The Pharmacology of Plant Toxins

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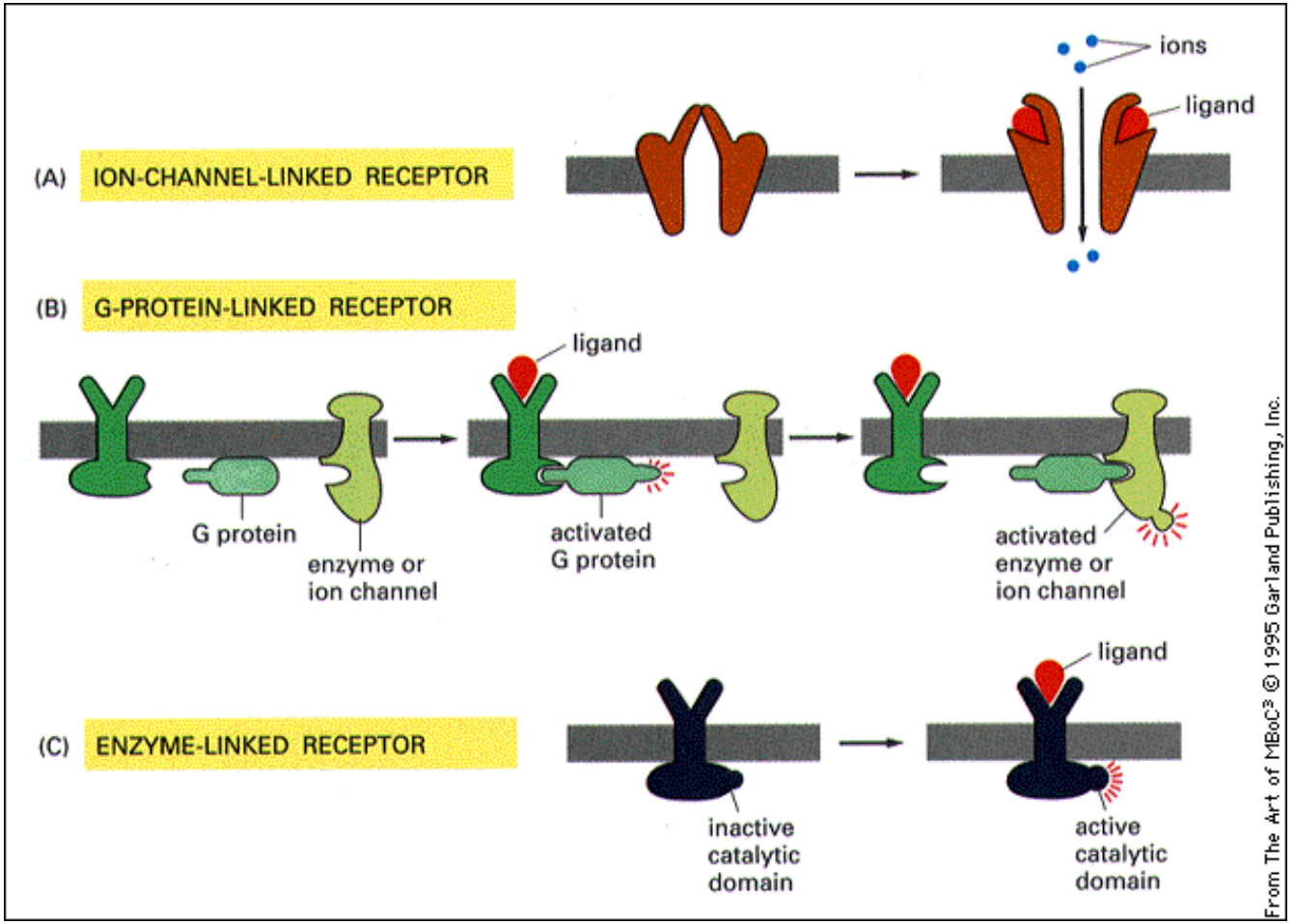
What is Pharmacology?

- **Defined as**: The study of drugs, their sources, preparations, and therapeutic uses.
- **Pharmacodynamics:** The study of mechanisms underlying drug action in the body.
- **Pharmacokinetics:** The study of drug disposition in the body.
- **Pharmacotherapeutics:** The identification and development of clinical applications for drugs to palliate, prevent, or cure disease.

Drug-Receptor Interactions

- The interaction of a chemical (ligand) with specific protein sites (receptors) either in the cell or on its surface.
  - Main classification of drugs.
    - Agonist, a drug that produces a biological effect.
    - Antagonist, a drug that opposes the actions of an agonist.

