Evaluation of Delayed Treatment of Focal Cerebral Ischemia With Three Selective \(\kappa\)-Opioid Agonists in Cats

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Background and Purpose The purpose of this study was to determine the therapeutic efficacy of three \(\kappa\)-opioid agonists used for delayed treatment of experimental focal cerebral ischemia.

Methods Forty halothane-anesthetized cats underwent permanent occlusion of the right intracranial internal carotid, middle cerebral, and anterior cerebral arteries via a transorbital, microsurgical approach. Six hours after occlusion, animals received a blinded bolus injection, and a subcutaneous osmotic pump was implanted to provide continuous release for 7 days. The injection and pump contained either saline or one of three \(\kappa\)-agonists: dynorphin (1-13), U-50,488, or DuP E3800. Survival, neurological function, tissue damage, and brain weight were assessed.

Results As a group, \(\kappa\)-agonist–treated animals had higher survival \((P<.02)\), less tissue damage \((P<.02)\), and lower brain weight \((P<.05)\) than saline controls. U-50,488 more effectively improved survival \((P<.03)\) than dynorphin \((P<.07)\) or E3800 \((P<.07)\). Each of the three \(\kappa\) compounds improved tissue damage (dynorphin, \(P<.02\); U-50,488, \(P<.05\); E3800, \(P<.05\)). Greater improvement in neurological function was seen after treatment with dynorphin \((P<.05)\) than with U-50,488 \((P<.6)\) or E3800 \((P<.7)\). The only significant reduction in brain weight was seen after dynorphin treatment \((P<.01)\).

Conclusions Compounds that act at the \(\kappa\) subclass of opiate receptors are effective in increasing survival, improving neurological function, and decreasing tissue damage and edema in a cat model of focal cerebral ischemia. The current study provides support for the benefits of treatment of acute cerebrovascular ischemia with \(\kappa\)-opioid agonists. The agents may prove to be of superior clinical utility because of efficacy even when administered 6 hours after the onset of stroke. (Stroke. 1994;25:2047-2054.)

Key Words • brain edema • cerebral ischemia, focal • opioid receptors • cats

A prominent difficulty with the clinical treatment of stroke is the extended time often present between the onset of the ischemic insult and patient presentation.\(^1\) Successful experimental agents whose therapeutic action necessitates pretreatment or administration within minutes after the onset of ischemia may not be amenable to widespread patient application, a situation in which presentation is frequently as long as 4 to 6 hours after the onset of stroke.

Treatment with opioid compounds may tolerate such a time lag. In a paradigm involving initiation of drug treatment at 6 hours after occlusion, dynorphin, a putative endogenous \(\kappa\)-receptor agonist, has been shown to reduce neurological deficit and increase length of survival in a feline model of focal cerebral ischemia.\(^2\) In 1986, Silvia and Tang\(^3\) demonstrated that the \(\kappa\)-opioid agonist U-50,488 had protective effects following focal cerebral ischemia when treatment was initiated 4 hours after occlusion. Birch et al.\(^5\) beginning treatment 6 hours after occlusion, recently showed that...
Animals were carefully evaluated every half hour on the day of surgery until the late evening hours (at least 12 hours after occlusion). No investigator was aware of which animals received the IP bolus or osmotic pump. Immediately after each pump placement, the animal was given an intraperitoneal bolus injection. Both the pump and bolus injection contained identical compounds. Animals were carefully evaluated every half hour on the day of surgery until the late evening hours (at least 12 hours after occlusion), again starting in the early morning of the next day, and several times daily thereafter. Antibiotics and fluids were administered daily.

We anticipated that animals showing signs of postoperative pain or distress would be treated with analgesics, and those animals whose pain did not subside after treatment would be killed. Vocalizations, agitation, irritability, and hyperreactivity were our initial indicators of pain or distress. We also assessed heart rate by palpation over the chest wall. Because the animals did not exhibit signs of distress, we did not find it necessary to measure physiological variables such as blood pressure. No animal required analgesics or euthanasia because of pain or distress, and all were carefully observed and assessed with this specific concern in mind.

