REVERSAL OF MORPHINE AND STIMULUS-PRODUCED ANALGESIA BY SUBTOTAL SPINAL CORD LESIONS

ALLAN I. BASBAUM *, NICHOLAS J.E. MARLEY, JOHN O'KEEFE and CHARLES H. CLANTON

Departments of Neurology, Physiology, and Anatomy, University of California, San Francisco, Calif. 94143 (U.S.A.) and Department of Anatomy, University College London, Gower Street, London WC1E 6BT (Great Britain)

(Accepted July 21st, 1976)

SUMMARY

This study examined the hypothesis that descending inhibitory pathways from brain stem to spinal cord mediate the analgesic effect of both electrical brain stimulation and morphine. In the first set of experiments, the effect of subtotal midthoracic spinal cord lesions on the analgesic effect of electrical stimulation in the periaqueductal gray matter of the rat was examined. In the second, the effect of similar cord lesions on the analgesic effect of intraperitoneal morphine was studied. In both cases, a lesion of the dorsal part of the lateral funiculus (DLF) reduced or abolished the analgesia of the hindlimbs. Analgesia of the forelimbs was unaffected. Lesions of the dorsal columns, which include the corticospinal tract, or lesions of the ventral part of the lateral funiculus had no effect on analgesia. It is concluded that an inhibitory pathway, which descends in the dorsal part of the lateral funiculus and which probably originates in the nucleus raphe magnus of the medulla, mediates the descending control found in both morphine and stimulus-produced analgesia.

INTRODUCTION

The recent demonstration of a morphine-like analgesic compound in mammalian brain [14,15,25,32,34] strongly supports the hypothesis that there is an endogenous system involved in pain modulation. Electrical stimulation of certain brain stem and diencephalic sites produces profound analgesia [1,3,
Furthermore, many of these sites are anatomically coextensive with brain regions rich in opiate-binding substances [32] and are sensitive to locally injected opiate analogs [7,24,38].

Earlier investigations suggest that part of the analgesic action of both morphine and stimulus-produced analgesia (SPA) depends on descending connections from supraspinal centers to the spinal cord. For example, electrical stimulation in the periaqueductal gray (PAG) which produces analgesia also blocks flexor withdrawal reflexes [19]. Electrophysiological studies have demonstrated that PAG stimulation inhibits spinal dorsal horn neurons in the cat [12,22], and Satoh and Takagi have shown that spinal transection disrupts morphine’s action on splanchnic-evoked ventral quadrant responses [30].

The present studies were undertaken to test the hypothesis that both SPA and opiate analgesia depend on descending connections to spinal cord. To this end, the effects of lesions of various spinal cord pathways on the analgesic properties of morphine and brain stimulation were examined. A preliminary report of this work has been published [6].

METHODS

Female albino rats weighing between 200 and 250 g were used in both brain stimulation and morphine studies. The rat was chosen for these studies because most subtotal spinal cord lesions can be made without impairing the rat’s normal response to nociceptive stimuli [4]. Furthermore, since the corticospinal tract in the rat is isolated in the ventral part of the dorsal columns [39], selective destruction of different descending pathways is more feasible.

Surgical procedures

Surgical procedures for SPA were performed under a fluothane, nitrous oxide, oxygen anesthetic mixture. Bipolar electrodes (250 µm diameter insect pins, insulated except for a 500 µm conical tip) were implanted bilaterally in each rat, using stereotaxic coordinates taken from the atlas of König and Klippell [16]. Trains of 50 Hz sine waves lasting 100 msec were presented at a rate of 3 trains/sec. Current intensities for the production of analgesia ranged from 20 to 1000 µA.

Subtotal cord lesions were made in 8 of the rats implanted for brain stimulation. A laminectomy of the appropriate vertebra (usually T3) was performed. The dura was then reflected, and the lesions made by crushing portions of the spinal cord with jeweler’s forceps. A lesion of the ventral part of the lateral funiculus required slight rotation of the cord. To achieve this, a blunt instrument was placed on the exposed lateral surface, and the cord was rotated away from the side of the lesion. Finally, a piece of Gelfoam was placed over the exposed cord, and the muscle and overlying skin were sutured. Four rats in the SPA series underwent a second cord lesion at T3.

