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Receptor partial agonism and method to express receptor partial activation with respect to novel Full Logistic Model of mixture toxicology

Martin Ezechiáš[a,b], Tomáš Cajthaml[a,b,*]

[a] Laboratory of Environmental Biotechnology, Institute of Microbiology of the CAS, v.v.i., Vídeňská 1083, Prague, 142 20, Czech Republic
[b] Institute for Environmental Studies, Faculty of Science, Charles University in Prague, Albertov 6, Prague, 128 43, Czech Republic

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ABSTRACT

Living organisms interact with various chemical compounds via receptors, which is described by the receptor theory. The affinity of the biologically active compounds toward receptors and their ability to trigger a biological or toxic signal vary substantially. In this work, we describe a new insight into understanding of the mode of action of receptor partial agonists and the receptor theory using a Full Logistic Model (FLM) of mixture toxicology. We describe the hypothesis that the effect of a partial agonist can be mathematically described via separation of agonistic and antagonistic behavior of the partial agonist where the antagonistic effect is described as an action of the compound producing zero effect. In this way, a competitive antagonist can be considered as an agonist with zero effect. This idea is also placed into a context with classical concepts, e.g., Gaddum's equation. Using the assumption that competitive antagonists are agonists with no effect, equations describing the microscopic and macroscopic equilibrium constants have been derived. Accordingly, we show that the constants could be calculated from the measured partial agonistic dose-response curve. As a consequence, we provide a simple mathematical tool for comparison of dose-response curves of drugs according to their affinities and efficacies.

1. Introduction

Human organisms are exposed daily to various chemicals, drugs and environmental pollutants that may cause health adverse effects. The receptor theory is a commonly accepted concept of how a chemical or drug interacts with organisms. The receptor theory states that chemicals (agonists) act through macro-molecules (receptors) and interact with specific binding sites of the receptors. These interactions may cause activation or inactivation of the respective receptors and consequent biochemical reactions. An agonist can be recognized either as a full agonist or as a partial agonist according to its ability to elicit the maximum response mediated by a specific type of receptor. Receptor full agonists, irrespective of their different receptor binding affinities, are all capable of causing full maximum response. In contrast, receptor partial agonists are unable to elicit full maximum response regardless of their concentration (Zhu, 1996). This situation occurs when only part of the receptors occupied by the agonist convert to an active form and remains inactive (Jenkinson et al., 1995; Neubig et al., 2003). This situation in toxicology is described as:

$$L + R \overset{K_1}{\Leftrightarrow} LR \overset{K_2}{\Leftrightarrow} LR^{+} \quad (1)$$

$$K_1 = \frac{[LR]}{[L]\cdot[R]}$$

$$K_2 = \frac{[LR^{+}]}{[LR]}$$

where L is a ligand, R is a receptor, LR is a receptor-ligand complex and LR^+ is the active form of the receptor-ligand complex. The labels in the square brackets in the following equations represent the respective concentrations. K_1 and K_2 are microscopic equilibrium association constants. In contrast to a full agonist where the receptor-ligand complex automatically converts to the active form, in partial agonism some amount of the inactive form (LR) should be present at equilibrium; however, in our experiments we are not usually able to quantify this inactive form of the receptor-ligand complex. The macroscopic equilibrium constant of the whole reaction is given by Eq. (2) (Neubig et al., 2003).

$$K = \frac{K_1 \cdot K_2}{1 + K_2} \quad (2)$$

where K is a macroscopic equilibrium constant and K_1 and K_2 are the microscopic equilibrium constants from the previous scheme.

* Corresponding author at: Laboratory of Environmental Biotechnology, Institute of Microbiology of the CAS, v.v.i., Vídeňská 1083, Prague, 142 20, Czech Republic.
E-mail address: cajthaml@biomed.cas.cz (T. Cajthaml).

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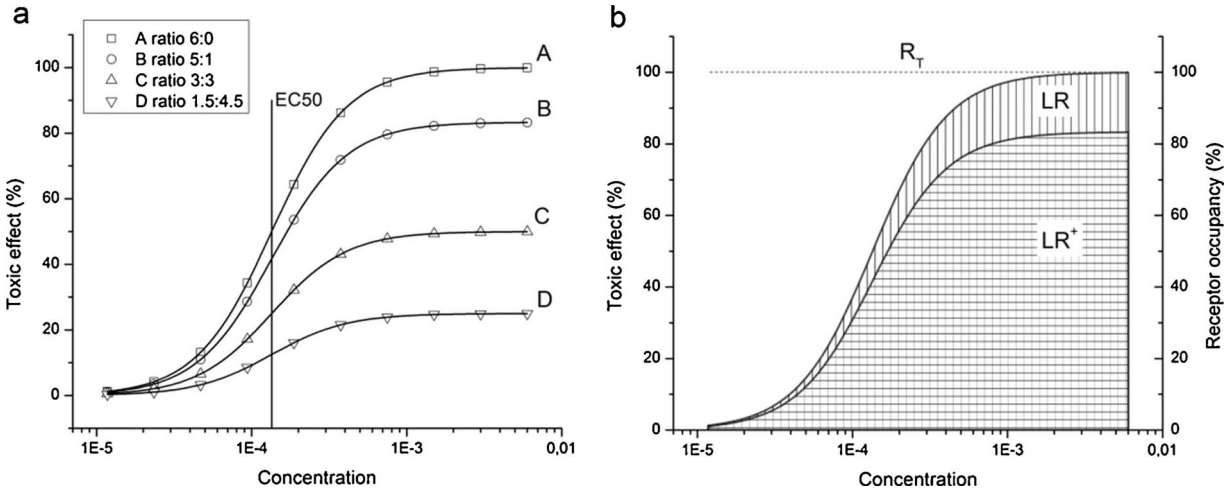

Fig. 1. Dose-response curves in the presence of competitive antagonist. (a) The dose-response curves for an agonist in the co-presence of a competitive antagonist with the same affinity. The individual curves represent different concentration ratios of agonistic and antagonistic moieties and equal 6:0; 5:1; 3:3; 1.5:4.5 for curves A; B; C; D respectively. The x axis displays the sum of the concentrations for both parts. (b) The dose-response curve of a partial agonist which can activate only 83.3% of the receptors. The rest of the receptors are also occupied by an agonist but remain inactive (LR area) and represent a complement to the curve to the full agonistic curve with the same inflection point.