**Table 1. Treatment Groups**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>IP Bolus</th>
<th>Osmotic Pump</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>0.4 mL/kg</td>
<td>10 μg/h</td>
</tr>
<tr>
<td>Dynorphin</td>
<td>2.0 mg/kg</td>
<td>50 μg/h</td>
</tr>
<tr>
<td>U-50,488</td>
<td>0.5 mg/kg</td>
<td>400 μg/h</td>
</tr>
<tr>
<td>E3800</td>
<td>0.0025 mg/kg</td>
<td>1.0 μg/h</td>
</tr>
</tbody>
</table>

Animals received one of the four treatments beginning 6 hours after occlusion.

**Reagents**

The compounds tested were dynorphin A (1-13), U-50,488, and DuP E3800. Dynorphin, a putative endogenous agonist at κ-receptors, was manufactured at Peninsula Laboratories. U-50,488 (trans-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzeneacetamide methane sulfonate hydrate) has been used extensively as a selective κ-agonist and has greater than 60-fold selectivity for the κ₁-receptor over the κ₂, κ₃, or μ-receptor subtypes. E3800 ([±]-trans-3,4-dichloro-N-methyl-2-[(1-pyrrolidinyl-1-yl)-6-hydroxy-1,2,3,4-tetrahydronaphth-1-yl]benzeneacetamide, phosphate), the phosphate salt of DuP X7648, is greater than 20-fold more selective for the κ over the μ-receptor subtypes and is 40-fold more potent than U-50,488 in behavioral assays.

**Surgery**

Forty male cats weighing 2.5 to 7.0 kg were sedated with 11 mg/kg ketamine hydrochloride combined with 0.03 mg/kg atropine and anesthetized with 4% halothane by mask until endotracheal intubation was performed. Thereafter, anesthesia was maintained with 1.1% halothane in oxygen. The animals were ventilated with a Harvard respirator, with volume and rate set to maintain arterial Pco₂ near 35 mm Hg. Body temperature was monitored with a rectal probe and normothermia maintained with a heating pad. One milliliter of Combiotic (200 000 U penicillin G per 0.5 g dihydrostreptomycin) was administered intramuscularly before surgery and daily thereafter.

The head of each cat was immobilized in a head holder. After a lateral canthotomy and removal of the conjunctiva, the globe was incised and its contents evacuated. Using both unipolar and bipolar electrocautery, the orbital contents were exenterated. Working under magnification using the operating microscope, the optic foramen was enlarged with a high-speed drill and the dura incised. The bifurcation of the internal carotid artery, forming the middle cerebral and anterior cerebral arteries, was identified and dissected free of arachnoid. The three arteries and all of their branches were permanently occluded by bipolar coagulation for a distance of 2 mm from their junction. After coagulation, the three arteries were transected with microscissors to ensure complete occlusion. The orbit was filled with methyl methacrylate cement, and the orbital skin was sutured closed. Concurrently, a small incision was made in the lumbar region, and a subcutaneous pocket was created for later placement of an Alzet osmotic minipump.

Each animal was assigned to one of four treatment groups (Table 1). The optimal drug doses were determined in previous dose-response trials. No investigator was aware of which animals were assigned to which groups. Each treatment group contained 10 cats. At 6 hours after occlusion, the animal was again anesthetized with 4% halothane by mask. An Alzet 2-mL, 10-μL/h osmotic minipump was placed into the lumbar subcutaneous pocket. Immediately after each pump placement, the animal was given an intraperitoneal bolus injection. Both the pump and bolus injection contained identical compounds.

For assessment of the amount of tissue damage, two categories of tissue damage were identified: fully stained (healthy) and abnormally stained (damaged). Photographic slides of each face of each section were taken within 1 week of staining.

