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REVIEW ARTICLE

Determination of the Intrinsic Efficacies of β_2-adrenergic Agonists

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ABSTRACT

β-adrenergic agonists have been traditionally classified as strong or weak. Attempts to express their effectiveness in quantitative terms has led to the concepts of potency, which designates the concentration range over which the agonist becomes effective, and the intrinsic activity, which designates the maximal effect produced by agonist at saturating concentrations. In the present review we describe developments in which the molecular effects of the common β-adrenergic agonists on their cognate receptors can be related to their effectiveness. This approach is based on the activation/inactivation cycle of G proteins. It has been formalized so that the effectiveness (that is the efficacy) of each individual β-adrenergic agonist can be expressed as a single numerical value. The agonists may, therefore, be listed is order of efficacy. For the β-adrenergic agonists for which there is accurate data the order is : epinephrine > fenoterol≈procaterol > albuterol≈zinterol≈terbutaline > dobutamine > tulobuterol > ephedrine. The formal model of β-adrenergic agonism also allows a novel approach to the question of agonist specificity and a more rational appraisal of which drugs might be most useful for particular purposes.

KEY WORDS

efficacy, epinephrine, fenoterol, procaterol, β_2-adrenergic agonist

INTRODUCTION

This review concentrates on assessing the relative abilities of the β-adrenergic agonists to activate adenylyl cyclase. *A priori* the ideal approach to measuring those abilities should be able to order the agonists from the strongest to the weakest and be usable in all tissues. It should be quantitative, rather than merely descriptive at the verbal level. It should be associated with a quantitative system of measuring tissue response which allows for prediction of experimental results as well as mere description of experimental results already obtained. In this review we describe how beta-adrenergic agonist efficacy has been related to the ability of agonist to promote GTP/GDP exchange in the Cassel-Selinger[1] cycle of adenylyl cyclase activation. The relationship between this ability and the traditional measurements of agonist effectiveness (potency and intrinsic activity) is straightforward. Following Furchgott[2] we will define this ability as efficacy. In subsequent sections we show how the relationship was developed and show how it may be measured and used in practice.

CLASSICAL DESCRIPTION OF TISSUE RESPONSE TO A DRUG

Figure 1 illustrates the classic descriptors for a dose-response to a drug. The effect measured is for adenylyl cyclase activity for a preparation of Human Embryonic Kidney cells (HEK293 cells) transfected with additional human beta-adrenergic receptor. The measurement of adenylyl cyclase activities in membrane preparations from these cells has been described in detail.[3] It is obvious that the maximal response at saturating epinephrine concentrations is greater than that for zinterol, while the EC_{50} for zinterol is less that that of epinephrine. In other words, the epinephrine has a greater "intrinsic activity" than the zinterol, but the zinterol is more "potent" than the epinephrine. In the classical approach to the description of drug response, both potency and intrinsic activity are necessary in this approach to define the relationship between response and drug concentration. There is no obvious relationship between the two parameters and it is not clear which should be considered the "strongest" agonist.[4] Epinephrine produces

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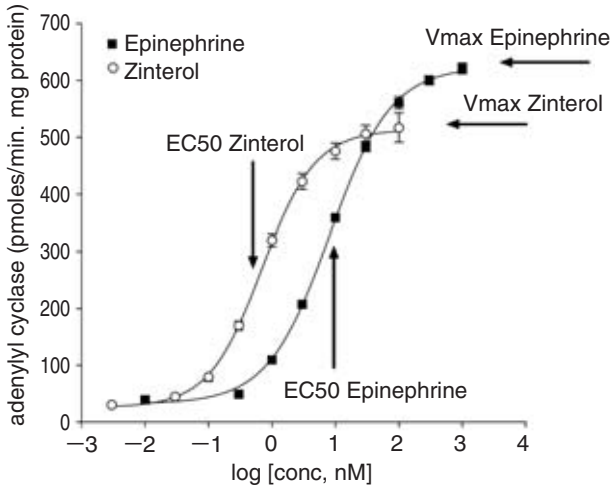

Fig. 1 The adenylyl cyclase activity in membranes prepared form HEK293 cells transfected with additional β-adrenergic receptor in response to epinephrine and zinterol. The EC50 and Vmax for both agonists are indicated by arrows.

