Insecticide Mode of Action

Training slide deck

IRAC MoA Workgroup

Version 1.0, April 2019

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What is an Insecticide's 'Mode of Action'?

The Mode of action defines the process of how an insecticide works on an insect or mite at a molecular level

Why is it good to know the Mode of Action of an Insecticide?

Knowing the Mode of action of an insecticide is key to managing resistance

The Insecticide Resistance Action Committee (IRAC) is a coordinated industry response to resistance management

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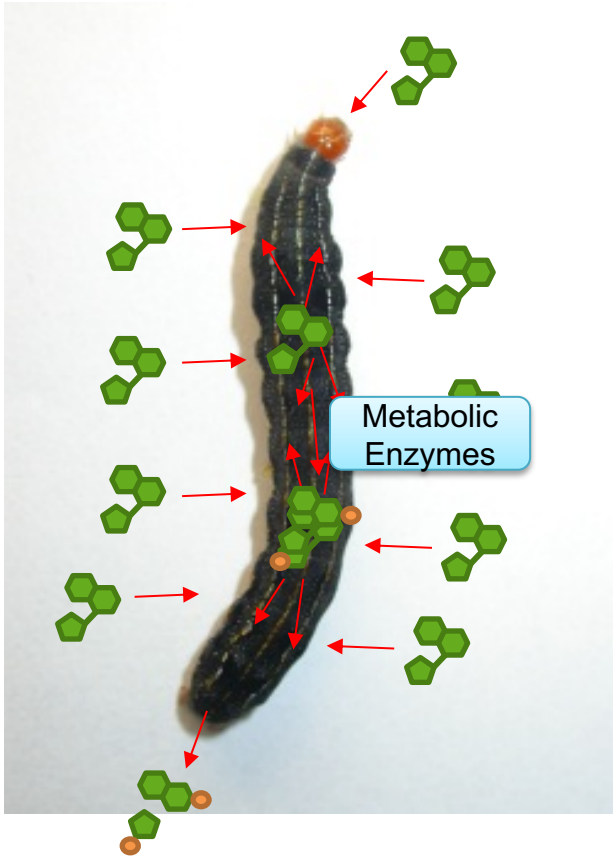
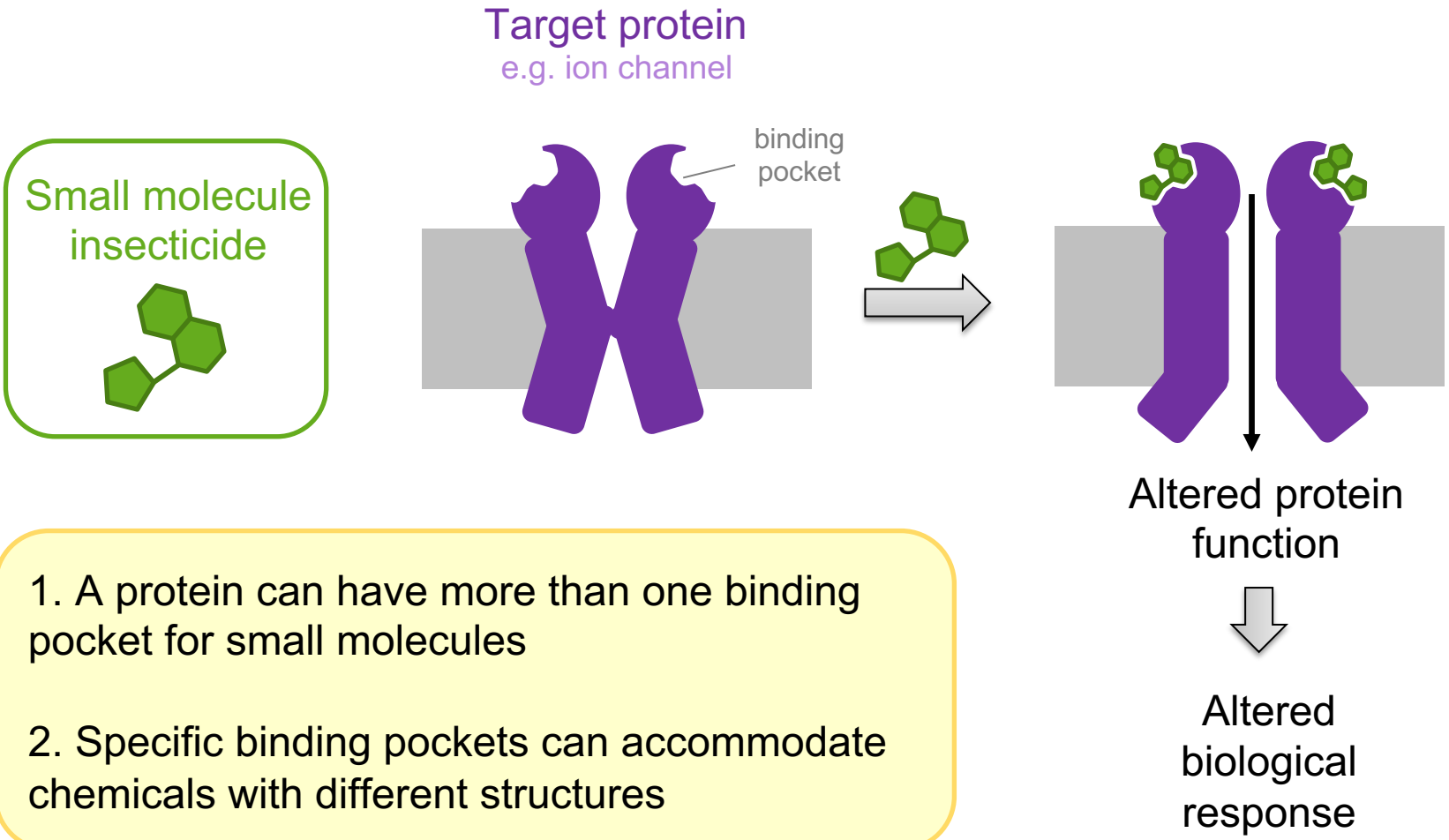
ADME is an important factor in an insecticide's bioavailability

- **Absorption**
  - Through the cuticle
  - Orally through consumption
  - Inhaled through spiracles as vapor
- **Distribution**
  - Through the body to target sites
- **Metabolism** (Break down)
  - By insect defense mechanisms
- **Excretion**



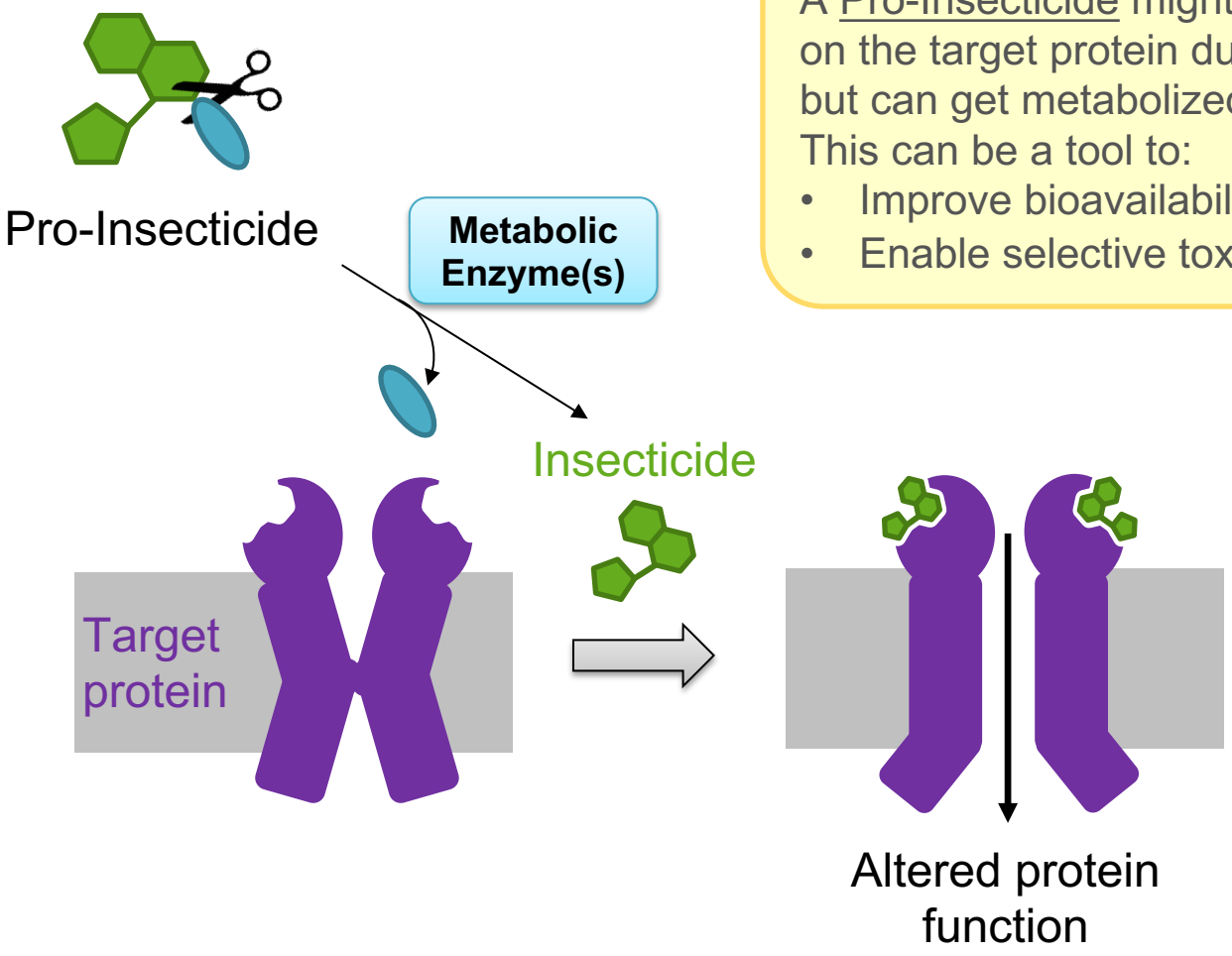
Insecticides act on key functional proteins that regulate vital processes



1. A protein can have more than one binding pocket for small molecules

2. Specific binding pockets can accommodate chemicals with different structures

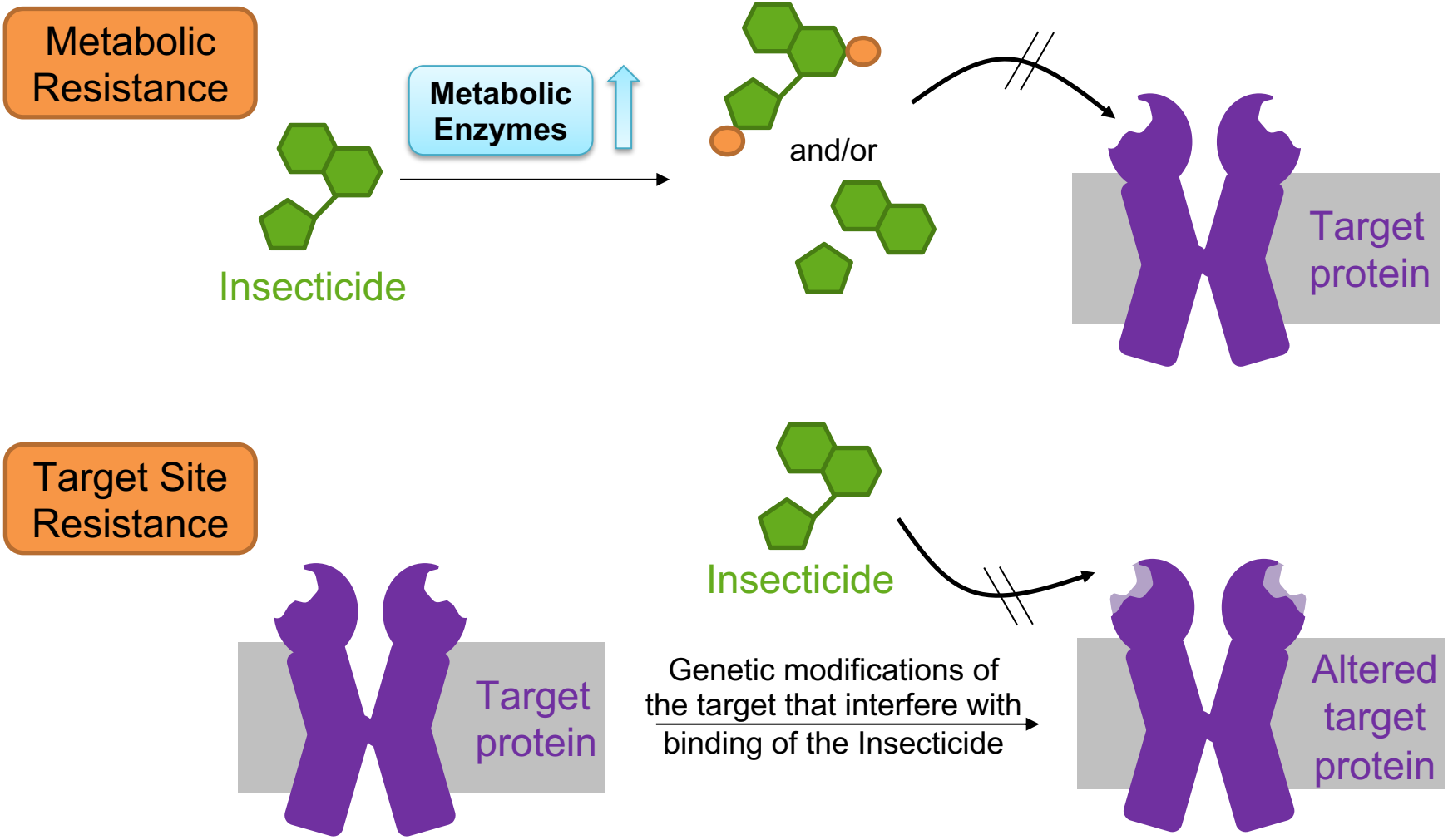
The Pro-Insecticide concept



A Pro-Insecticide might have negligible activity on the target protein due to protecting groups, but can get metabolized *in vivo* to its active form. This can be a tool to:

- Improve bioavailability
- Enable selective toxicity

Major mechanisms of Insecticide Resistance



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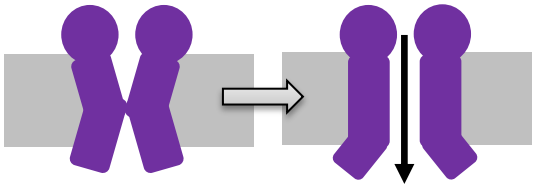
Key functional proteins that are targets for Insecticides

Ion channels

essential for bioelectricity



Na^+ Ca^{2+} K^+ or Cl^-

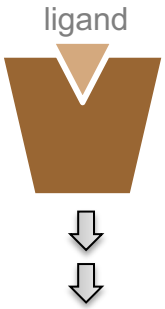
Enzymes

biocatalysts

Proteins accelerating chemical reactions

Receptors

signal transducer



Binding of a ligand triggers a response

Insecticide Mode of Action
Major classes

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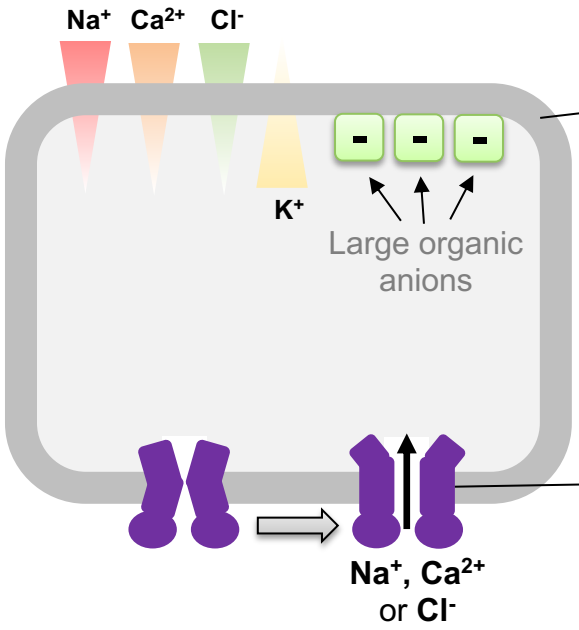
Ion channels are important targets of neuromuscular disruptors



Cells are surrounded by a cell membrane, which acts like an insulator separating two conducting media

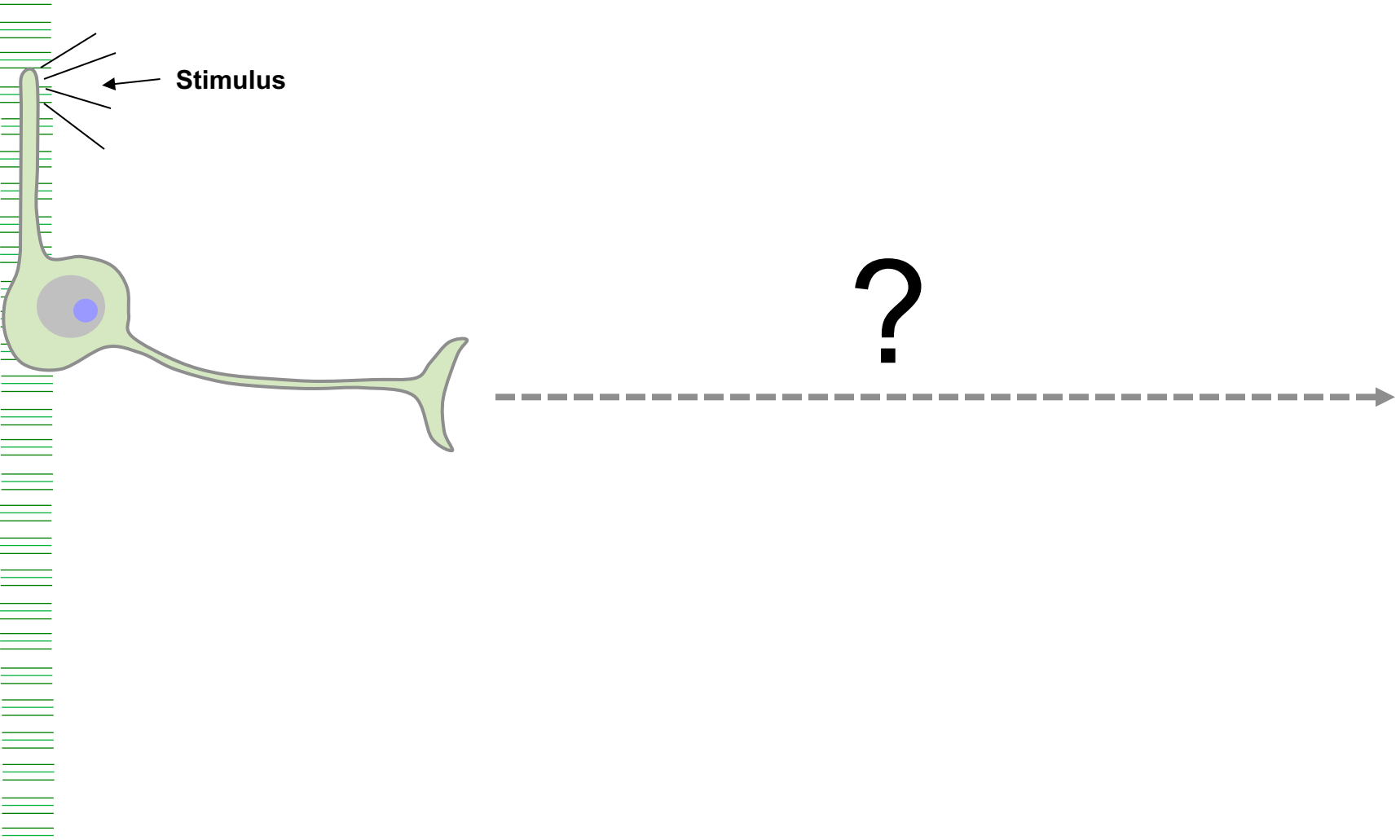
An asymmetric separation of charges across the cell membrane makes the inside negative compared to the outside of the cell (membrane potential)

Ion channels are pore-forming membrane proteins that transduce signals by controlling the flux of ions across the cell membrane. Their concentration gradients together with the membrane potential determine the direction of ion flux.

In electrically excitable cells (neurons, muscle cells) ion channels play an important role in fast signal transduction over long distances

- *Gating:* Trigger for channel opening (voltage, ligand, etc.)
- *Ion selectivity:* Ion preference of the channel

The Insect Neuromuscular system: Translating a stimulus into (muscle) action



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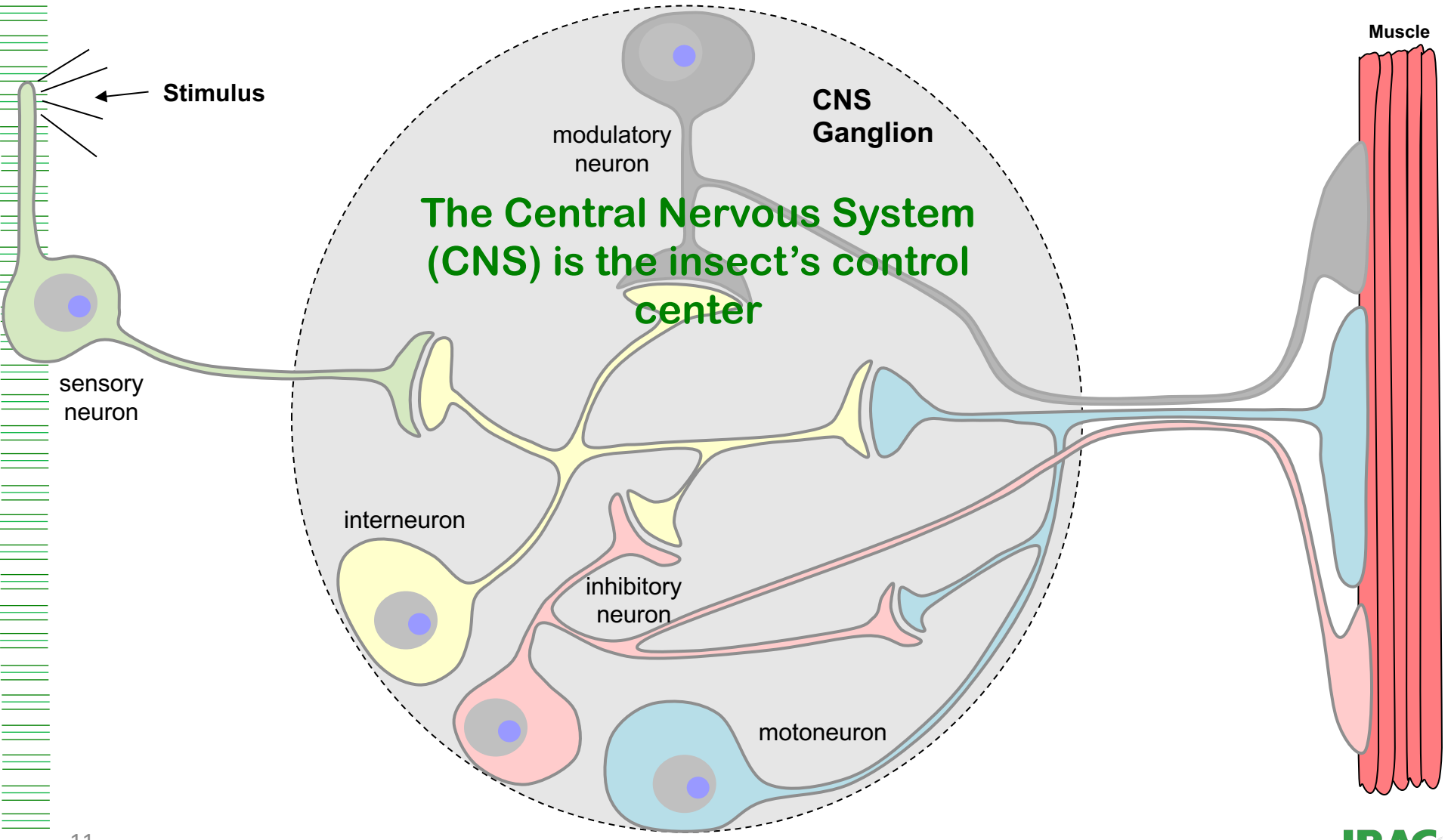
Different types of neurons are involved in signal transduction and fine tuning



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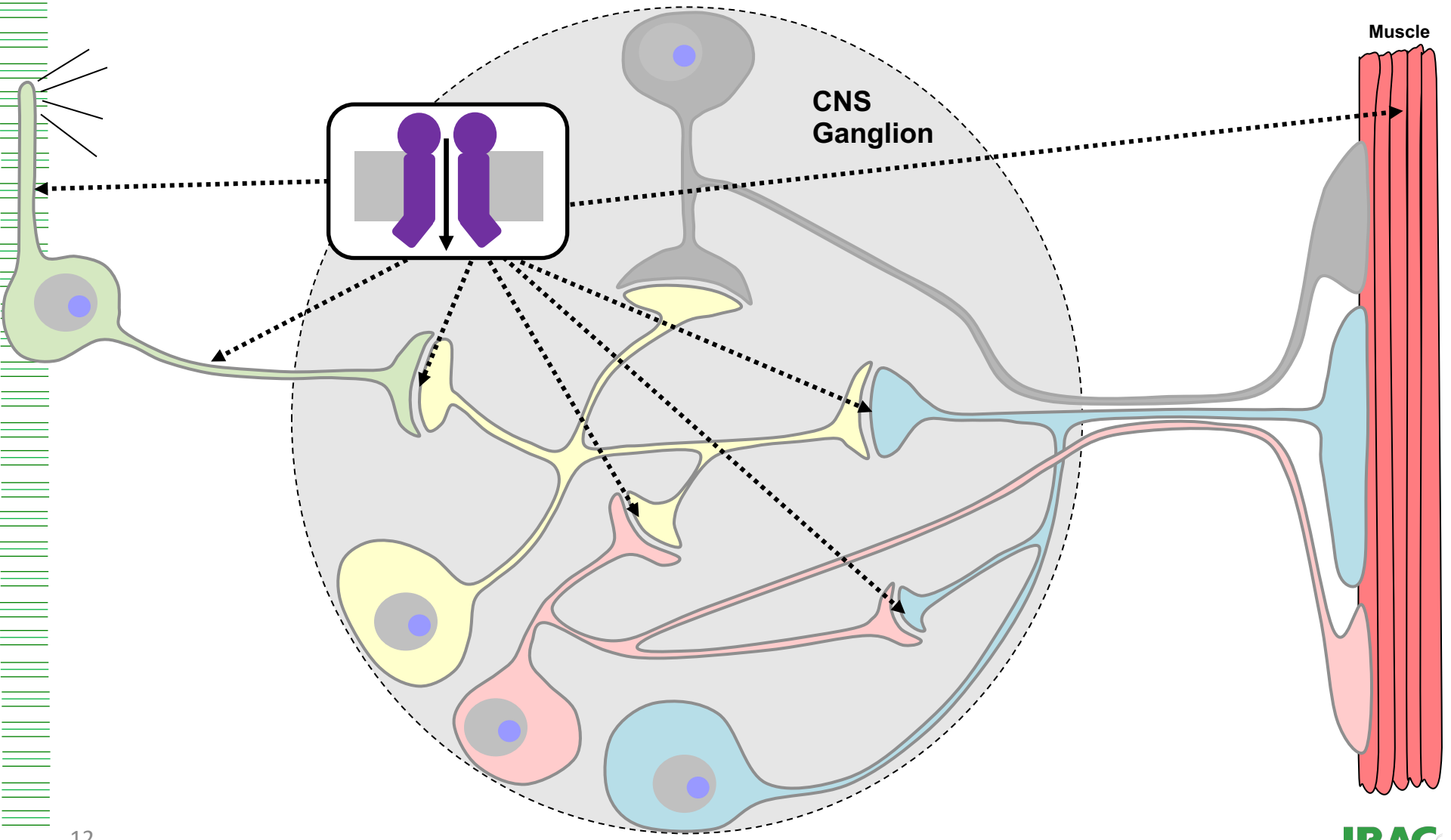
Ion channels play diverse roles within the neuromuscular system