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**Statistical Analyses**

We examined the effects of κ-agonist treatment as a whole compared with vehicle as well as the relative efficacy of each compound. All data except survival are expressed as mean ± SEM. The probability of survival was analyzed using Fisher's exact test.
TABLE 2. Neurological Assessment

A. Motor Function
10: Normal gait 100% of the time, no deficit
9: Normal gait >80% of the time
8: Normal gait >50% of the time, moderate hemiparesis, may stumble or slide
7: Normal gait <50% of the time, walks for short distances
6: Barely walks, moderate hemiparesis, momentary weight bearing
5: Unable to walk, slight weight bearing on paws but not on footpad for slight forward movement
4: Unable to walk, slight weight bearing on paws with no forward movement
3: Unable to walk, severe hemiparesis, limb movement but no weight bearing or forward movement
2: Unable to walk, extremely severe hemiparesis, limb movement barely perceptible
1: Unable to walk, hemiplegia

B. Forepaw
7: Normal function
6: Weight bearing, placed normally >50% of the time, may slide or rest on metacarpals
5: Weight bearing, placed abnormally, placed on metacarpal
4: Briefly weight bearing, slips out
3: Non-weight bearing, moves well
2: Barely moves, hemiparesis
1: No movement, hemiplegia

C. Hindpaw
6: Normal function
5: Weight bearing, placed normally, may slide or rest on metacarpals
4: Briefly weight bearing, slips out
3: Non-weight bearing, moves well
2: Barely moves, hemiparesis
1: No movement, hemiplegia

D. Circling
5: Normal, no circling
4: Intermittent circling
3: Broad circling
2: Broad to tight circling
1: Tight circling
0: Does not walk or circle

E. Sensory, Forepaw
4: Normal reaction, immediate withdrawal from painful stimulation
3: Slow reaction, withdrawal is long in latency or slow in action
2: Severely blunted reaction, small twitch
1: No response

F. Sensory, Hindpaw
4: Normal reaction, immediate withdrawal from painful stimulation
3: Slow reaction, withdrawal is long in latency or slow in action
2: Severely blunted reaction, small twitch
1: No response

G. Level of Consciousness
4: Normal, alert, awake
3: Awake but not alert, no startle response
2: Drowsy, stuporous
1: Comatose

Percent tissue damage across the distance of the brain and brain weight of left and right hemispheres were analyzed using the mixed, two-factor ANOVA. Planned comparisons of individual drug treatment effects on tissue damage were further analyzed using the mixed, two-factor ANOVA. The effects of each treatment on tissue damage at discrete locations of the brain were analyzed using the two-tailed Student’s t test. The Tukey test was performed for individual drug treatment comparisons for brain weight analyses. Differences between drug treatments in predrug function were analyzed using a Kruskal-Wallis one-way ANOVA for ordinal data. Additionally, predrug function comparisons between saline and each κ compound were carried out using the Mann-Whitney U test. For control of any differences in neurological function that may have been present before drug treatment and determination of whether drug treatment improved neurological function over pretreatment levels, each animal’s baseline score was subtracted from its posttreatment score for each assessment. This measure was called improvement in neurological function. Differences between drug treatments on improvement in neurological function were analyzed at each time point using a Kruskal-Wallis one-way ANOVA for ordinal data. Additionally, comparisons of each drug at each time point were carried out using the Mann-Whitney U test. Because errors of interpretation can frequently exist when adjustments for multiple statistical comparisons are made, no adjustments were made in the present study other than those stated above.

Results

Survival

Overall, treatment with κ compounds significantly improved survival (κ, 16/30; saline, 1/10; P < .02). Considering each compound individually, U-50,488 significantly increased survival to 60% (P < .03). Dynorphin and E3800 each produced a strong trend toward increased survival (both P < .07, Table 3).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Survivors/Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>1/10</td>
</tr>
<tr>
<td>Dynorphin</td>
<td>5/10</td>
</tr>
<tr>
<td>U-50,488</td>
<td>6/10*</td>
</tr>
<tr>
<td>E3800</td>
<td>5/10</td>
</tr>
</tbody>
</table>

*Higher than saline, P < .03.
Tissue Damage

As seen in Fig 1, treatment with κ compounds significantly reduced the percentage of the brain that suffered tissue damage (κ, 36.0±6.31%; saline, 50.9±3.9%; P<.02). To determine which compounds contributed to the κ effect, we compared each compound with saline. Tissue damage was significantly reduced in each group of animals receiving κ treatment (dynorphin, F(1,18)=8.13, P<.01; U-50,488, F(1,18)=6.61, P<.05; E3800, F(1,17)=5.34, P<.05; Fig 1).