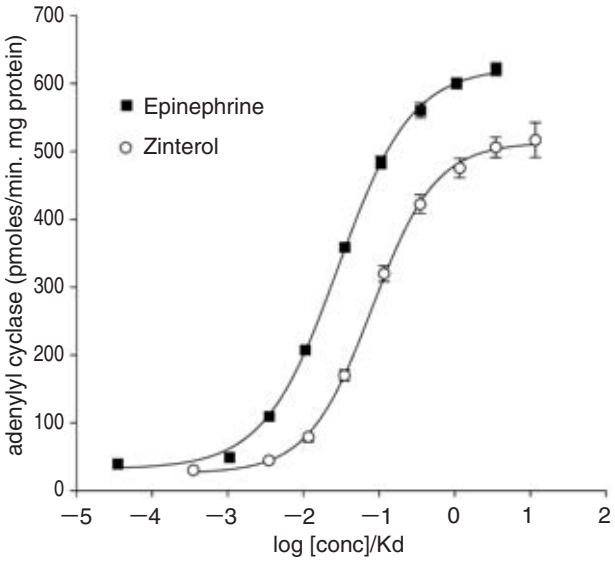

Fig. 2 A replot of the data shown in Figure 1, but with the agonist concentrations normalized to their dissociation constants on the β-adrenergic receptors. With this type of plot positions on the abscissa correspond to equal receptor occupancy for both agonists.

greater effects at saturating concentrations, but at any equal concentration of the two drugs below 10 nM zinterol causes a greater effect.

This problem of which drug is inherently stronger is alleviated to some extent by comparing the drugs at equal occupancies of the receptors. This is achieved by plotting the effects of the drug against its concentration divided by its dissociation constant (K_d). Figure 2, where the data from Figure 1 are plotted in this manner, is an example of such a plot. In this type of plot the value 0 on the x-axis corresponds to a drug concentration to K_d ratio ([concentration]/K_d) of 1 and, therefore, to 50% occupancy of the receptors by the drug. The EC_{50} for zinterol occurs when [concentration]/K_d is about 0.1 and the EC_{50} for epinephrine occurs when [concentration]/K_d is about 0.02. A plot of this type makes it clear that epinephrine gives more stimulation at all receptor occupancies and should presumably be described as a "stronger" agonist than zinterol. It is still not clear, however, even from a plot of this type how their relative strengths should be measured. Figure 3 extends the data in Figure 2 to many more agonists measured with the same membrane preparation. It may be seen (with one small exception) that the curves do not cross. That is, in comparing any two agonists, the stronger agonist is stronger at all fractions of receptor occupancy. The exception in these data applies to procaterol and fenoterol. At low receptor occupancies fenoterol gives a greater response at higher concentrations it is procaterol with the greater response. This feature will be discussed later once the rational approach to measurement of agonist efficacy has been described. The formal, empirical equation which relates agonist concentration, intrinsic activity (V_{max}), potency (EC_{50}), dissociation constant (K_d) and response (v) is :

$$v = \frac{V_{max}\left(\frac{h}{K_d}\right)}{\frac{EC_{50}}{K_d} + \left(\frac{h}{K_d}\right)} \qquad (1)$$

USING THE CASSEL-SELINGER CYCLE OF G PROTEIN ACTIVATION TO A RATIONAL DEFINITION OF EFFICACIES

Beta-adrenergic agonists work by binding to their cognate receptors and in combination with them catalyzing the exchange of GTP for GDP on Gs. Diagrammatically this is shown in Figure 4.[1] It has been shown by Whaley *et al.*[5,6] that the rate of exchange is proportional to the number of receptors present in the preparation or tissue and to the identity of the drug. By noting that in the steady state of G protein activation the rate of activation and inactivation must be the same it was possible to derive the following equation which relates drug response to drug concentration and to the rate constants for activation and inactivation of the G protein.[5,6] The equation is :

$$v = \frac{V_{100}\frac{k_1 r}{k_1 r + k_{-1}}\left(\frac{h}{Kd}\right)}{\frac{k_{-1}}{k_1 r + k_{-1}} + \left(\frac{h}{Kd}\right)} \qquad (2)$$