J Vet Intern Med 2004;18:586–588

The Effect of Hypocretin Replacement Therapy in a 3-Year-Old Weimaraner with Narcolepsy

Scott J. Schatzberg, Katherine Cutter-Schatzberg, Daryl Nydam, Jennifer Barrett, Richard Penn, James Flanders, Alexander deLahunta, Ling Lin, and Emmanuel Mignot

A 3-year-old male neutered Weimaraner dog presented to the Cornell University Hospital for Animals with a chief complaint of acute onset cataplectic attacks, triggered by emotional events such as playing or eating.[a] The diagnosis of narcolepsy and cataplexy was made based on clinical signs and evaluation of cerebrospinal fluid (CSF) that contained a dramatically decreased hypocretin-1 concentration (<100 pg/mL; normal reference range, 200–350 pg/mL).[1] To evaluate clinical signs on a repetitive basis during the course of treatment, the dog was trained to conduct food-elicited cataplexy tests (FECTs).[a] Both the number of attacks (NA) and elapsed time in collapse (ET) were measured as an index of cataplexy severity. Further supporting the diagnosis of narcolepsy and cataplexy, we measured a dramatic response to IV yohimbine (Figs 1, 2; NA and ET with no treatment: median, 6 collapses and 50.5 seconds, respectively; NA and ET with 0.048 μg/kg IV: median, 0.5 collapses [$P = .004$] and 9.5 seconds [$P = .005$, Wilcoxon rank sum test], respectively).[2]

Narcolepsy in dogs has been shown to affect more than 17 breeds.[3,4] Two forms of the disease exist. In Doberman Pinschers, Labrador Retrievers, and Dachshunds, a familial form with early onset (≤6 months of age) and autosomal recessive transmission has been reported. The familial form is caused by mutations in the hypocretin-receptor-2 gene.[5,6] In most other cases, the disease is sporadic, the age of onset is variable, and the disease is associated with a loss of the hypocretin ligand.[7] This more common form of narcolepsy in dogs is particularly interesting because it may be an equivalent of the human disorder. In humans, most cases are sporadic, with onset around adolescence, and patients typically have low concentrations of hypocretin-1 in CSF.[1] The disease in humans is associated closely with human leukocyte antigen HLA-DQ, and autoimmune destruction of hypocretin-containing cells has been proposed as the cause of the disorder.[8] Studies have yet to demonstrate a DLA-DQ association in sporadic cases of narcolepsy in dogs.[9]

Given the acute presentation in the dog of this report (episodes of cataplexy began less than 1 week before presentation), we began immunosuppressive therapy with prednisone 1mg/kg PO q12h for 3 weeks. The dog was considered unusual because it is rare to diagnose human patients in such temporal proximity to disease onset. FECTs were performed both at home by the owner (who was trained to perform FECTs) and at Cornell University on a weekly basis. Clinical signs remained static according to the owner, and objective testing with FECTs failed to demonstrate a substantial reduction in clinical signs. Consequently, this therapeutic strategy was abandoned (Figs 1, 2). The lack of response to immunosuppressive doses of prednisone in this dog fails to support the hypothesis of an autoimmune pathogenesis in hypocretin-deficiency narcolepsy. However, the autoimmune destruction of hypocretin-containing cells could have been too far advanced in this dog to be reversible at the time of therapy.

We next elected to assess the efficacy of IV and centrally administered hypocretin-1. FECTs were conducted after (15 minutes, 30 minutes, 1 hour, and 2 hours) IV injections of 0.86 μg/kg to 96 μg/kg hypocretin-1. No anticataplectic effects were detected (data not shown). Similar results were reported in another hypocretin-deficient dog at Stanford University.[10] To allow us to study the effects of centrally administered hypocretin, the owner consented to the surgical implantation of an indwelling intrathecal catheter, which was connected to a subcutaneous infusion pump.[b]