Accordingly, partial agonists which bind to receptors include a certain portion that remains inactive after binding. In this way, the concentration of the compound can be divided into two parts. One part is represented by the properties of a full agonist where every receptor-ligand complex automatically transforms to its active form. The other part consists of competitive antagonists which compete for the same binding site, but remain inactive after binding. However, both parts should have the same affinity towards the binding site of the receptor.

Recent studies from the field of mixture toxicology have brought novel opportunities for how partial agonists could be described in mixtures (Ezechias and Cajthaml, 2016; Howard and Webster, 2009). These studies follow the concept of concentration addition and provide two novel mathematical models for calculation of mixture effects. In this article, we use the Full Logistic Model (FLM) from the article of Ezechias and Cajthaml (2016) and the equation of Generalized Concentration Addition (GCA) from the article of Howard and Webster (2009) expressed in this study as Eqs. (3) and (4), respectively.

$$E_{mix} = \left(MAX_1 + \frac{MIN_1 - MAX_1}{1 + \left(\frac{c_1}{EC_{50_1}} + \frac{c_2}{EC_{50_2}} \right)^{p_1}} \right) \cdot \left(\frac{\frac{c_1}{EC_{50_1}}}{\frac{c_1}{EC_{50_1}} + \frac{c_2}{EC_{50_2}}} \right) + \left(MAX_2 + \frac{MIN_2 - MAX_2}{1 + \left(\frac{c_2}{EC_{50_2}} + \frac{c_1}{EC_{50_1}} \right)^{p_2}} \right) \cdot \left(\frac{\frac{c_2}{EC_{50_2}}}{\frac{c_2}{EC_{50_2}} + \frac{c_1}{EC_{50_1}}} \right) \quad (3)$$

$$E_{mix} = \frac{MAX_1 \cdot \frac{c_1}{EC_{50_1}} + MAX_2 \cdot \frac{c_2}{EC_{50_2}}}{1 + \frac{c_1}{EC_{50_1}} + \frac{c_2}{EC_{50_2}}} \quad (4)$$

E_{mix} in these equations is the calculated mixture effect. The parameters MAX_1, MAX_2, MIN_1 and MIN_2 are the respective maximum and minimum of the individual dose-response curves of the compound 1 and 2; the parameters p_1, p_2 and EC_{501}, EC_{502} are the respective Hill coefficients and the inflection points of the individual dose-response curves of the compounds 1 and 2, respectively. c_1 and c_2 represent concentrations of the respective compounds 1 and 2.

These new models generally allow us to use dose-response curves of partial agonists (MAX < MAX of a full agonist); however, the models can also incorporate compounds with no agonistic effect (MAX = 0). This is a substantial advantage compared to previously published models which cannot calculate the mixture effect for compounds with no agonistic effect on their own (Howard and Webster, 2009).

In this study, we apply these new methods to the paradigm of partial agonists. The models are used so as to separate the agonistic and antagonistic behavior of a partial agonist where the antagonistic effect is described separately as an effect of the compound producing zero effect. This also leads to a general hypothesis that any competitive antagonist is nothing more than an agonist with no effect. This concept may significantly enhance our understanding of the receptor theory and the mode of action of receptor partial agonists. This assumption allowed us to derive the equations describing the microscopic and macroscopic equilibrium constants. In this way, we can show how these constants could be calculated and also obtained from the measured partial agonistic dose-response curve. As a result, we describe a simple mathematical tool for how the dose-response curves of drugs could be compared on the basis of their affinities and efficacies.

2. Results and discussion

2.1. Dose-response curves for agonists in the presence of antagonist

The assumption that some portion of the molecules of a partial agonist which is bonded to a receptor remains inactive, could be mathematically described as a combination of two compounds where one compound exhibits zero effect on its own ($MAX_2 = 0$). The actual concentration of the partial agonist could be also split into c_{ago} and c_{antago} where c_{ago} represents the concentration of the molecules which convert to an active form (LR^+) after binding to a receptor and $c_{anatago}$ represents the concentration of the molecules which remain inactive (LR). A partial agonistic dose-response curve can be obtained by substituting these parameters into Eqs. (3) and (4). The maximum effect of this curve is dependent on the ratio of concentrations c_{ago} and c_{antago}. A few examples of a hypothetical compound calculated by the FLM model with different ratios of c_{ago}:c_{antago} are shown in Fig. 1a.

The full agonistic curve resulted only when $c_{antago} = 0$; changing the ratio in favor of c_{antago} resulted in diminishing the maximum effect of the curve (Fig. 1a).

The assumption that combination of an agonist with its competitive antagonist resulted in the partial agonistic dose-response curve is not completely new. Zhu also showed that this combination resulted in the form of a partial agonistic dose-response curve. The only difference is that he assumed a hybrid compound which covalently linked molecules of an agonist with the antagonist (Zhu, 1996). This hybrid compound formation resulted in a situation where the molar concentration of the agonistic and antagonistic parts are always equal but differ in their affinities towards the receptor. In our situation, we considered the