and a similar mechanism for action myoclonus in CRSM as that postulated by Van Woert [12] for post-hypoxic action myoclonus. This hypothesis would receive more support had we been able to measure 5-hydroxyindoleacetic acid levels in cerebrospinal fluid, but this procedure was not available. Nevertheless, our data extend the findings of Franceschetti and associates [8] and suggest that 5-HTP as a supplement to anticonvulsants produces sustained improvement in CRSM.

Presented in part at the 15th Annual Meeting of the Child Neurology Society, Boston, MA, Oct 1986.

References

1. Gonatas NK, Terry RD, Winkler R, et al. A case of juvenile lipidosis: the significance of electronmicroscopic and biochemical observations of cerebral biopsy. J Neuropathol Exp Neurol 1963;22:557–580
2. Goldstein M, Kolodny EH, Gascon GG, Gilles FH. Macular cherry red spot myoclonic epilepsy and neurovisceral storage in a 17-year-old girl. Trans Am Neurol Assoc 1974–1975;99:29–32
3. Rapin I, Katzman R, Engel J Jr. Cherry red spots and progressive myoclonus without dementia: a distinct syndrome with neuronal storage. Trans Am Neurol Assoc 1975;100:39–42
4. O'Brien JS. Neuraminidase deficiency in the cherry red spot–myoclonus syndrome. Biochem Biophys Res Commun 1977; 79:1136–1141
5. Rapin I, Goldfisher S, Katzman R, et al. The cherry red spot–myoclonus syndrome. Ann Neurol 1979;3:234–242
6. Lowden JA, O'Brien JS. Sialidosis: a review of human neuraminidase deficiency. Am J Hum Genet 1979;31:1–18
7. Engel J Jr, Rapin I, Giblin D. Electrophysiological studies in two patients with cherry red spot–myoclonus syndrome. Epilepsia 1977;18:73–87
8. Franceschetti S, Uziel G, Di Donata S, et al. Cherry red spot–myoclonus syndrome and alpha neuraminidase deficiency: neurophysiological and biochemical study in an adult. J Neurol Neurosurg Psychiatry 1980;43:934–940
9. Walters A, Hening W, Cote L, Fahn S. Dominantly inherited restless legs with myoclonus and periodic movement of sleep: a syndrome related to the endogenous opiates? In: Fahn S, Marsden CD, Van Woert MH, eds. Myoclonus: advances in neurology, Vol 43. New York: Raven Press, 1986:309–319
10. Duvoisin RC. Essential myoclonus: response to anticholinergic therapy. Clin Neuropharmacol 1984;7:141–147
11. Chokroverty S, Manocha MK, Duvoisin RC. A physiologic and pharmacologic study in anticholinergic-responsive essential myoclonus. Neurology 1987;37:608–615
12. Van Woert MH, Sethy VH. Therapy of intention myoclonus with L-5-hydroxytryptophan and a peripheral decarboxylase inhibitor, MK 484. Neurology 1975;25:135–140

A Double-Blind Randomized Crossover Trial of Bromocriptine and Placebo in Restless Legs Syndrome

Arthur S. Walters, MD,*† Wayne A. Hening, MD, PhD,† Neil Kavey, MD,‡ Sudhansu Chokroverty, MBBS, FRCP,*† and Steve Gidro-Frank, BA‡

A double-blind randomized crossover study of 7.5 mg bromocriptine at bedtime versus placebo was conducted in 30-day phases (with a 2-week washout period between phases) in 6 patients with idiopathic restless legs syndrome. Five patients experienced partial subjective improvement in restlessness and paresthesias on bromocriptine as opposed to placebo and expressed a desire to continue on the medication. On bromocriptine, the patients showed polysomnographically a mean decrease of 43% from control and a mean decrease of 57% from placebo in the number of periodic movements of sleep per hour of sleep ($p < 0.025$). Two of 3 patients with abnormally decreased total sleep time and sleep efficiency showed an improvement in these measures on therapy. The dopamine agonist bromocriptine may be a useful therapy in some patients with restless legs syndrome.