A standard dorsal laminectomy was performed at the level of the 3rd cervical vertebra, and a small bore catheter was advanced to the level of the foramen magnum through a small defect made in the dura matter. Confirmation of the catheter location was made by intraoperative fluoroscopy and by injecting contrast material (1 mL Iohexal[c]) into the catheter. The intrathecal catheter was attached via a surgical steel connector to a larger-gauge catheter that was connected to the Medtronic fluid pump (secured subcutaneously in the dorsal cervical area). Such pumps are used routinely in humans for chronic intrathecal administration of drugs, and we hypothesized that this technique could also be used in dogs. During implantation, an IV bolus dose (96 μg/kg) of hypocretin-1 was injected, and plasma and hypocretin-1 concentrations were measured before and 15 and 45 minutes after injection. A large increase in plasma hypocretin-1 concentration was detected (preinjection, not detectable; 15 minutes postinjection, 175,850 pg/mL; 45 minutes postinjection, 94,500 pg/mL) with insignificant increases in CSF hypocretin-1 concentration (preinjection, 82 pg/mL; 15 minutes postinjection, 91 pg/mL; 45 minutes postinjection, 276 pg/mL), further suggesting that peripheral administration of hypocretin-1 is unlikely to provide therapeutic relief in patients with narcolepsy.

One month after the surgery, the Medtronic pump was

From the Animal Medical Center, New York, NY (Schatzberg); the Department of Clinical Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY (Cutter-Schatzberg, Nydam, Barrett, Flanders, deLahunta); the Department of Surgery, Pritzker School of Medicine, University of Chicago, Chicago, IL (Penn); and Stanford University Center For Narcolepsy, Palo Alto, CA (Lin, Mignot).

Reprint requests: Scott Schatzberg, DVM, PhD, The Bobst Hospital of the Animal Medical Center, 510 East 62nd Street, New York, New York 10021; e-mail: sjs13@twcny.rr.com.

Submitted October 10, 2003; Revised January 27, 2004; Accepted March 29, 2004.

0891-6640/04/1804-0024/$3.00/0

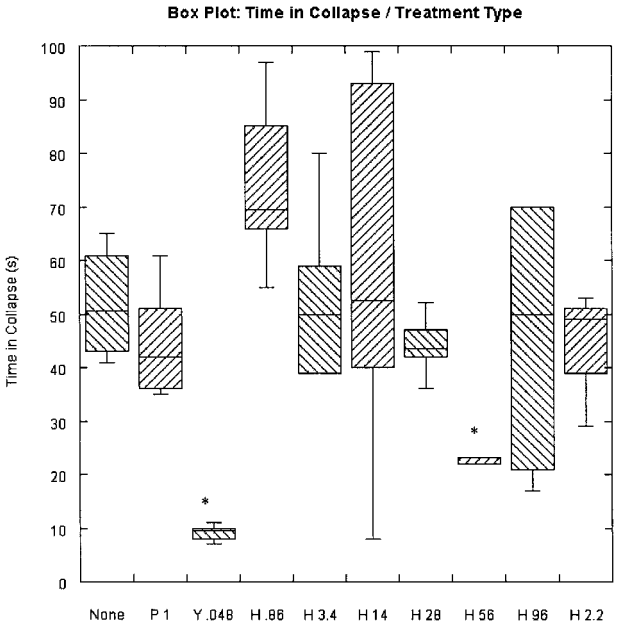

Fig 1. Box-and-whisker plot of time in collapse for each treatment type. For each group, the horizontal bar within the each box represents the median time in collapse, the top of the box represents the 3rd quartile, the bottom of the box represents the 1st quartile, and the "whiskers" represent the range of data within each treatment group. None = no treatment; P1 = prednisone at 1 μg/kg; Y.048 = yohimbine at 0.048 μg/kg; H .86 = hypocretin at 0.86 μg/kg; H 3.4 = hypocretin at 3.4 μg/kg; H 14 = hypocretin at 14 μg/kg; H 28 = hypocretin at 28 μg/kg; H 56 = hypocretin at 56 μg/kg; H 96 = hypocretin at 96 μg/kg; and H 2.2 = hypocretin at 2.2 μg/kg q24h at constant rate. *$P < .05$ for that treatment group, Wilcoxon rank sum test; absence of * means no significant difference from no treatment.

