

NEUROLOGY

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Carl W. Bazil, Douglas Short, David Crispin and Wei Zheng
Neurology 2000;55;1746-1748

This information is current as of April 20, 2006

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Patients with intractable epilepsy have low melatonin, which increases following seizures

Article abstract—Melatonin, which is used to treat sleep disorders, has anticonvulsant properties. The authors measured salivary melatonin and cortisol, at baseline and following seizures, in patients with intractable temporal lobe epilepsy and controls. Melatonin was reduced in patients with epilepsy at baseline compared with controls, and increased threefold following seizures. Cortisol also increased following seizures. Patients with intractable epilepsy have low baseline melatonin levels that increase dramatically following seizures.

NEUROLOGY 2000;55:1746–1748

Carl W. Bazil, MD, PhD; Douglas Short, MPH; David Crispin, MD; and Wei Zheng, PhD

Despite many new antiseizure drugs and improvements in surgical treatment, intractable epilepsy is common. Patients with intractable epilepsy are affected by seizures, by sleep disorders, and by postictal lethargy, which can last for days following even a brief seizure.¹

Melatonin has been advocated in the treatment of sleep disorders, particularly those associated with circadian rhythm disturbance such as jet lag and shift work.² In addition, studies in both animals³ and humans^{4,5} suggest that melatonin has anticonvulsant properties. Seizures are known to affect other hormones (e.g., prolactin and cortisol); therefore, it is possible that melatonin plays a role in seizure control or sleep regulation in patients with epilepsy. The effects of chronic epilepsy on melatonin and cortisol levels, both at baseline and following complex partial seizures are discussed below.

Methods. All eligible patients admitted to the Epilepsy Monitoring Unit at Columbia–Presbyterian Medical Center were asked to participate. To control for possible variations between seizure types, only patients with temporal lobe epilepsy were included. All patients gave informed written consent. Use of sedative-hypnotic drugs, alcohol, and caffeine was prohibited for 24 hours before the testing period. Patients included in the study usually continued anticonvulsant treatment but were not taking benzodiazepines or barbiturates. Anticonvulsants were typically tapered during the hospitalization. Control subjects had no known sleep disturbance and no neurologic disease likely to interfere with sleep, melatonin, or cortisol. None were taking steroids during the collections.

Patients and controls had saliva collected at 3-hour intervals (2, 5, 8, 11, 14, 17, 20, and 23 hours) by chewing a salivette, beginning no earlier than the second hospital day. Lights remained dim throughout nighttime sampling. Baseline measurements began following an interval of at least 24 hours seizure-free, and consisted of a 24-hour period with no seizure. Seizure measurements began follow-

ing a documented seizure (complex partial or secondarily generalized), and continued for 24 hours.

Samples were stored at -4°C until analysis and protected from light. Melatonin and cortisol were measured by radioimmunoassay using commercially available kits (DiagnosTech International, Inc., Osceola, WI). Both area under the saliva concentration-time curve (AUC) and maximal saliva concentration (C_{max}) were calculated for each 24-hour period. All results are presented as $\pm\text{SEM}$, and significance was determined by Wilcoxon signed-rank test (for paired data) or rank sum test.

Results. More than 90% of the patients asked to participate in the study agreed to do so. Eleven patients had suitable measurements under both baseline and seizure conditions (age 41 ± 3 ; range: 26 to 55 years). Temporal lobe epilepsy was verified by video-EEG recording of typical seizures. Six control patients were also obtained (age 38 ± 2 ; range: 33 to 46 years). Control patient diagnoses included MG, transverse myelitis, MS, and vertigo.

The times of melatonin peak for a representative patient and control are shown in figure 1. The control patient has a fairly normal distribution, with a peak at 2 AM. Under baseline conditions, the patient had an overall lower amount secreted and a peak at 11 PM. Following a secondarily generalized seizure at 4:25 PM, a melatonin surge compared with baseline occurred, with a peak over the next 24 hours at 2 AM. Results for all patients are summarized in figure 2. Baseline melatonin for patients under baseline conditions was less than control patients (45 ± 7 versus 87 ± 15 pg/mL-h; $p < 0.05$). Melatonin increased in patients following seizures, to 142 ± 52 pg/mL-h ($p < 0.05$). Peak melatonin levels (for all seizures) under patient baseline, seizure, and control conditions were 8 ± 2 , 23 ± 9 , and 15 ± 3 pg/mL; these differences were not statistically significant. When only secondarily generalized seizures were included ($n = 8$) the pattern was similar for AUC (see figure 2), with peak melatonin levels also significantly elevated following seizures (28 ± 11 versus 7 ± 2 pg/mL for patient baseline).

Figure 3 shows salivary cortisol under the same conditions. AUC was increased following seizures (4.2 ± 0.7 versus 10.9 ± 2.5 $\mu\text{g/dL-h}$; $p < 0.05$). Baseline levels were not statistically significantly different between patients and controls.