Walters AS, Hening WA, Kavey N, Chokroverty S, Gidro-Frank S. A double-blind randomized crossover trial of bromocriptine and placebo in restless legs syndrome. Ann Neurol 1988;24:455–458

Idiopathic restless legs syndrome (RLS), when severe, is frequently associated with seven features [1–3]:

1. Restlessness, manifested by floor pacing, foot rubbing, tossing and turning in bed, and sometimes marching in place or body rocking.
2. Paresthesias, usually in the legs.
3. Periodic movements of sleep (PMS), which are stereotypical flexion movements involving the legs much more than the arms. They usually recur at regular 20- to 40-second intervals during non–rapid-eye-movement (NREM) sleep and, although

From the *Movement Disorder Group, Department of Neurology, UMDNJ—Robert Wood Johnson Medical School, New Brunswick, the †Neurophysiology Section, Neurology Service, Lyons VA Medical Center, Lyons, NJ, and the ‡Sleep Disorders Center, Columbia Presbyterian Medical Center, New York, NY.

Received Jan 12, 1988, and in revised form Mar 16, 1988. Accepted for publication Mar 24, 1988.

Address correspondence to Dr Walters, Department of Neurology, CN19, UMDNJ—Robert Wood Johnson Medical School, New Brunswick, NJ 08903-0019.

originally called nocturnal myoclonus, they are rarely as fast as true myoclonus [2].

4. "Dyskinesias while awake." These involuntary flexions also involve the legs more than the arms and occur primarily at rest when the patients are lying or sitting quietly. Some are fast and jerky; others are more sustained. The clinical impression of different observers is that the faster "dyskinesias while awake" represent true myoclonus [1, 3]. The "dyskinesias while awake" are often stereotypical and repeat periodically (like PMS), aperiodically, or they may occur in clusters with, for example, four, five, or more rapid jerks of the legs occurring in quick succession [1].
5. Sleep disturbances.
6. A tendency to be worse at night.
7. A positive family history for RLS may also be present in some cases [1, 3].

Because the dopamine precursor L-dopa has been reported to relieve the symptoms of RLS [4, 5] and because of a report that 2 patients with RLS subjectively improved with the dopamine agonist bromocriptine [4], we conducted a double-blind randomized crossover trial of bromocriptine versus placebo in 6 patients who were severely affected with idiopathic RLS, and quantitated results polysomnographically.

Materials and Methods

Six patients with a history of restlessness and paresthesias that were worse at night and did not occur secondary to neuroleptics, neuropathy, or other causes were entered into the study. Four men and 2 women (mean age 61 years; range 40–68 years) had long-term symptoms (mean 19 years; range 10–39 years). All 6 also had a history of sleep disturbances and jerking of the arms or legs either during wakefulness or sleep. Informed consent was obtained from all patients.

Over a 30-day period, patients were given gradual increments of drug or placebo to a total of 3 tablets in 1 or 2 divided doses 1 to 3 hours prior to sleep (total dose of bromocriptine, 7.5 mg). Patients were studied polysomnographically [6, 7] on 2 nights prior to the first phase and 2 nights at the end of each phase of the study. There was a 2-week washout period between phases when the patient did not take either set of tablets. Patients were questioned about whether restlessness or paresthesias had changed during each phase of the study. Using established polysomnographic methods, PMS were quantitated by electromyogram (EMG) of the legs (electrodes placed at a minimum on both tibial anterior muscles) and videotape [2, 6]. To be counted as PMS, at least five periodic movements of sleep had to be present in a row [2]. Because the semicontinuous tossing and turning in bed in RLS occurs mostly during the waking state [1, 3], discrete involuntary movements that occur during sleep, such as PMS, are generally unobscured by these semicontinuous restless movements on EMG and can thus be distinguished from them. Sleep parameters were quantitated by electroencephalogram using standard scoring techniques [6, 7] (electrodes placed at a minimum on O_1-A_2 and C_4-A_1), electro-oculogram (left outer canthus and right outer canthus), mentalis EMG, abdominal excursion, nasal air flow, and electrocardiogram. Analysis of variance for objectively collected data was performed by using the individual numerical values (not the average of the two values) for the duplicate studies. If the analysis of variance showed that a particular parameter was statistically significant among the three conditions (control, placebo, drug), a second analysis of variance was done comparing placebo to drug for that particular parameter.

