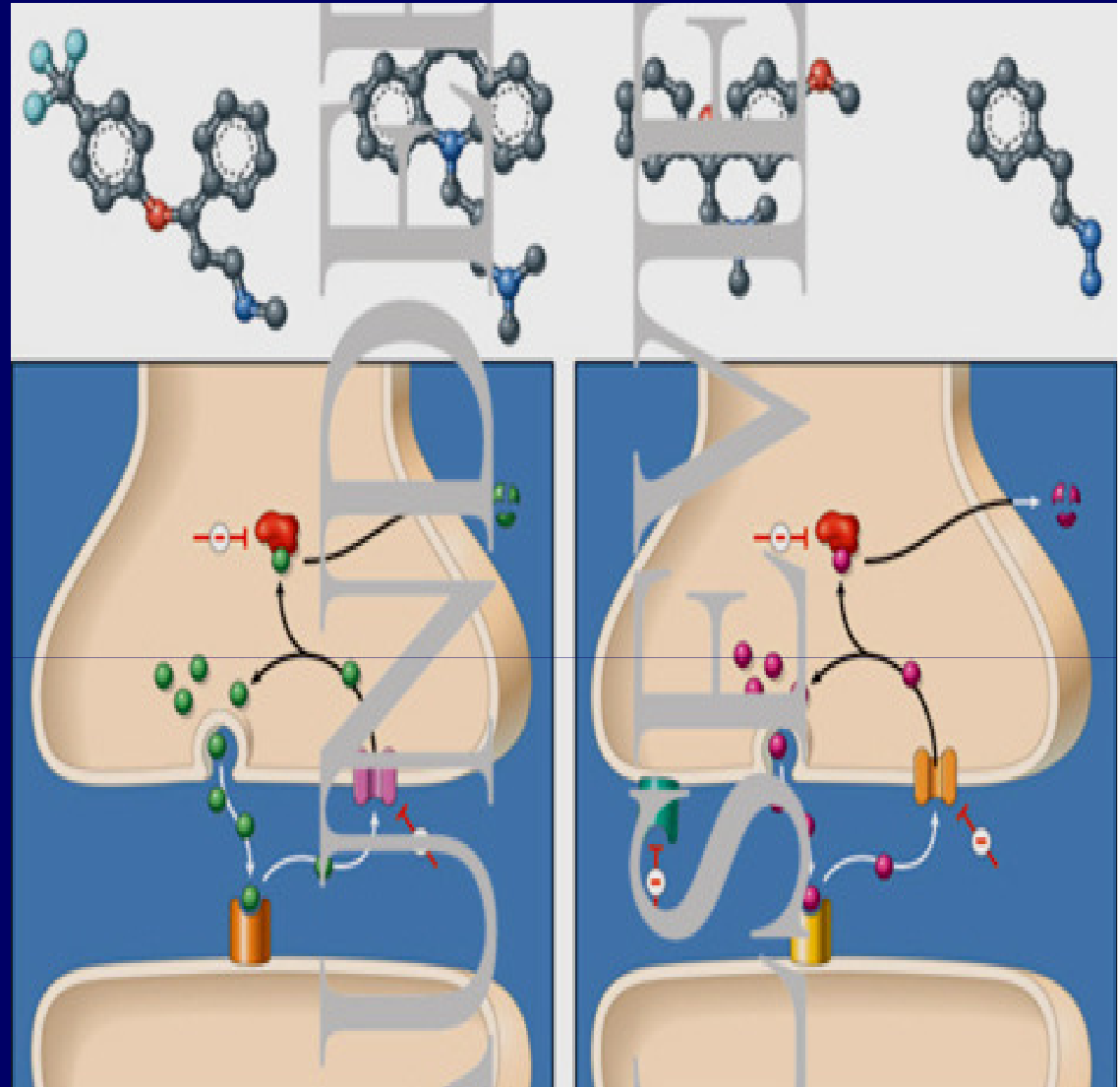




C.6



Coupling response quantification

See: www.veterinarypharmacon.com

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Currently there are several hypotheses regarding the relationship between drug and receptor, from which **three theories** have been established:

the “Occupancy” theory (Clark’s)

the intensity of a drug's effect depends on *the number of occupied receptors* (this theory has many variations)

the “Speed” theory (Paton’s)

where the intensity of the effect is the result of **speed combined with the receiver.**

the “Activation” theory

claims that the pharmacodynamic effect is produced by converting receptors from an **"inactive"** form into an **"active"** form.