Classes of Receptors



Levy, 2003

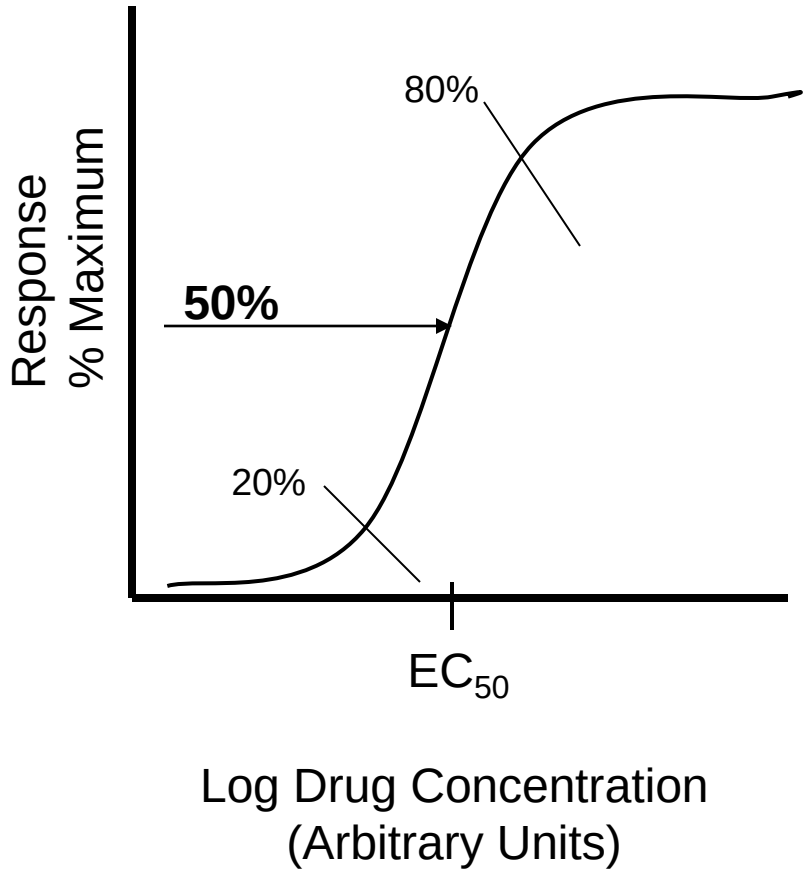
Pharmacological Definition of Receptors

The receptor must allow for the recognition and binding of a drug and must satisfy the following criteria:

- **Saturability** – receptors exists in finite numbers.
- **Reversibility** – binding must occur by weak intermolecular forces (H-bonding, van der Waal forces).
- **Stereoselectivity** – receptors should recognize only one of the naturally occurring optical isomers (+ or -, d or l, or S or R).
- **Agonist specificity** –related drugs should bind well, while physically dissimilar compounds should bind poorly.
- **Tissue specificity** – Drug concentrations should be physiologically relevant and binding should occur in in tissues known to be sensitive to the endogenous ligand.

Concentration-Effect Relationships of Agonists

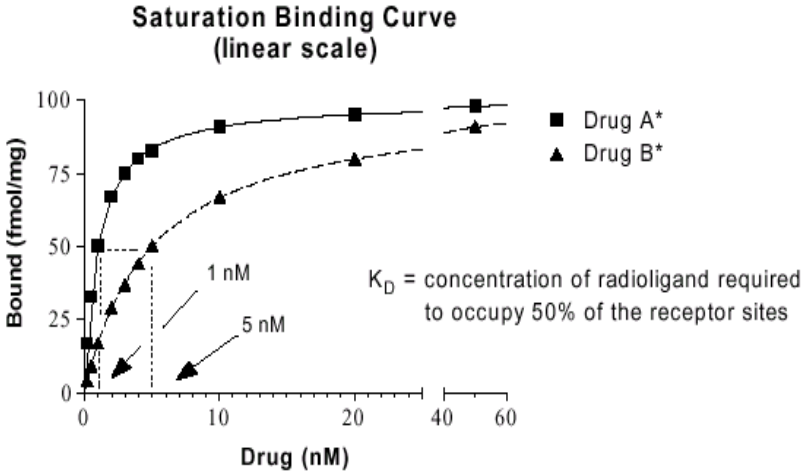
- Agonist activity is correlated with its concentration at the receptor.
- This relationship can be plotted as a concentration-effect curve.
- Drug concentration is plotted on the x-axis against graded changes in the magnitude of drug effect on the y-axis.