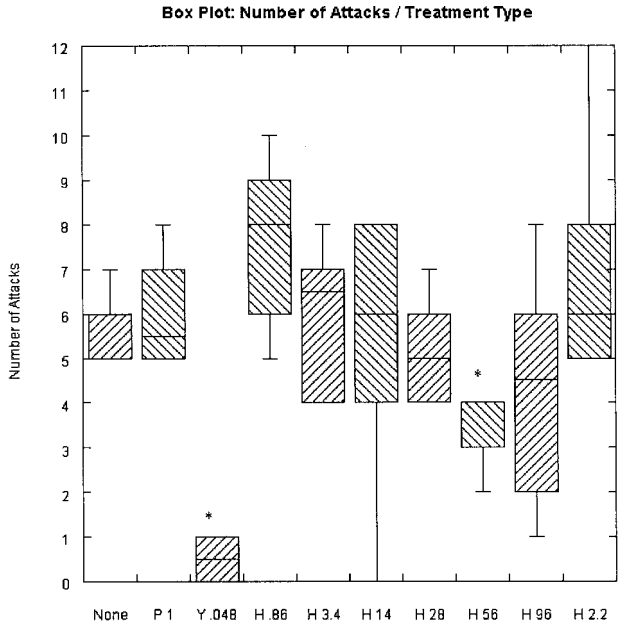

Fig 2. Box-and-whisker plot of the number of attacks during food-elicited cataplexy tests for each treatment type. See Figure 1 for interpretation.

programmed to administer increasing intrathecal boluses of hypocretin-1, with doses ranging from 0.86 to 96 μg/kg. Doses were calculated based upon doses of hypocretin-1 known to have strong wake-promoting effects when injected intracerebroventricularly in dogs (28.5 to 106.9 μg).[10] Temperature, electrocardiogram, and respiratory rate were assessed at 30-minute intervals for 6 hours after bolus administration. No significant changes were observed in vital parameters for any of the boluses tested at any time. The dose was increased every 3 days up to a final dose of 96 μg/kg (0.86, 3.4, 14, 28, 56, and 96 μg/kg all were assessed). Two FECTs were performed at 30 minutes, 2 hours, and 6 hours after each administration. Blood samples also were collected 1 hour after intrathecal injection to measure plasma hypocretin-1 concentration (preinjection plasma concentrations, undetectable for all boluses; postinjection plasma concentrations, undetectable for 0.86- and 3.4-μg/kg boluses, 230 pg/mL for 13-μg/kg boluses, 683 pg/mL for 56-μg/kg boluses, and 1,149 pg/mL for 96-μg/kg boluses). When we started at a dose of 56 μg/kg, the dog was subjectively more alert. Statistically significant reductions in both NA and ET were observed at the 56-μg/kg dose (NA and ET with no treatment: median, 6 collapses and 50.5 seconds, respectively; NA and ET with 56-μg/kg hypocretin bolus: median, 3 collapses [$P = .004$] and 22 seconds [$P = .004$, Wilcoxon rank sum test], respectively). However, the dog's cataplexy was not adequately controlled at this dose or after the highest dose administered (96 μg/kg). The 96-μg/kg dose was associated with a large increase in plasma hypocretin-1 concentration, suggesting leakage from CSF to plasma. When we considered that sustained CSF concentrations of hypocretin (rather than CSF surges of hypocretin) might promote wakefulness and reduce cataplexy, we ultimately decreased the dosage to a constant-rate intrathecal infusion of 2.2 μg/kg q24h (0.17 μg/kg q1h during the day; 0.017 μg/kg q1h during the night) and discharged the dog for observation. However, during the 2 months of this therapy, no significant differences in NA or ET were observed on FECTs (see Figs 1, 2), and the owner did not appreciate a subjective change in the dog's clinical signs.

Three months later, the dog was started on symptomatic treatment PO with the alpha-2 antagonist yohimbine.[2] Excellent control of cataplexy was achieved with this treatment for 3 months, at which point resistance developed. Currently, the clinical signs are moderately well controlled with a monthly regimen alternating between desipramine (3 mg/kg PO q12h) and yohimbine (0.045 mg/kg PO q12h). These 2 drugs are established treatments for cataplexy in dogs with narcolepsy.[11] Cataplexy is a clinical sign of abnormal rapid eye movement (REM) atonia known, as is REM sleep itself, to be most sensitive to adrenergic and cholinergic drugs. Desipramine, an adrenergic reuptake inhibitor, was used as the initial treatment. It was selected in preference to other antidepressants, because cataplexy is well known to be most sensitive to antidepressants that inhibit adrenergic rather than serotoninergic reuptake.[11–13] Similarly, yohimbine, an alpha-2 antagonist, is known to activate adrenergic transmission presynaptically, thereby reducing cataplexy. Although yohimbine is an effective treatment for cataplexy in dogs, tolerance to the drug's effect has been demonstrated previously.[2]

We report for the first time the use of centrally administered hypocretin supplementation in hypocretin-deficient narcolepsy. The lack of efficacy after intrathecal administration of hypocretin-1 was disappointing. When administered in the lateral ventricle, 1.06 to 3.95 μg/kg hypocretin-1 (1% of the highest dose administered in this study) has profound wake-promoting effects in healthy dogs.[10] With these data, we anticipated greater amelioration of the cataplexy in this dog.