Sixteen rats in the morphine series underwent cord surgery. Ten rats had unilateral cord lesions, all at T3 (Table II). Four animals underwent simulta-
neous bilateral lesions, also at T3. In two rats, serving as sham-operated con-
trols, a laminectomy was performed at T3, the dura was opened, but no cord
lesion was made.

**Evaluation of analgesia**

Analgesia was evaluated by observing the response to application of a
toothed alligator clip before, during, and after brain stimulation or morphine
sulfate administration *.

The response to the clip was graded as follows: **+ = a complete response,
as found in non-analgesic animals, with vocalization, rapid localization of the
clip, and vigorous attempts to remove it; + = a reduced response — in these
cases, some aspects of the response were present, but the affective compo-
nent of the response was significantly reduced or absent; and 0 = absence of
these responses to the clip. The latter constituted complete analgesia. Each
of the 4 limbs was tested separately.

All tests in the morphine series were performed double blind. Since there
is some variability in the effective dose for analgesia, an appropriate test dose
was established prior to surgery. After a one week postoperative recovery
period, the effects of the cord lesions on the analgesic properties of mor-
phine were assessed. The rats were tested every other day, both before and
after morphine administration, beginning with the preoperatively established
dose. Because tolerance to morphine developed rapidly, the number of post-
operative tests was less than for the SPA studies.

Rats in the SPA series were also tested for self-stimulation. A bar was
introduced into the test box, which the rat could press to self-administer
brain stimulation. Only the presence or absence of self-stimulation and thresh-
old currents were established. All electrodes which produced analgesia also
supported self-stimulation at thresholds slightly lower or equal to those for
analgesia.

**Histology**

After all tests were completed, the rats were anesthetized with "Equi-
thesin" and perfused intracardially with buffered isotonic saline followed by
10% formol—saline. The brain and spinal cord were removed. Electrode tip
positions in the midbrain were established by the gliosis at the electrode site,
as seen in 60 μm frozen sections stained with cresyl fast violet. Serial 30—50
μm frozen sections containing the spinal lesions, as well as the neighboring

---

* This is a reliable noxious stimulus which always elicited pain when applied to the experi-
menters and elicits a predictable response from normal rats including behavior mediated
by supraspinal structures, in addition to spinal withdrawal reflexes. Because of the reli-
ability of the response, the presence or absence of analgesia could be assessed by a single
brief application of the noxious stimulus and the number of applications could be kept to
the minimum. To further minimize discomfort to the animal, the clip was removed or, where
appropriate, the analgesic brain stimulation was begun immediately after the onset
of the response.
Fig. 1. Photomicrographs of representative lesions. On the left are 3 examples of lesions of the dorsal part of the lateral funiculus, in two cases, with involvement of the dorsal columns. On the right side are: top: a bilateral lesion of the dorsal columns; middle and bottom: a small and large lesion of the ventral part of the lateral funiculus, respectively. Cresyl fast violet.
RESULTS

(1) Stimulus-produced analgesia

Electrode placements which produced profound analgesia were concentrated within or adjacent to the dorsal raphe of the midbrain (Fig. 2). Because of the electrode arrangement, analgesia was usually obtained from one or the other of the bipolar electrodes in the assembly, but not both. In 3 animals, one pair was located within the dorsal raphe, and the second was outside the PAG (P16, 20, 23). In 3 animals, both electrodes produced anal-

Fig. 2. Reconstruction of electrode tip locations illustrated on appropriate frontal planes from the stereotaxic atlas of König and Klippell [15]. Circles represent electrode sites where stimulation produced profound analgesia of the 4 limbs. The effects of spinal cord lesions on SPA were studied in these rats (Table I). Squares represent electrode sites where SPA was not equally profound over the 4 limbs. Triangles represent sites from which stimulation failed to produce analgesia.

rostral and caudal segments from the spinal cord were cut and the tissue stained with cresyl fast violet. Every tenth section was stained with solochrome cyanide for normal myelin. The lesions were plotted onto schematics from appropriate levels of a normal rat cord. Photomicrographs of representative lesions are shown in Fig. 1.
gesia, but they were not equally effective (P10, 17, 22). In some animals, the analgesia was equally profound over all 4 limbs but, in others, only the hind-limb ipsilateral to the effective electrode showed strong analgesia. Analgesia appeared within seconds of stimulus onset and sometimes outlasted stimulation for several minutes. In agreement with previous studies [19], most negative sites (triangles, Fig. 2) were found more rostrally and laterally.