Affinity

$$[\text{ligand}] + [\text{receptor}] \underset{k_{off}}{\overset{k_{on}}{\longleftrightarrow}} [\text{ligand} \bullet \text{receptor}]$$

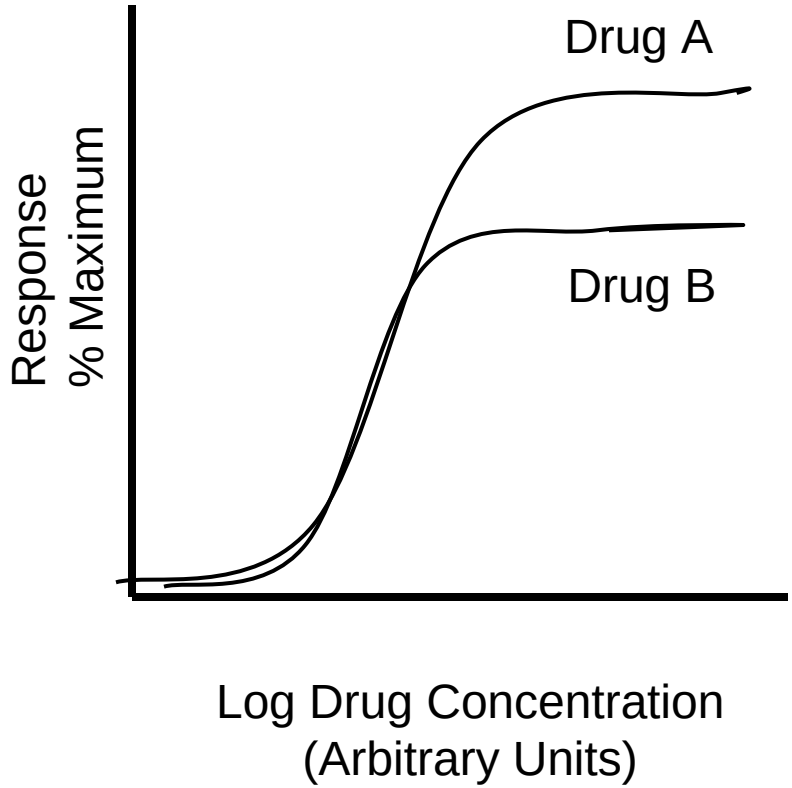
- : The tenacity by which a drug its receptor.
- noles/liter) expresses the affinity g for a receptor.
  = [ligand] which occupies half receptors.
- ned by the use of radiolabelled I)-ligand.
- is often lower than the tration required to elicit a *half-l biological response* (EC_{50}).



Levy, 2003

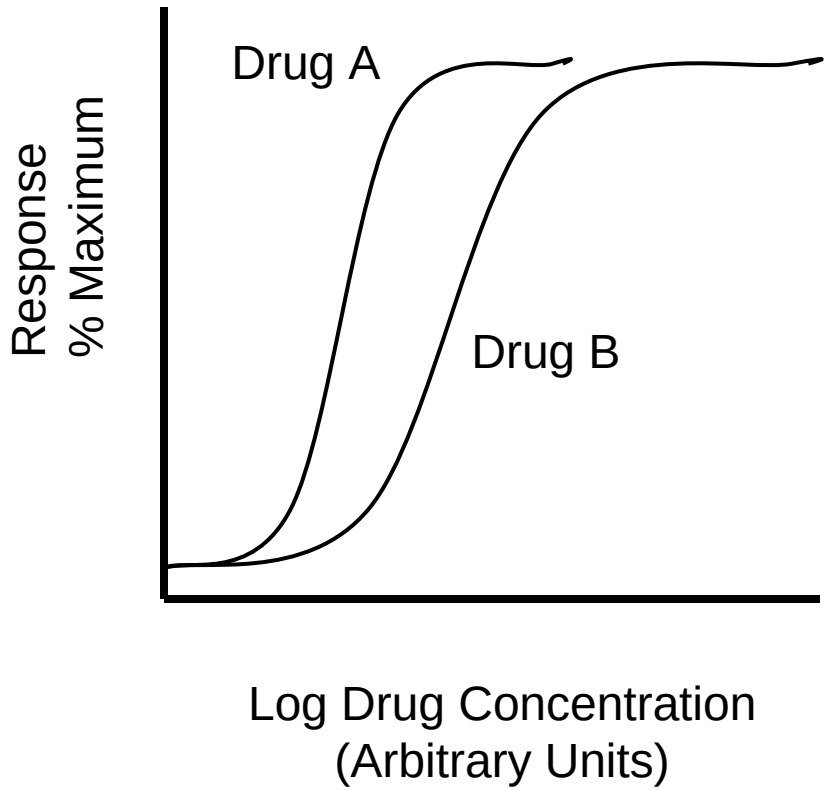
Efficacy

- [redacted]: also known as activity". The a drug to produce al biological e relative to other xpressed as E_{max}.
- [redacted]e antagonists intrinsic efficacy.



