermore, the trigeminal serves as the motor nerve for the masticatory muscles. Since NE and 5-HT have been shown to provide analgesia at the spinal level it would seem reasonable that TCA's which block reuptake of these substances would provide analgesia.

It has been shown that alpha-adrenergic agonists such as NE administered to the spinal cord produced thermal analgesia[10] and inhibition of the response to

Substance P (SP) given intrathecally (i.t.),[9] a test of antinociception using SP as the chemical noxious stimulus. Likewise, serotonin administered i.t. in rats produced thermal analgesia and inhibition of the response to SP given i.t.[8] By studying the levels of antinociception produced by different TCA's administered either spinally or systemically, we sought to determine the relative importance of spinal and supraspinal sites of action.

METHODS

Nociception was produced in mice by i.t. SP injection, a chemically mediated noxious stimulus with a more complex behavioral response than the tail flick test.[7] When SP is injected i.t., a mouse will bite and scratch at its adbomen as if an irritant had been injected into the abdominal skin. Since some investigators had failed to see thermal reflex analgesia with TCA's, we reasoned the non-reflexive SP assay might reveal an analgesic effect not apparent in the reflexive assays. The technique of i.t. injection involves injecting a substance through the skin, between two lumbar vertebrae, through the meninges into the cauda equina.[6]

Two routes of administration for TCA's were used in this study, subcutaneous and intrathecal. The subcutaneous route was chosen to study the systemic effect of these drugs and the intrathecal route to study spinal action. Following i.t. injection of SP, biting and scratching behaviors were counted for 60 seconds. This time frame is sufficient to see SP action and assures that the peptide has not travelled to the brain and that the behaviors observed were the result of a spinal rather than cerebral response.

In the first series of experiments, groups of 6-10 male Swiss-Webster mice were injected subcutaneously with 10ml/kg of a 0.9% saline solution containing various amounts of the TCA as follows: protriptyline & desipramine — zero, 10mg/kg, 25mg/kg, 50mg/kg, 100mg/kg; fluoxetine — zero, 3mg/kg, 10mg/kg & 30mg/kg. After a period of 60-90 min, when the mice were minimally sedated, a dose of 10ng SP was injected i.t. and the number of characteristic behaviors (caudally directed biting and scratching) were counted for 60 seconds.

To study the spinal effect of these drugs, groups of 6-10 male Swiss-Webster mice were injected i.t. with the following doses of drugs: 5μl .01N HOAc in 0.9% saline (vehicle), 1.15μg 3μg 6μg and 12μg TCA along with 10 ng SP. SP behaviors were again counted for 60 seconds.

To evaluate the possible interaction between non-specific locomotor effects, locomotor behavior was also tested in an open field experiment. Mice were released individually onto a rectangular grid 25cm x 40cm containing 32 equal squares immediately after the i.t. injection and 60-90 minutes following the subcutaneous injection. Then the number of squares occupied by the mouse's hind feet were counted for 60 seconds.

RESULTS

Systematically administered protriptyline produced dose-related (3-25mg/kg) analgesia in the SP behavioral assay (Fig. 1). On the other hand, these mice were hyperactive in the locomotor function tests performed (52 vs 23 mean squares occupied, p<.01). A similar inhibitory effect on SP-induced behavior was observed with systemic desipramine (25mg/kg) but the effect was not as profound. Fluoxetine was inactive systemically.
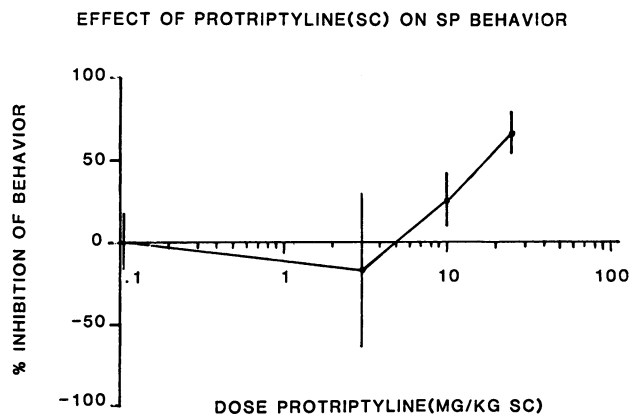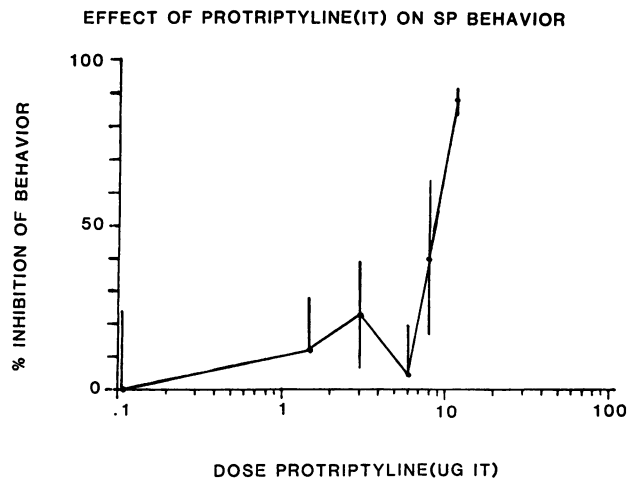
FIGURE 1