Additional examination of the tissue damage at discrete locations of the brain revealed that the locations at which κ treatment reduced the percentage of damaged tissue included 12 mm (κ, 14.7±3.6%; saline, 36.0±6.9%; P<.01) and 6 mm (κ, 36.8±5.0%; saline, 62.7±3.7%; P<.01) anterior to the optic chiasm and 12 mm (κ, 17.3±3.3%; saline, 32.5±6.2%; P<.05) and 18 mm (κ, 5.2±2.1%; saline, 19.3±9.7%; P<.05) posterior to the optic chiasm (Fig 1).

Further analysis of the κ effects revealed which compounds contributed to the reduced tissue damage at discrete brain locations. Treatment with dynorphin reduced damage at 12 and 6 mm anterior and 12 and 18 mm posterior to the optic chiasm (both P<.02, Fig 1). Treatment with U-50,488 reduced tissue damage at 12 and 6 mm anterior to the optic chiasm (both P<.02, Fig 1). Treatment with E3800 reduced tissue damage at 6 mm anterior to the optic chiasm (P<.01, Fig 1).

Improvement in Neurological Function

Before initiation of drug therapy, all animals demonstrated comparable neurological function (mean score=24.4, Kruskal-Wallis=5.17, P<.2; Fig 2). In addition, predrug function of animals later treated with κ compounds did not differ from predrug function of animals later given saline (κ versus saline, Mann-Whitney U=106, P<.2; Fig 2).

Because 8 of the 10 saline animals died during the first 24 hours, assessments of function on only the first day were used for comparisons of κ and saline functions. A significant effect of treatment was seen at various postdrug trials, with improvement in neurological function (Kruskal-Wallis one-way ANOVA: 1 hour, P<.05; 1.5 hours, P<.02; 2.5 hours, P<.03). Comparison of each compound using the Mann-Whitney U test revealed that only dynorphin-treated animals showed significantly better postdrug improvement than saline animals and at only 2.5 hours postdrug (P<.05, Fig 2). Additionally, as seen in Fig 2, animals treated with dynorphin showed statistically significant postdrug improvement compared with animals treated with U-50,488 or E3800 at various postdrug trials (dynorphin > U-50,488: 0.5, 1.0, 1.5, 2.0, 2.5, and 3.0 hours postdrug; dynorphin > E3800: 3.5, 5.0, 5.5, and 6.0 hours postdrug). The superior improvement in neurological function by animals treated with dynorphin tended to be on the measures of motor function, forepaw and hindpaw function, and forepaw sensory function (Table 4). Overall, neurological function improved 2.7 points across days in the κ-agonist treatment groups [F(6,90)=3.84, P<.002].

Brain Weight

Treatment with κ compounds produced a significant reduction in brain weight [F(1,38)=5.58, P<.03; Table 5]. Comparisons using the Tukey test correction revealed that dynorphin was particularly effective in reducing brain weight in the occluded and nonoccluded hemispheres (both P<.05). ANOVA confirmed that no differences in body weight existed between the four treatment groups [4.7±0.16 kg, F(3,36)=1.27, P<.3].

Discussion

The results of the current study suggest that treatment with κ-opioid agonists increases survival, improves neurological function, and decreases tissue damage and brain edema secondary to focal cerebral ischemia. The potential clinical significance of the current study is amplified by the demonstration of improved outcome...
TABLE 5. Brain Weight

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Left</th>
<th>Right (Occluded)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>10.22±0.37</td>
<td>10.59±0.40</td>
</tr>
<tr>
<td>Dynorphin</td>
<td>8.83±0.14*</td>
<td>9.00±0.25*</td>
</tr>
<tr>
<td>U-50,488</td>
<td>10.00±0.32</td>
<td>10.00±0.49</td>
</tr>
<tr>
<td>E3800</td>
<td>9.60±0.34</td>
<td>9.66±0.20</td>
</tr>
</tbody>
</table>

Values are mean±SEM expressed in grams.
*Less than saline, $P<.01$.

even though treatment was delayed for 6 hours after insult.