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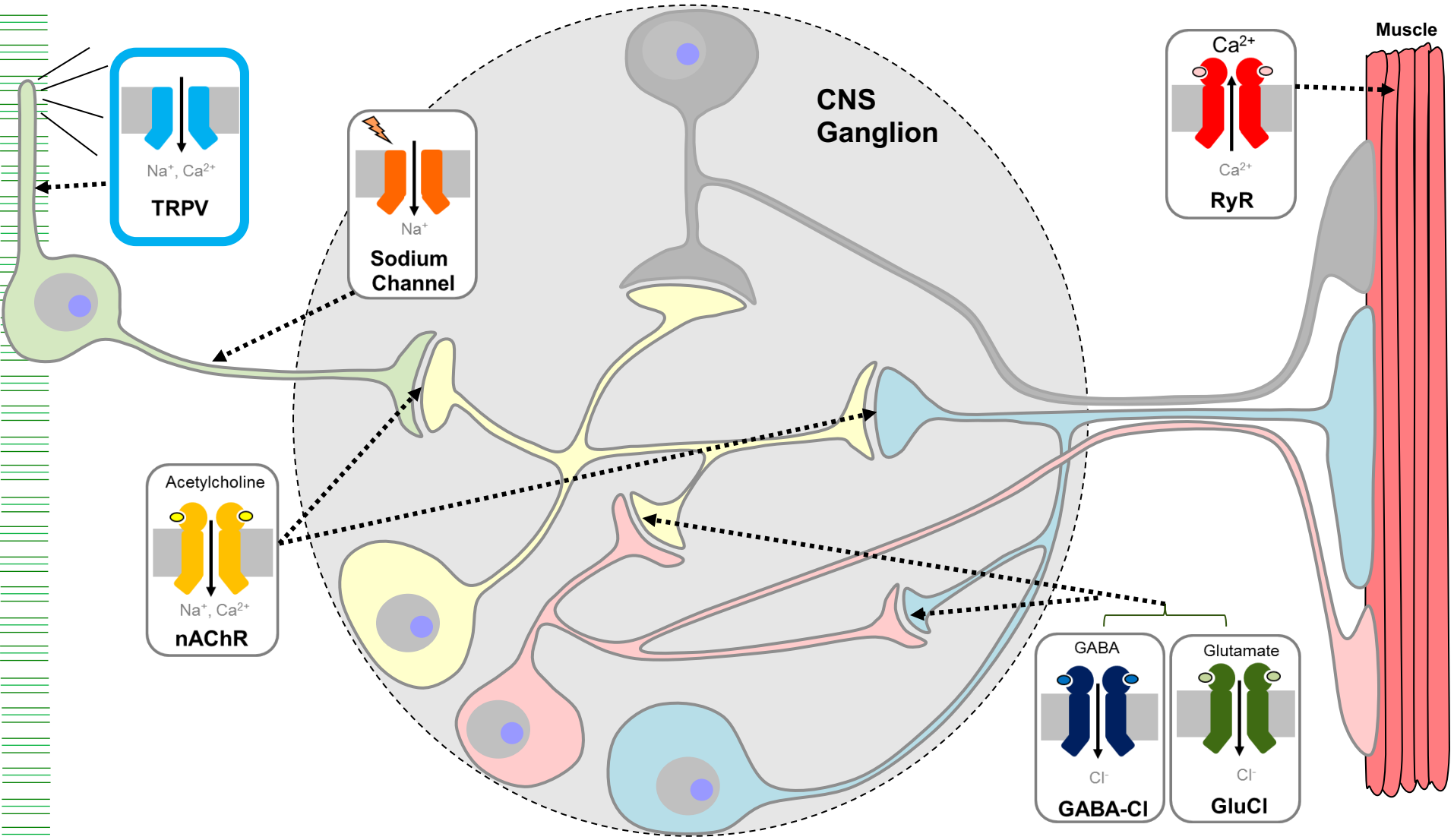
Overview of ion channels targeted by neuromuscular disruptors



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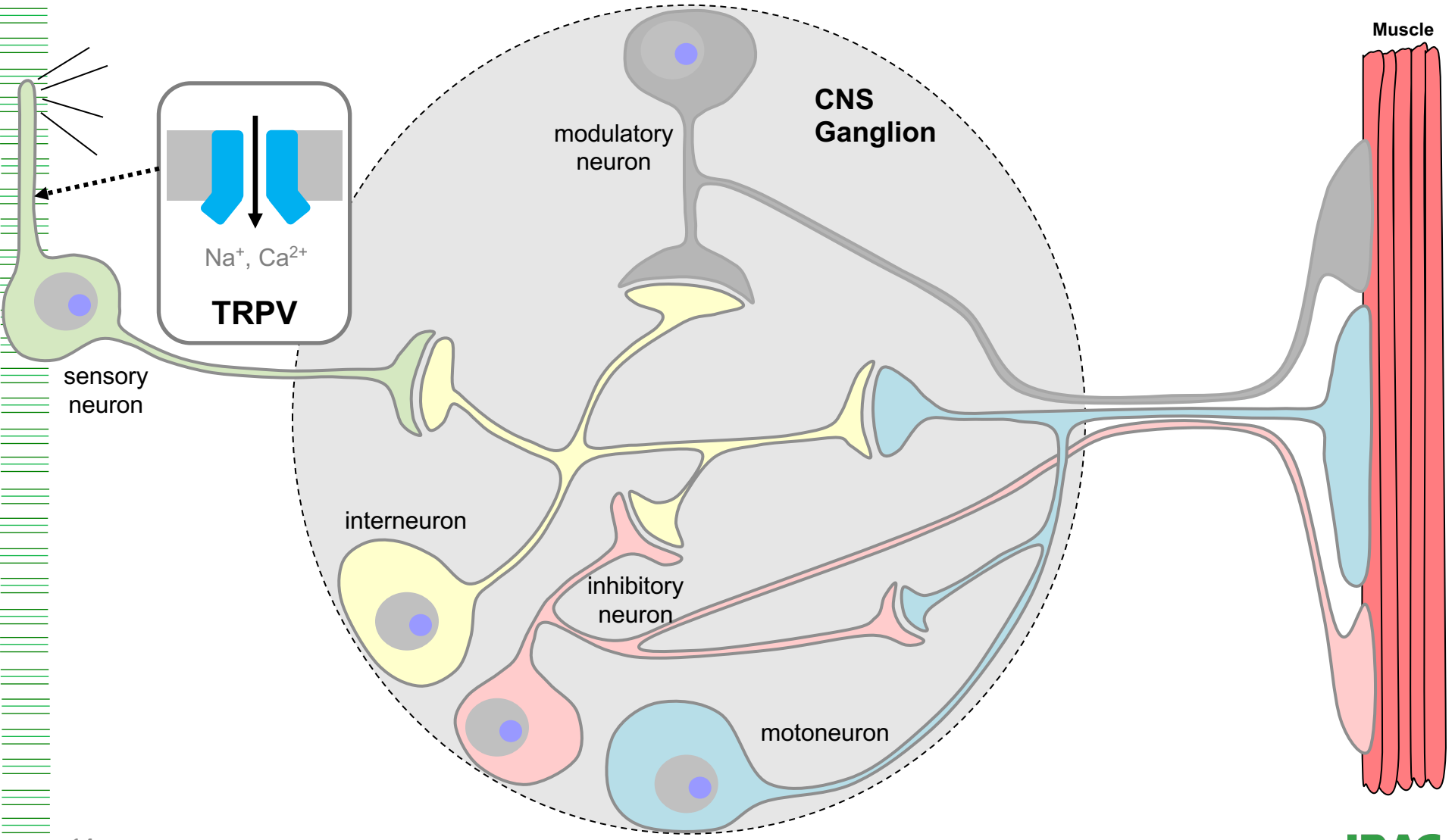
The TRPV channels exist in specialized sensory neurons that detect stretch



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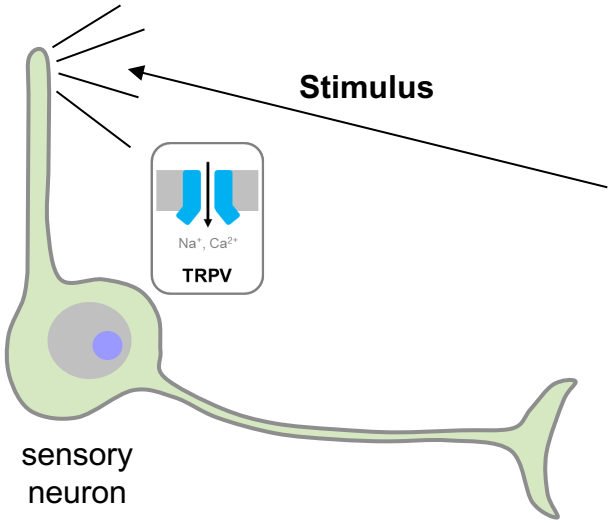
TRPV channels play an important role in insect stretch receptor signaling (Chordotonal Organ)

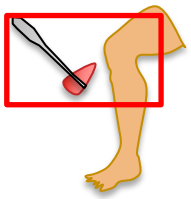


- Sight
- Taste
- Smell
- Touch
- Hearing (antenna)
- Gravity (antenna)
- Proprioception* (joints)
- Others

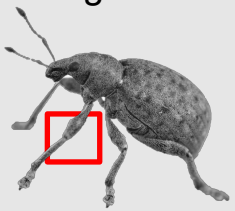
Sensed by stretch receptors

*Proprioception is the detection of the relative position and motion of body parts

When a doctor tests reflexes with a rubber hammer (knee jerk reflex) local stretch receptors are activated that signal to the spinal cord and back to the target muscle.



Insects also have stretch receptors that detect joint bending forces



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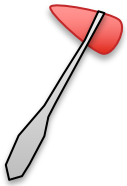
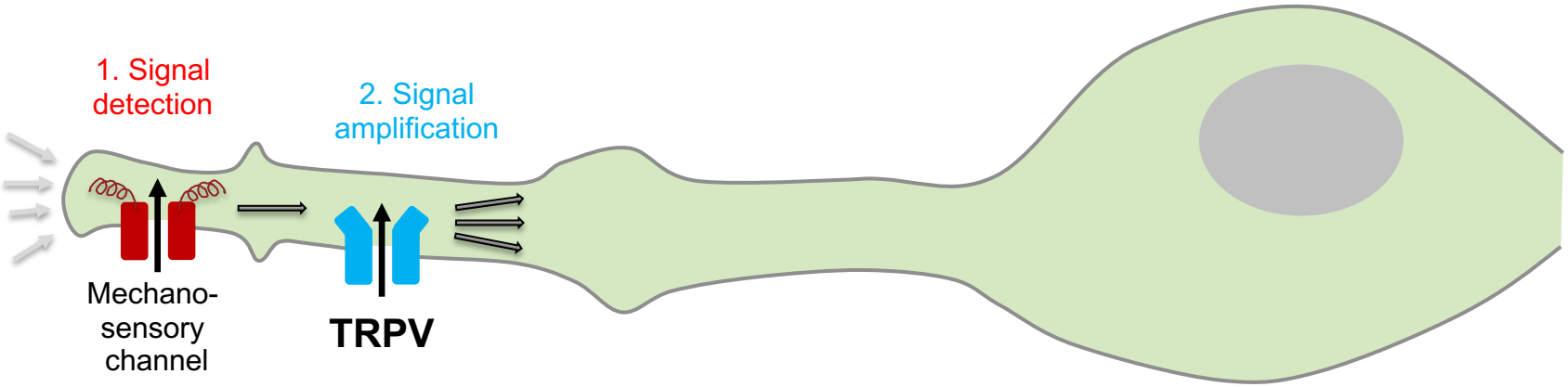
Insecticides acting on TRPV channels interfere with stretch receptor signaling

- TRPV channel modulators affect Chordotonal organs (COs), stretch receptors in the insect joints that sense relative position of body parts (proprioception)

Leg extension caused by a TRPV modulator (can be imagined as a 'molecular' rubber hammer)

