pA_2 Calculation (Potency of a Competitive Reversible Antagonist)

The potency of a competitive reversible antagonist is expressed as a **pA_2** value. The pA_2 value is the negative logarithm of the molar concentration of antagonist which causes a twofold shift of the concentration-response curve for agonist. The larger the pA_2 the more potent the antagonist.

The pA_2 value is derived from the formula:

$pA_2 = pA_x + \log (x-1)$

where pA_x is the negative log of the concentration of antagonist used and x is the concentration-ratio.

The concentration-ratio (x in the formula) is the ratio of the concentration of agonist that gives the same response (usually the 50% maximum response) in the presence and absence of the antagonist.

The concentration can be derived either from the EC_{50} values,

Concentration-ratio = $\frac{EC_{50} \text{ (presence of antagonist)}}{EC_{50} \text{ (absence of antagonist)}}$

or from the pD_2 values:

Concentration-ratio = Antilog [pD_2 (absence of antagonist) - pD_2 (presence of antagonist)].

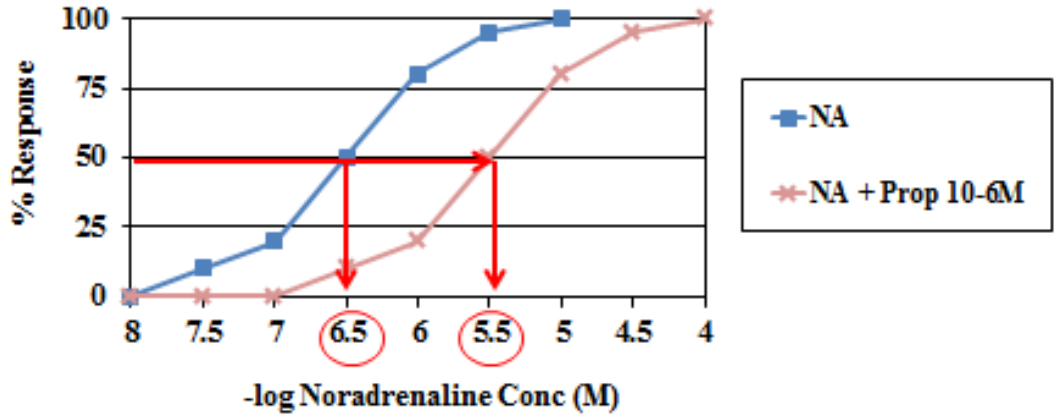

Figure 1: The effects of propranolol (1μM) on the contractile response of rat aorta to noradrenaline.

Using the above concentration-response curves, the first step is to determine the EC_{50} / pD_2 values in the presence and absence of antagonist. I've drawn the lines on the graph so you can see the process, with the resulting values:

Presence of antagonist: $pD_2 = 5.5$, $EC_{50} = 3 \times 10^{-6}$M
Absence of antagonist: $pD_2 = 6.5$, $EC_{50} = 3 \times 10^{-7}$M

We can now work out the concentration ratio (x):

Concentration-ratio = Antilog [pD_2 (absence of antagonist) - pD_2 (presence of antagonist)]
= Antilog (6.5 – 5.5)
= 10

Note: Antilog is 10^x on your calculators

or

Concentration-ratio = $\frac{EC_{50} \text{ (presence of antagonist)}}{EC_{50} \text{ (absence of antagonist)}}$

$= \frac{3 \times 10^{-6} M}{3 \times 10^{-7} M}$

= 10

pA_X = -log antagonist conc
= -log (1×10^{-6})
= 6

pA_2 = pA_x + log (x-1)
= 6 + log (10-1)
= 6 + 0.95
= 6.95

Calculator Lesson: When entering 1×10^{-6} in to your calculator you need to press 1 then EXP then -6. There is no need to enter the 10, which is just a way of indicating the exponential value.

pD_2' Calculation (Potency of a Competitive Irreversible or Non-Competitive Antagonist)

The potency of an antagonist that causes a depression of the maximum response to an agonist is expressed as a **pD_2'** value (not the pD_2 value). The pD_2' value is the negative logarithm of the molar concentration of antagonist which causes a halving of the maximal response of the agonist. The larger the pD_2' value the more potent the antagonist. pD_2' values are derived from the formula:

$$pD_2' = pD_x + \log (x - 1),$$

where pD_x is the negative logarithm of the molar concentration (mol/L, M) of antagonist used and x is the depression of the maximal response.

$$x = \frac{\text{Maximal response in absence of antagonist}}{\text{Maximal response in presence of antagonist}}$$

When the maximal response is halved in the presence of an antagonist, x = 2, log (x - 1) = O, and the $pD_2' = pD_x$ value.

NOTE: A pD_2 value is a measure of the potency of an AGONIST whereas a pD_2' value is the measure of the potency of a competitive irreversible or non-competitive antagonist.

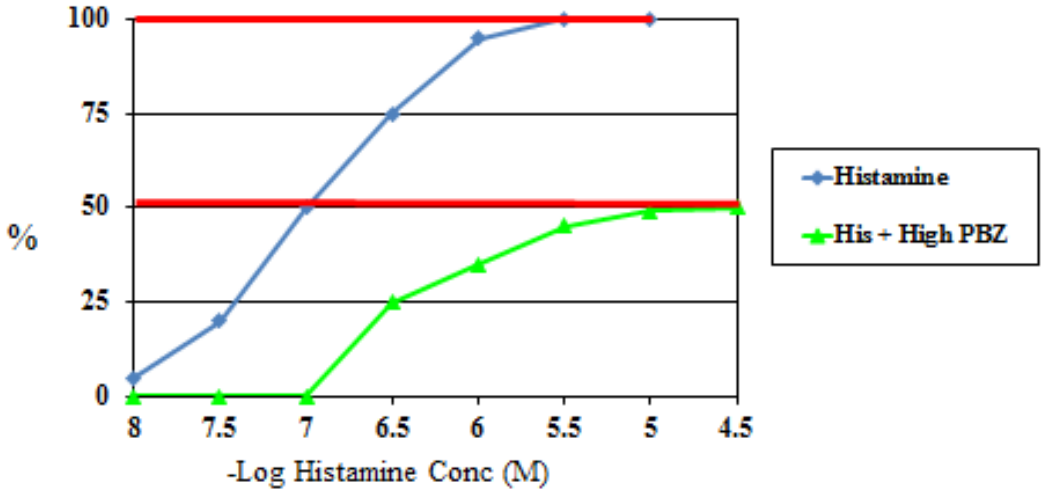

Figure 2: The effects of phenoxybenzamine (3μM) on the contractile response of guinea pig ileum to histamine.

Using the above concentration-response curves, the first step is to determine the maximum responses in the presence and absence of antagonist. I've drawn the lines on the graph so you can see the process, with the resulting values:

Maximal response in absence of antagonist: 100%
Maximal response in presence of antagonist: 50%

We can now work out x:

$$x = \frac{\text{Maximal response in absence of antagonist}}{\text{Maximal response in presence of antagonist}}$$

$x = \frac{100}{50}$

$x = 2$

pD_x = -log antagonist conc

= $-\log (3 \times 10^{-6})$

= 5.5

$pD_2' = pD_x + \log (x - 1)$

$= 5.5 + \log (2 - 1)$

$= 5.5$