The possibilities for treatment failure are numerous. First, contrary to our expectations, hypocretin-1 may not have backflowed sufficiently through the foramen magnum and may have failed to reach critical brain structures (eg, locus ceruleus, dorsal raphe) after cisternal administration. Second, hypocretin deficiency may be associated with a deficiency in hypocretin receptor function. The hypocretin gene has been screened for mutations in dogs (as in human patients) with late-onset hypocretin deficiency, but no mutations have been identified.[14] A 3rd possibility is that hypocretin deficiency is associated with down-regulation of hypocretin receptors, and such a consideration needs to be assessed by hypocretin ligand binding studies. Finally, cataplexy may be a secondary phenomenon that develops slowly as a consequence of hypocretin deficiency and may be extremely difficult to reverse. In support of this hypothesis, the cataplectic component of human narcolepsy is slightly delayed in onset after the clinical manifestation of sleepiness. Additional studies in hypocretin-deficient animals by using a centrally penetrable hypocretin agonist or a sustained hypocretin infusion into the lateral ventricle may be necessary to address these important considerations, which could provide important information about treatment for this disabling disorder.

Footnotes

[a]http://www.med.stanford.edu/school/Psychiatry/narcolepsy/
[b]Subcutaneous infusion pump, Medtronic Inc, Minneapolis, MN
[c]1 mL Iohexal, Hovione LL, East Windsor, NJ

References

1. Mignot E, Lammers GJ, Ripley B, et al. The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. Arch Neurol 2002;59:1553–1562.

2. Nishino S, Haak L, Shepherd H, et al. Effects of central alpha-2 adrenergic compounds on canine narcolepsy, a disorder of rapid eye movement sleep. J Pharmacol Exp Ther 1990;253:1145–1152.

3. Tonokura M, Fujita K, Morozumi M, et al. Narcolepsy in a hypocretin/orexin-deficient chihuahua. Vet Rec 2003;152:776–779.

4. Mignot E, Guilleminault C, Dement W, et al. Genetically determined animal models of narcolepsy, a disorder of REM sleep. In: Driscoll D, Birkhauser M, eds. Genetically Determined Animal Models of Neurobehavioral Dysfunction. Cambridge, MA: Boston Inc; 1992:90–110.

5. Lin L, Faraco J, Li R, et al. The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. Cell 1999;98:365–376.

6. Hungs M, Fan J, Lin L, et al. Identification and functional analysis of mutations in the hypocretin (orexin) genes of narcoleptic canines. Genome Res 2001;11:531–539.

7. Ripley B, Fujiki N, Okura M, et al. Hypocretin levels in sporadic and familial cases of canine narcolepsy. Neurobiol Dis 2001;8:525–534.

8. Mignot E, Lin L, Rogers W, et al. Complex HLA-DR and -DQ interactions confer risk of narcolepsy-cataplexy in three ethnic groups. Am J Hum Genet 2001;68:686–699.

9. Wagner JL, Storb R, Storer B, et al. DLA-DQB1 alleles and bone marrow transplantation experiments in narcoleptic dogs. Tissue Antigens 2000;56:223–231.

10. Fujiki N, Yoshida Y, Ripley B, et al. Effects of IV and ICV hypocretin-1 (orexin A) in hypocretin receptor-2 mutated narcoleptic dogs and IV hypocretin-1 replacement therapy in a hypocretin ligand deficient narcoleptic dog. Sleep 2003;26:953–959.

11. Nishino S, Mignot E. Pharmacological aspects of human and canine narcolepsy. Prog Neurobiol 1997;52:27–78.

12. Mignot E, Renaud A, Nishino S, et al. Canine cataplexy is preferentially controlled by adrenergic mechanisms: Evidence using monoamine selective uptake inhibitors and release enhancers. Psychopharmacology (Berl) 1993;113:76–82.

13. Nishino S, Arrigoni J, Shelton J, et al. Desmethyl metabolites of serotonergic uptake inhibitors are more potent for suppressing canine cataplexy than their parent compounds. Sleep 1993;16:706–712.

14. Peyron C, Faraco J, Rogers W, et al. A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. Nat Med 2000;6:991–997.