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Review

Isobolographic analysis of the mechanisms of action of anticonvulsants from a combination effect

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Diazepam (PubChem CID: 3016)
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Ethosuximide (PubChem CID: 3291)
Etomidate (PubChem CID: 36339)
Felbamate (PubChem CID: 3331)
Gabapentin (PubChem CID: 3446)
Glutamate diethyl ester (PubChem CID: 73961)
Ifenprodil (PubChem CID: 3689)
Ketamine (PubChem CID: 3821)
Lamotrigine (PubChem CID: 3878)
Levetiracetam (PubChem CID: 5284583)
Loreclezole (PubChem CID: 3034012)
Losigamone (PubChem CID: 6918049)
LY233053 (PubChem CID: 15928273)
LY235959 (PubChem CID: 131938)
LY354740 (PubChem CID: 213056)
Memantine (PubChem CID: 4054)
MeTHIQ (PubChem CID: 92214)
Muscimol (PubChem CID: 4266)
NBQX (PubChem CID: 3272524)
Oxcarbazepine (PubChem CID: 34312)
Phenobarbital (PubChem CID: 4763)
Phenytoin (PubChem CID: 1775)
Pregabalin (PubChem CID: 5486971)
Procyclidine (PubChem CID: 4919)
Propofol (PubChem CID: 4943)
Retigabine (PubChem CID: 121892)
Riluzole (PubChem CID: 5070)
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ABSTRACT

The nature of the pharmacodynamic interactions of drugs is influenced by the drugs' mechanisms of action. It has been hypothesized that drugs with different mechanisms are likely to interact synergistically, whereas those with similar mechanisms seem to produce additive interactions. In this review, we describe an extensive investigation of the published literature on drug combinations of anticonvulsants, the nature of the interaction of which has been evaluated by type I and II isobolographic analyses and the subthreshold method. The molecular targets of antiepileptic drugs (AEDs) include Na^+ and Ca^{2+} channels, GABA type-A receptor, and glutamate receptors such as NMDA and AMPA/kainate receptors. The results of this review indicate that the nature of interactions evaluated by type I isobolographic analyses but not by the two other methods seems to be consistent with the above hypothesis. Type I isobolographic analyses may be used not only for evaluating drug combinations but also for predicting the targets of new drugs.

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Stiripentol (PubChem CID: 5311454)
Talampanel (PubChem CID: 164509)
Tiagabine (PubChem CID: 60648)
Topiramate (PubChem CID: 5284627)
Trihexyphenidyl (PubChem CID: 5572)
Valproate (PubChem CID: 3121)
Vigabatrin (PubChem CID: 5665)
Zonisamide (PubChem CID: 5734)
α-Aminoadipic acid (PubChem CID: 469)
γ-Hydroxybutyric acid (PubChem CID: 10413)

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Subthreshold method
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Contents

1. Introduction

Multiple drug therapy (in which two or more drugs are administered together) is routinely used in various drug therapies. The effects of a given drug combination are analyzed in preclinical studies in various disease models. The pharmacodynamic interactions between two drugs are called synergistic, additive, or antagonistic when the magnitude of the effects is large, equal, or small compared to the effects of the individual drugs, respectively (Chou, 2006). The molecular mechanisms of individual drugs can be expected to influence the pharmacodynamic interaction of the drugs.

There are two distinct types of analytical methods for investigating drug interactions. One is the type I isobolographic analysis, which evaluates combinations of two drugs using the two drugs' effective doses. The other type of analytical method is comprised of both the type II isobolographic analysis and the subthreshold method, both of which evaluate combinations using the effective dose of a drug with a subthreshold dose of another drug (Greco et al., 1995). In contrast to these two methods, the type I isobolographic analysis is thought to be the most robust method to analyze the nature of the interaction between two drugs in terms of synergy, additivity, or antagonism (Berenbaum, 1989).

It has been hypothesized that the interaction of two drugs that have the same mechanisms usually results in an additive or antagonistic interaction, and that two drugs with different mechanisms produce a synergistic interaction (Czuczwar and Borowicz, 2002; Deckers et al., 2000). However, this theory does not account for the conflicting conclusions obtained by different modeling methods for exactly the same combinations of drugs. For instance, when oxcarbazepine (OXC) is combined with conventional antiepileptic drugs (AEDs) (Luszczki and Czuczwar, 2003), and when pregabalin (PGB) is combined with lamotrigine (LTG), OXC, or topiramate (TPM) (Luszczki et al., 2010b), the combinational effects identified using a type I isobolographic analysis are not always comparable to the effects identified using the subthreshold method. Moreover, synergistic effects are found more often by the subthreshold method compared to isobolographic analyses (Jonker et al., 2007). The inconsistent conclusions seem to be associated with the different modeling methods.

In this review, we evaluate the published studies on the nature of interactions of drug combinations which have been analyzed by a type I or type II isobolographic analysis or the subthreshold method. We focus on anticonvulsant drugs (whose mechanisms have been characterized by electrophysiological and biochemical methods), and on two animal models: the maximal electroshock seizures (MES) and pentylenetetrazole (PTZ)-induced clonic seizures in mice. We discuss how the analytical methods used to evaluate drug interactions influence the conclusions regarding the nature of the interactions, and we suggest the analytical methods that would be the most appropriate for deducing the mechanisms of action of drugs.