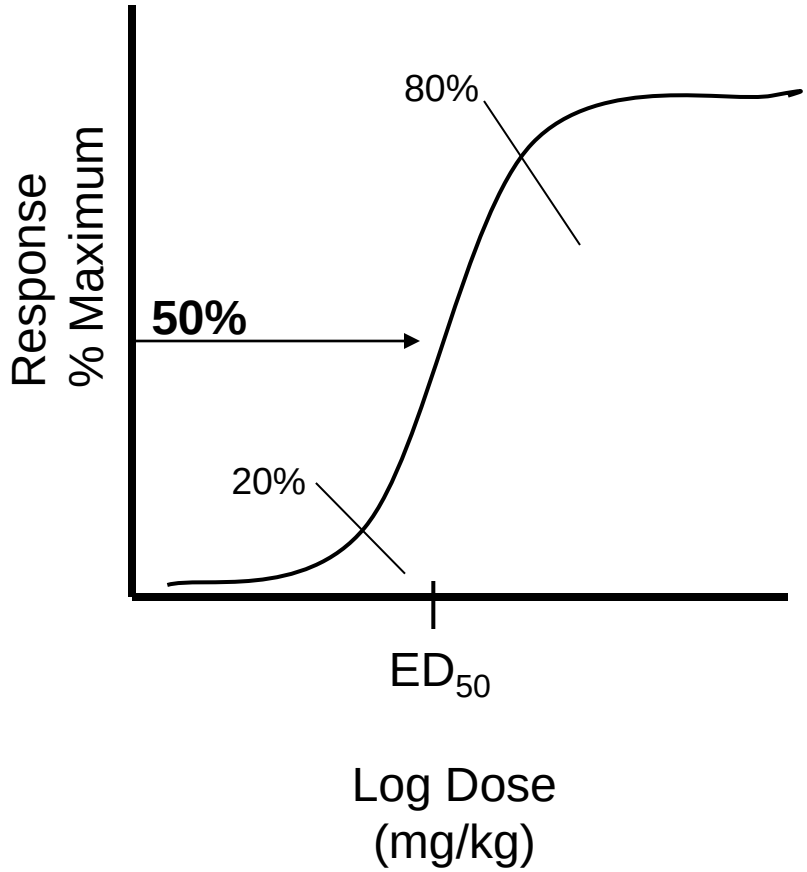
Potency

- [redacted]: ability of a drug to measured al change relative to gs.
- [redacted]d tissue or cell ssays potency must ssed as the 50% concentration



Dose

- The quantity of drug usually represented as milligram of drug per kilogram of body weight (mg/kg).
- The dose of a drug that cause a half maximal response in an organism is known as the 50% effective dose (ED_{50}).



Affinities verses Potency of Selected Agonists From Plants

Toxin	Plant	Affinity, K_i (**nM**) α7-nAChR	Potency (**μM**) α7-nAChR
Nicotine	Common Tobacco *Nicotiana tabacum*	400	18
Anabasine	*Tree Tobacco* *Nicotiana glauca*	58	16.8
Anabaseine	*Tree Tobacco* *Nicotiana glauca*	58-759	6.7
Lobeline	Indian Tobacco *Lobelia inflata*	11000	No Effect

Sharples, C. G. V., and S. Wonnacott. 2001. Neuronal nicotinic receptors. Tocris Reviews No. 19.

Drug Potencies Vary by Receptor Type

Toxin	Potency (**μM**) α7-nAChR	Potency (**μM**) $\alpha_4\beta_2$-nAChR	Potency (**μM**) $\alpha_3\beta_4$-nAChR
Nicotine	18	0.3	5
Anabasine	16.8	N.D.	N.D.
Anabaseine	6.7	4.2	N.D.
Lobeline	No Activation	N.D.	N.D.

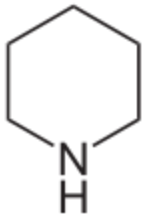
Sharples, C. G. V., and S. Wonnacott. 2001. Neuronal nicotinic receptors. Tocris Reviews No. 19.

Cell-Based Assays

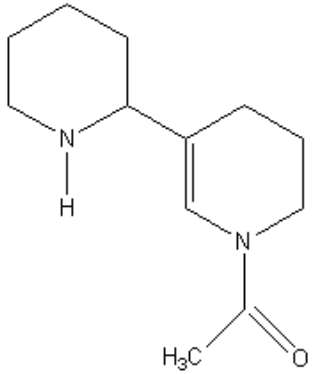
- TE-671 cells
  - Express fetal human muscle-type nAChR ($\alpha 1_2 \beta 1 \gamma \delta$).
- SH-SY5Y cells
  - Express autonomic type nAChRs containing α3 and β4 subunits.