Discussion. This study shows decreased melatonin in patients with temporal lobe epilepsy compared with controls, and increased melatonin and cortisol

From the Department of Neurology (Drs. Bazil, Short, and Crispin) and Pharmacology (Dr. Zheng), Columbia University College of Physicians and Surgeons, New York, NY.

Supported by a grant from the Epilepsy Foundation of America.

Received March 6, 2000. Accepted in final form August 2, 2000.

Address correspondence and reprint requests to Dr. Carl W. Bazil, the Neurological Institute, 710 West 168th Street, New York, NY 10032; e-mail: cwb11@columbia.edu

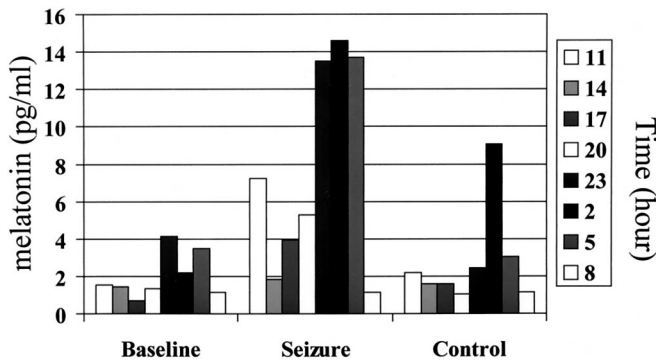


Figure 1. Melatonin levels in a patient with temporal lobe epilepsy, under baseline and seizure conditions. The patient is a 26-year-old woman; a secondarily generalized seizure occurred at 16:25 and lasted 4 minutes and 16 seconds. A control patient, a 45-year-old woman with vertigo, shown for comparison, manifests a normal diurnal pattern.

in the 24-hour period following seizures. This has three important implications. First, as melatonin has anticonvulsant properties, treatment with exogenous melatonin could improve seizure control in these patients. Second, a melatonin surge following seizures may be protective against repetitive seizures. Finally, better regulation of melatonin could improve sleep and, therefore, symptoms of postictal lethargy.

Previous studies of melatonin in patients with epilepsy showed variable results, probably because they were not controlled for seizure occurrence. The secretion of several hormones was compared in 12 patients with epileptic and nonepileptic seizures and 28 normal control subjects.⁶ Serum cortisol (along with prolactin, thyrotropin, and growth hormone) was increased postictally, but melatonin remained within normal limits. Other studies have suggested

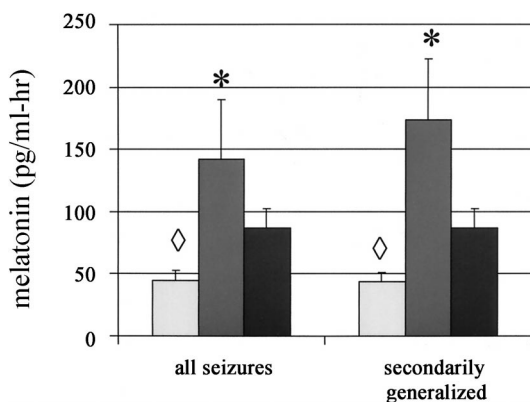


Figure 2. Melatonin levels (area under the saliva concentration-time curve for 24 hours) in patients with temporal lobe epilepsy under baseline and seizure conditions, compared with control patients. Data are shown for all seizures, and for only patients with secondarily generalized seizures. Light gray bars = baseline; dark gray bars = seizure; black bars = controls. Asterisks indicate $p < 0.05$ compared with patient baseline; diamonds indicate $p < 0.05$ compared with control patients.

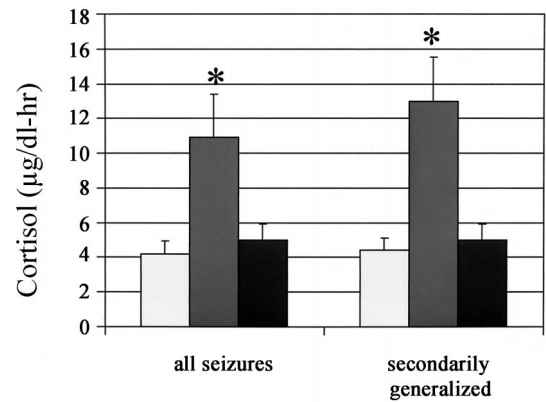


Figure 3. Cortisol levels (area under the saliva concentration-time curve for 24 hours) in patients with temporal lobe epilepsy under baseline and seizure conditions, compared with control patients. Data are shown for all seizures, and for only patients with secondarily generalized seizures. Light gray bars = baseline; gray bars = seizure; black bars = control. Asterisks indicate $p < 0.05$ compared with patient baseline.

that seizures do alter melatonin secretion. Single serum melatonin levels from children with epilepsy, combined to give a 24-hour profile, suggested disruption of the diurnal pattern with epilepsy.⁷