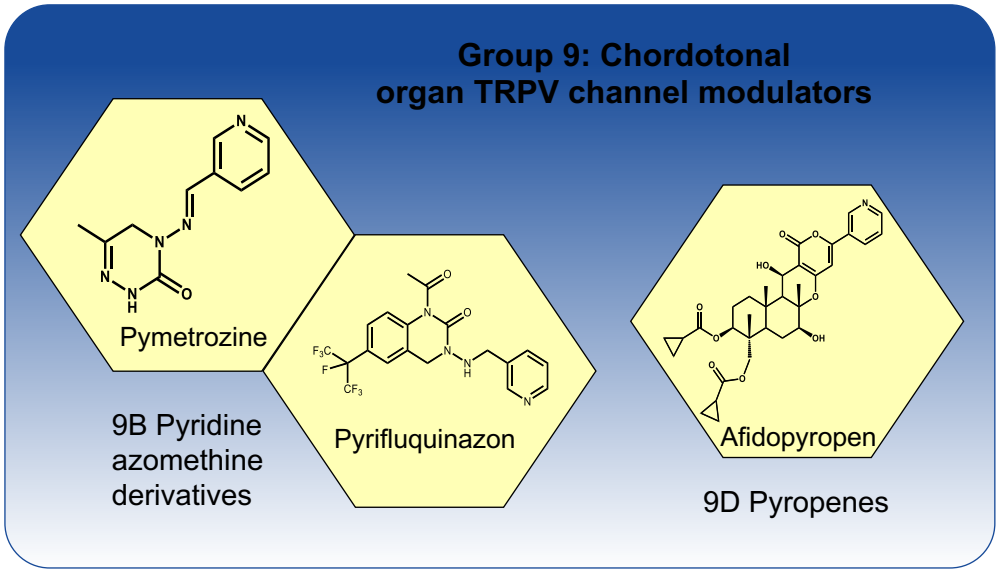


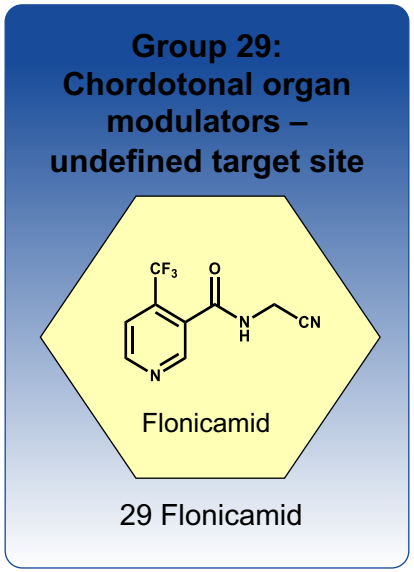
- TRPV channels amplify the weak mechanosensory signal in chordotonal neurons



- Modulation of TRPV channels generates continuous chordotonal nerve signals independent of joint movement. This leaves insects deaf and uncoordinated, resulting in rapid feeding cessation, leading to starvation and ultimately death

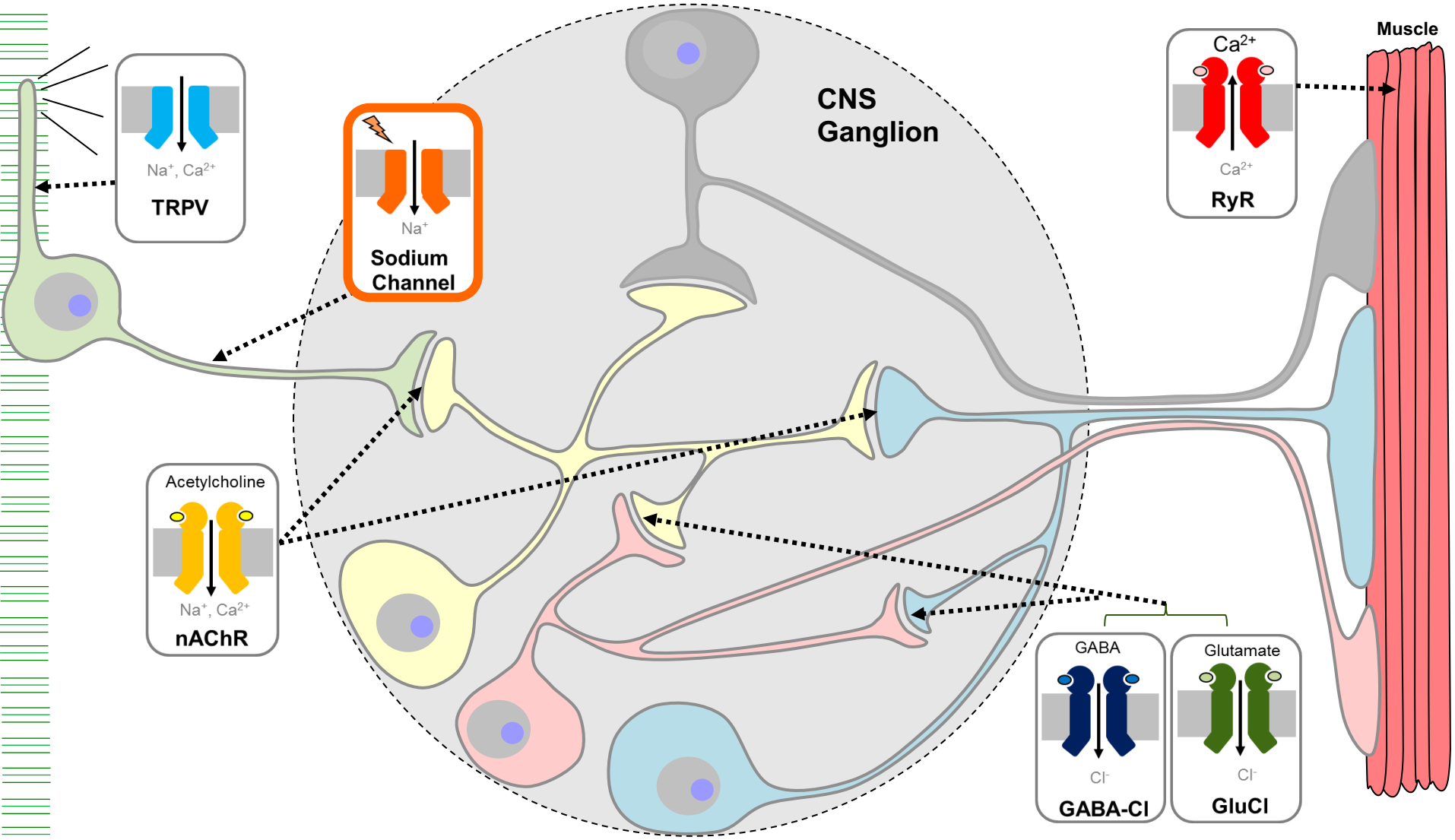
TRPV channel and chordotonal organ modulators





Flonicamid produces symptoms similar to TRPV channel modulators and like its more active metabolite affects chordotonal organs. However, Flonicamid appears not to act directly on TRPV channels, suggesting a different target site in chordotonal organs.

Overview of ion channels targeted by neuromuscular disruptors



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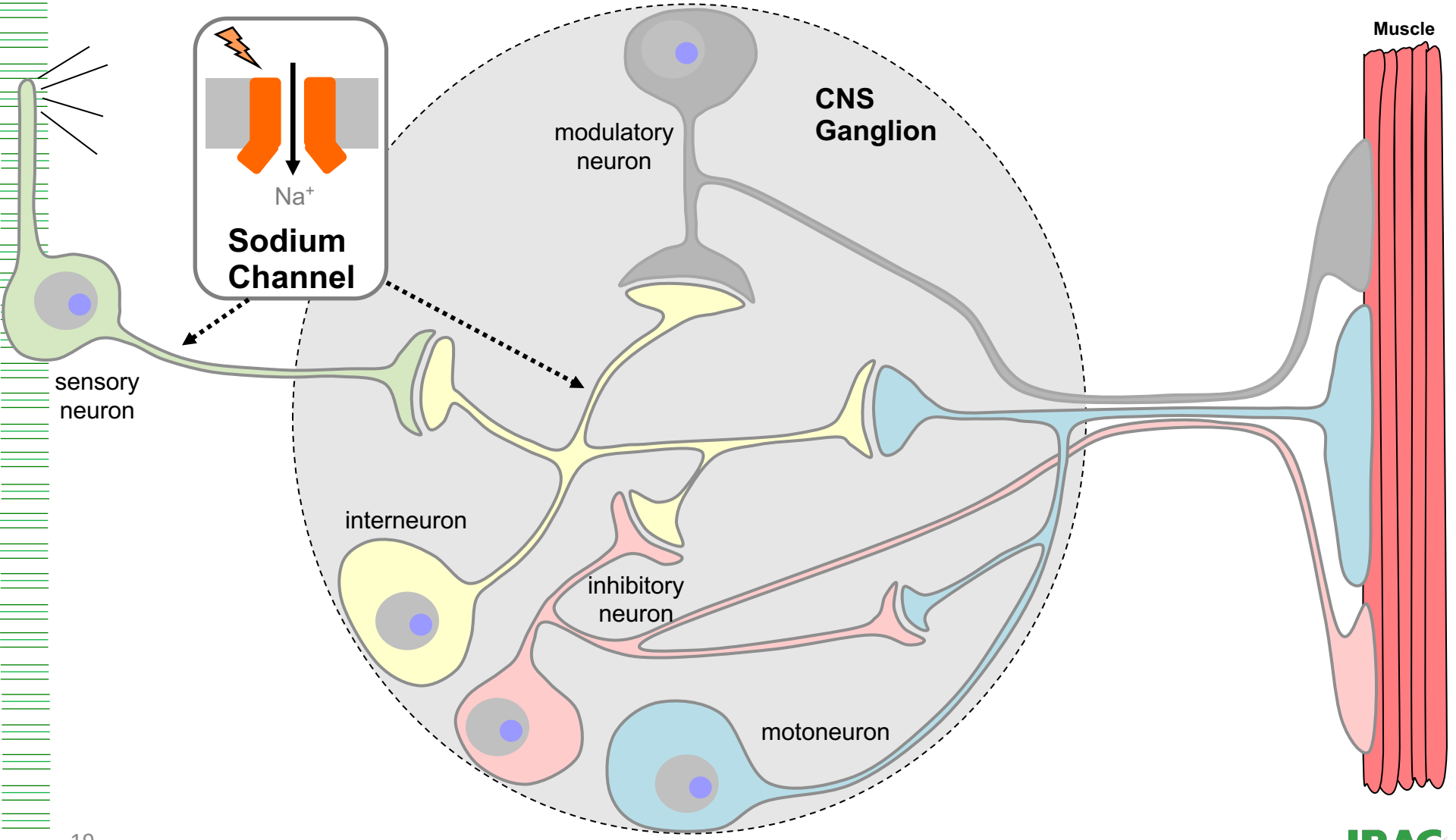
Insecticides acting on Sodium channels



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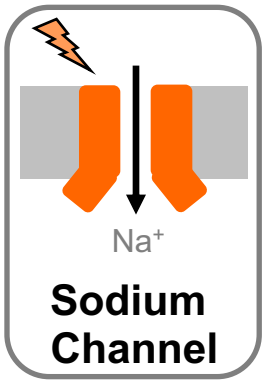
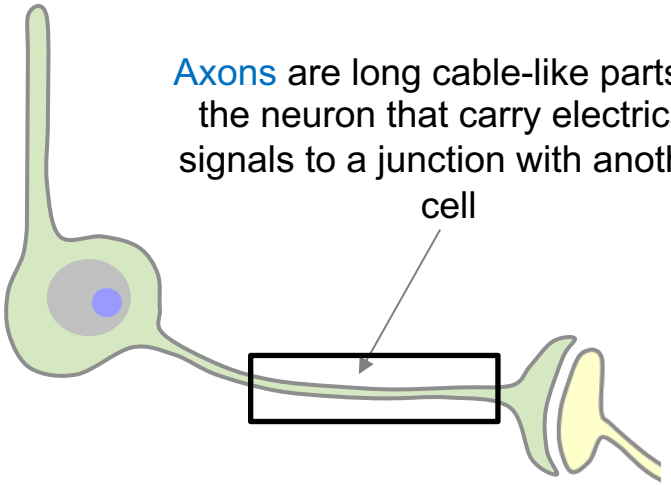
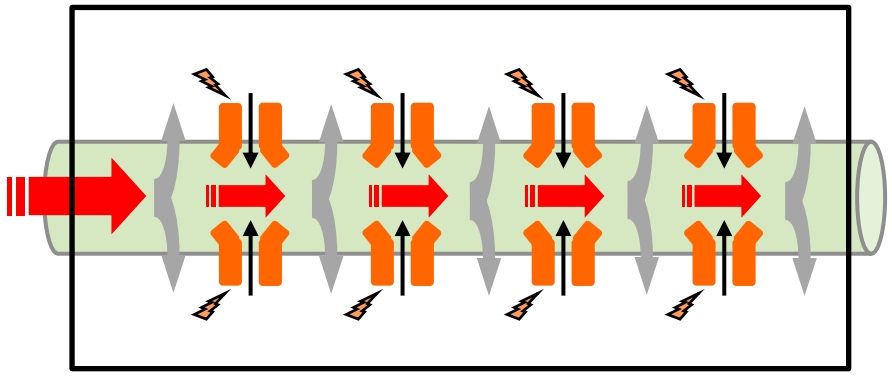
Sodium channels play a crucial role in signal propagation in excitable cells







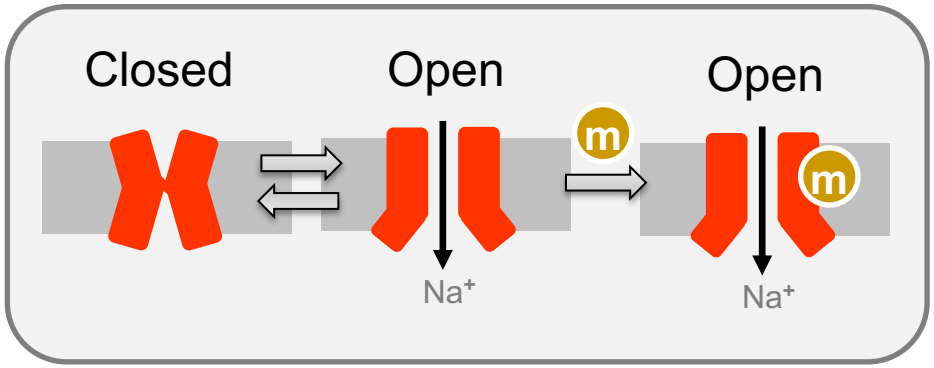
Voltage-dependent sodium channels contain a built-in voltage sensor which detects local positive changes in membrane potential