Survival was increased from 10% to 53% in the
K-treated animals. This is in agreement with other studies that have demonstrated increased survival in cats with
focal cerebral ischemia treated with K-agonists.2,3,16

Each of the three compounds reduced tissue damage. Previous studies that reported no change in tissue
damage after treatment with K-agonists in experimental focal cerebral ischemia have relied on assessment of
tissue damage from a single coronal section through the
optic chiasm.2,2 Had tissue damage in the present study
been assessed at only the optic chiasm, there would,
again, have been no significant improvement seen after K-agonist treatment.

K-Agonists produced a trend toward improvement from predrg levels in neurological function. However,
we did not assess whether one drug had a greater
analgesic or sedative effect than another. The functional
ability of the animals in the various treatment groups
may have been differentially altered by their sedation
level.

Because there was no difference in brain weight be-
tween the two hemispheres, it appeared that any edema
secondary to the vascular occlusion occurred bilaterally.
Normal, adult, feline brains weigh approximately 9.5 g per
hemisphere (unpublished data). This weight was similar to
the brain weight of the experimental animals treated with K
compounds. Therefore, K treatment may have reduced
brain water content to its preischemic level.

In general, the three agonists had comparable effects
on survival and tissue damage. However, dynorphin had
superior effects on neurological function and brain
weight, and U-50,488 had somewhat superior effects on
survival. Several explanations may account for the dif-
ferential effects. The differences may be related to
variation in the relative affinities for the K receptor
subtypes. Both dynorphin and U-50,488 have a 70-
to 80-fold higher affinity for K$_r$ over K$_G$-receptor
subtypes.12 Therefore, part of the efficacy of these com-
ounds may be mediated via the K$_r$-receptor. Dynorphin
has a 10-fold higher affinity for K$_r$ than K$_G$-receptors,
whereas U-50,488 has an 80-fold higher affinity for K$_r$
over K$_G$.12 This may explain the differential effects of
these two compounds. Although subcutaneous admin-
istration of K-agonists, including dynorphin, has been
shown to be an effective route of administration in both
normal and injured animals,2,21 each compound may
be absorbed to a greater or lesser extent than the others.
Another possibility is that, although each
compound is a K-agonist, there may be very different
effects of each substance at some other, unnamed
receptor that may alter outcome. The peptide nature of
dynorphin, as compared with the other two nonpeptide
compounds, could favorably influence its pharmaco-
bio-dynamics. Any or all of these effects may account for the
minor differences observed with each drug.

It is unclear whether the K-agonists improved out-
come because of central or peripheral actions or a
combination of the two. It is likely, however, that the
therapeutic efficacy of the K-agonists is centrally medi-
ated, because the beneficial effects of naloxone have
been shown to be unrelated to changes in systemic
variables, including blood pressure and heart rate.20
Additionally, recent studies have demonstrated the abili-
ty of K-agonists to cross the blood-brain barrier in
experimental focal cerebral ischemia.21 Furthermore, a
classic effect of K-agonism, increased diuresis, has not
been seen after administration of a K-agonist that
specifically does not cross the blood-brain barrier.22
Although a variety of pathophysiological mechanisms have been implicated in cerebral ischemia, it is unclear which derangements produce the majority of tissue damage, functional loss, and mortality seen in this disease. A number of mechanisms may be involved in the neuroprotection seen in the present study, including reduction of neurotoxicity related to excess dopamine release, excess glutamate release, excess calcium accumulation, or increased brain edema.

Reduction of dopamine neurotoxicity may be a mechanism by which κ-agonists improve outcome after cerebral ischemia. κ-Opioids can reduce potentially damaging levels of extracellular dopamine in several brain regions. Decreased levels of dynorphin, seen in focal cerebral ischemia, may lead to excessive dopamine release and exacerbation of ischemic damage. Exogenously administered κ-opioids may reduce the elevation in dopamine and thereby decrease ischemic damage.