Today it is considered, that the **allosteric activation** of the receptors, is a necessary process to obtain a drug effect.

Knowing the **type of responses** produced by a drug they can also be completed by measuring the:

- **response size** and respectively the
- **drug quantity**, in order to make it possible to study the dose-effect relationship.

The procedure known as “**quantitative bioassay**” has allowed for several active substances to be used with a reasonable accuracy from a dosing point of view.

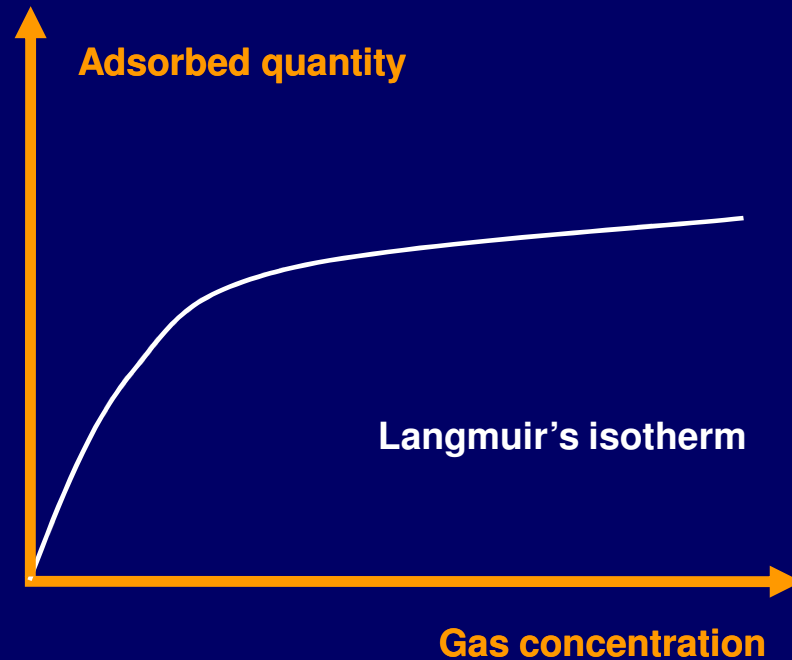
The bioassay can also be applied for the **identification of a drug** whose effect is characteristic or, for which an identified antagonist is known.

Clark's theory (of occupation)

and its variants

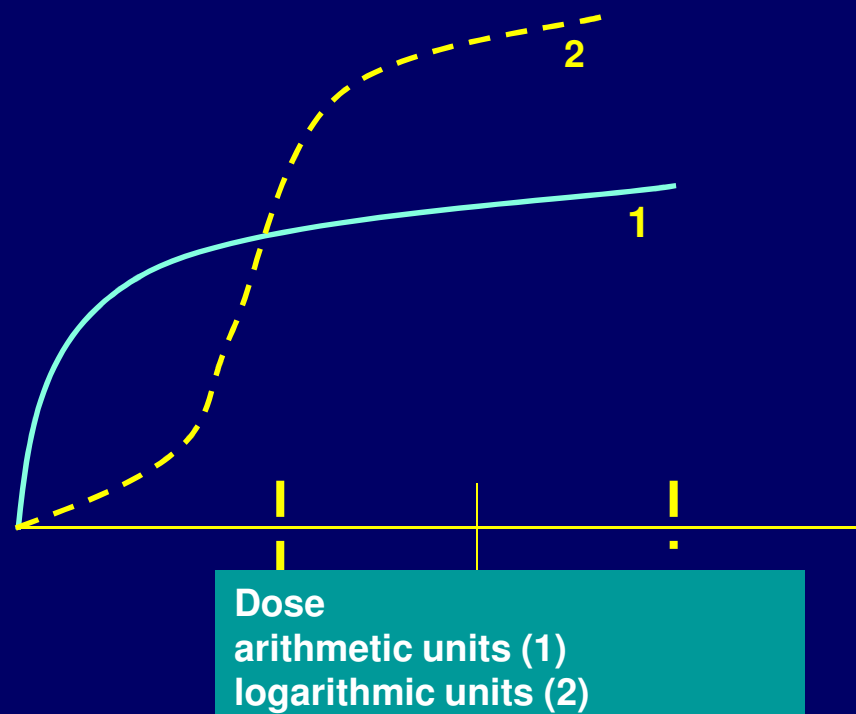
Clark observed the similarity between **Langmuir's** adsorption isotherm form and many dose-response curves.

