β-Endorphin-like immunoreactivity increases in human lumbar cerebrospinal fluid following routine metrizamide myelography

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Much interest has recently been focused on the possible role of the endogenous opiates in the perception of pain in humans. Several investigators have examined the levels of these substances in human cerebrospinal fluid (CSF) in attempts to identify the mechanisms by which electrical stimulation of the brain might induce analgesia. Most of these CSF samples were collected at the time of ventriculography or myelography. In the present study, the levels of β-endorphin in the CSF of 22 patients undergoing myelography were examined before and after the injection of a contrast agent. β-Endorphin increased an average of 356% (p < 0.0005) 15 to 20 minutes following the injection of contrast material into the lumbar subarachnoid space. Thus, routine myelography may have a profound effect on the levels of β-endorphin measured by radioimmunoassay in human CSF, and great care must be taken in interpreting the significance of changes seen in β-endorphin levels in CSF collected from patients at the time of myelography or ventriculography. The effect of the injection of contrast material on β-endorphin immunoreactivity must be distinguished from the postulated effects of any analgesia-inducing therapy.

KEY WORDS • cerebrospinal fluid • neurochemistry • opiates • myelography • pain • periaqueductal gray matter

The discovery of endogenous opiate-like substances in the brain has raised many questions concerning the possible role of these peptides in the perception of pain. Recently, attempts have been made to treat chronic pain syndromes with electrical stimulation of parts of the brain thought to be rich in these endogenous opiates. Reynolds first reported the induction of potent analgesia in the rat by stimulation of the periaqueductal gray matter. Subsequently, many investigators have demonstrated the effectiveness of electrical stimulation of the periventricular gray (PVG) matter for the relief of chronic pain syndromes in humans.

Recent work has suggested that the analgesic effect may be mediated by the release of endogenous opiates. The pain relief induced by the electrical stimulation of PVG has been reported to be totally reversed by the specific opiate antagonist, naloxone. Intraventricular administration of β-endorphin produces a prolonged analgesic effect in humans. Stimulation of the PVG has been reported to be effective only in patients who are responsive to narcotics, and tolerance to PVG stimulation-induced analgesia results in cross-tolerance to morphine analgesia.

Much of the evidence suggesting that the endogenous opiates might mediate the analgesic effects of PVG stimulation comes from the levels of β-endorphin measured in human cerebrospinal fluid (CSF) before and after stimulation. Hosobuchi, et al., found a 60% to 260% increase in levels of β-endorphin in the CSF 15 minutes after cessation of PVG stimulation. Akil, et al., reported greater than a 10-fold increase in levels of β-endorphin in the CSF 10 to 15 minutes after the cessation of PVG stimulation. Both these studies involved the collection of CSF at the time of electrode placement. The CSF was collected before and after the injection of contrast agents through a ventricular catheter. Very little work has been done to investigate normal levels of β-endorphin in the CSF of humans.

We have examined serial CSF samples from 22 patients before and after metrizamide myelography to see how this procedure might affect the levels of β-endorphin measured by radioimmunoassay.
**Clinical Material and Methods**

The 22 patients included individuals undergoing myelography for a variety of diagnoses. These are shown in Table 1. The study involved nine men and 13 women, with an average age of 44 years.

The CSF was obtained in 2-cc samples immediately after placement of the spinal needle in the lumbar subarachnoid space. These samples were immediately frozen on dry ice. Metrizamide (Amipaque, 10 to 15 cc) was then injected into the lumbar subarachnoid space of each patient. Between 15 and 20 minutes after the injection of metrizamide, a second 2-cc sample of CSF was collected and frozen on dry ice. The samples were then stored at -90°C until they were assayed.

β-Eendorphin was assayed with a radioimmunoassay kit.* This assay has a 50% cross-reactivity with β-lipotropin, and less than 0.01% cross-reactivity with α-endorphin, leucine enkephalin, methionine enkephalin, and α-MSH (melanocyte-stimulating hormone).

**Results**

The results are shown in Table 2. All 22 patients exhibited a rise in β-endorphin levels in CSF 15 to 20 minutes following metrizamide myelography. The mean levels of β-endorphin were 37.9 ± 3.11 pg/ml (standard error of the mean) before and 173 ± 20.62 pg/ml after injection of contrast material. The increase ranged from 23.6% to 1209%, with a mean increase of 356.4%. The magnitude of the increase in β-endorphin level did not correlate with the patient’s age or sex. The increases seen were somewhat higher in the three patients with spinal stenosis (average 903%) and somewhat lower in the four patients with spinal cord tumors (average 186%).

**Discussion**

In this study, we found increases in the levels of β-endorphin measured in humans 15 to 20 minutes after metrizamide myelography as compared with baseline levels. This increase was found in all 22 patients investigated. All the myelograms were performed with metrizamide as the contrast material. These results suggest that metrizamide myelography produces a significant rise in β-endorphin immunoreactivity as measured by radioimmunoassay 15 to 20 minutes after the addition of the contrast material.

There are several possible mechanisms by which myelography may result in elevated β-endorphin immunoreactivity in the CSF. The myelogram itself may actually induce higher levels of β-endorphin in the CSF. One of the components of the contrast medium may either induce the release of β-endorphin or inhibit its breakdown. Similarly, the transient physical stress produced by withdrawing CSF and injecting metrizamide into the lumbar subarachnoid space may affect the production or metabolism of β-endorphin.

Another possibility is that the rise in β-endorphin immunoreactivity seen after myelography may be an artifact in the assay, and does not represent a true change in the level of β-endorphin. Several lines of information suggest that this may be the true mechanism. The rise in β-endorphin was seen in all 22 patients regardless of age, diagnosis, medications, or the pain associated with their condition. The increases were seen within 15 minutes of the injection of metrizamide, and represented huge increases of several hundred percent. Finally, recent work in this laboratory (unpublished data) suggests that metrizamide, as well as several other contrast agents, produces an increase in β-endorphin levels as measured by radioimmunoassay when added to samples of CSF after myelography. The possible

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* Radioimmunoassay kit manufactured by New England Nuclear, 549 Albany Street, Boston, Massachusetts.
mechanisms of this interaction are currently being investi-gated.

Many investigators have examined levels of β-endorphin in human CSF in attempts to identify the mechanisms by which various methods of analgesia work. Almost all of these studies have used CSF samples that have been gathered following the injection of contrast medium during myelography or ventriculography. No attempts were made to isolate the possible effects of electrical stimulation of the brain and injection of contrast material on β-endorphin immunoreactivity. The eight patients in the series of Hosobuchi, et al., and Akil, et al., showed an average increase of 882%, with a range of 58% to 1900% in β-endorphin levels following ventriculography and stimulation of the PVG. These increases are similar in magnitude to those we found in 22 patients following metrizamide myelography. Thus, the increase of β-endorphin measured in human CSF may be a nonspecific effect of the injection of contrast agents in the CSF. The levels of β-endorphin measured may have little to do with concomitant interventions designed to alleviate the perception of pain. We conclude that great care must be taken in evaluating the significance of elevated levels of β-endorphin as measured by radioimmunoassay in human CSF during ventriculography or myelography, especially when positive contrast agents are used. The effects of the injection of contrast medium must be distinguished from the postulated effects of any analgesia-inducing therapy.

References


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