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REVIEW

Current understanding of the mechanism of action of the antiepileptic drug lacosamide

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Summary The antiepileptic drug lacosamide [(*R*)-2-acetamido-*N*-benzyl-3-methoxypropanamide], a chiral functionalized amino acid, was originally identified by virtue of activity in the mouse and rat maximal electroshock (MES) test. Attention was drawn to lacosamide because of its high oral potency and stereoselectivity. Lacosamide is also active in the 6 Hz seizure model but inactive against clonic seizures in rodents induced by subcutaneous pentylenetetrazol, bicuculline and picrotoxin. It is also ineffective in genetic models of absence epilepsy. At doses greater than those required to confer protection in the MES test, lacosamide inhibits behavioral and electrographic seizures in hippocampal kindled rats. It also effectively terminates seizures in the rat perforant path stimulation status epilepticus model when administered early after the onset of seizures. Lacosamide does not exhibit antiepileptogenic effects in kindling or post-status epilepticus models. The profile of lacosamide in animal seizure and epilepsy models is similar to that of sodium channel blocking antiepileptic drugs, such as phenytoin and carbamazepine. However, unlike these agents, lacosamide does not affect sustained repetitive firing (SRF) on a time scale of hundreds of milliseconds or affect fast inactivation of voltage-gated sodium channels; however, it terminates SRF on a time scale of seconds by an apparent effect on sodium channel slow inactivation. Lacosamide shifts the slow inactivation curve to more hyperpolarized potentials and enhances the maximal fraction of channels that are in the slow inactivated state. Currently, lacosamide is the only known antiepileptic drug in clinical practice that exerts its anticonvulsant activity predominantly by selectively enhancing slow sodium channel inactivation.

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Introduction

The antiepileptic drug (AED) lacosamide was derived from synthetic chemistry efforts focusing on small molecules referred to as functionalized amino acids, which contain a *N*-benzyl-2-acetamidopropionamide core structure. In 1985, Harold Kohn and colleagues at the University of Houston identified N-acetyl-alanine-*N*-benzylamide as having protective activity in the mouse maximal electroshock (MES) test (Cortes et al., 1985), a widely used screening model for potential AEDs (Castel-Branco et al., 2009). Functionalized amino acids have substitutions on the C(2) carbon giving rise to a chiral center so that the molecules exist as (*R*) and (*S*) enantiomers. Subsequently, it was noted that anticonvulsant activity resides exclusively in the (*R*)-enantiomers whereas the (*S*)-enantiomers are virtually inactive (Choi et al., 1996; Kohn et al., 1988). The stereoselectivity was unusual for an AED and stimulated extensive exploration of derivatives to define the structural features conferring seizure protection. The project was enabled by the Anticonvulsant Screening Project (ASP) of the National Institute of Neurological and Communication Disorders and Stroke, a resource, directed at the time of lacosamide's discovery by Harvey Kupferberg, that provides testing in animal models. Over 250 functionalized amino acids were subsequently synthesized and evaluated by the ASP. Within a series of 2-substituted *N*-benzyl-2-acetamidopropionamide analogs, the methyl ether derivative *N*-benzyl-2-acetamido-3-methoxypropionamide (originally designated as ADD 234037, SPM 927, harkoseride and erlosamide and currently known by the United States Adopted Name lacosamide; Fig. 1) exhibited particularly potent oral activity and a low propensity to cause motor toxicity in the rotorod test, conferring it with a wide therapeutic window (Choi et al., 1996). Activity in the MES test resided exclusively in the (*R*)-enantiomer (eudismic ratio > 22), as was generally the case with *N*-benzyl-2-acetamidoacetamide derivatives such as the lead compound *N*-acetyl-alanine-*N*-benzylamide.

Lacosamide ($C_{13}H_{18}N_2O_3$; MW 250.29) displays amphiphilic properties, which means that it is lipophilic enough to be orally bioavailable and penetrate the blood–brain barrier yet it is sparingly but sufficiently soluble in aqueous solution to permit the development of a 10 mg/ml parenteral formulation without adding a solubilizing agent (Hovinga, 2003). A 10 mg/ml oral solution (syrup) is also available.

Following initial identification, the properties of lacosamide were more extensively characterized in various animal models by the ASP. A summary of the results of these studies is provided in the next section. Pre-clinical studies using in vitro electrophysiological approaches revealed that lacosamide has a novel mechanism of action in that it selectively enhances the slow inactivation of voltage-gated sodium channels (VGSCs). Conventional sodium-channel blocking AEDs are believed to protect against seizures primarily by interacting with the fast inactivated state of VGSCs (Rogawski and Löscher, 2004). Lacosamide does not affect fast inactivation of VGSCs. While the precise mechanism by which lacosamide exerts its antiepileptic effect in humans remains to be fully elucidated, a review of our current understanding is presented in the following sections.

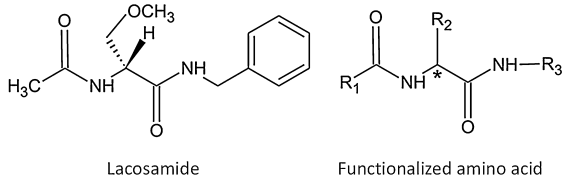

Figure 1 Chemical structure of lacosamide and a functionalized amino acid.