Hypocretin Administration as a Treatment for Human Narcolepsy


J.M. Siegel, PhD
Neurobiology Research VA GLAHS Sepulveda, Dept. of Psychiatry, UCLA School of Medicine, Los Angeles CA

THE REPORT IN THE CURRENT ISSUE OF SLEEP BY FUJIKI ET AL. REINFORCES PRIOR WORK THAT SUGGESTS THAT HYPOCRETIN (HCRT, ALSO KNOWN AS OREXIN) ADMINISTRATION WILL BE AN EFFECTIVE TREATMENT FOR HUMAN NARCOLEPSY. Most human narcolepsy is caused by a loss of hypocretin neurons.1-3 That finding suggested that Hcrt administration might be an effective treatment for narcolepsy. Work in our laboratory showed that intravenous (IV) Hcrt administration reduced symptoms of canine genetic narcolepsy.4 Although the Fujiki et al. paper emphasizes technical problems associated with studying these effects, it confirms key aspects of these hopeful findings.

SYSTEMIC HCRT AS A TREATMENT FOR NARCOLEPSY

It is obvious that any treatment for human narcolepsy that required intracerebroventricular (ICV) administration of Hcrt would be impractical. However, several lines of evidence have suggested that systemic administration would be effective.

Studies of Hcrt penetration into the brain parenchyma after IV administration concluded that Hcrt-1 crosses the blood-brain barrier (BBB) rapidly by a non-saturable mechanism.5-6 In vitro work suggested that many of Hcrt’s central effects may be mediated by its role in stimulating the release of amino acids.7 In vivo work found that IV administration of as little as 3-4 µg/kg of Hcrt-1 produced an increase in central levels of Hcrt in the brain parenchyma8 and robust increases in central glutamate release.9 The Fujiki et al. paper also shows a substantial (2.4 fold) increase in Hcrt-1 levels in cerebrospinal fluid (CSF) after systemic administration, although their use of a logarithmic Y axis in Figure 4, to increase in Hcrt-1 levels in cerebrospinal fluid (CSF) after systemic administration of as little as 3-4 µg/kg of Hcrt-1 produced an increase in central levels of Hcrt in the brain parenchyma8 and robust increases in central glutamate release.9 The Fujiki et al. paper also shows a substantial (2.4 fold) increase in Hcrt-1 levels in cerebrospinal fluid (CSF) after systemic administration, although their use of a logarithmic Y axis in Figure 4, to display the increases in both blood plasma and CSF Hcrt levels after IV administration, makes it difficult to discern the change in CSF levels. Evaluation of this curve must also take into account the limitations of these investigator’s RIA assay for Hcrt-1. Although strong increases in central Hcrt-1 can be seen at the larger IV doses employed here, changes in Hcrt concentration become undetectable at low doses. Kastin et al.’s findings5,6 indicate that no threshold is involved in Hcrt-1 penetration of the BBB, but the sensitivity of the RIA assay used in the current study may not be sufficient to detect functionally important changes in CSF Hcrt-1 concentration at lower doses. Moreover, the relevant measures of effective penetration are the levels of Hcrt found in the brain parenchyma, not those in the CSF, since CSF levels reflect parenchymal levels at a significant time delay and are greatly reduced relative to brain tissue levels.

Given that Hcrt-1 crosses the BBB, can it effectively be used to treat narcolepsy? A unique feature of the Fujiki et al. paper is the study of an “idiopathic” narcoleptic dog. The pathology in such dogs is likely to mirror that of the human narcolepsy syndrome more closely than the pathology of any of the genetic animal models. As Figure 5 shows, IV administration of Hcrt-1 produced a dramatic reduction in cataplexy symptoms. Although the number of trials at each dose is small, resulting in wide error ranges, the decrease in cataplexy is clear and is proportional to dose (Figure 5c).

DOSE

Two important issues are the size of an adequate dose and the comparability of the doses used in the Fujiki et al. study with those used in prior studies. The authors imply that the doses required for a potent effect on cataplexy are too high to be of practical value. However, the authors report, in agreement with our prior study,4 that effective doses and all doses up to the maximum tested did not cause any apparent side effects. No GI upset, appetite or heart rate changes, seizures, vocalizations indicating distress or other signs of toxicity were seen. These findings bode well for the development of systemically administered Hcrt or Hcrt analogs for the treatment of narcolepsy or other disorders of arousal.

The current study found marked reductions in cataplexy in the idiopathic narcoleptic dog with IV Hcrt-1 administration at 50 µg/kg, with further improvement seen at doses of up to 384 µg/kg. (The doses most effective in the idiopathic narcoleptic dog were not administered to the Hcrt receptor-2 mutant dogs.) Amphetamines, modafinil and other therapeutic agents commonly used in the treatment of human narcolepsy are given at dosages comparable to or considerably higher than the doses employed in the idiopathic narcoleptic dog. These Hcrt-1 doses are not “high” in a pharmacological, physiological or clinical sense. What is high is the monetary cost of effective doses. Using commercial research sources, one injection at an effective dose reported in our study would cost at least $300 for a 75 kg human. However, one can hope that treatment costs would fall as production increased.

