Current Concepts of Cerebrovascular Disease — Stroke

Opiate Antagonists in the Treatment of Stroke

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DURING the past two years the rapidly growing experimental and clinical literature on the use of opiate receptor antagonists (e.g., naloxone) in the treatment of stroke has produced conflicting findings and generated a considerable degree of controversy. Some of the interlaboratory differences may have resulted from differences in methodology or design: for example, choice of species, ischemic model, or treatment dose in the experimental studies or in patient population and dose schedule in the clinical studies. Much of the present confusion may also result from a trivialization of the complexities of endogenous opioid systems or of the mechanism of action of opiate antagonists. The purpose of the present report is to summarize some of these complexities, to review critically both the experimental and clinical studies, and to suggest a more rational approach for future studies in this area.

Endogenous Opioids and Opiate Receptors

Since the discovery of the opiate receptor in 1973 and of the first endogenous ligands for these receptors in 1975, there have been rapid developments in the opioid field. Five distinct classes of opiate receptors have now been identified within the central nervous system, termed μ, δ, κ, σ, and ε. In addition, there is increasing experimental support for the idea of isoreceptors, that is, opiate receptor subtypes for the various opiate receptor classes. For example, some evidence has been demonstrated for multiple μ receptors subtypes (μ₁, μ₂), as well as for multiple κ receptors subtypes. Paralleling the expansion in the number of identified opiate receptors has been an equally rapid expansion in the number of identified endogenous opioid substances (endorphins).

Three of these classes of opioids have been proposed as the endogenous ligands for specific receptors: (1) β-endorphin for the κ receptor, (2) enkephalins for the δ receptor, and (3) dynorphin for the κ receptor. Each of these three classes of opioids has a distinct pharmacological profile and a distinct distribution within the central nervous system and derives from a distinct prohormone. In addition, fragments of some of these opioids exist with pharmacological activity and tissue concentrations which differ from the larger peptide. Given this complexity of opioid systems and receptors, it becomes meaningless to talk about generic endorphin effects. Moreover, opiate antagonists may have variable effects and affinities for the various opiate receptor populations, thereby complicating the interpretation of results obtained with a given antagonist.

Opiate Antagonists

A number of opiate antagonists have been produced by modifying potent opiate alkaloids. One of the earliest and most utilized of these compounds is naloxone. Naloxone has been termed a specific opiate receptor antagonist and has been used for many years as a tool to infer the actions of endogenous opioids. However, naloxone is not a specific opiate receptor antagonist. At some doses and under certain conditions, it may have some agonist properties. Moreover, while naloxone has preferential action at the μ or morphine receptor, in higher doses it can antagonize effects at the other opiate receptors. Moreover, at high doses it has a number of properties which may not be opiate receptor mediated, including effects on calcium flux and lipid peroxidation; at high doses it may also have potent anti-GABA (gamma aminobutyric acid) activity.

Other potent opiate antagonists have been produced with different pharmacological properties (Table 1). Among the most utilized have been (1) naltrexone, a μ-selective antagonist which is orally efficacious and which possesses a longer half-life than naloxone but which has more agonist properties; (2) ICI 154,129, a δ-selective antagonist; (3) WIN 44,441-3, an antagonist which is selective for the κ and μ receptors; (4) β-funaltrexamine (β-FNA), an antagonist highly selective for the μ receptor; and (5) naloxonazine, an antagonist selective for the μ receptor. Stereo-isomers (the mirror-image form of some of these antagonists have also been produced) possess no activity at the opiate receptor and, therefore, may be used to provide further evidence for a receptor mechanism of action.