This triggers opening of the channels and sodium entry

Entry of sodium results in a more positive membrane potential that in turn activates adjacent sodium channels thus propagating the signal along the axon

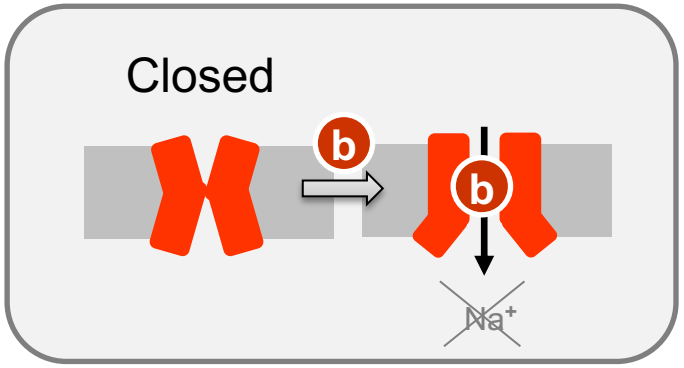
Sodium channel modulators & blockers

Sodium channel modulators



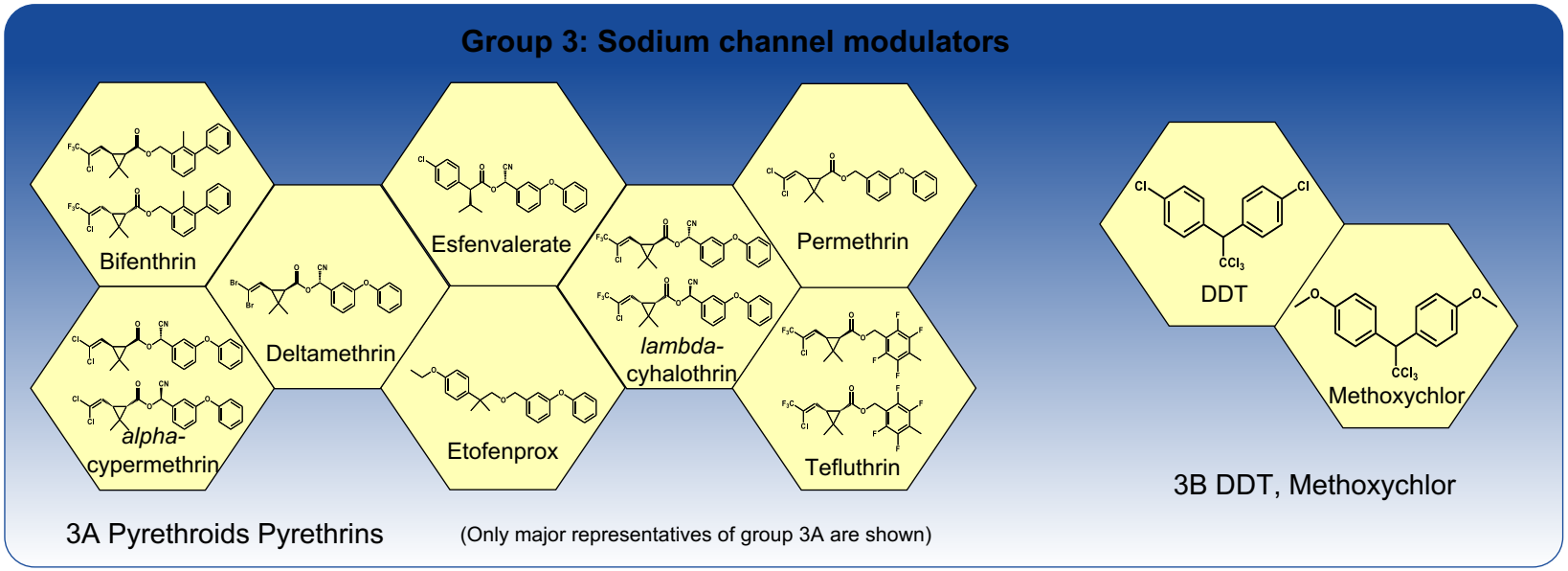
- prolonged opening of sodium channels
- prolonged action potentials
- restimulation of the nerve and repetitive firing
- hyperexcitation

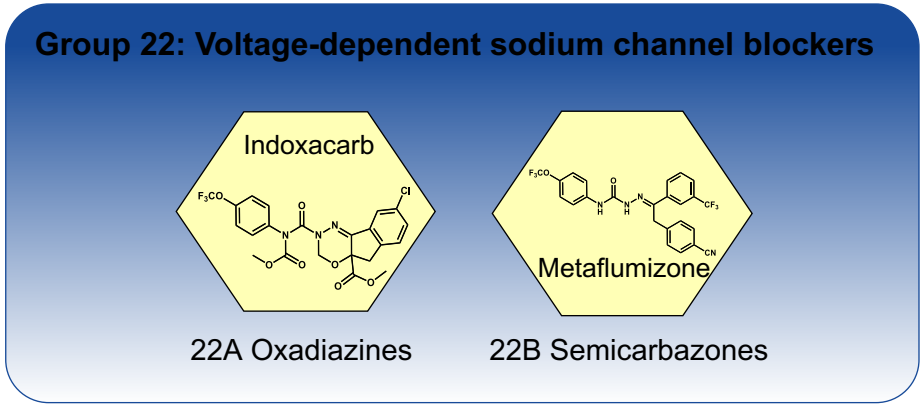
Sodium channel blockers



- obstruction of the sodium channel pore
- block of nerve action potentials
- paralysis

Insecticides acting on Sodium channels





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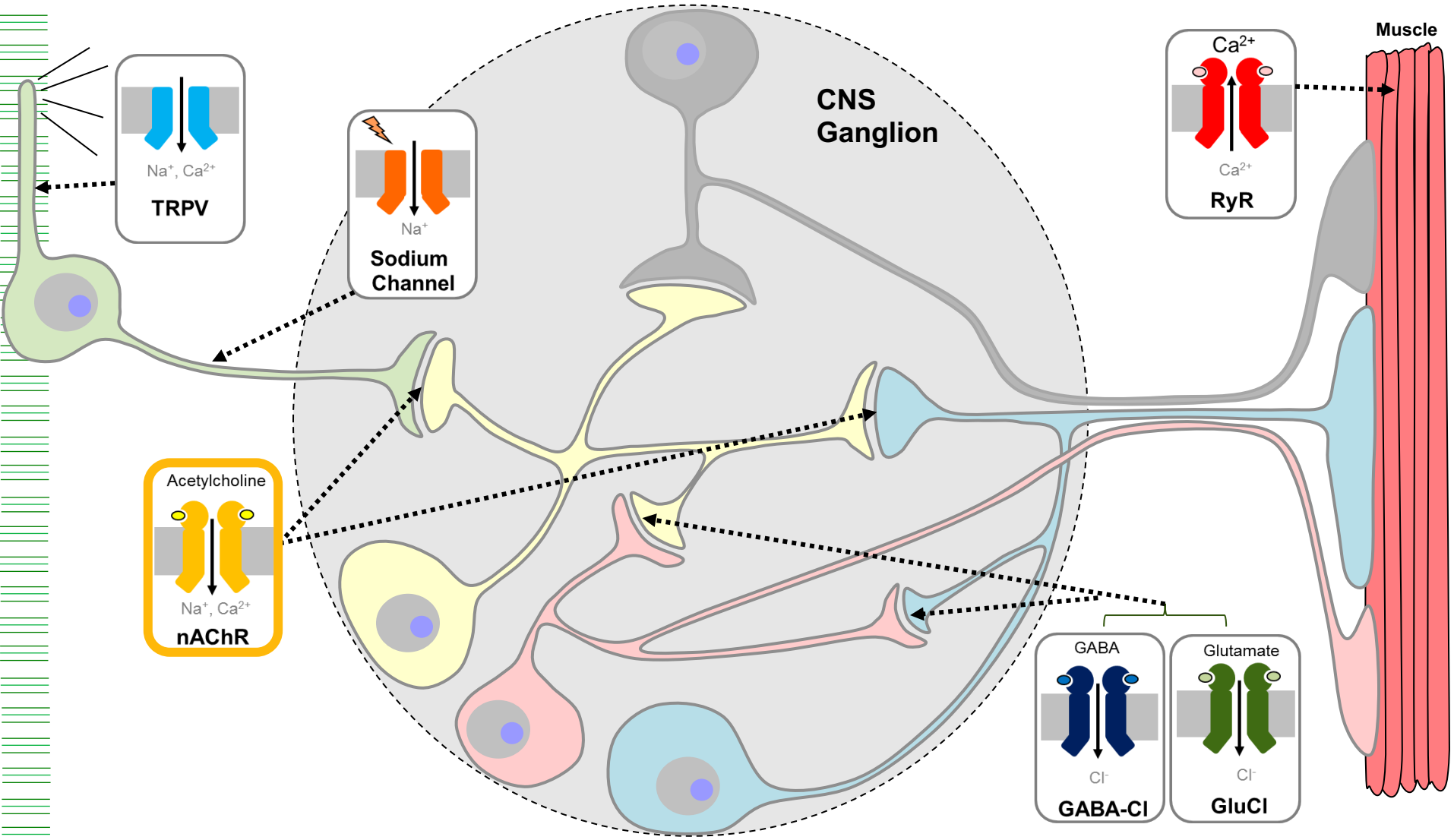
Overview of ion channels targeted by neuromuscular disruptors



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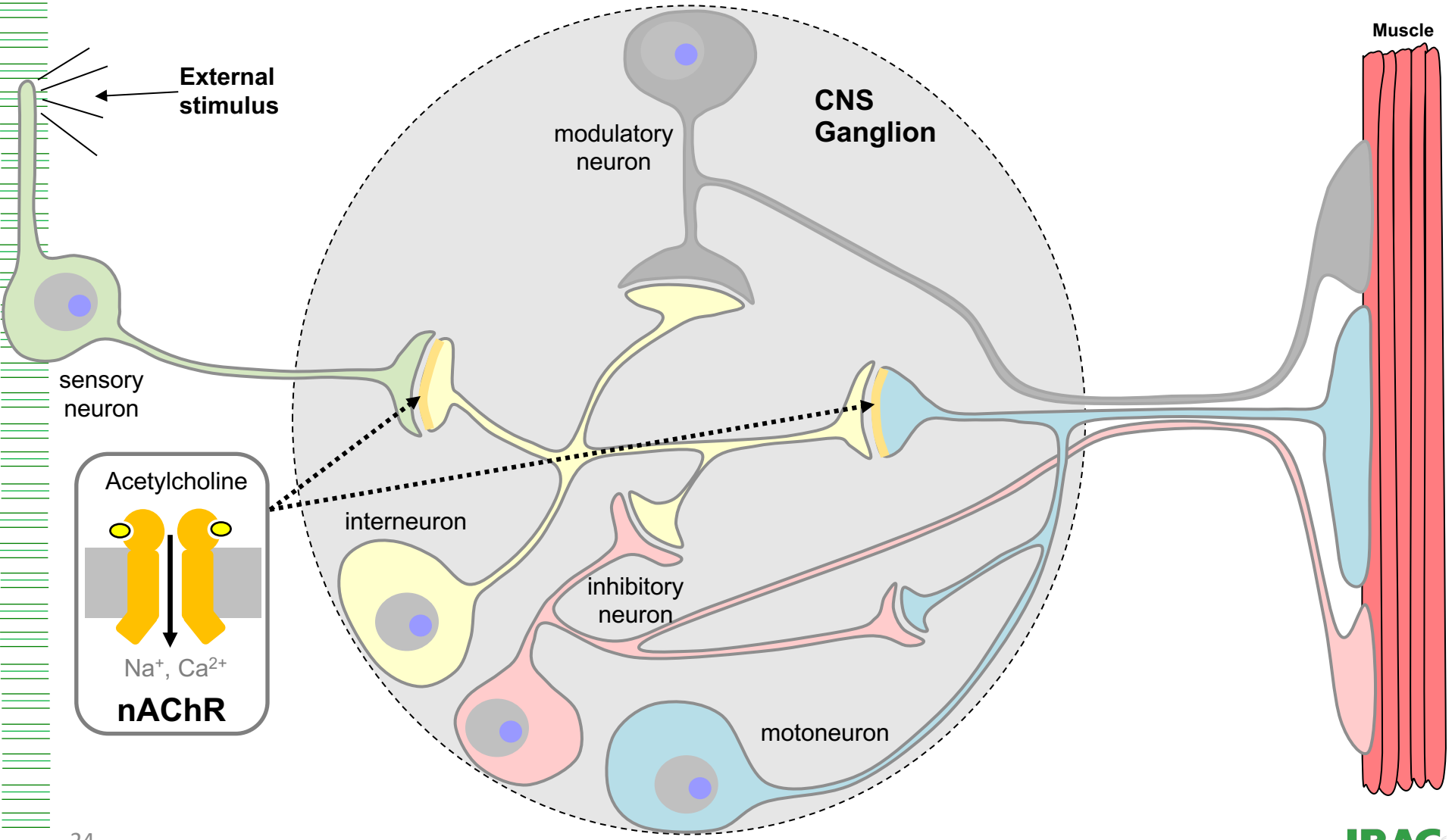
Insecticides acting on nicotinic Acetylcholine receptors (nAChR)