Our effective doses were much smaller than some of those reported here. Hcrt-1 can be easily degraded and the details of the preparation, delay between preparation and administration and precise method of administration of Hcrt-1 are important for preserving its potency. The disulfide bond in Hcrt-1 is critical to its activity and can be easily degraded.10 The use of PE tubing in the lateral ventricles in the current study may reduce the effective potency of Hcrt-1, because it would be degraded.10 The use of PE tubing in the lateral ventricles in the current study may reduce the effective potency of Hcrt-1, because it would be degraded.10 However, the authors report, in agreement with our prior study,4 that effective doses and all doses up to the maximum tested did not cause any apparent side effects. No GI upset, appetite or heart rate changes, seizures, vocalizations indicating distress or other signs of toxicity were seen. These findings bode well for the development of systemically administered Hcrt or Hcrt analogs for the treatment of narcolepsy or other disorders of arousal.

Another issue is the duration of the effect. The current study did not explore this in detail but implied that long term effects were not seen, while our prior study14 saw some effects lasting many hours. More work will be needed to resolve this issue. Whatever the duration of the therapeutic effects, time release preparations of Hcrt-1 or Hcrt analogs could be developed to provide very long duration clinical improvements for the treatment of human narcolepsy.

The text accompanying Figure 1 emphasizes a lack of effect of IV Hcrt-1 administration on cataplexy measures in genetically narcoleptic dogs. But inspection of the figure reveals that all doses reduced cataplexy, as measured by elapsed time, changes in number of attacks and number of attacks relative to the saline control, for at least 120 min. (Our prior study tested cataplexy at 4 min after IV administration of
Hcrt-1, using a somewhat different type of test.) Using the presented data and a nonparametric U test (the appropriate test for ordinal data), it appears that the reduction in cataplexy attacks following IV Hcrt-1 administration in genetically narcoleptic dogs was significant (p<0.01, n1=3, n2=12, U=36), as are other changes shown in the figure. Figure 2 (upper right) also shows a trend of increased wakefulness in both narcoleptic and normal dogs with increasing dose, although the n is small and the standard errors are large. Certainly the data do not convincingly show a lack of effect.

ICV AND INTRAVENOUS ADMINISTRATION

Fujiki et al. suggest that ICV administration of Hcrt had no effect in genetically narcoleptic dogs, whereas ICV administration in normal control dogs produced increased wakefulness. There are two Hcrt receptors. Prior work demonstrated that genetically narcoleptic dogs have a homozygous mutation in the Hcrt receptor-2 gene, but have a normal Hcrt receptor-1 gene. Several studies have shown that activation of the locus coeruleus by ICV or direct injection of Hcrt-1 is sufficient to activate noradrenergic cells and produce motor activation and increased wakefulness. The locus coeruleus contains predominantly or exclusively Hcrt receptor-1. Kisanuki et al. showed that mice with both Hcrt receptor-1 and -2 genes deleted are more symptomatic, with more severe cataplexy and more disrupted waking, than those with only Hcrt receptor-2 gene deletions, indicating that the Hcrt type 1 receptor has an important role in Hcrt mediated arousal. But Fujiki et al. conclude that ICV administration has no effect on cataplexy or waking duration in the Hcrt receptor-2 mutant dog, implying that receptor-1 activation by Hcrt-1 has no effect on waking arousal. These results are difficult to understand in light of prior results.

Fujiki et al. also report that the same Hcrt receptor-2 mutant narcoleptic dogs showed a significant reduction in REM sleep (by 40%; equivalent to a significant increase in NREM + waking values) with ICV administration of Hcrt (not illustrated in a figure). This REM sleep suppression finding demonstrates that the Hcrt receptor-2 mutation does not prevent REM sleep suppression by Hcrt-1 administration. It suggests a role for Hcrt receptor-1 in the arousing effects of Hcrt administration and supports prior results that showed REM sleep suppression with IV or ICV administration. REM sleep suppression is a common characteristic of drugs that are effective against cataplexy. The simplest way to reconcile the lack of effect on waking of Hcrt-1 administered ICV to Hcrt receptor-2 mutant narcoleptic dogs in the current study and the suppression of REM sleep by the same ICV administration, with the positive Hcrt receptor-1 mediated results in many prior studies, is to hypothesize that technical difficulties, as discussed above, or the small n in the current study did not allow detection of the wake altering effects of Hcrt-1.

There might be little economic incentive for pharmaceutical company development of the use of the native Hcrt-1 peptide as a treatment for narcolepsy, compared to the development of new, patentable, Hcrt analogs. However, one would expect that new peptide analogs would be more likely to have significant side effects or toxicity than would the naturally occurring peptide.

TREATMENT PROSPECTS

To summarize, the positive effects of systemic administration of Hcrt-1 in narcoleptic animals in this and in our prior study suggests that similar treatments will be effective in humans. Treatments might use inhalants or timed release preparations and will necessitate the development of new, less expensive techniques for synthesizing the peptide. Such developments would offer real hope to individuals with narcolepsy.

REFERENCES