EFFECT OF PROTRIPTYLINE(SC) ON SP BEHAVIOR

DOSE PROTRIPTYLINE(MG/KG SC)

FIGURE 2

EFFECT OF PROTRIPTYLINE(IT) ON SP BEHAVIOR

DOSE PROTRIPTYLINE(UG IT)

Both protriptyline (Fig. 2) and desipramine given intrathecally inhibited SP behavior at a dose of 12μg. Protriptyline's effect was not accompanied by any motor deficits (data not shown). On the other hand desipramine's toxic effect was manifested by flaccidity of the hind limbs. Fluoxetine i.t. had a biphasic effect, being analgesic at the 1.25μg dose and having no effect at the 5μg dose (Fig. 3) on pooled biting and scratching data. Fluoxetine action was accompanied by increased scratching (43% vs 22% of total behaviors) relative to biting.

EFFECT OF FLUOXETINE(IT) ON SP BEHAVIOR

DOSE FLUOXETINE(UG IT)
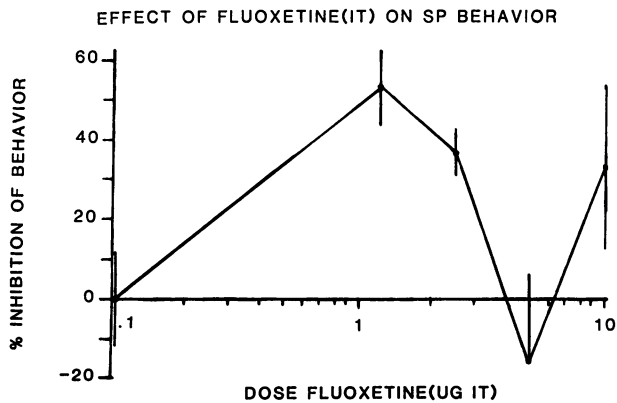
DISCUSSION

The TCA's with predominantly noradrenergic activity tested (desipramine and protriptyline) had an inhibitory action in the SP assay, which may indicate an analgesic effect. Hwang and Wilcox (unpublished observation) have reported that despiramine, is analgesic in the tail flick assay at 4µg (i.t.). This result in a thermal nociceptive assay supports the results reported here. The significance of this new information obtained from the SP assay is that it suggests TCA's may have an inhibitory effect on the ascending pain pathways. In contrast to relexive thermal assays (e.g. tail flick) where stimuli elicit action via a reflex arc, the SP assay incorporates complex behavior requiring transmission of afferent signals to the midbrain and thalamus.

The intrathecal action of the noradrenergic TCA's indicates a spinal site of action for these drugs. Protriptyline's effect was more selective than that of desipramine whose action was coincident with motor toxicity. Perhaps these TCA's ameliorate pain in humans by a similar action.

Fluoxetine's action intrathecally was interesting because it mimicked the action of intrathecal serotonin observed by Hylden and Wilcox.[8] This is not surprising since fluoxetine's action is primarily the result of blocking 5-HT reuptake at serotonin nerve terminals. In addition, we observed an almost two-fold increase in scratching behavior in agreement with the results of Hylden and Wilcox.[8]

In summary, these results indicate that TCA's, notably protriptyline and fluoxetine, may produce analgesia at the spinal level in rodents. Such an action may underly the successful therapeutic use of TCA's in chronic pain syndromes.

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