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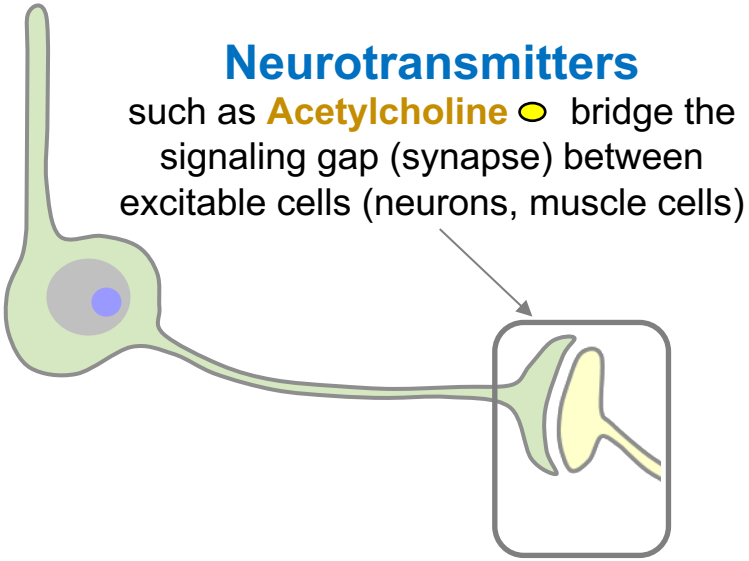
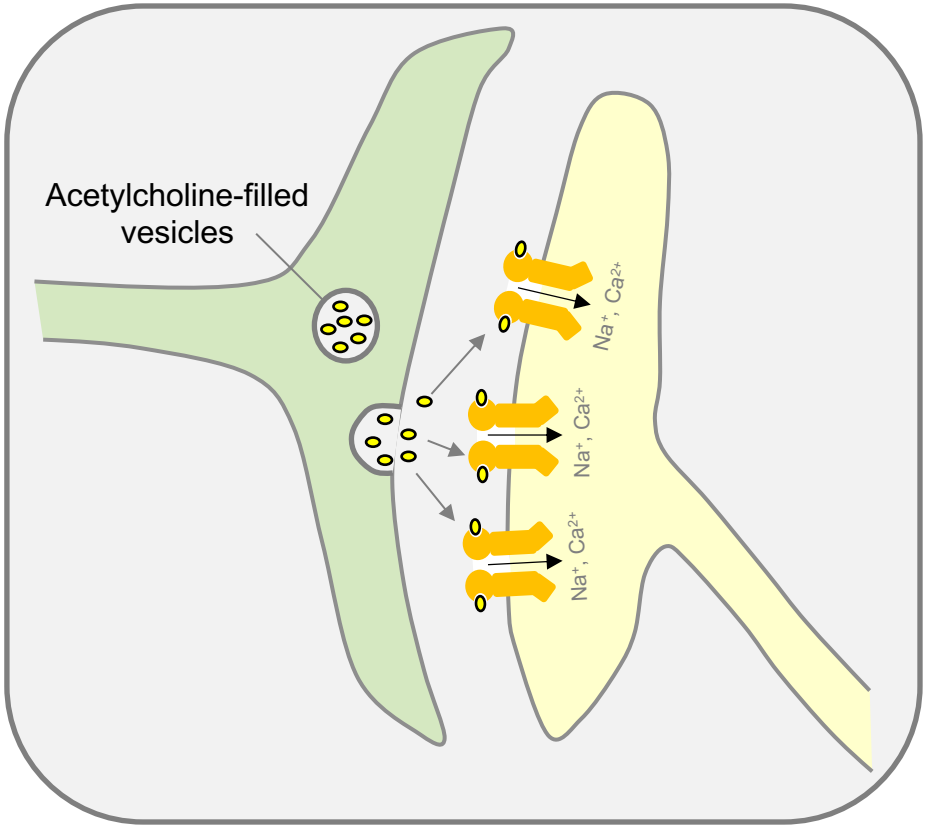


Neurotransmitters
such as **Acetylcholine** bridge the signaling gap (synapse) between excitable cells (neurons, muscle cells)



- Most fast excitatory synapses in the insect CNS use **Acetylcholine** as the neurotransmitter
- Synaptic vesicles store **Acetylcholine** that can be released into the synapse in response to nerve impulses and in turn activate postsynaptic nAChRs

Insecticides acting on nAChR

nAChR competitive modulators

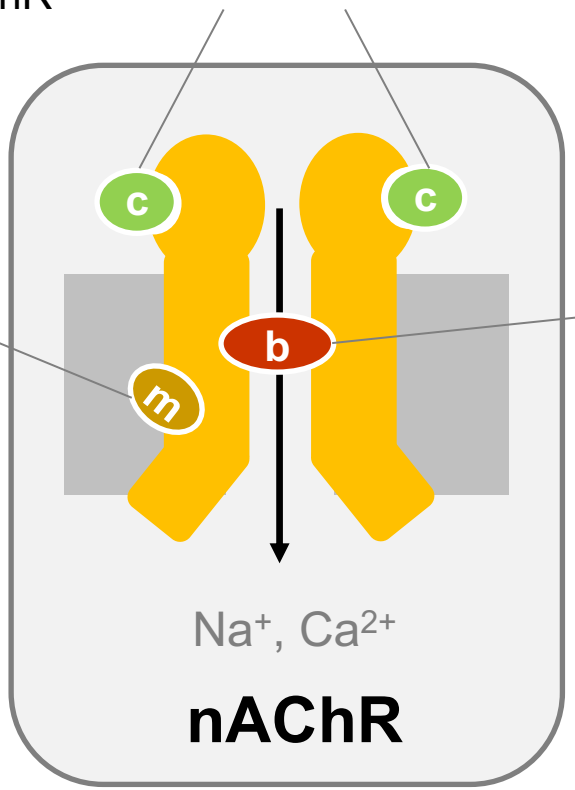
- Bind to the same site as acetylcholine
- desensitize nAChR

Can cause hyperexcitation and/or inhibitory paralysis

nAChR allosteric modulators

- Bind to the acetylcholine-opened channel form at a different (allosteric) site and keep channels open

Can cause hyperexcitation and contractive paralysis

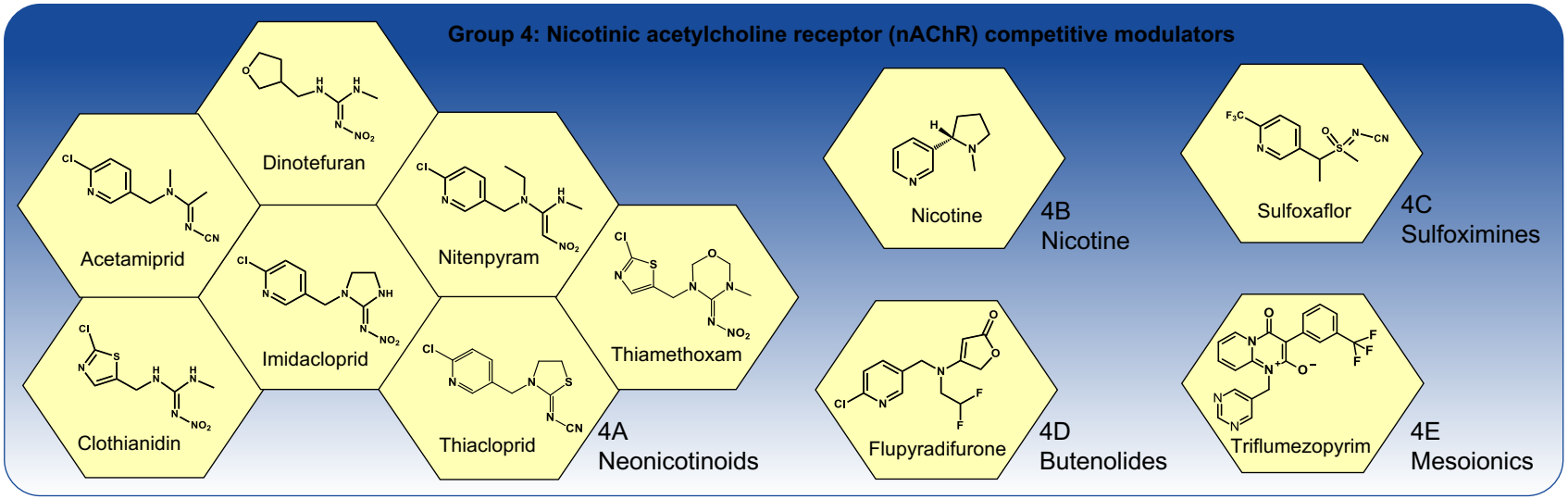


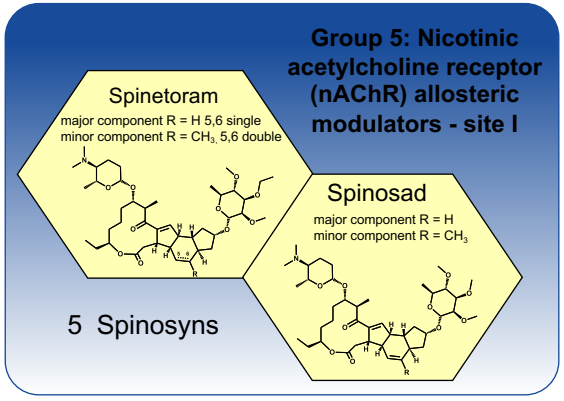
nAChR channel blockers

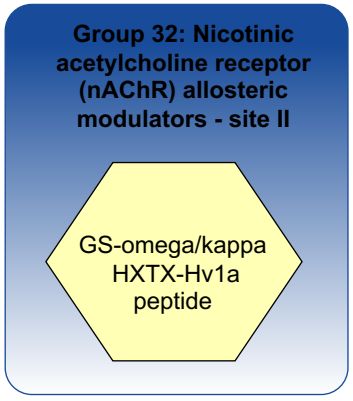
- Obstruct the pore and prevent ion flow
- prevent acetylcholine signal transduction

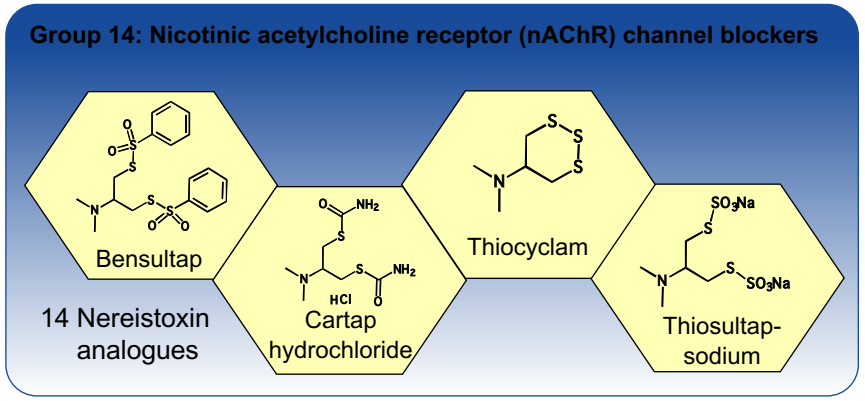
Can cause flaccid paralysis

Summary of Insecticides acting on nicotinic Acetylcholine receptors (nAChR)









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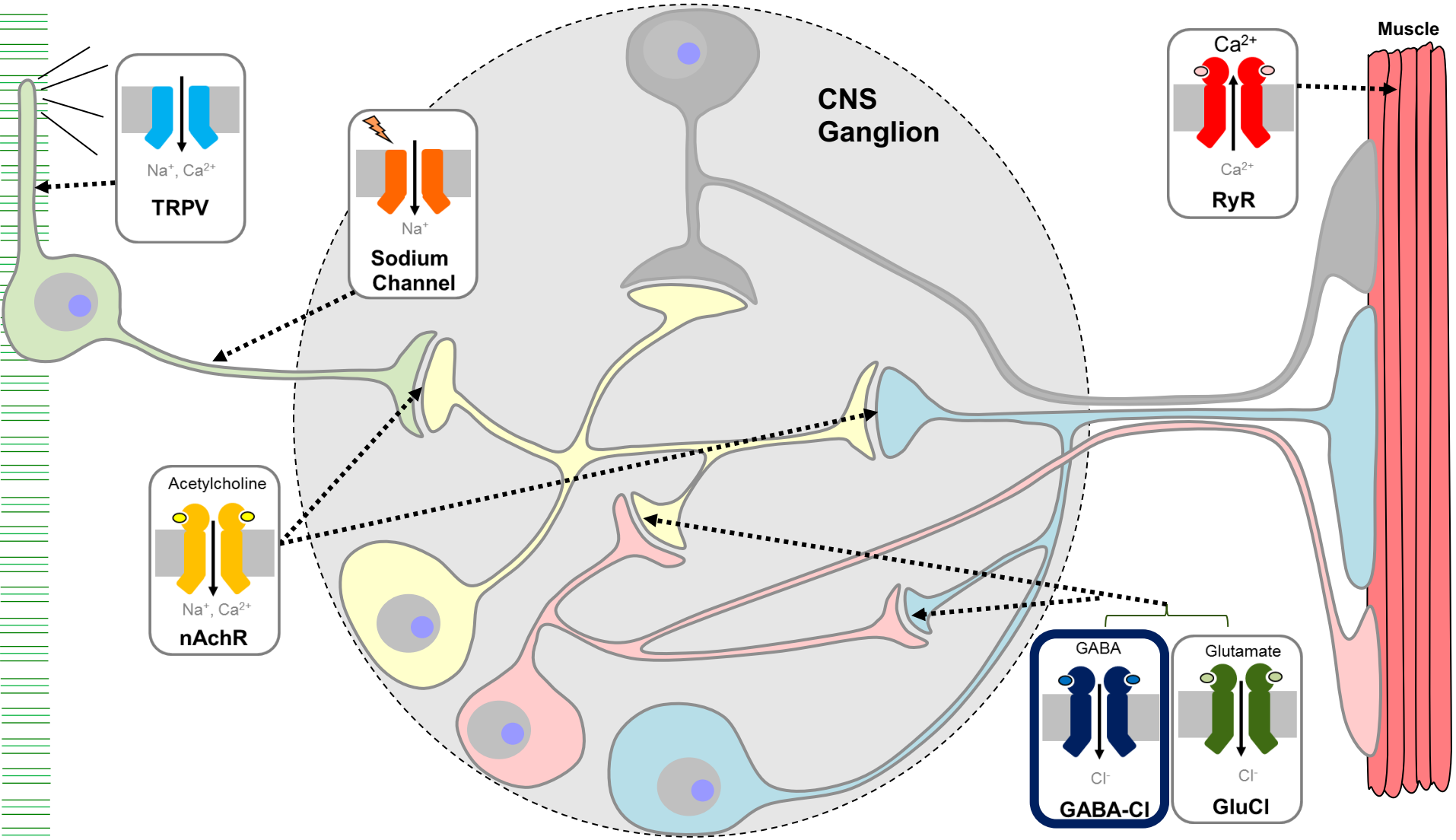
Overview of ion channels targeted by neuromuscular disruptors



