The effect of analgesic doses of morphine on regional cerebral glucose metabolism in pain-related structures

ROBERT M. LEVY, HOWARD L. FIELDS, MICHAEL P. STRYKER and MARY M. HEINRICHER

Departments of Neurological Surgery, Physiology and Neurology, School of Medicine, University of California, San Francisco, California (U.S.A.)

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The effect of morphine on regional cerebral glucose metabolism was measured in rats using high resolution \[^{14}\text{C}]2\text{-deoxyglucose autoradiography} with concurrent confirmation of morphine-induced analgesia measured by tail-flick latency to noxious heat. Within the limits of resolution of this technique, doses of morphine sufficient to inhibit the tail-flick reflex had no significant effect on glucose metabolism in structures implicated in the modulation of pain.

While the antinociceptive effect of morphine is well-known, a direct effect of this opiate on glucose metabolism in regions of the central nervous system implicated in pain modulation has not been well-characterized. While the effects of morphine on regional cerebral glucose metabolism (RCGM) have been reported\(^9,11\), behavioral testing was not used to confirm morphine analgesia. Results obtained for RCGM during activation of pain-modulating systems by electrical stimulation of the periaqueductal gray may not be comparable with the effects of systemically administered morphine\(^4\). In the experiments reported here, we used tail-flick (TF) latency to noxious heat in rats to document morphine analgesia concurrently with measurement of RCGM in pain-related structures.

Fourteen adult male Sprague-Dawley rats were anesthetized with pentobarbital (50 mg/kg, ip) and jugular venous and femoral arterial and venous catheters were placed. Body temperature was maintained at 38 °C with a circulating water pad. Rats were maintained in a lightly anesthetized state using a continuous infusion of methohexital (15-30 mg/kg/h, iv), which prevented spontaneous movement and signs of discomfort but allowed TF responses at stable latencies. TF latency was tested by focusing a projector lamp onto the blackened ventral surface of the rat's tail. A thermistor probe placed in contact with the tail provided the signal for feedback control of the heat stimulus. TF usually occurred 3-4 s after the onset of heat. If no TF occurred, the heat was turned off at 10 s to prevent tissue damage.

After stable TF latencies were obtained, either morphine sulfate (MS) (5 mg/kg, iv) or saline was administered; Levine et al.\(^10\) have shown that this dose of morphine induces profound analgesia without significant sedation. TF testing was repeated 2 min after administration of MS or saline; in all rats injected with MS, TF increased to cutoff. \[^{14}\text{C}]2\text{-deoxyglucose} (100 \mu\text{Ci/kg, 56 mCi/mmol, Amersham CFA562, iv}) was then administered by continuous infusion over 15 min. Isotope was not administered by bolus injection\(^13\) because of evidence\(^2,6\) that some morphine-sensitive cells in the rostral ventral medulla undergo spontaneous cycles of activity that last up to several minutes. Infusion for an extended period produced a prolonged period of availability of tracer in plasma; therefore, values of RCGM should reflect glucose utilization averaged over several cycle times for these cells. Arterial blood samples were obtained.

Correspondence: R.M. Levy, c/o The Editorial Office, Department of Neurological Surgery, 1360 Ninth Avenue, Suite 210, San Francisco, CA 94122, U.S.A.
Fig. 1. A: Nissl-stained section taken through the rostral rat medulla that shows the nucleus paragigantocellularis and nucleus raphe magnus. B: [$^{14}$C]2-deoxyglucose autoradiograph of the section shown in A. Despite the high resolution of this technique, no focal areas of increased [$^{14}$C]2-deoxyglucose uptake are seen after morphine administration.
The effect of morphine on regional cerebral glucose metabolism

Values are expressed as (RCGMregion/RCGMcerebellum) × 100 and S.E.M.