Only 8 of these rats (Fig. 2, circles) were chosen for spinal lesions. Brain stimulation did not disrupt the behavior of these 8 rats. They explored novel objects, ate normally, and did not show abnormal motor patterns which may arise with electrode placements situated more ventrally, near the decussation of the superior cerebellar peduncle. Furthermore, analgesia in these rats was equally profound over both fore- and hindlimbs. All behavioral responses to the clip, including flexor withdrawal reflexes, were abolished. Therefore, any changes in the analgesia of the hindlimbs after midthoracic cord lesions could be studied while complete analgesia of the forelimbs was maintained.

Fig. 3 Diagrams of spinal cord lesions from rats in the SPA series. Hatched lines indicate total extent of lesion reconstructed from superimposed serial sections.
TABLE I
EFFECTS OF CORD LESIONS ON ANALGESIC PROPERTIES OF BRAIN STIMULATION

Abbreviations: DLF = dorsal part of lateral funiculus; DC = dorsal columns; VLF = ventral part of lateral funiculus; RT = right; LT = left.

<table>
<thead>
<tr>
<th>Rat</th>
<th>Cord lesion</th>
<th>Degree of response to noxious stimulus **</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LT fore</td>
</tr>
<tr>
<td>P10</td>
<td>RT DLF (T3)</td>
<td>0</td>
</tr>
<tr>
<td>P16</td>
<td>RT DLF (T3)</td>
<td>0</td>
</tr>
<tr>
<td>P17</td>
<td>RT DLF (T3)</td>
<td>0</td>
</tr>
<tr>
<td>P22</td>
<td>RT DLF (T3)</td>
<td>0</td>
</tr>
<tr>
<td>P18</td>
<td>RT DLF (T3)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>LT DLF (T8) *</td>
<td>0</td>
</tr>
<tr>
<td>P19</td>
<td>Bilat. DC (T3)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>RT VLF (T8)</td>
<td>0</td>
</tr>
<tr>
<td>P20</td>
<td>RT DC (T8)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>LT Lissauer tr. (T8)</td>
<td>0</td>
</tr>
<tr>
<td>P23</td>
<td>LT DC (T3)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>LT DLF (T8)</td>
<td>0</td>
</tr>
</tbody>
</table>

* This lesion was performed after analgesia had returned to right and left hind limbs.
** ++ = full response, no analgesia; + = reduced response, moderate analgesia; 0 = no response, complete analgesia (see text).

Thus, the forelimbs of each animal served as control for disruption of analgesia observed in the hindlimbs.

Response of operated rats. One to 2 weeks after surgery, the animals were retested for self-stimulation and analgesia. None of the surgical procedures affected the normal response to the clip. In unstimulated rats, the only detectable difference between the fore- and hindlimb response was a slight difficulty in localizing the clip ipsilateral to a unilateral lesion of the dorsal part of the lateral funiculus (DLF). In the latter cases, the animal vocalized and usually explored both hindlimbs until the clip was located, at which time the animal made vigorous attempts to remove the clip.

Self-stimulation was never altered by a spinal cord lesion (Fig. 3). In contrast, certain cord lesions produced a marked reduction of the analgesic effect of brain stimulation (see Table I). A unilateral lesion of the dorsal part of the lateral funiculus, ipsilateral to the effective stimulating electrode, completely abolished analgesia of the hindlimb caudal and ipsilateral to the cord lesion (P10, 16, 17, 18, 22). During PAG stimulation, application of the clip to the hindlimb ipsilateral to the DLF lesion elicited the response seen in the non-stimulated animal, including vocalization and attempts to remove the clip or attempts to escape from the test box. Flexor withdrawal reflexes were also seen in the ipsilateral hindlimb.

In all cases, the contralateral hindlimb showed a slight reduction of analgesia. Vocalization was not always present, and the distress produced by the
clip was much less than for the ipsilateral limb. Analgesia of the forelimbs was unaffected by any thoracic cord surgical procedures.