Results

Clinical Features

All 6 patients experienced restlessness and paresthesias. Six patients exhibited PMS polysomnographically and these were quantitated in 4 (Tables 1, 2). Five patients polysomnographically had "dyskinesias while awake" as previously defined [1] (not quantitated). All 6 patients historically had sleep disturbances, but these were polysomnographically severe in only 3 (Patients 1, 2, and 7) (see Table 2). Family history in 4 patients suggested RLS.

Therapeutic Response

RESTLESSNESS AND PARESTHESIAS. Five patients under blinded conditions identified bromocriptine as the drug that partially relieved restlessness and paresthesias. The sixth patient had no subjective improvement from either phase of the study. The 5 responders expressed a desire to continue on the medication and 2 of our early patients (Patients 2 and 7) continue with bromocriptine as an adjunctive therapy after 8 and 12

Table 1. Average Response of Periodic Movements of Sleep and Sleep Parameters to Bromocriptine and Placebo in 6 Patients with Restless Legs Syndrome

PMS and Sleep Parameters	Control	Placebo	Drug
Total PMS/night of sleep (n = 4)	278	302	193[a]
PMS/hour sleep (n = 4)	65	86	37[a]
% REM (of sleep period time) (n = 6)	10	10	10
% Stages 1 and 2 (of sleep period time) (n = 6)	43	48	58
% Stages 3 and 4 (of sleep period time) (n = 6)	10	17	12
Total sleep time (minutes) (n = 6)	224	234	275
Sleep efficiency (n = 6)	55%	60%	70%

[a] $p < 0.025$ by analysis of variance as compared to placebo. Nos. of PMS per hour of sleep decreased 43% from control subjects and 57% from placebo.

PMS = periodic movements of sleep; REM = rapid eye movement.

Table 2. Individual Response of Periodic Movements of Sleep and Sleep Parameters to Bromocriptine and Placebo in 6 Patients with Restless Legs Syndrome[a]

Patient No.		PMS/Night Sleep	PMS/Hour Sleep	Total Sleep Time	Sleep Efficiency (%)	% Stages 1 & 2	% Stages 3 & 4	% REM
1	Control			88	23	34	0	1
	Placebo			205	59	41	23	6
	Drug			148	43	65	2	13
2	Control	299	120	146	42	48	5	6
	Placebo	257	184	98	30	47	3	4
	Drug	308	78	250	73	68	9	1
7[b]	Control			16	6	12	0	0
	Placebo			13	5	56	0	0
	Drug			103	35	40	5	2
4	Control	245	44	336	93	65	18	15
	Placebo	332	54	372	94	56	25	16
	Drug	191	31	370	95	61	19	15
5	Control	220	33	400	87	50	21	17
	Placebo	342	52	399	88	44	38	11
	Drug	174	26	405	91	59	26	6
6	Control	350	59	360	78	49	15	20
	Placebo	276	52	319	84	49	16	20
	Drug	98	16	374	83	52	13	23

[a]Each value listed represents an average of two polysomnographic studies.
[b]Patient 3 did not complete the study and was replaced by Patient 7.

PMS = periodic movements of sleep; REM = rapid eye movement.

months, respectively. The only side effects from bromocriptine were encountered in 1 patient who experienced some transient nasal stuffiness and lightheadedness.

PERIODIC MOVEMENTS IN SLEEP. For the group as a whole, on bromocriptine there was a significant decrease in the total number of PMS per night of sleep ($p < 0.025$) and the PMS per hour of sleep (43% decrease from control and 57% decrease from placebo) ($p < 0.025$) (see Table 1).