Opiate Antagonists in Stroke: Experimental Studies

Because of the beneficial effect of naloxone in experimental spinal injury, particularly its ameliorative effect on spinal cord flow, a number of groups have examined the therapeutic effects of this opiate antagonist in experimental stroke (Table 2). Hosobuchi et al. first reported the beneficial effect of naloxone on neurological function following common carotid occlusion in the gerbil. In this model approximately 40% of gerbils developed contralateral hemiplegia; naloxone at a dose of 1 mg/kg administered intraperitoneally was reported to reverse the hemiplegia in each of 10
TABLE 2 Naloxone in Stroke (Experimental Studies)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Species</th>
<th>Model</th>
<th>Dose</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hosobuchi et al. 20 1982</td>
<td>Gerbil</td>
<td>Permanent CCA occlusion</td>
<td>1 mg/kg ip or 10 mg ip pellets</td>
<td>+ (Improved function)</td>
</tr>
<tr>
<td>Holaday, D'Amato 21 1982</td>
<td>Gerbil</td>
<td>Permanent CCA occlusion, bilateral temporary CCA occlusion</td>
<td>5 mg/kg iv</td>
<td>- (No effect on function)</td>
</tr>
<tr>
<td>Kastin et al. 22 1982</td>
<td>Gerbil</td>
<td>Permanent CCA occlusion</td>
<td>0.1, 1.0, and 10.0 mg/kg ip</td>
<td>- (No effect on function)</td>
</tr>
<tr>
<td>Levy et al. 23 1982</td>
<td>Gerbil</td>
<td>Permanent CCA occlusion</td>
<td>1.0 mg/kg ip</td>
<td>- (No effect on function or pathology)</td>
</tr>
<tr>
<td>Faden et al. 24 1982</td>
<td>Dog</td>
<td>CCA air embolization</td>
<td>2 mg/kg iv plus 2 mg/kg hr infusion</td>
<td>+ (Improved CSER and CBF)</td>
</tr>
<tr>
<td>Levy et al. 25 1982</td>
<td>Cat</td>
<td>Permanent MCA occlusion</td>
<td>2 mg/kg iv</td>
<td>+ (Improved function)</td>
</tr>
<tr>
<td>Dullien et al. 28 1982</td>
<td>Rat</td>
<td>Spontaneous stroke prone</td>
<td>1.0 mg/kg ip</td>
<td>+ (Reduced hyperirritability)</td>
</tr>
<tr>
<td>Baskin et al. 26 1982</td>
<td>Baboon</td>
<td>Permanent MCA occlusion</td>
<td>4.7 mg/kg iv</td>
<td>+ (Improved function)</td>
</tr>
<tr>
<td>Zabramski et al. 27 1983</td>
<td>Baboon</td>
<td>Permanent MCA occlusion</td>
<td>5 mg/kg iv</td>
<td>+ (Improved function; decreased pathology)</td>
</tr>
<tr>
<td>Nehls et al. 30 1983</td>
<td>Monkey</td>
<td>Permanent MCA occlusion, temporary MCA occlusion</td>
<td>10 mg/kg iv plus 10 mg/kg hr infusion</td>
<td>- (No change in function, CSF, or pathology)</td>
</tr>
<tr>
<td>Faden et al. 29 1983</td>
<td>Rabbit</td>
<td>Spinal ischemic injury</td>
<td>2.0, 10.0 mg/kg iv injections X 4</td>
<td>+ (Improved function)</td>
</tr>
</tbody>
</table>

Abbreviations: MCA = middle cerebral artery; CCA = common carotid artery; CSER = cortical somatosensory evoked response; CBF = cerebral blood flow.

animals so treated. Unfortunately, three independent groups (Holaday and d’Amato, 21 Kastin et al.,22 and Levy et al.23) failed to replicate these results in the gerbil, even though they utilized similar methods and treatment schedules.

In contrast to the experiments in the gerbil which collectively failed to support the beneficial effect of naloxone, naloxone therapy has proved effective in a variety of other models.24-29 We have shown that naloxone administered one hour after air embolization of the carotid artery in the dog significantly improves the cortical sensory-evoked response and limits the multifocal areas of critically low blood flow characteristic of this model.24 Hosobuchi’s laboratory has reported that naloxone treatment improves neurological function following middle cerebral artery occlusion in the cat25 and baboon.26 Similarly, Zambramski et al27 have found improved function as well as less pathological change following middle cerebral artery occlusion in the baboon. Dullien et al28 have noted that naloxone treatment reduced the hyperirritability characteristic of early stroke in stroke-prone rats fed a high salt diet.

Recently, we have shown that naloxone treatment improves functional recovery in a rabbit “spinal stroke” model produced by temporary aortic occlusion.29 Of the non-gerbil studies only one has failed to show a beneficial effect of naloxone: Nehls et al.30 did not find significant effects on neurological function, blood flow, or histopathology with naloxone treatment administered to monkeys subjected to either permanent or temporary middle cerebral artery occlusion. However, in this study there did appear to be a trend in favor of naloxone-treated animals; thus, the lack of significant beneficial effects may have resulted from an inadequate sample size.

