Similarities in Mechanisms and Treatments for Epileptic and Nonepileptic Myoclonus

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Myoclonus is a disordered movement that may be an ictal phenomenon or may be due to various injuries in brain and spinal cord motor structures. Many epileptic and nonepileptic myoclonic conditions are associated with abnormalities in inhibitory neurotransmission. γ-Aminobutyric acid type A ($GABA_A$)-receptor antagonists may trigger myoclonus. Several antiepilepsy drugs (AEDs) effective against myoclonic seizures [valproic acid (VPA), clonazepam (CZP), levetiracetam (LEV)] enhance GABAergic neurotransmission and improve myoclonic movement disorders. Together these associations suggest links between episodic disorders involving synchronous cortical discharges (seizures) and hyperkinetic movement disorders.

Introduction

Nikolaus Friedreich (1) introduced the term *paramyoclonus* more than 100 years ago to differentiate sudden body jerks due to motor disorders from seizure-related myoclonus. Many interesting similarities exist, however, in the mechanisms and treatments for myoclonus and epilepsy.

Myoclonus is defined as sudden jerks typically lasting 10 to 50 milliseconds, with the duration of movements rarely longer than 100 milliseconds (1). Myoclonus is usually a positive phenomenon, causing synchronized muscle contractions in single or multiple muscle groups. Negative myoclonus consists of sudden brief loss of muscle tone with associated loss in electromyogram (EMG) activity. Myoclonic jerks can be irregular, rhythmic, or even oscillatory, and occur with dysfunction in cortical, brainstem, or spinal motor systems. Cortical injuries that cause myoclonus also are frequently associated with seizures. Patients with diffuse cortical hypoxic injuries, for example, may develop both focal motor seizures with central spikes and cortical myoclonus. Neurodegenerative syndromes, encephalitis, and toxic-metabolic disorders (e.g., late stages of Alzheimer dementia, Jakob-Creutzfeldt disease, drug overdoses) may cause myoclonus and seizures.

In addition to motor system disorders associated with seizures, myoclonus occurs as an ictal phenomenon in many epilepsy syndromes. These include idiopathic (e.g., juvenile myoclonic epilepsy or JME), symptomatic (e.g. myoclonic epilepsy of infancy) and progressive disorders (e.g., Lafora body disease). Striking similarities are found in the electrophysiologic features of myoclonus and myoclonic events associated with epileptic syndromes. Cortical myoclonus is often associated with a giant central sensory-evoked potential (SEP) linked to movements on EMG back-averaging, suggesting that the sensorimotor cortex is hyperexcitable. These patients often also have central spikes on EEG. In JME, jerk-locked averaging showed an EEG polyspike complex, with a frontal maximum transient that precedes the myoclonic jerk by 10 milliseconds. Patients with JME also have reduced motor-evoked potential inhibition during transcranial magnetic stimulation, suggestive of impaired cortical inhibitory mechanisms (2). These findings suggest that the cortical discharges producing epileptic and posthypoxic myoclonus may involve similar cortical motor pathways and mechanisms. In addition, electrophysiologic studies can help in the differential diagnosis of myoclonus and movement disorders that mimic myoclonus, such as psychogenic jerks, spasms, and tremors (3,4). A recent study suggested that increased coherence of EMG and midline EEG activity may be a more sensitive marker of cortical myoclonus than cortical SEP back-averaging (5), indicating that more advanced methods of evaluating patients will lead to better diagnostic accuracy and better understanding of the pathogenesis of these disorders.

Some types of seizures and myoclonic movement disorders may share similar neuronal mechanisms. Seizures are due to synchronized discharges of action potentials, which are regulated by voltage-dependent ion channels (6) and synaptic interactions. Myoclonus, however, may be caused by hyperexcitability of populations of neurons at different levels of the affected motor system as a result of neuronal injury or degenerative disorder. Alterations of inhibitory control mechanisms

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may explain the neuronal hyperexcitability that underlies some forms of myoclonus. GABA mediates the majority of fast inhibitory synaptic transmission in the CNS; glycine is the inhibitory transmitter for some neurons in the brainstem and spinal cord. The postsynaptic receptors for GABA and glycine are pentameric arrangements of subunits around a central pore that conducts chloride when opened by transmitter binding, thereby inhibiting the postsynaptic cell. $GABA_A$ antagonists, such as bicuculline, can induce myoclonus as well as seizures when injected in rat lateral ventricles in a dose-dependent manner (7). Picrotoxin, a $GABA_A$-receptor antagonist, applied to motor cortex, striatum (caudate and putamen), and nucleus reticularis, elicits myoclonus. Glycinergic antagonists in spinal cord can induce motoneuronal oscillations, the neuronal correlate of myoclonus.