He applied to drug-receiver interactions, **principles and kinetics** used to reproduce a hypothetical model for the reactions occurring at **a surface level.**



Clark was pleased with this model because, in many cases, the form of dose - effect curves experimentally obtained matched the obtained form of a relationship that involved:

- **interaction type: molecule - molecule;**
- **tiny proportion from administered drugs that bind to receptors;**
- **the proportion from the maximum effect that can be achieved: dependent on the administered drug concentration (its affinity is constant)**



Explanation:

The adsorption isotherm has derived as a result of studying the adsorption rate of a gas at a constant temperature by the material prepared (considered impermeable surface).

The curve shows how **the adsorbed gas concentration increases**, once the applied concentration increases:

- first **very quickly**,
- then, **much more slowly**, (as the adsorbent is approaching **saturation level**).

In the vicinity of a **certain threshold** it will no longer reach a higher adsorbed concentration, regardless of how much the applied concentration increases.

Drug binding on the cell surface was assumed to be based on the principle:

“A drug molecule per receptor”, just like the case of a molecular reaction between a gas and a solid surface.

Adsorbent surface saturation has been equated with:

occupying all available receptors, corresponding to the point of dose-response curve, in which the effect is maximal.

From this it was deduced that:

▶ a lower proportion of receptor occupancy could produce a weaker effect.

Assuming that each occupied receiver produces a constant unit of response, the effect would be directly proportional to the receptor occupancy, because the occupying rate and stimulus are cumulating.

Another assumption was that:

adsorption on the surface did not produce a significant reduction in the concentration of a gas or free drug.

When **various gases** are present, in the same molecular concentrations at the adsorbent surfaces (that have the same area and are from the same structure) under standard conditions of temperature and pressure, it is obvious that the extent to which different concentrations of adsorbed gas differ at the time of equilibrium, **depends** on **its individual coefficients of adsorption**.

If it is considered that drug-receptor interaction is realized in a closed system ("in vitro"), it can be assumed that the process follows the principles of the **mass action law**:

When the effect level **is stable** in the presence of an administered drug, there exists **a balance** at which **the association and dissociation rates** of complex **are equal**.

A difficulty in this theory was found for "**dualists**", also called **partial agonists**.

A partial agonist is unable to produce the maximum effect compared to a full agonist, when reacting with the same population of receptors (it does not produce the same level of response).

Ariens theory

**Clark's theory assumed that:
each coupling of any drug with any receiver from
the same population will have the same efficiency
in producing response units.**

Partial agonists have shown that it is not like that!

In order to introduce this observation in the theory, a second property of drugs, was invoked:

▶ **one that is quantitative non-dependent on affinity**

While **the affinity** remains the property which determines the ability of a drug to bind to receptors,

▶ **Ariens** proposed another property: **the intrinsic activity.**

The concept of intrinsic activity

Allows, the understanding of another set of observations that do not correspond to the theory of occupancy. Like, when agonists are administered in mixtures, and the result (answer) is sometimes weaker than the one that is expected (due to an addition of effects of receptor occupancy).

In the presence of a partial agonist, for example, the **concentration of a potent agonist** (which under normal circumstances is sufficient to cause a maximum response) turns out to be, not as effective.

This is due to **the occupancy of a receptor fraction** by a partial agonist that **will be able to produce** only sub-maximal stimuli.

Stephenson's theory

Another alternative extension of Clark's theory was the one of Stephenson, who proposed a modified theory that incorporates the following observation:

For some drugs, the production of a **maximum effect** can be achieved by **receptor occupancy** in a proportion of **less than 100%**.

He invoked the concept of **efficiency**, whose value expresses the relative ability of the receptor occupied by the drug in question to "**donate**" a unit of **biological stimulation (S)** to the cell.

$$S \sim r e$$

(where e = efficacy)

A drug with high efficiency can produce a **maximum response** after occupying only **a small** proportion of the receptor population leaving a number of **spare receptors**.