Teratogenic Activity Profile

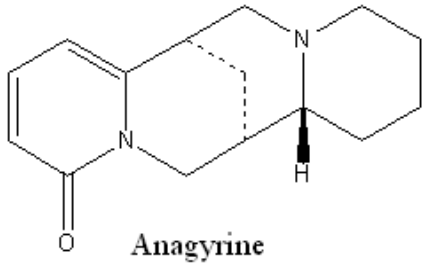
- Piperidine alkaloids
- Carbon side chain of at least three carbons or larger attached to the carbon alpha to the piperidine nitrogen increased teratogenic activity.
- A methyl group attached to the nitrogen reduced teratogenic activity.
- A double bond at the nitrogen or carbon side chain increases teratogenic activity



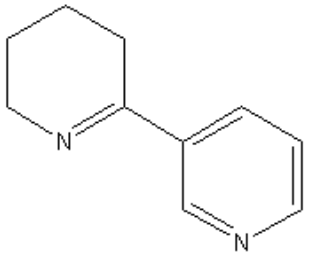
Piperidine



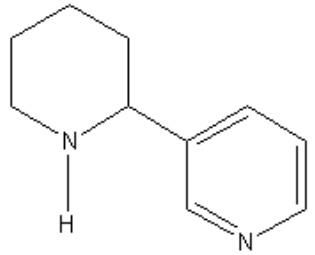
Ammodendrine



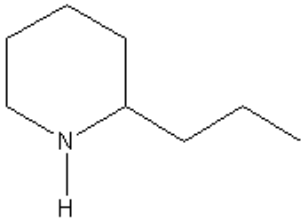
Anagyrine



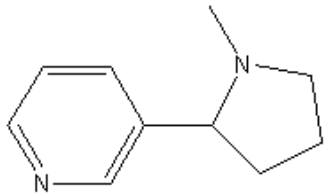
Anabaseine



Anabasine



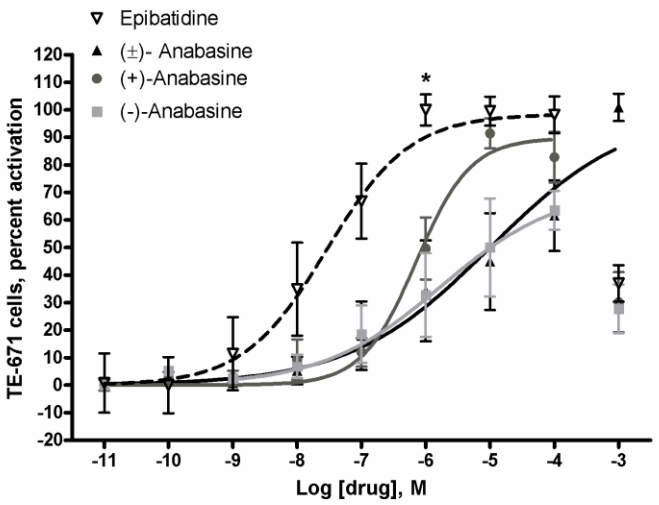
Coniine

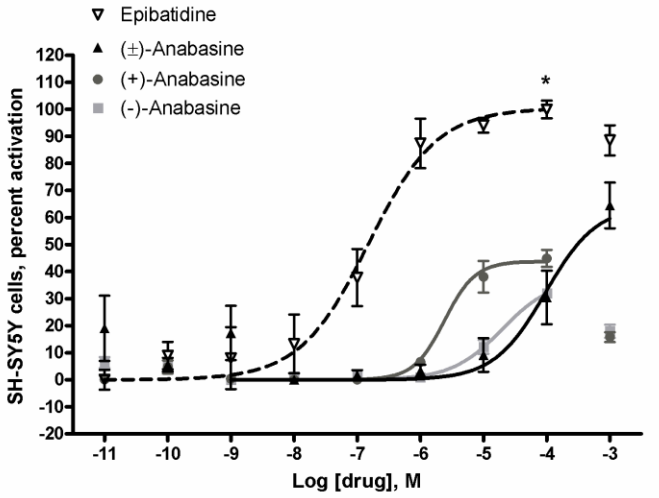


Nicotine

Anabasine

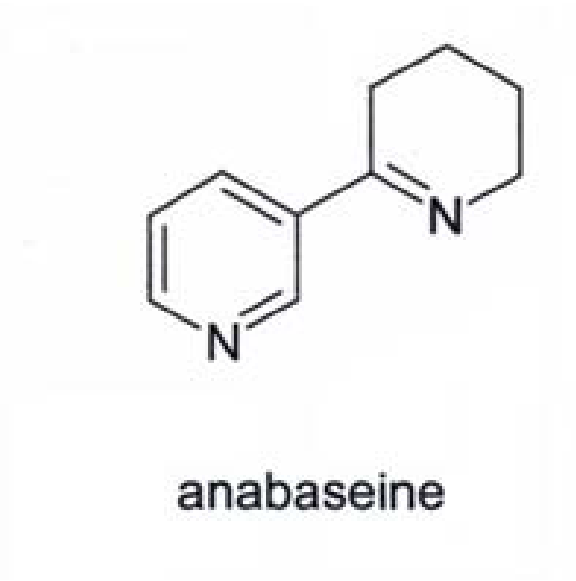
- Piperidine Alkaloid
  - •Isolated from *N. glauca* (tree tobacco)
  - •Agonist
  - •Present in the plant as a racemate.