Animal models of myoclonus have been generated by producing alterations of postsynaptic $GABA_A$ or glycine receptors. Mice genetically engineered to lack the β_3 subunit of the $GABA_A$ receptor have myoclonus and seizures. Associated with reduced neuronal responses to GABA, these mice have epileptiform EEG abnormalities suggesting cortical hyperexcitability (8). A form of hereditary myoclonus, hyperekplexia, is caused by a mutation in the glycine receptor that reduces its function (9). Recently a mutation in the α_1 subunit of the $GABA_A$ receptor was found in a large family with autosomal dominant JME (10). All of these findings demonstrate that alterations in inhibitory synaptic transmission may produce myoclonus or myoclonic syndromes of the epileptic type. So far, data are lacking to implicate these mechanisms for cortical and other types of myoclonus. However, drugs that augment GABAergic transmission are useful in all types of myoclonus, suggesting that common mechanisms may be involved in myoclonic movement disorders and epilepsy.

Defects in serotonin neurotransmission also have been implicated in posthypoxic myoclonus in animal models and in humans. Posthypoxic audiogenic myoclonus in rats emulates features of the human disorder, and serotonin agonists improve myoclonus in both. A link between serotonergic transmission and epilepsy has been suggested by several lines of evidence. Decreased serotonin facilitates long-term potentiation (LTP) and kindled seizures. Genetically epilepsy-prone rats (GEPRs) appear to have deficiencies in the serotonin system, and drugs that increase extracellular serotonin ameliorate their seizures (11). Mice lacking the 5-HT2C receptor exhibit audiogenic seizures (12). Serotonin is not, however, involved in producing generalized absence seizures in the GAERS model of epilepsy.

Drugs that augment GABAergic transmission are useful in all types of myoclonus, and clonazepam (CZP) and valproic acid (VPA) are the first-line treatments. CZP augments the GABA action at the $GABA_A$ receptor. VPA's effect against myoclonus has been linked to the GABAergic system, perhaps through increasing brain levels of the transmitter and not through interaction with the receptor. Approximately 50% of patients respond to treatment, although often partially (13). Piracetam and levetiracetam (LEV) are structurally related compounds that show efficacy in the treatment of myoclonus. Piracetam, which has only weak antiseizure properties in experimental models, is a standard treatment for myoclonus in Europe, but is not available in the United States. LEV, an effective AED, blocks the effects of negative $GABA_A$-receptor modulators such as zinc (14). Preliminary studies indicate that LEV is effective for treating cortical and spinal myoclonus (15–19). Barbiturates are less effective than these agents, perhaps because they affect $GABA_A$ receptors differently. The AEDs that reduce myoclonus—VPA, CZP, LEV—do not necessarily reduce myoclonus through the same GABAergic mechanisms that reduce seizures. The anticonvulsant effect of LEV on rodent audiogenic seizures, for example, correlates with binding to a novel neuronal receptor. Piracetam, however, does not bind to this receptor, yet shares effects on myoclonus.

The AEDs shown to be effective for myoclonus are broad-spectrum agents, effective against both partial-onset and primary generalized seizures. One hypothesis is that because these AEDs enhance GABA-mediated neurotransmission, they correct defective inhibitory mechanisms such as those in posthypoxic myoclonus and in some of the generalized epilepsies that have been characterized (e.g., familial JME). This raises the possibility that other drugs effective for generalized epilepsy that affect GABAergic transmission might be effective for myoclonus. Topiramate (TPM) increases the frequency of $GABA_A$-receptor channel opening, suggesting it also may be a potential treatment for myoclonus. Tiagabine (TGB) also increases synaptic GABA and has antimyoclonic action in animal models, but has not been assessed in humans and is not effective for myoclonic epilepsy. Zonisamide (ZNS) blocks sodium channels and modulates T-type calcium channels, but also binds to the GABA ionophore without changing chloride flux.

It would be helpful to explore whether AEDs that occasionally trigger myoclonus—gabapentin (GBP), pregabalin (PGB), carbamazepine (CBZ), lamotrigine (LTG)—might indirectly affect GABA neurotransmission (20). It also would be interesting to explore similarities in mechanisms and treatments for negative myoclonus and atonic seizures. Atonic and myoclonic seizures in myoclonic-astatic epilepsy of early childhood, for example, have similar spike patterns (21). The links between GABAergic neurotransmission and treatment of hyperkinetic movement disorders and myoclonic seizures suggest an interesting therapeutic avenue, and several compounds in development specifically target this receptor complex.

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