**PHARMACODYNAMICS**

**Dose-response relationships and receptor activation by agonists:** An important concept of Pharmacodynamics is the dose-response relationship i.e. how much does a response changes when you increase drug dose. We use dose-response curves to: 1) determine a drug's **potency** and **efficacy** in order to compare its effects with other drugs (agonists) producing the same response and 2) determine how safe a drug is to use. In Fig 1 (below), ISO, EPI and NE all interact with the same and produce the same maximal effect (indicated by the vertical arrow labeled **EFFICACY**). Thus ISO, EPI and NE are equally effective or efficacious. Efficacy is proportional to the number of receptors activated, so ISO, EPI and NE all activate the same number of receptors and are described as **full agonists**. But the dose-response curves don't look the same - what's different?

**Fig.1**

The difference is the **dose** (i.e. the amount of drug) required to activate a similar number of receptors. In order to compare the 3 drugs, we assess the concentration of each which produces a half-maximal increase in response. Since the maximal response for ISO, EPI and NE is 100%, the half-maximal response is 50%. But how much of each drug is required to cause that 50% increase in response? 1 mg of ISO (see the vertical red arrow), 3 mg of EPI (see vertical blue arrow - a dose 3 times higher than that for ISO) and 10 mg of NE (see vertical green arrow - a dose 10 times higher than that for ISO).

The difference between the 3 drugs is their **POTENCY**. ISO is more **potent** than EPI and EPI is more potent than NE (ISO > EPI > NE), but all 3 drugs are equally effective (i.e. produce the same max. response).

**Fig.2**

**Dose-Response Curves for Full and Partial Agonists:** Fig 2 shows 4 drugs that differ in potency (EPI > NE > phenylephrine > ephedrine). Notice that EPI, NE and phenylephrine are equally effective (producing a 30% increase in blood pressure), but the maximal response to ephedrine is only a 20% increase in blood pressure. Since the size of the response is proportional to the number of receptors activated, ephedrine activates fewer receptors than EPI, NE or phenylephrine. Thus ephedrine is an agonist (i.e. binds to a receptor and produces a response) which is only partially as effective as EPI, NE or phenylephrine. Therefore ephedrine is described as a **partial agonist**.

**Fig. 3**
Effects of antagonists on agonist dose-response relationships: Many therapeutic agents are designed to block the body’s responses to naturally-occurring receptor agonists. In order to do this, these drugs must bind to agonist receptors, but must not activate them. Drugs which bind to receptors, do not activate them and prevent agonists from binding are called antagonists.

Antagonists will also have an effect on the dose-response curves for receptor agonists. In Fig 3 (below), EPI's potency (i.e. that concentration of EPI producing a half-maximal increase) is 0.1 mg (see the red curve, solid line). When we examine the EPI dose-response curve in the presence of 1 mg of prazosin (red curve, dashed line), we notice that it takes 0.1 mg of EPI to produce a half-maximal response (i.e. EPI's potency has decreased from 0.1 to 0.3 mg/kg body wt). This is 3 times the amount of EPI it takes in the absence of prazosin (red curve, solid line). When the dose of prazosin in increased to 10 mg, EPI's potency is 1 mg/100 kg body wt (now EPI's potency has decreased from 0.1 mg to 1 mg or it is 1/10 as potent in the presence of prazosin) However, prazosin alone (i.e. when EPI concentration is 0) has no effect by itself (gray triangles and line), while blocking (i.e. antagonizing) the ability of EPI to do so. When prazosin is present at a fixed concentration, low doses of EPI have less of an opportunity to bind to the receptor. Since the number of receptors activated determines the size of the response, those receptors occupied by prazosin do not contribute to EPI's response. Because prazosin antagonizes EPI's effects, and reduces EPI's potency but not its efficacy, prazosin is described as a competitive antagonist.

Notice how the drug phenoxybenzamine affects EPI's dose-response curve (red curve, dashed line). Once again EPI's potency has been reduced, but something else has changed as well -- EPI's maximum response has been reduced to 70% of the response to EPI alone. Since the response to EPI is proportional to the number of receptors it can activate, this means that phenoxybenzamine has prevented some receptors from being activated, no matter how high the concentration of EPI. Unlike the situation with prazosin, no amount of EPI can overcome the blockade of EPI receptors by phenoxybenzamine. Since EPI cannot compete for the receptors occupied by phenoxybenzamine, phenoxybenzamine is defined as a non-competitive antagonist.