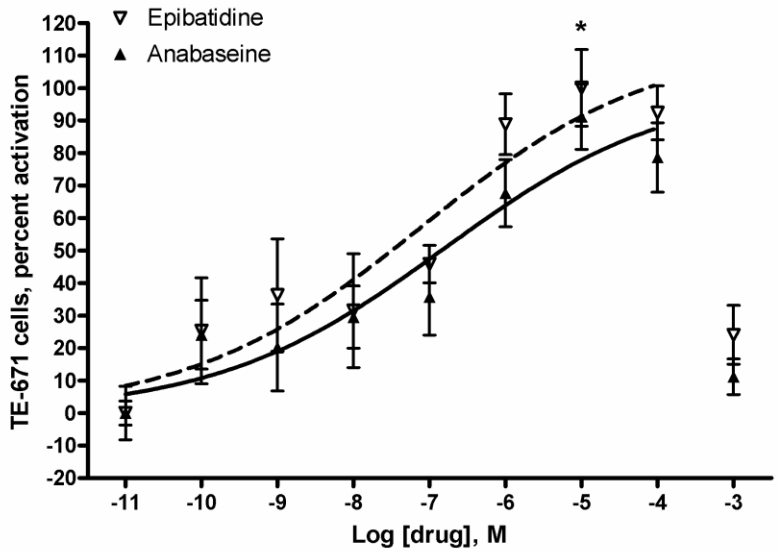


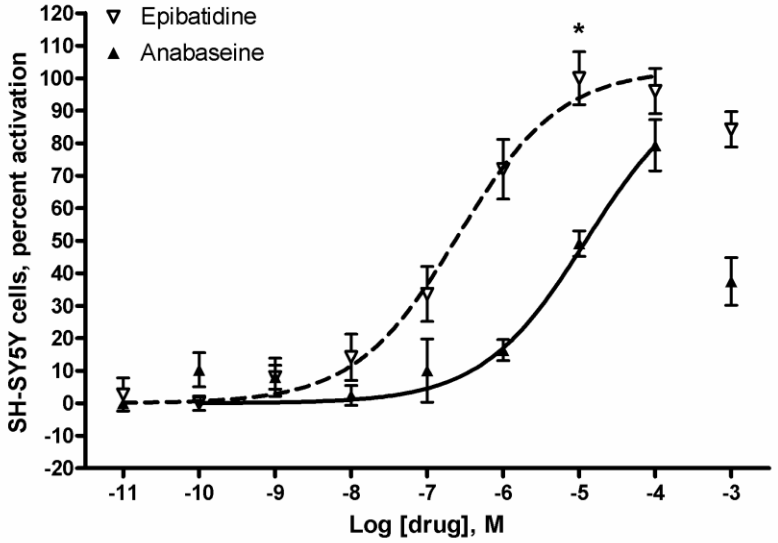


Anabaseine

- Carnivorous marine worm toxin
- Potent at neuromuscular receptors.
- Double (imine) bond between positions 1 and 2 of the piperidine ring.
- Isolated and identified from *Paranemertes peregrina* (purple ribbon worm).