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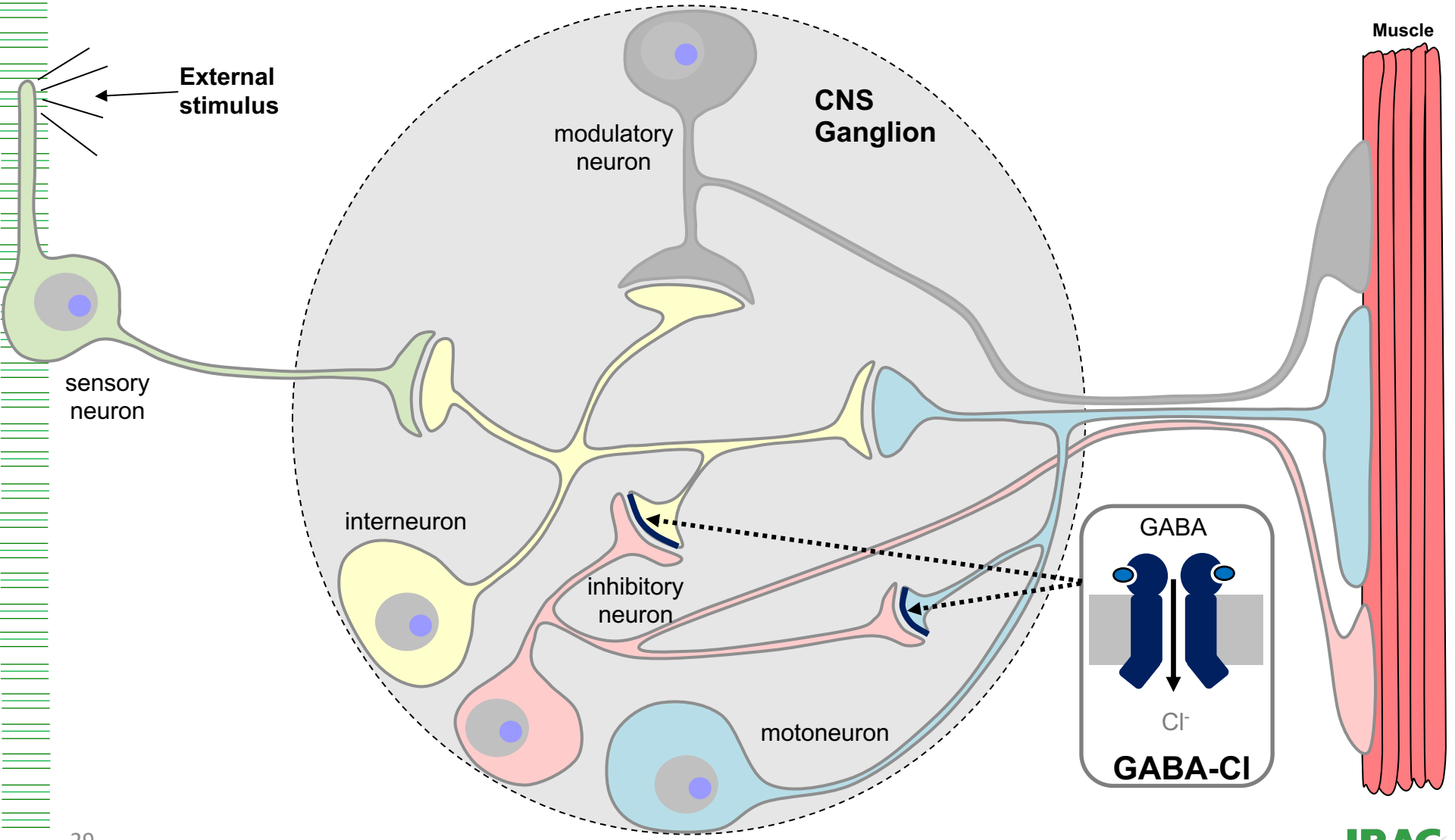
Insecticides acting on GABA-gated chloride channels (GABA-Cl)



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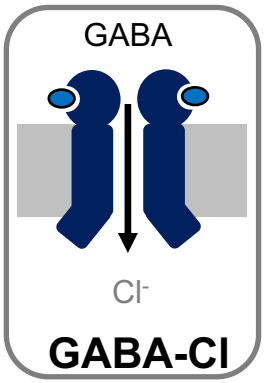
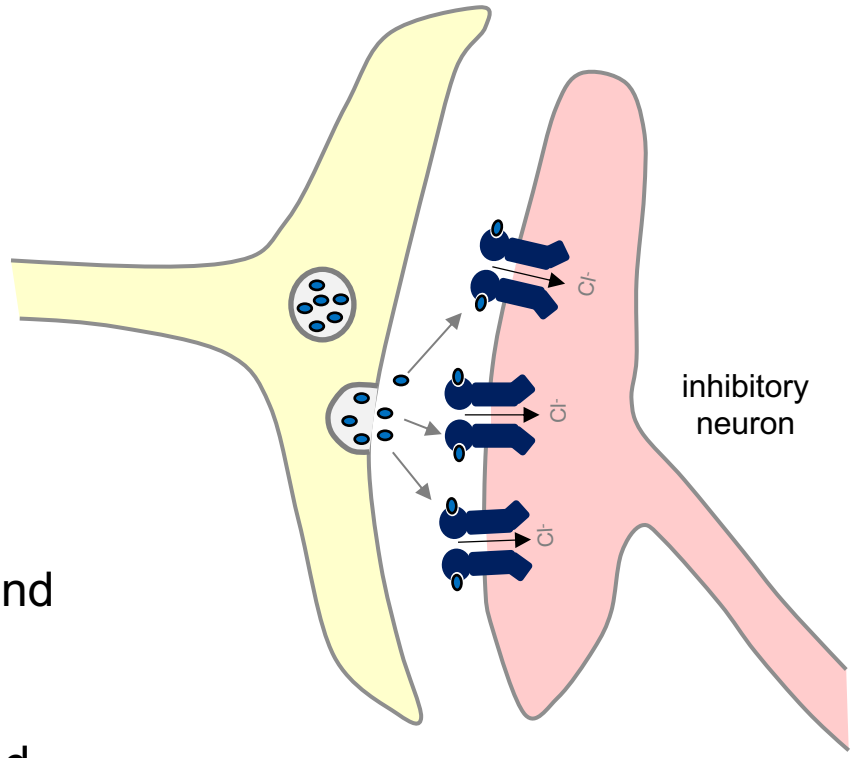


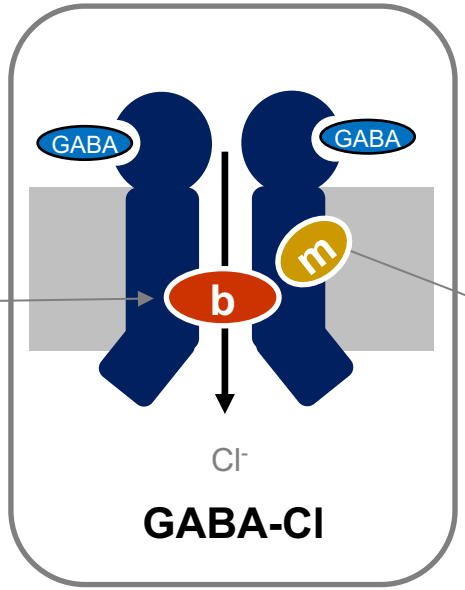


- GABA is a major inhibitory neurotransmitter in the CNS and neuromuscular synapses
- Influx of the negatively charged Cl- ions has an inhibitory effect, counteracting excitatory signals

Insecticides acting on GABA-gated chloride channel (GABA-Cl)

GABA-Cl antagonists

- Block the pore and prevent chloride influx, interfering with the channel's inhibitory function



GABA-Cl allosteric modulators

- Binding of modulators negatively affects GABA-Cl, interfering with the channel's inhibitory function

Pore blockers and negative modulators both cause convulsions and death

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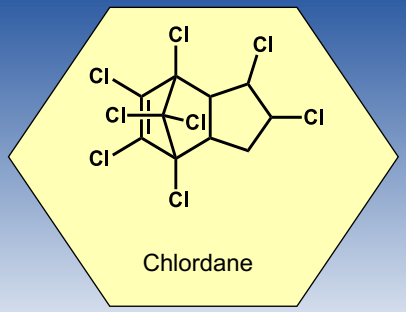
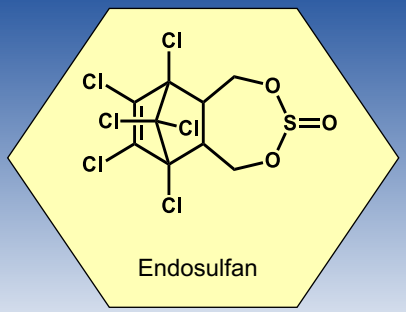
Summary of Insecticides acting on GABA-Cl

Group 2: GABA-gated chloride channel antagonists

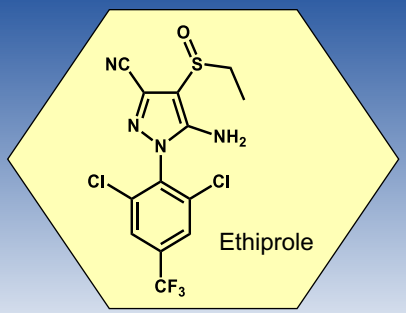


Chlordane

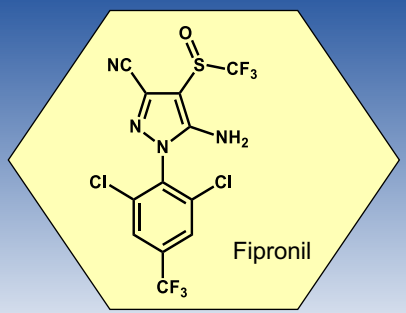


Endosulfan

2A Cyclodiene Organochlorines



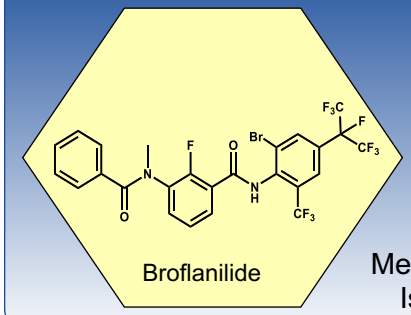
Ethiprole



Fipronil

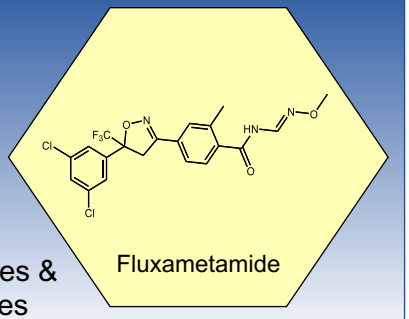
2B Phenylpyrazoles (Fiproles)

Group 30: GABA-gated chloride channel allosteric modulators



Broflanilide

Meta-diamides & Isoxazolines



Fluxametamide

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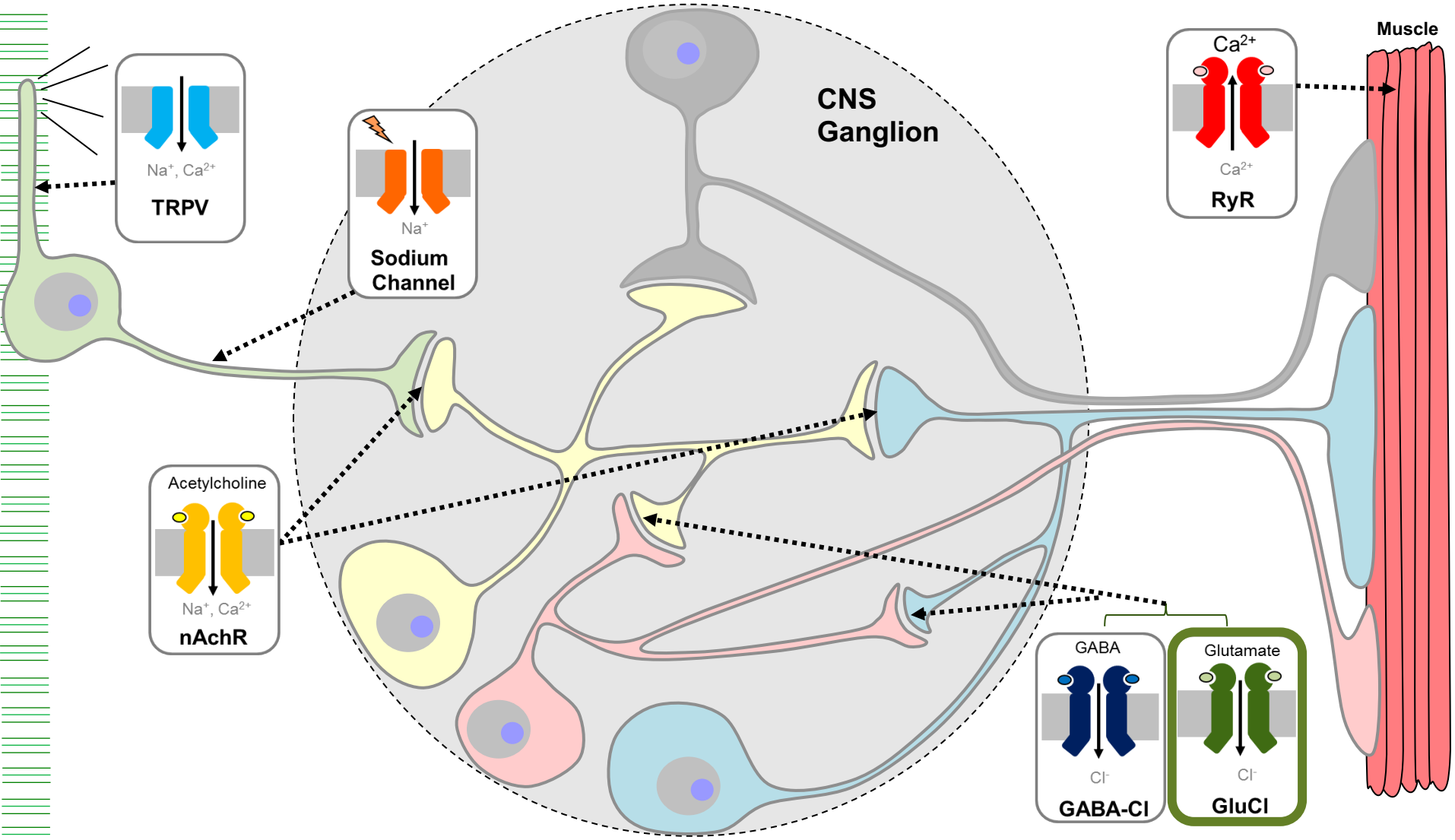
Overview of ion channels targeted by neuromuscular disruptors