Some of the interlaboratory differences with regard to naloxone’s therapeutic effects may have resulted from methodological differences. For example, most of the experimental studies demonstrating a beneficial effect have utilized doses of naloxone in the range of 2 to 5 mg/kg administered intravenously. In contrast, Nehls et al utilized a dose of 10 mg/kg followed by infusion with 10 mg/kg/hr. This high dose of naloxone has proved less effective than a dose of 2 mg/kg following experimental shock in the rat.31 Similarly, we recently demonstrated that naloxone doses of 10 mg/kg
are less effective than a dose of 2 mg/kg following ischemic spinal cord injury in the rabbit (manuscript in preparation). Thus, as shown in experimental shock and experimental spinal cord injury, naloxone effects appear to be optimal at a dose between 2 and 5 mg/kg. These dose requirements are orders of magnitude higher than those utilized in clinical studies reported to date.

Opiate Antagonists in Stroke: Clinical Studies

Baskin and Hosobuchi\textsuperscript{32} initially reported that naloxone treatment at a dose of 0.4 mg (approximately 0.006 mg/kg) reversed the functional neurological deficit in two patients with cerebral ischemia and diminished level of consciousness following intraoperative procedures but was not effective in another patient with radiographically demonstrated cerebral infarction. Three subsequent studies have found minimal to no beneficial effect for low dose naloxone treatment in human stroke\textsuperscript{33-35} (Table 3). Bredesen et al.\textsuperscript{33} showed no effect of naloxone at doses between 0.4 and 0.8 mg iv in ten unselected patients with stroke, including six patients with ischemic cerebral infarction, one with hemorrhagic infarction, two with intracerebral hemorrhage, and one with subarachnoid hemorrhage. Most of these patients were treated many hours to as long as two weeks after initiation of the stroke. Jabaily and Davis\textsuperscript{34} noted some functional recovery after naloxone treatment in three of seven patients with cerebral ischemia or infarction, treatment being given between 4 and 36 hours after the cerebral event at a dose of 0.8 to 1.2 mg iv. The neurological deficit returned within one hour of drug administration in two of the three patients showing some response. Finally, Fallis et al.\textsuperscript{35} evaluated naloxone in a double-blind trial with 15 patients (14 with cerebral infarction) and found no beneficial effects with regard to neurological function. Patients were treated between 8 and 60 hours after onset of symptoms with a dose of 0.4 to 4.0 mg.

It should be noted that each of these clinical studies was performed on patients many hours after onset of neurological deficit, using doses far below any shown to have a beneficial effect in experimental animals. Given these facts, it is perhaps not surprising that clinical studies to date have not been impressive. What is clearly required are controlled studies in highly selected patients with acute ischemia of relatively short duration (probably less than eight hours), employing naloxone doses in the range which has proved effective for experimental animals. Since such doses have never been demonstrated to be safe in humans, a Phase I trial of naloxone is necessary to establish the safety of the drug at doses which may be therapeutically effective.

Unresolved Questions

Although the weight of experimental evidence supports a beneficial effect for naloxone (at high doses) in stroke, the mechanism by which naloxone exerts its therapeutic effects is as yet unknown. Whether the high doses required reflect actions at non-\(\mu\) opiate receptors or from nonopiate actions of the drug, such as effects on lipid peroxidation or calcium flux, remains to be determined. One approach would be to compare the therapeutic effects of receptor-selective opiate antagonists. We have begun such studies and have found that the \(\delta\) selective antagonist ICI 143,129 was not effective after "spinal stroke" in the rabbit, thus suggesting that naloxone’s beneficial effects in this model are not mediated by \(\delta\) receptors.\textsuperscript{36} Another important question is whether naloxone has direct effects on the cerebral microcirculation. An important first step would be to determine whether opiate receptors or endogenous opioids are found on cerebral vessels or whether cerebral vessels are sensitive to administration of selected opioids.

Conclusions

The weight of experimental evidence to date suggests that at high doses (2 to 5 mg/kg) naloxone is effective in improving physiological variables or functional recovery following acute cerebral ischemia. In contrast, the limited clinical literature to date has not been impressive, in part because of poor selection of patients, lack of early treatment, and use of inadequate doses. Utilization of newer and more selective opiate antagonists will help to define the mechanism of action of opiate antagonists in cerebral ischemia, as well as to suggest development of more specific pharmacological strategies. Given the high doses of naloxone which are likely to be required in human stroke, widespread use of this drug for stroke should be deferred pending outcome of phase I studies and controlled clinical trials.

References

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