<table>
<thead>
<tr>
<th>Region</th>
<th>Control</th>
<th>Morphine</th>
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<tbody>
<tr>
<td>N. reticularis paragigantocellularis</td>
<td>93.8 ± 3.7</td>
<td>86.4 ± 1.9</td>
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<tr>
<td>N. raphe magnus</td>
<td>87.6 ± 3.5</td>
<td>81.9 ± 2.6</td>
</tr>
<tr>
<td>N. reticularis gigantocellularis</td>
<td>88.6 ± 3.8</td>
<td>82.8 ± 1.8</td>
</tr>
<tr>
<td>Facial nerve nucleus</td>
<td>97.6 ± 5.1</td>
<td>91.0 ± 3.1</td>
</tr>
<tr>
<td>Trigeminal nerve nucleus</td>
<td>90.0 ± 3.8</td>
<td>85.0 ± 1.3</td>
</tr>
<tr>
<td>Pyramidal tract</td>
<td>59.4 ± 3.4</td>
<td>62.2 ± 2.7</td>
</tr>
<tr>
<td>Superior olive</td>
<td>136.6 ± 10.6</td>
<td>129.9 ± 6.1</td>
</tr>
<tr>
<td>Periaqueductal gray</td>
<td>99.5 ± 5.6</td>
<td>92.0 ± 3.3</td>
</tr>
<tr>
<td>Midbrain reticular formation</td>
<td>90.2 ± 4.4</td>
<td>85.1 ± 2.6</td>
</tr>
<tr>
<td>Inferior colliculus</td>
<td>115.1 ± 4.8</td>
<td>107.9 ± 2.2</td>
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These findings are consistent with the results of a number of studies that showed acute morphine administration had no specific effect on the RCGM of structures implicated in the mechanisms of morphine analgesia. Sakurada et al. found diffuse decreases in RCGM of rats after 5–30 mg/kg of morphine was administered. In more detailed studies, this group found that doses of 1.0 or 2.5 mg/kg of morphine had no effect on RCGM measured 1 h after administration of the opiate. Administration of 5.0 mg/kg of morphine caused changes in RCGM of the substantia nigra, mammillary body and medial division of the lateral habenular nucleus, but had no effect on RCGM overall. Hiesiger et al. measured RCGM 10 min after administration of 5.0 mg/kg of morphine and found that while there was a diffuse decrease in RCGM, a statistically significant reduction in RCGM was found only in the medial thalamus and habenula.

Because the antinociceptive effects of morphine were not documented in animals in which RCGM was measured in any of these studies, it is possible that either profound sedation or a failure to produce analgesia in all morphine-treated animals may have obscured any effect of morphine in pain-related structures. In a study of the effects of electrical stimulation of the periaqueductal gray on RCGM in rats, Beitz and Buggy documented analgesia before determination of RCGM. They found increases in RCGM in nucleus reticularis paragigantocellularis, the ventral portion of the nucleus reticularis giganto-cellularis and nucleus cuneiformis, and in the spinal trigeminal nucleus and the substantia gelatinosa. Their data are difficult to evaluate, however, and
electrical stimulation may have had a non-specific effect on RCGM. Moreover, the effects of morphine and electrical stimulation of the periaqueductal gray on RCGM may not be comparable. In the experiments reported here, RCGM was measured during behaviorally documented morphine-induced analgesia. We found no statistically significant changes in RCGM in the midbrain periaqueductal gray, the nucleus raphe magnus, or in the nucleus reticularis paragigantocellularis.

It was shown recently that different classes of cells in the rostral ventral medulla in the region of the nucleus raphe magnus have predictable and differential changes in spontaneous discharge and, presumably, metabolic rate after administration of morphine systemically. Although these populations of cells in the rostral ventral medulla are either activated or inhibited by systemic morphine under the exact conditions of this experiment, we observed no changes in RCGM in this region after morphine administration.

Values for RCGM reported here were measured for regions delineated on Nissl-stained sections; there was no obvious anatomical compartmentalization with respect to the effects of morphine on neuronal activity. Moreover, direct measurement of RCGM from the autoradiographs provided no evidence that morphine altered metabolic activity in small, discrete regions of the rostroventral medulla. Electrophysiologic experiments have not determined whether neurons excited by morphine are concentrated in areas that are larger than the limit of resolution of our autoradiographic technique, which is calculated to be greater than 100 μm. Thus, regions in which RCGM is increased after administration of morphine may be so small that they were not detected with this technique. It is also not clear whether the metabolic activity of these neurons, measured at their somata, is closely coupled to their discharge frequency; close coupling may be the rule in cerebral cortex, but there appear to be some exceptions for brainstem neurons.

It is also probable that cells in the rostral ventral medulla that are either activated or inhibited by morphine administration are not spatially segregated; thus, despite profound effects on individual morphine-sensitive neurons, there may be no overall effect on RCGM. Results of our previous studies suggest that it is unlikely that the population of morphine-sensitive cells in the rostral ventral medulla is so small that significant stimulation of these cells is not sufficient to alter the overall RCGM in these areas.

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