SLEEP PARAMETERS. There was no change on bromocriptine in the percent of sleep period time spent in REM sleep or Stages 3 and 4 of sleep (deep sleep) (see Table 1). However, patients on bromocriptine spent an extra 10 to 15% of their sleep period time in Stages 1 and 2 (light sleep) (see Table 1). For the group as a whole, there was also an increase in total sleep time and a 10 to 15% increase in sleep efficiency (see Table 1). None of these changes were statistically significant, but the changes in total sleep time and sleep efficiency were almost entirely due to improvement in these parameters in 2 patients who initially had very poor sleep patterns (Patients 2 and 7) (see Table 2). Although a third patient with very poor sleep patterns (Patient 1) also showed improvement in total sleep time and sleep efficiency while on bromocriptine, he, in addition, showed an improvement on placebo (see Table 2). The remaining 3 patients objectively had relatively good sleep under control conditions (Patients 4, 5, and 6) and did not experience any improvement in sleep on the drug (see Table 2).

Discussion

Other authors have reported that L-dopa [4, 5] and dopamine agonists [4] ameliorate the symptoms of idiopathic RLS. Our data indicate that the D_2 receptor agonist bromocriptine may decrease PMS and ameliorate restlessness, paresthesias, and sleep disturbances in some patients with RLS. Others have reported that dopamine antagonists exacerbate the symptoms of RLS or cause restlessness of the type associated with neuroleptics (neuroleptic-induced akathisia) [8]. This latter point is important because the restlessness of RLS and neuroleptic-induced akathisia look clinically similar, i.e., each may present with floor pacing, body rocking, or marching in place [1, 8]. Thus dopamine agonists and antagonists have opposite effects on motor restlessness and the dopaminergic system may therefore be implicated in the pathogenesis of RLS.

The dopamine system may not be the only neurotransmitter system involved pathogenetically in RLS because opioid agonists and antagonists [9–11] and adrenergic agonists and antagonists [12–14] also have opposite effects on symptoms such as restlessness and PMS. Thus the endogenous opioid system and the adrenergic system may also play a role in RLS. As a

corollary, opioid agonists [9–11] and adrenergic antagonists [12, 13] both seem to be therapeutically useful in RLS, and we might add that the effect of bromocriptine in decreasing the number of PMS in RLS patients is certainly modest compared to that of the opioids [10, 11]. The relative contribution and sites of central nervous system action of these neurotransmitter systems might be further elucidated by a positron emission tomographic scan study with receptor-specific ligands [15].

This work was funded by a grant from the Sandoz Corporation.

We thank Ms LuAnn Thorne for typing this manuscript and Donna Smith, Mitch Rubinstein, and Ramone Ramos for their technical assistance.