The implications of the changes seen in melatonin are unclear at present. However, an extensive body of literature supports the anticonvulsant properties of melatonin in a wide variety of animal models of epilepsy, and in humans. In gerbils, pinealectomy causes seizures, an effect which is reversed with exogenous melatonin use.⁸ In rats, melatonin inhibits amygdala-kindled seizures,³ and antibodies to melatonin induced seizures.⁹

Human studies have been indirect, but support an anticonvulsant role for melatonin.⁴ A single preliminary study of melatonin treatment in 10 children with severe epilepsy has been published.⁵ All were given open label melatonin (5 to 10 mg) 1 hour before bedtime. Six showed decreased seizure frequency by seizure calendar, and eight showed improvement in sleep according to a subjective rating scale. Interestingly, salivary melatonin measured in six patients suggested decreased melatonin compared with controls, which was restored to normal by melatonin treatment. It is unclear whether improvement in seizures resulted from improved sleep, a direct anticonvulsant effect of melatonin, or to a placebo effect.

Considerable evidence indicates that melatonin has anticonvulsant properties. This study demonstrates that patients with temporal lobe epilepsy have low melatonin compared with controls. Although it is possible that anticonvulsant treatment contributed to this finding, these agents are not known to affect melatonin levels or pattern of secretion. Whether low melatonin represents the cause or effect of seizures remains uncertain. It is possible that melatonin, through a more general inhibitory effect, prevents large ensembles of neurons from syn-

chronous discharge. The lack of sufficient basal level of melatonin in patients with refractory epilepsy could thereby facilitate seizures. Alternatively, repeated seizures could alter the feedback regulatory mechanisms coordinated by the pineal gland. Thus, the low level of melatonin reflects, at least partially, a disorder in neuroendocrine regulation among these patients. The increased melatonin seen following seizures could be a protective mechanism against repetitive seizures. Increased melatonin may also contribute to tiredness following temporal lobe seizures, although seizures are known to disrupt sleep structure and particularly REM sleep.¹⁰ Restoring melatonin to the normal level, perhaps using oral melatonin supplements, is worthy of further study. Randomized clinical trials are needed to further clarify the influence of melatonin on intractable epilepsy.

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A placebo-controlled crossover trial of creatine in mitochondrial diseases

Article abstract—To test the efficacy and safety of creatine (Cr) monohydrate in mitochondrial diseases, 16 patients with chronic progressive external ophthalmoplegia or mitochondrial myopathy were randomized in a crossover design to receive double-blind placebo or 20 g Cr/day for 4 weeks. Cr was well tolerated, but there were no significant effects with regard to exercise performance, eye movements, or activities of daily life. The power of this pilot study was limited and future multicenter trials are needed.

NEUROLOGY 2000;55:1748–1751

T. Klopstock, MD; V. Querner, MD; F. Schmidt; F. Gekeler, MD; M. Walter, MD; M. Hartard, MD; M. Hennig, Dipl-Stat; T. Gasser, MD; D. Pongratz, MD; A. Straube, MD; M. Dieterich, MD; and W. Müller-Felber, MD

Creatine (Cr) is a naturally occurring compound that plays a pivotal role in the regulation of energy metabolism. The highest Cr concentrations are found in muscle and brain, where the enzyme creatine kinase catalyzes the phosphorylation of Cr and the dephosphorylation of phosphocreatine (PCr). This acts as a

high-energy phosphate-buffering system allowing the resynthesis of adenosine triphosphate (ATP). Supplemental Cr ingestion in doses of 10 to 20 g/day for 4 to 6 days is well tolerated by healthy subjects and causes an increase of approximately 20% in muscle Cr and PCr,^{1,2} and may increase maximal power output in anaerobic activities up to 20%.³

Cr supplementation may be of particular benefit to patients with mitochondrial diseases in which depletion of ATP leads to increased dephosphorylation of PCr. MR spectroscopy (MRS) of these patients shows reduced resting PCr and delayed postexercise recovery of PCr in skeletal muscle⁴ as well as a reduced PCr/ATP ratio in the brain.⁵

A recent controlled trial showed that the administration of Cr monohydrate increased the strength of anaerobic and aerobic activities in a group of seven patients with mitochondrial diseases, comprising six patients with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes

From the Department of Neurology (Drs. Klopstock, Querner, Gekeler, Gasser, Straube, and Dieterich) and the Friedrich-Baur-Institut (Drs. Walter, Pongratz, and Müller-Felber), Ludwig-Maximilians-Universität München; and the Department of Sports Medicine (Dr. Hartard) and the Institute for Medical Statistics and Epidemiology (M. Hennig), Technische Universität München, Germany.

The investigators received no financial incentives such as equity interest, patent rights, corporate affiliation, or any other support.

Presented in part at the 51st annual meeting of the American Academy of Neurology; Toronto, Canada; April 1999.

Received September 13, 1999. Accepted in final form August 17, 2000.

Address correspondence and reprint requests to Dr. Thomas Klopstock, Department of Neurology, Klinikum Grosshadern, Ludwig-Maximilians-Universität München, D-81366 München, Germany; e-mail: klopstock@brain.nefo.med.uni-muenchen.de

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This information is current as of April 20, 2006

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