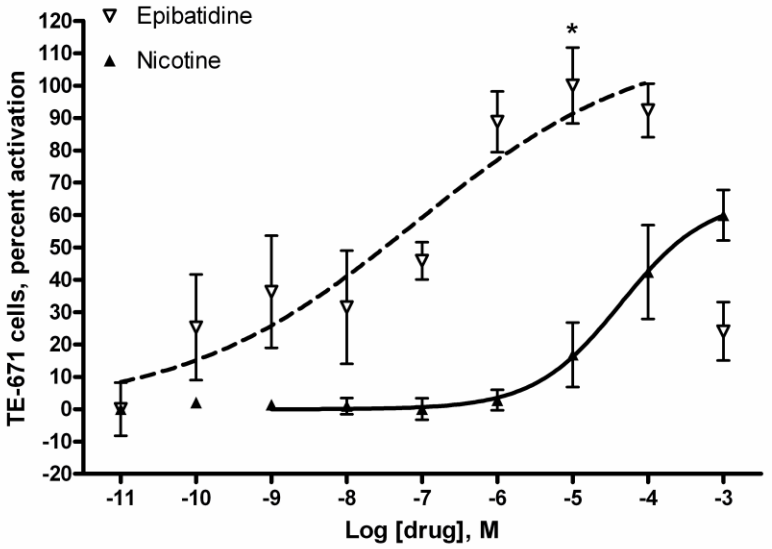


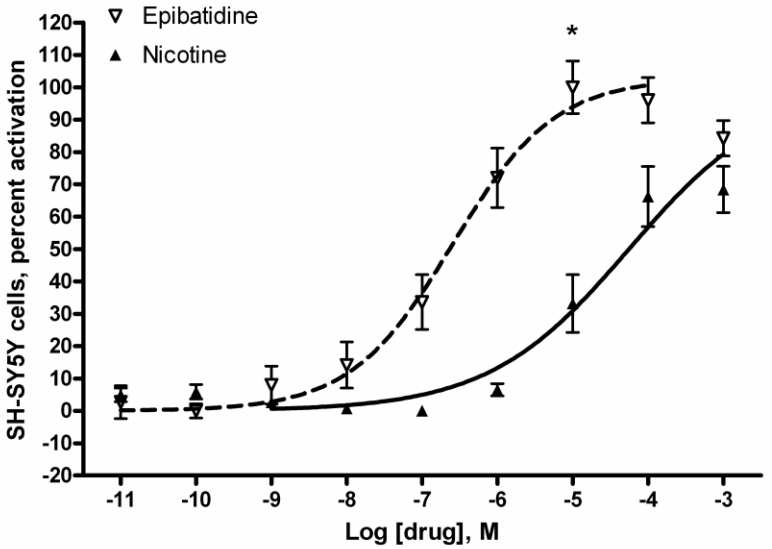




Nicotine

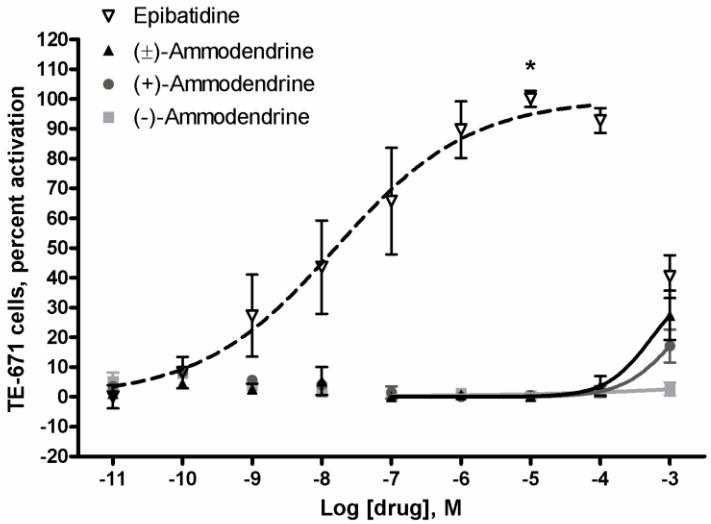
- Pyridine Alkaloid
- *N. tabacum*
- Not very teratogenic when compared to the piperidine alkaloids.

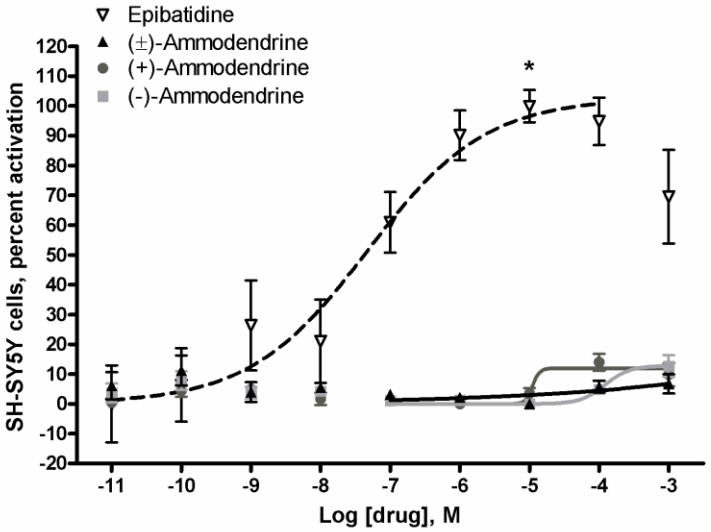




Ammodendrine

- *Lupinus* Spp.
- Piperdine alkaloid
- Teratogenic in cattle





Relationship between potency, percent maximum response, and affinity of the teratogenic alkaloids.