References

1. Walters A, Hening W, Chokroverty S. Frequent occurrence of myoclonus while awake and at rest, body rocking and marching in place in a subpopulation of patients with restless legs syndrome. Acta Neurol Scand 1988;77:418–421
2. Coleman R, Pollak CP, Weitzman ED. Periodic movements in sleep (nocturnal myoclonus): relation to sleep disorders. Ann Neurol 1980;8:416–421
3. Boghen D, Peyronnard JM. Myoclonus in familial restless legs syndrome. Arch Neurol 1976;33:368–370
4. Akpinar S. Restless legs syndrome treatment with dopaminergic drugs. Clin Neuropharmacol 1987;10:69–79
5. Montplaisir J, Godbout R, Poirier G, Bedard MA. Restless legs syndrome and periodic movements in sleep: pathophysiology and treatment with L-dopa. Clin Neuropharmacol 1986;9:456–463
6. Guilleminault C, ed. Sleeping and waking disorders: indications and techniques. Menlo Park, CA: Addison-Wesley, 1982
7. Rechtschaffen A, Kales A, eds. A manual of standardized terminology, techniques, and scoring system for sleep stages of human subjects. Los Angeles: UCLA Brain Information Service and Brain Research Institute, 1968
8. Munetz MR, Cornes CL. Distinguishing akathisia and tardive dyskinesia: a review of the literature. J Clin Psychopharmacol 1983;3:343–350
9. Trzepacz PT, Violette EJ, Sateia MJ. Response to opioids in three patients with restless legs syndrome. Am J Psychiatry 1984;141:993–996
10. Walters A, Hening W, Côté L, Fahn S. Dominantly inherited restless legs with myoclonus and periodic movements of sleep: a syndrome related to the endogenous opiates? In: Fahn S, Marsden CD, Van Woert MH, eds. Myoclonus: advances in neurology, Vol 43. New York: Raven, 1986:309–319
11. Hening WA, Walters A, Kavey N, et al. Dyskinesias while awake and periodic movements of sleep in restless legs syndrome: treatment with opioids. Neurology 1986;36:1363–1366
12. Handwerker JV, Palmer RF. Clonidine in the treatment of restless legs syndrome. N Engl J Med 1985;313:1228–1229
13. Ware JC, Pittard JT, Blumoff RL. Treatment of sleep-related myoclonus with an alpha-receptor blocker. Sleep Res 1981; 10:242
14. Ware JC, Brown FW, Moorad PJ, et al. Nocturnal myoclonus and tricyclic antidepressants. Sleep Res 1984;13:72
15. Frost JJ, Dannals RF, Ravert HT, et al. Imaging opiate receptors with positron emission tomography. J Nucl Med 1984;25:P73

Brain Neurotransmitters in Glycine Encephalopathy

Stephen J. Kish, PhD,*†‡ Lori M. Dixon, BSc,*
W. McIntyre Burnham, PhD,‡ Thomas L. Perry, MD,‖
Lawrence Becker, MD,¶ Jerome Cheng, BSc,‡
Li-Jan Chang, MSc,* and Michelle Rebbetoy, BSc*

We measured neurotransmitter markers in autopsied brain of infants with glycine encephalopathy (GE). Because patients with GE develop intractable seizures, special attention was devoted to those neurotransmitter systems implicated in human epilepsy. Mean levels of glycine in the frontal cortex of GE patients were three times higher than control values. No abnormalities were observed for concentrations of gamma-aminobutyric acid (and related receptors), other major neurotransmitter amino compounds, or activities of cholineacetyltransferase and aspartate aminotransferase. Mean acetylcholinesterase activity was significantly elevated by 46%. As experimental data suggest, glycine markedly potentiates the action of the excitatory neurotransmitter glutamic acid. To the extent that the brain seizures in patients with GE can be explained by this mechanism, pharmacotherapy with excitatory amino acid antagonists may represent a new approach to the treatment of GE.

Kish SJ, Dixon LM, Burnham WM, Perry TL, Becker L, Cheng J, Chang L-J, Rebbetoy M. Brain neurotransmitters in glycine encephalopathy. Ann Neurol 1988;24:458–461

Glycine encephalopathy (GE, nonketotic hyperglycinemia) is an autosomal recessive disorder of infants characterized biochemically by altered glycine metabolism and clinically by intractable seizures, lethargy, spasticity, severe mental retardation, and early death [1]. In GE, marked elevation of glycine is observed in cerebrospinal fluid and brain [2] consequent to a defect in the glycine cleavage enzyme [3].

Apart from biochemical studies of glycine and its metabolizing enzymes, little information is available with respect to studies of the behavior of major nonglycinergic neurotransmitter systems in the brains

From the *Clarke Institute of Psychiatry, Toronto, the Departments of †Psychiatry, ‡Pharmacology, and §Neuropathology, University of Toronto, ¶Hospital for Sick Children, Toronto, Ontario, Canada, and the ‖Department of Pharmacology, University of British Columbia, Vancouver, BC, Canada.

Received Dec 7, 1987, and in revised form Mar 16, 1988. Accepted for publication Mar 24, 1988.

Address correspondence to Dr Kish, Human Brain Laboratory, Clarke Institute of Psychiatry, 250 College St, Toronto, Ontario M5T 1R8 Canada.