Lesions of the dorsal columns (DC) were performed in 3 rats and did not interfere with the analgesic effect of brain stimulation (P19, 20, 23). These lesions sever the corticospinal tract, which lies in the ventralmost part of the dorsal funiculus. Thus, the corticospinal tract is not a necessary component of the descending inhibitory action of analgesia-producing brain stimulation. These 3 rats with lesions sparing the DLF served as controls for possible disruptive effects of the surgery itself on SPA.

The latter 3 rats underwent a second operation, ipsilateral to the first lesion and 5 segments caudal (T). Unilateral section of the DLF (P23) abolished the SPA in the ipsilateral hindlimb, confirming the previous 5 cases. In contrast, disruption of analgesia was not produced by a subsequent section of Lissauer’s tract (P20) or of the ventral part of the lateral funiculus (VLF) (P19).

The disruptive effects of DLF section on SPA subsided somewhat with time. After 2 months, partial return of analgesia was found in 3 of the 5 rats with unilateral DLF lesions (P10, 16, 17). In another, P18, there was complete return of analgesia within 7 weeks. No differences between the two hindlimbs or between fore- and hindlimbs were then detectable. No apparent relationship between the size or locus of the lesion and the return of analgesia was found. To test whether contralateral descending fibers mediated the return of analgesia in P18, a second DLF section was performed at T, contralateral to the first. The second operation, however, failed to disrupt the analgesia.

(2) Morphine analgesia

In the normal rat, with few exceptions, approximately 3–5 mg/kg i.p. morphine abolishes all the behavioral responses to the alligator clip within 15–30 min after administration. In some animals, analgesia is associated with a paucity of movement, however, an effective dose can be established which produces analgesia without signs of generalized nervous system depression. The rats continue to explore the test box and respond to noises or objects placed in the visual field. After an appropriate morphine dose was established for each rat, the animals were subjected to various spinal cord lesions (see Methods). Reconstructions of these lesions are shown in Fig. 4.

Table II summarizes the results from 14 rats. Ten rats had unilateral lesions at T, and two rats were sham controls (M1, 4). Of the 4 rats that had bilateral lesions at T, only two (M13, 16) are included in Table II. In two rats (M14, 15), the lesions encompassed the lateral funiculi on both sides and disturbed the normal pattern of response to the clip, making adequate assessment of morphine’s effect impossible.

Unilateral lesions of the cord, which included the dorsal part of the lateral funiculus (M2, 3, 7, 8, 9, 10), significantly reduced or eliminated the analgesic effect of morphine in the limbs caudal to the lesion. The loss of analgesia was not consistently restricted to the ipsilateral hindlimb (Table II). In
Fig. 4. Diagrams of spinal cord lesions from rats in the morphine series. Hatched lines indicate total extent of lesion reconstructed from superimposed serial sections. All lesions in morphine series were made at T3.

3 rats (M2, 7, 8), a reduction in analgesia over both hindlimbs was observed. In all cases, the analgesia of the forelimbs was maintained.

A sufficiently large dose of morphine (20–25 mg/kg) produced analgesia of both the fore- and hindlimbs, indicating that the antagonistic effects of a DLF lesion can be overcome. This observation is consistent with studies which have demonstrated a direct spinal cord action of morphine [17,37] which may be independent of its supraspinal effects.

With repeated testing, tolerance to morphine developed. By the fourth or fifth session, up to 20 mg/kg was required to obtain analgesia of the forelimbs. Nevertheless, the reduction or loss of analgesia in the hindlimbs was still demonstrable.

Lesions of the dorsal columns, either unilateral (M6) or bilateral (M11), did not interfere with the analgesic effect of morphine on the hindlimbs. This implies that the loss of analgesia in rats with combined DC-DLF lesions is not attributable to the DC involvement. If the VLF was extensively damaged (M12), the response to the clip after morphine was quite variable. Signs
TABLE II
EFFECTS OF CORD LESIONS ON ANALGESIC PROPERTIES OF MORPHINE

