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Interactions between drugs and occupied receptors☆

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Abstract

This review has 2 parts. Part I deals with isobolographic procedures that are traditionally applied to the joint action of agonists that individually produce overtly similar effects. Special attention is directed to newer computational procedures that apply to agonists with dissimilar concentration–effect curves. These newer procedures are consistent with the isobolographic methods introduced and used by Loewe, however, the present communications provides the needed graphical and mathematical detail. A major aim is distinguishing super and sub-addictive interactions from those that are simply additive. The detection and measurement of an interaction is an important step in exploring drug mechanism and is also important clinically. Part II discusses a new use of isoboles that is applicable to a single drug or chemical whose effect is mediated by 2 or more receptor subtypes. This application produces a metric that characterizes the interaction between the receptor subtypes. The expansion of traditional isobolographic theory to this multi-receptor situation follows from the newer approaches for 2-drug combination analysis in Part I. This topic leads naturally to a re-examination of competitive antagonism and the classic Schild plot. In particular, it is shown here that the Schild plot in the multi-receptor case is not necessarily linear with unit slope. Both parts of this review emphasize the quantitative aspects rather than the many drugs that have been analyzed with isobolographic methods. The mathematical exposition is rather elementary and is further aided by several graphs. An appendix is included for the reader interested in the mathematical details.
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Keywords: Isobole; Synergism; Additivity; Receptor interaction; Schild plot; Knockout animals; Muscarinic receptors

Contents

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1. Drug combinations

1.1. Introduction

The simultaneous presence of 2 or more drugs is a common occurrence in clinical settings and in numerous experimental designs aimed at studying mechanism. When 2 drugs (or chemicals) that produce overtly similar effects are simultaneously present it is important to detect and characterize any interaction that leads to either exaggerated or reduced effects. That characterization requires measurement, that is, quantitation yielding a metric that distinguishes between the expected and the actual effect magnitudes. Obtaining that metric is an important step in the exploration of mechanism. Even when a single drug is administered to a living system it is present in a sea of endogenous chemicals. Thus, studies of drug action are enhanced by models that apply to drug combination situations. Interactions between drugs can be inhibitory or potentiating. This first part of this article is devoted to isobolar methods for measuring interactions between agonist drugs. The second part introduces a novel strategy for determining interactions between 2 or more receptors that are occupied by the same drug. For convenience in expression I will often refer to the compounds as "drugs" whether these are actual drugs, experimental compounds or other chemicals. Drug pairs that involve competition between an agonist and antagonist at the same receptor, though well characterized quantitatively, are not generally amenable to isobolar methods for reasons that will be discussed here. However, the well-known models of competition for a single-receptor will be shown to be very relevant to the topic of the second part of this communication.

Of special interest are those cases in which 2 drugs that individually produce overtly similar effects yield a superadditive (synergistic) effect when they are present together. Superadditivity refers to an effect that is above that which is *expected* from the individual dose effect relations. This invites the questions, what is the criterion on which that expectation is based? And what is meant by *additivity*, whether it describes 2 drugs or 2 receptors stimulated by the same drug? These are key topics that are addressed in this review.

Numerous possible mechanisms might explain why the action of agonist drug B is enhanced by agonist drug A. For example, any one or more than one of the following might apply: (1) Drug A might enhance the affinity of B for its receptor, (2) cause release of some effect enhancing chemical, (3) promote increased delivery of B to its receptor, (4) decrease the elimination of B, (5) enhance guanine nucleotide exchange (activation of G-protein), (6) activate an enzyme, (7) affect feedback control, etc. Often the intimate mechanism is unknown. Sometimes the effect of the combination is greatly enhanced, indicating synergism. If synergism is detected, and this is a quantitative pursuit, then that finding can help illuminate the mechanism of both the single and combined drug action. It may also help guide new drug development, reduce toxic interactions, aid therapy and, almost certainly, guide the direction of new experimental designs. Distinguishing synergism from normal additivity is an important first step in the further exploration of mechanism and it is that topic that begins this review.

1.2. Drug combinations and isoboles

Studies of combinations of chemicals in the early 20th century had agricultural aims. Pesticide development motivated early investigations, for example, insects placed on a screen were dosed with individual and combination chemicals to assess their effectiveness. Determining the percent that were killed in each case provided a metric for assessing combination action. A quantitative method for evaluating combinations of drugs was introduced by Loewe and Muischnek (1926). This is a graphical method that, in subsequent communications (Loewe, 1927, 1928, 1953), became ultimately known as isobolographic analysis. This analysis employs a graph known as an *isobologram* which will be defined and extensively discussed in this review.

While the isobole was introduced in the 1920's it seems to have had limited use, though several notable later studies did employ the methodology (e.g., Smith & Corbascio, 1966; Gessner & Cabana, 1970; DiFazio et al., 1972; Pircio et al., 1978; Masusda et al., 1981) and, in one study, the method was even expanded to deal with interactions among 3 drugs (Gershwin & Smith, 1973). More recent studies using isobolographic methods, often with analgesics and other CNS drug combinations, suggest an increase in the use of this methodology (e.g., Horan et al., 1992; Raffa et al., 1993; Kimmel et al., 1997; Bolan et al., 2002; Field et al., 2002; Miranda et al., 2002; Tallarida, 2002b). There have been several reviews dealing with isobolographic analysis and its application to various drug combinations (Wessinger, 1986; Berenbaum, 1989; Tallarida, 1992, 2000, 2001, 2006). Certain recent works by this author, referenced throughout this communication, deal with some of the newer applications of isobolographic methodology and focus on the question of how an isobole is actually constructed from the dose–response data of the individual drugs, regardless of their shape. Of special interest is how the isobole method leads to a way of measuring the interaction between drugs. These are major topics in this communication, which takes a more in depth examination of the methodology and demonstrates its extension to situations to which the common method would not apply. The analysis starts with a determination of complete dose–effect data for the

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