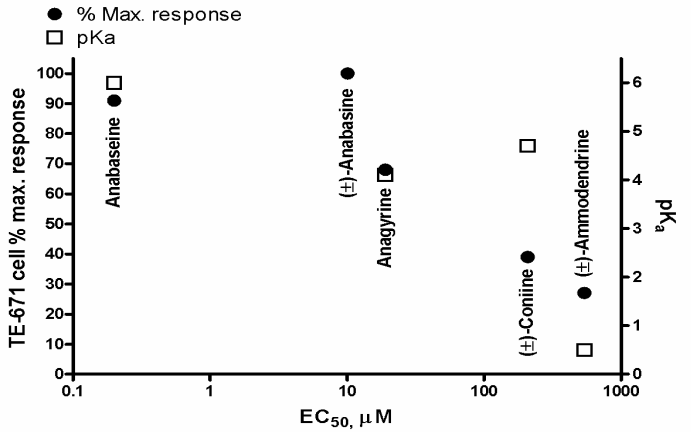
- Each figure presents the potency, and percent maximal response and the affinity (estimated, negative logarithm of the affinity value (pK_a), of the alkaloids in TE-671 cells (A) and SH-SY5Y cells (B).

- Suggest the actions of these alkaloids are efficacy dependent.

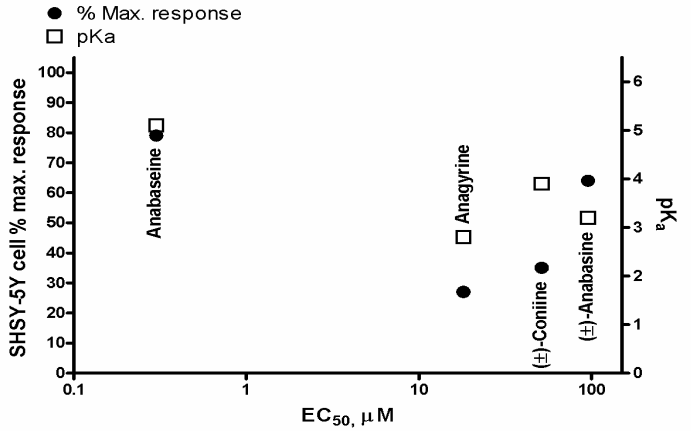
- High concentrations of affinity-dependent agonists are required to produce a near maximum biological response.

- Lower concentrations of efficacy-dependent agonists can produce a near maximum biological responses. Efficacy-driven agonists would have a greater potential to produce fetal defects at low concentrations relative to their pKa value.

A.

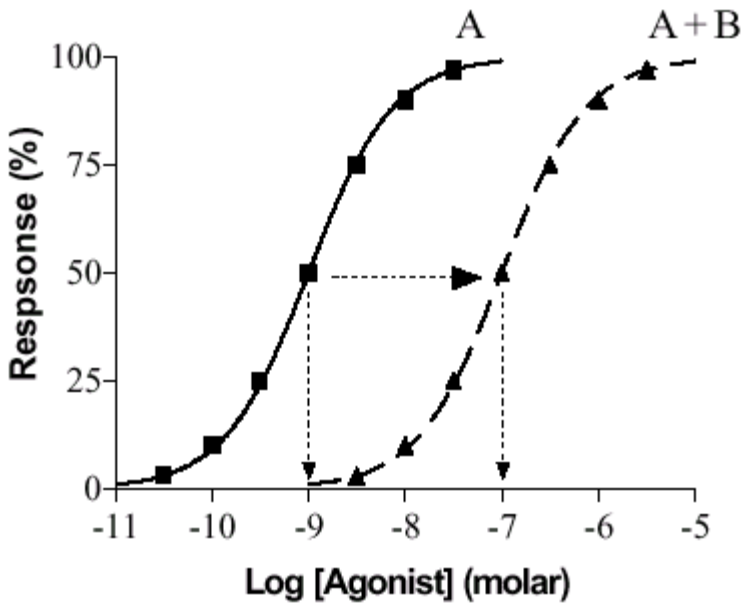


B.



Competitive Antagonists

- Competitive antagonists have
- These [redacted] mpete with a the bindi me recep educe the po gonists.
- The e comp gonist can b e by exces



A = agonist alone
B = antagonist (one concentration)
A+B = agonist + antagonist

Levy, 2003

Affinities of Selected Antagonists From Plants.

Toxin	Plant	Affinity, K_i (**nM**) α7-nAChR	Affinity, K_i (**nM**) $\alpha_4\beta_2$-nAChR
D-tubocurarine	*Chondodendron tomenosum*	25000	13.9
Methyllycaconitine (MLA)	*Delphinium spp.*	0.69	3700
Erysodine	*Erythrina spp.*	4000	5
Dihydro-β-erythroidine	*Erythrina spp.*	9000	3.2

Sharples, C. G. V., and S. Wonnacott. 2001. Neuronal nicotinic receptors. Tocris Reviews No. 19.

MLA

- Isolated from *Delphinium* Spp. (Larkspur)
- Classified as an antagonist
  - Lacks intrinsic efficacy.
- Acts at nAChR.