<table>
<thead>
<tr>
<th>Rat</th>
<th>Cord lesion *</th>
<th>Degree of response to noxious stimulus **</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LT fore</td>
</tr>
<tr>
<td>M2</td>
<td>RT DLF</td>
<td>0</td>
</tr>
<tr>
<td>M3</td>
<td>LT DLF</td>
<td>0</td>
</tr>
<tr>
<td>M7</td>
<td>LT DLF</td>
<td>0</td>
</tr>
<tr>
<td>M9</td>
<td>LT DLF</td>
<td>0</td>
</tr>
<tr>
<td>M8</td>
<td>LT DC + DLF</td>
<td>0</td>
</tr>
<tr>
<td>M10</td>
<td>LT DC + DLF</td>
<td>0</td>
</tr>
<tr>
<td>M11</td>
<td>Bilat. DC</td>
<td>0</td>
</tr>
<tr>
<td>M6</td>
<td>LT DC</td>
<td>0</td>
</tr>
<tr>
<td>M12</td>
<td>RT VLF (large)</td>
<td>0</td>
</tr>
<tr>
<td>M5</td>
<td>RT VLF (small)</td>
<td>0</td>
</tr>
<tr>
<td>M13</td>
<td>Bilat. DLF</td>
<td>0</td>
</tr>
<tr>
<td>M16</td>
<td>Bilat. DLF</td>
<td>0</td>
</tr>
<tr>
<td>M1</td>
<td>Sham-operated</td>
<td>0</td>
</tr>
<tr>
<td>M4</td>
<td>Sham-operated</td>
<td>0</td>
</tr>
</tbody>
</table>

* All lesions performed at T3. Abbreviations as in Table I.

of agitation with occasional vocalization were sometimes present; at other times, analgesia was complete. In contrast, a small VLF lesion (M5) had no effect on the analgesic effect of morphine. No changes in the analgesic effects of morphine were seen in the two sham-operated rats.

As described above, the effect of unilateral DLF section in the morphine series, although comparable to that in the brain stem stimulation series, did not consistently produce total loss of analgesia in the hindlimbs. Since morphine's action is bilateral, while brain stem stimulation was unilateral, we examined the effects of bilateral DLF section. Four rats had bilateral cord lesions at T3. Two of these (M13, 16) had lesions restricted to the DLF which did not interfere with the normal response to the clip. No analgesic effect of morphine on the hindlimbs could be demonstrated despite complete analgesia of the forelimbs. A comparable antagonistic effect of bilateral lesions of the DLF on the analgesic action of morphine using the tail-flick test in the rat has recently been found [13].

As mentioned above, the blockade of SPA in the hindlimbs by DLF lesions faded with time. Because of the rapid tolerance which developed to morphine, we did not test for a comparable reappearance of the analgesic effect of morphine after DLF lesions.

DISCUSSION

Although ascending mechanisms cannot be ruled out, these data provide considerable support for the hypothesis that both morphine and stimulus-
produced analgesia are mediated by descending systems which act on the spinal cord. Furthermore, the possibility that both morphine and SPA operate on a common neural substrate is strengthened by the comparable effects of DLF section on both analgesic agents. Unilateral DLF section had a more disruptive effect on the analgesia induced by unilateral PAG stimulation than on morphine analgesia. However, bilateral DLF section completely abolished the analgesic action of i.p. morphine on the hindlimbs. Since i.p. morphine must activate brain stem neurons bilaterally, it is, therefore, not unexpected that bilateral DLF section was required.

Since a direct projection from PAG to spinal cord via the DLF has not been described, it is likely that an indirect projection via a more caudal site mediates the descending inhibition. Using fluorescent-histochemical techniques, Dahlström and Fuxe [10] described a descending monoaminergic fiber system which originates in the caudal medulla and which courses, in part, in the dorsal part of the lateral funiculus. Since SPA and morphine analgesia have been correlated with serotonin levels in the brain and spinal cord [12,36] and since both are antagonized by prior administration of p-chlorophenylalanine [1,2], an inhibitor of serotonin synthesis, these serotonergic fibers in the DLF may subserve descending analgesic mechanisms.

The cells of origin of this descending serotonergic pathway lie in the midline raphe nuclei of the medulla [33]. A component of this system, the nucleus raphe magnus (NRM), has recently been implicated in SPA and morphine analgesia. Stimulation in NRM is a powerful analgesic agent in cats [23] and rats [21] and lesions of NRM antagonize the analgesic action of morphine [26]. Inhibition of spinal neurons responding to noxious stimulation by NRM stimulation has also been reported [11,17]. We have recently demonstrated that NRM stimulation in cats inhibits cells in both laminae I and V which respond to noxious stimulation, and that section of the DLF significantly reduces or abolishes this inhibitory action. NRM stimulation has no effect on cells in lamina IV which respond only to innocuous stimulation [11]. Taken together, these data offer a physiological correlate for the effects of DLF section on morphine and SPA described in this paper. It appears that DLF section reverses the analgesic effect of morphine and electrical stimulation, at least in part, by disrupting the inhibitory action of NRM on dorsal horn cells which respond to noxious stimulation.