On the contrary, a drug with **low** efficiency has to deal with **a higher proportion** of receptors, in order to produce a maximal response.

Partial agonist **does not manage** to induce a maximal response even when all receptors are occupied, because the value of its efficacy (**e**) is too low for the critical value of **S** to be reached.

And in this case, for an antagonist the value of **e** is zero.

Paton's theory

The inclusion of **"intrinsic"** and **"effectiveness activity"** in the occupancy theory of drug - receptor interactions has successively reduced the importance of the idea of a stable occupation of receptors, as a major determinant of response.

Rate theory for relations: **drug - receptor - response** (introduced by WDM Paton) led to a point where, the **occupancy** alone was considered **unimportant** for agonist activity.

Paton proposed the idea that the formation of a complex: **drug - receptor** generates toward **cell a stimulation unit** of the production response.

So:

- ▶ after drug **administration**,
- ▶ all tissular receptors are **available for coupling**
- ▶ the tissue will receive **the maximum stimulus** and
- ▶ will generate **a maximal response**.

for the answer to be maintained,

- ▶ **the complex must be decoupled and recovered**
- ▶ when the complex is **quickly disentangled**, couples will be **much more quickly** recovered.

So, for an agonist, **the rate of decoupling** complexes (governed by the dissociation constant) **is the one that determines potency**, because it dictates **the rate** at which new complexes can be achieved.

According to this hypothesis:

▶ **the antagonist binds fast, but the dissociation will happen slowly.**

Embracing this idea, Paton expressed some observations, inconsistent with the theory of occupancy (Clark).

For example, the fact that:

1. The same receptor set can be **stimulated** at first and then **blocked**.
2. the fact that **many active substances** produce a maximum effect **only after the first administration** (phenomenon called **tachyphylaxis**).

The first situation is considered “**partial agonism**”:

- when the drug stimulates at the moment of coupling, but because it dissociates relatively slowly, it **will persist** on receptors and thereby **will succeed in exerting** an antagonistic activity.

The second situation occurs, after repeated exposures to a drug, when

- **a part** of the previously administered dose **has remained** coupled to receptors (**reducing** the number of receptors available for coupling).

- For practical reasons, the experiments that are meant to test the rate theory **are difficult to perform.**
- Instantaneous registration of the response, is required to confirm that the installation of the maximal effect was achieved only under **experimental conditions.**
- The instantaneous termination of the response (consecutive removal of the drug from the tissue) requires **instant removal**, but the diffusion based on the concentration gradient is a **lengthy process.**

Activation theory
and other recent postulates

The continuing response requires the **release** and **regeneration** of receptors.

Recent comments have pushed this dynamic vision further, even questioning the very existence of receptors.

As stable populations, in terms of number, location or affinity, being proposed more complex patterns of interaction and modern drug - receiver.

For all the theory variants of the receptor, the postulate theory **is common**, which states:

- **an agonist drug** is combined with a site on the receptor, and the receptor **is activated**, thereby achieving **a response from the cell**.
- when **the drug disappears**, the receptor **returns to inactive status** (meaning, it regenerates).

This is essential for the subsequent cycles of response. **Upward or downward adjustment of the number of receptors** is another mechanism by which some drugs can act.

Enzymology theories

Expanding the concept of **allosteric sites** for drug-receptor interactions is another modern thesis suggested by researchers.

In **Enzymology**, allosteric sites are recognized as **adjacent locations to active sites** of enzymes, to which antagonists can bind, covering or distorting the active site so that it can no longer complex with the substrate.

In **Pharmacology**, the involvement of allosteric binding sites for antagonists was postulated for situations where the antagonism between two drugs moves **from competitive to non - competitive** as the **antagonist concentration increases** (e.g. acetylcholine and atropine act on smooth muscle).

Although the study of receptors has become a real science (**Receptology**), many questions about the receptors, still remain unanswered.

For example:

Why is it necessary that the cells possess specific structures that allow them to react to foreign substances?

The existence of receptors has already been demonstrated, and in time, all the attention has been focused on the **temporal, qualitative and quantitative** aspects of drug action, at cellular and molecular level, with advantageous consequences for pharmaceutical and pharmacological research.