Further reduction of neurotoxicity may result from κ-inhibited inhibition of glutamate excitotoxicity and calcium conductance. κ-Agonists have been shown to have potent anticonvulsant actions, particularly against N-methyl-d-aspartate-evoked seizures, and to interfere with glutamate activity. A component of the κ-decreased decrease in glutamate toxicity may involve reduction of calcium entry into the cells. κ-Agonists block calcium currents and inhibit calcium-induced release of glutamate. Inhibition of glutamate release may not be the primary mechanism of action in our model of focal cerebral ischemia, however, as antagonism of glutamate activity has been shown to be ineffective in reducing ischemia when treatment is delayed 4 or more hours after the onset of ischemia. Reduction of calcium conductance may protect the cells from ischemic damage by additional means, such as reducing damage to cell membranes secondary to excess calcium accumulation.

The dramatic decrease in brain weight seen in the dynorphin-treated animals suggests that a possible mechanism for the actions of dynorphin in acute stroke is reduction of brain edema. A salient property of the κ subclass of opiate agonists in a variety of species, including humans, is increased diuresis. 

The mechanism by which κ-agonists produce diuresis and also reduce brain edema has been suggested to be via an inhibition of arginine vasopressin (AVP). Although some reports have indicated that κ-opioids have no effect on or can increase rather than decrease AVP levels, the preponderance of evidence indicates that κ-opioids reduce AVP levels. Site of injection as well as dose and specificity of agonist may account for the differing results.

Separate from its effects on peripheral diuresis, AVP may be directly involved in water balance in the brain. AVP acts to elevate cerebrospinal fluid (CSF) directly from the brain, and CSF AVP levels can vary independently of plasma levels. Intracerebroventricular administration of AVP increases brain capillary permeability in monkeys and exacerbates brain edema in cats. Furthermore, AVP levels are elevated in CSF in stroke patients. Existing research suggests that dynorphin exhibits an autoregulatory effect on AVP secretion. An abundance of dynorphin exists within magnocellular neurons of the hypothalamus, and dynorphin has been shown to be colocalized with AVP in neurosecretory vesicles. Further, levels of dynorphin and AVP vary in parallel in response to physiological challenge. Since dynorphin has been shown to reduce voltage-dependent calcium conductance and dynorphin and AVP are coreleased, it has been suggested that dynorphin regulates the ability of hypothalamic magnocellular neurons to stimulate AVP release. Therefore, κ-opioids may inhibit central release of AVP, affecting cerebral edema by central effects and peripheral diuresis independently. Additionally, the actions of AVP may be inhibited by κ-induced alterations of second messenger levels or inhibition of ion channels. In future studies we plan to measure plasma and CSF levels of AVP and also measure urine output.

Some researchers have suggested that dynorphin may be neurotoxic and directly involved in the pathogenesis of cerebral ischemic damage. This hypothesis is based primarily on three lines of evidence. First, intrathecal dynorphin has been reported to produce paralytic effects. However, the spinal cord paralytic effect seen after intrathecal dynorphin is produced by immediate inhibition of motor neurons in the spinal cord rather than excitotoxic stimulation. Second, intrathecal dynorphin injections have resulted in pathological findings. However, in these studies dynorphin was given in millimolar doses. A large variety of peptides given in such large doses can cause damage, probably because of an inflammatory reaction to the introduction of such large amounts of peptide. The third line of evidence comes from the reports of elevations of dynorphin in head injury. However, this same lab reported no change in dynorphin in ischemia. Additionally, other labs and our own studies have shown that dynorphin is decreased in focal cerebral ischemia.

The results of the present study provide evidence for κ-opiostin neuroprotection even with delayed treatment onset. The current study, along with evidence from previous research, provides support for the possibility of treatment of acute cerebrovascular ischemia with κ-opioid agonists.

Acknowledgments

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