The anatomical substrate for this inhibition has been more precisely characterized [5]. Tritiated leucine was injected into NRM of cats and its descending projections studied with standard autoradiographic techniques. A dense projection is present in laminae I, II, and V of spinal dorsal horn, with a smaller projection to IV. Fibers from NRM course to the dorsal horn in the DLF, lateral to the corticospinal tract and medial to the dorsospino-cerebellar tract. In light of Dahlström and Fuxe's work [10], it is reasonable to expect that a similar projection of NRM to dorsal horn is present in the rat.

These data, however, do not suggest that NRM is the primary site of action of morphine or electrical stimulation. The original demonstration of
SPA was from the PAG [27], and this has been confirmed by subsequent studies [19]. The PAG is also a major locus for opiate receptor sites [25,32]. Tritiated morphine is found by autoradiographic analysis to accumulate in the PAG [35], and intracerebral microinjection of morphine is particularly effective in the PAG [24,38]. It appears likely, therefore, that the direct effect of morphine and electrical stimulation occurs on cells in the PAG-dorsal raphe, which in turn excite cells in NRM.

A direct anatomical projection from ventral PAG to NRM has recently been described in the cat [29], although it was not seen in the rat [8]. In preliminary physiological studies in the cat, we have found short latency excitation of cells in NRM from PAG stimulation. This suggests that an oligosynaptic circuit from PAG to spinal cord, via NRM, may underlie both SPA and morphine analgesia.

When SPA was first demonstrated, there was a suggestion that the concomitant rewarding effects of the brain stimulation produced an apparent analgesia. Certainly, many brain sites which support analgesia also support self-stimulation, an index of the rewarding properties of brain stimulation. Cox and Valenstein [9], however, demonstrated that rats do not prefer brain stimulation to the same stimulation coupled with foot shock, which suggested that an active suppression of the noxious stimulus had occurred. Later, Mayer and Liebeskind [18] demonstrated that many sites which did not support self-stimulation did produce analgesia. In fact, some sites that were effective for analgesia were exclusively aversive. Since testing for a response to a noxious stimulus during aversive brain stimulation is not feasible, the latter result was initially overlooked. However, if the rat was tested in the poststimulation period, when the aversive effects had disappeared, powerful and prolonged analgesia was discovered. In the present study, self-stimulation was unaffected by spinal cord lesions but analgesia of the hindlimb was abolished. It can be concluded that, despite overlapping sites for effective self-stimulation and SPA, the two phenomena can be completely dissociated.

ACKNOWLEDGEMENTS

We thank Professors P.D. Wall and H.J. Ralston, and Dr. H.L. Fields for help in generating this study and in preparation of this manuscript. We also thank Ms. S. Davis, Ms. M. Liu, Ms. L. Alberiri, and Mr. D. Akers for excellent technical assistance.

Supported by the SRC and MRC (England) the Foundations’ Fund for Research in Psychiatry, and by P.H.S. Grants NS70777, NS11529, NS05272, and NS11614.

REFERENCES

6 Basbaum, A.I., Marley, N. and O'Keefe, J., Effects of spinal cord lesions on the analgesic properties of electrical brain stimulation, Advanc. in Pain Res., in press.
10 Dahlström, A. and Fuxe, K., Evidence for the existence of monoamine neurons in the central nervous system. II. Experimentally induced changes in the intraneuronal amine levels of bulbo-spinal neuron systems, Acta physiol. scand., 64, Suppl. 247 (1965) 5–36.
14 Hughes, J., Isolation of an endogenous compound from the brain with pharmacological properties similar to morphine, Brain Res., 88 (1975) 295–306.
32 Snyder, S.H., Opiate receptor in normal and drug altered brain function, Nature (Lond.), 257 (1975) 185–189.
37 Yaksh, T.L. and Rudy, T.A., Analgesia mediated by a direct spinal action of narcotics, Science, in press.