For example:

- some pathological conditions in humans or animals have been demonstrated to be caused by **receptor depletion** (e.g. myasthenia gravis)
- **the efficiency loss of some drugs** due to consecutive **prolonged** administration was explained by **desensitization and / or depletion of receptors** (e.g. β - adrenoceptors, bronchodilators).

Conclusion

The term **receptor** identifies a location where a drug can bind and **induce an alteration** that is expressed under the form of an observed drug **effect**.

Different types of receptors have been identified:

- **cytosolic,**
- **coupled to pores**
- **or coupled to enzymes and different mechanisms of production of effects on cell:**
- **membrane depolarization,**
- **selective permeability changes,**
- **increasing or decreasing level of various cell regulators (enzymes, ions, degradation of the phospholipids).**



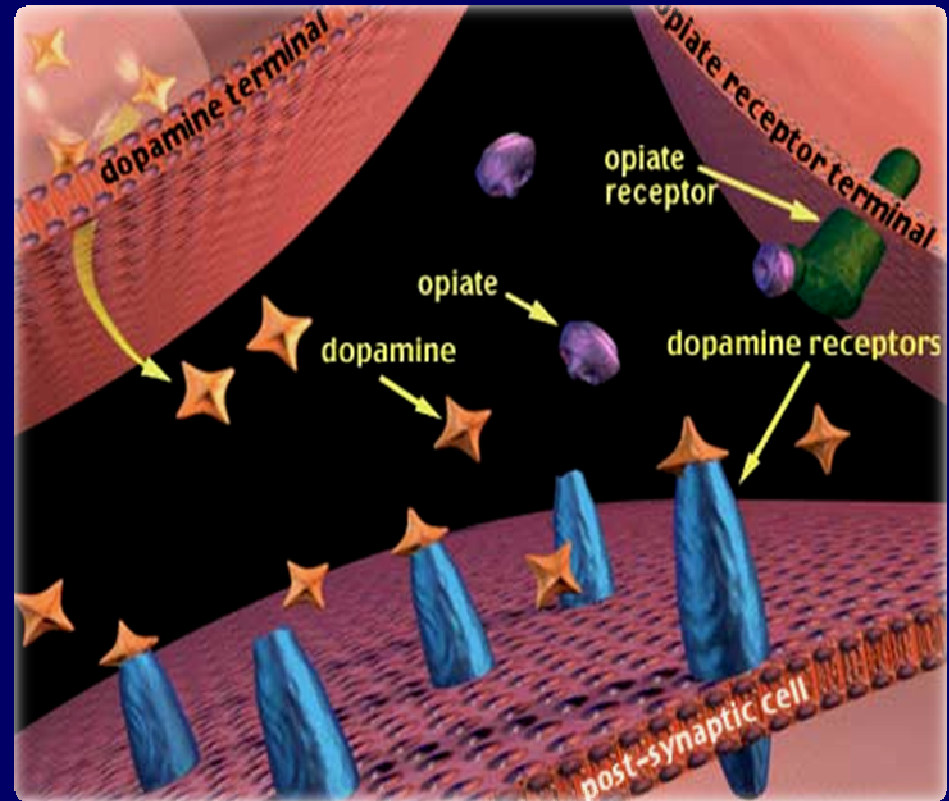
This makes it possible to understand why:

- some chemical messengers are acting **extremely fast**, (e.g. neurotransmitters through receptors coupled to pores over 1-2 ms) others,
- in a longer time, but a longer period (e.g. minutes for peptide hormones and receptor mediated enzymes), while
- others produce an effect only **after several hours** but have **an extended duration** of action (e.g. steroid hormones and functional proteins synthesized de novo by target cells).



E.g. antidepressants

The action mechanism



Opioids bind to specific receptors, where the signal will reach the dopaminic receiver (presented here, as part of another neuron) in order to release dopamine.

The dopamine binds to **dopamine receptors**, stimulating the **postsynaptic** cells and therefore a **positive** emotional feeling.

Thank you for your attention!

Images sources

http://whyfiles.org/225drug_receptors/images/opiate_receptors.jpg

<http://www.netterimages.com/images/vpv/000/000/012/12946-0550x0475.jpg>