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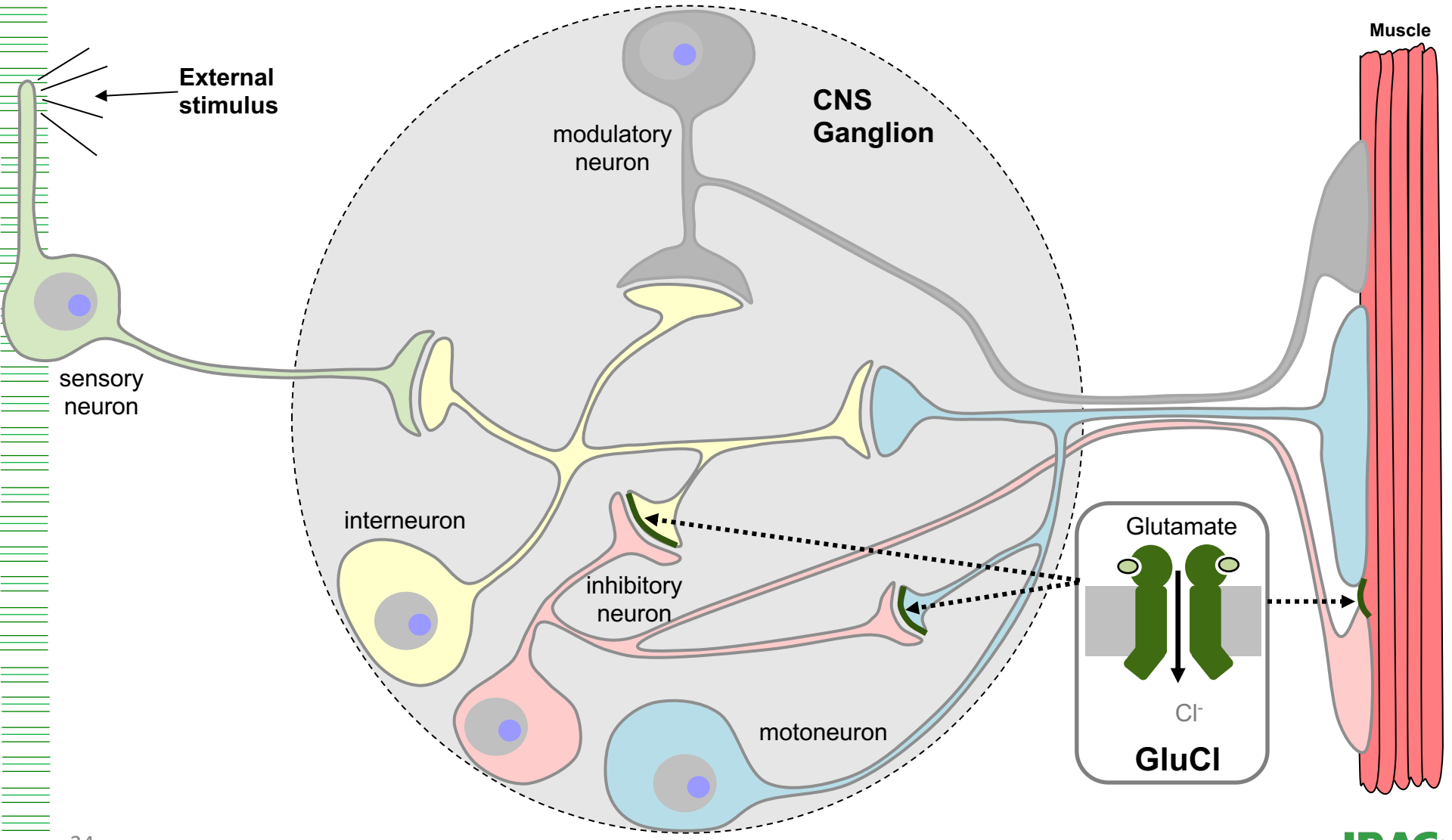
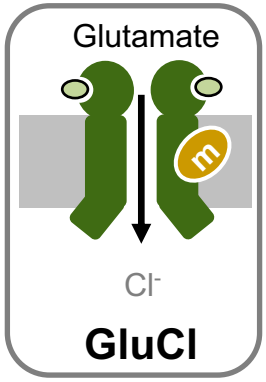
Insecticides acting on Glutamate-gated chloride channels (GluCl)

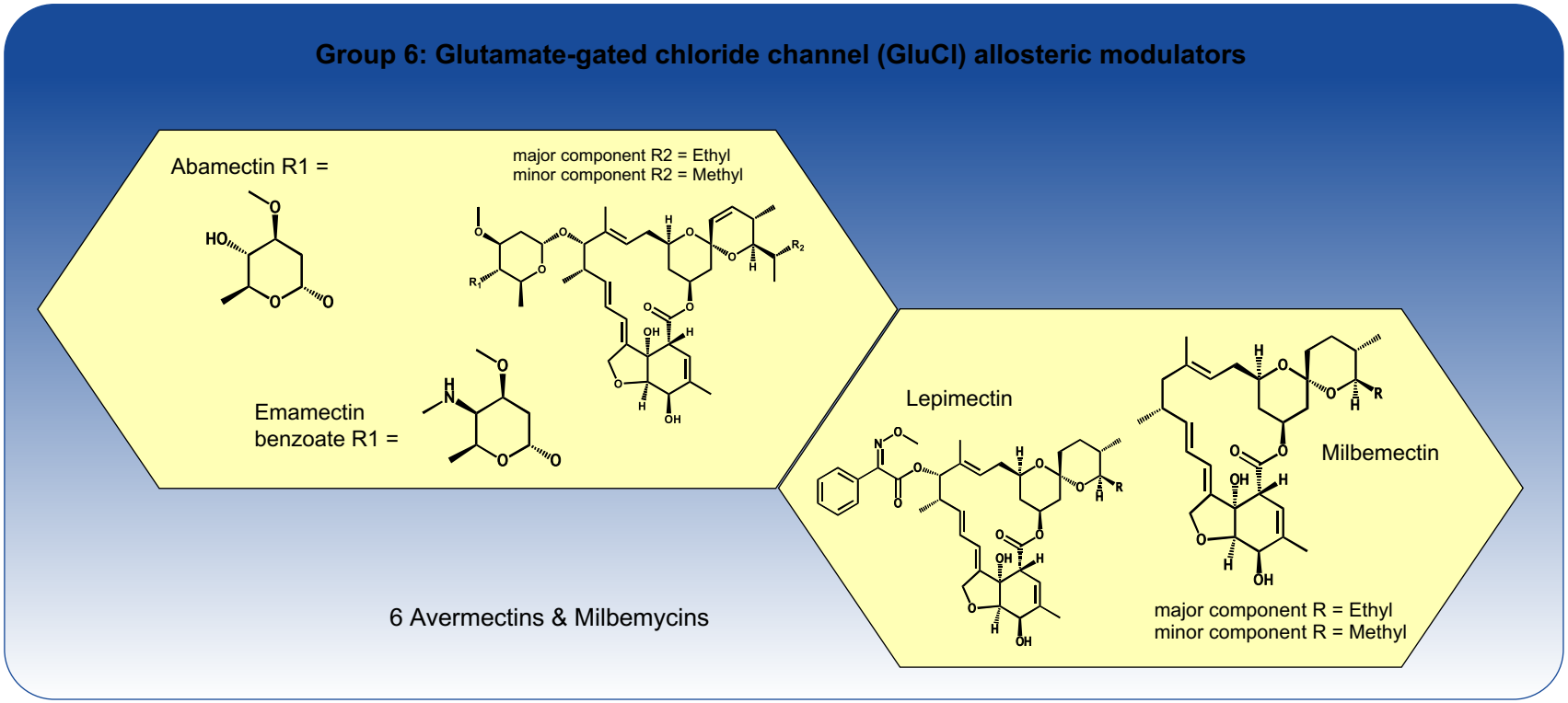


Allosteric modulators of Glutamate-gated chloride channels (GluCl)

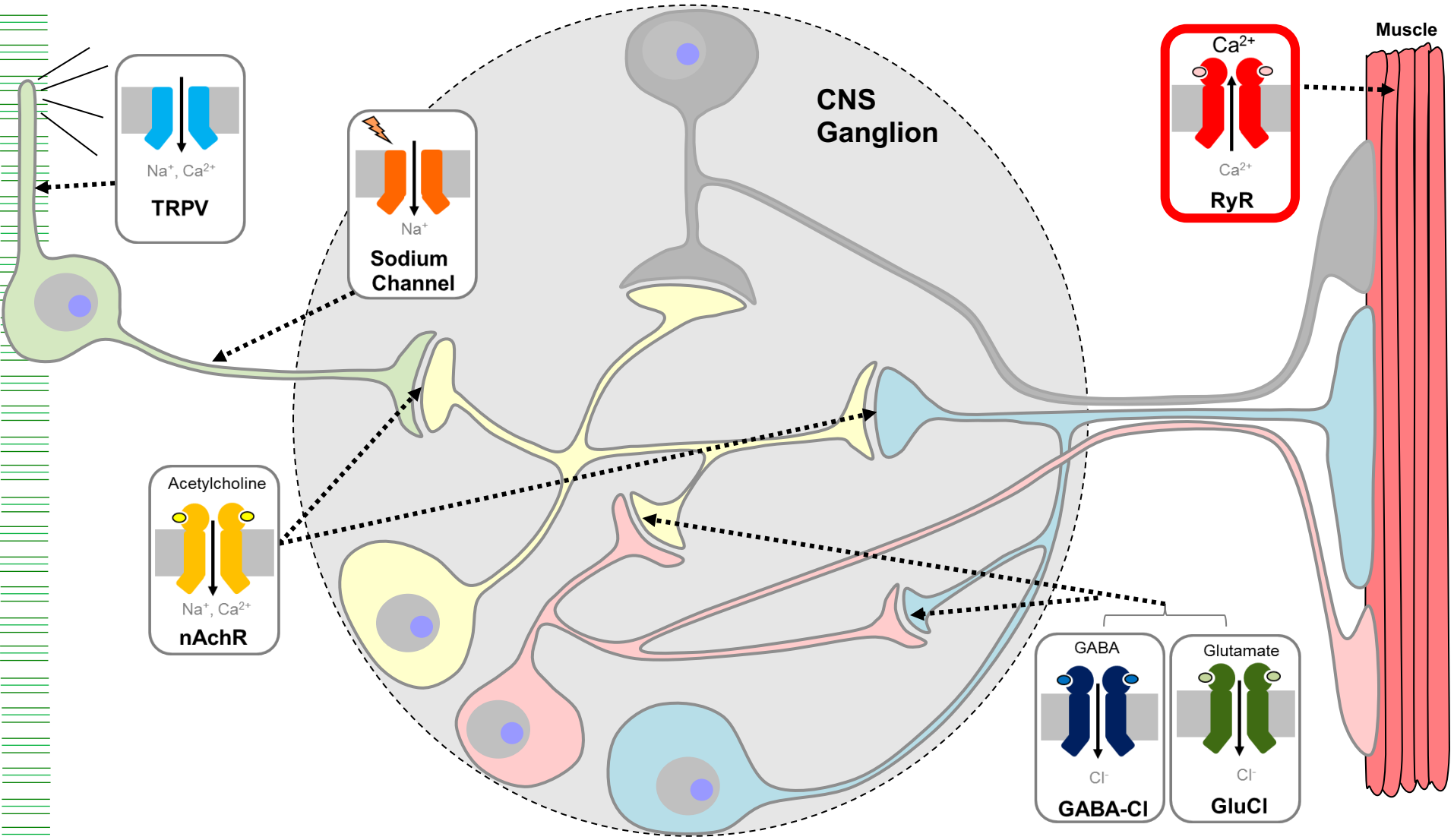


- Inhibitory Glutamate-gated chloride channels (GluCl) are widespread on insect nerve and muscle cells and likely function in inhibitory neurotransmission
- GluCl modulators activate chloride influx, causing flaccid paralysis

Allosteric modulators of Glutamate-gated chloride channels (GluCl)

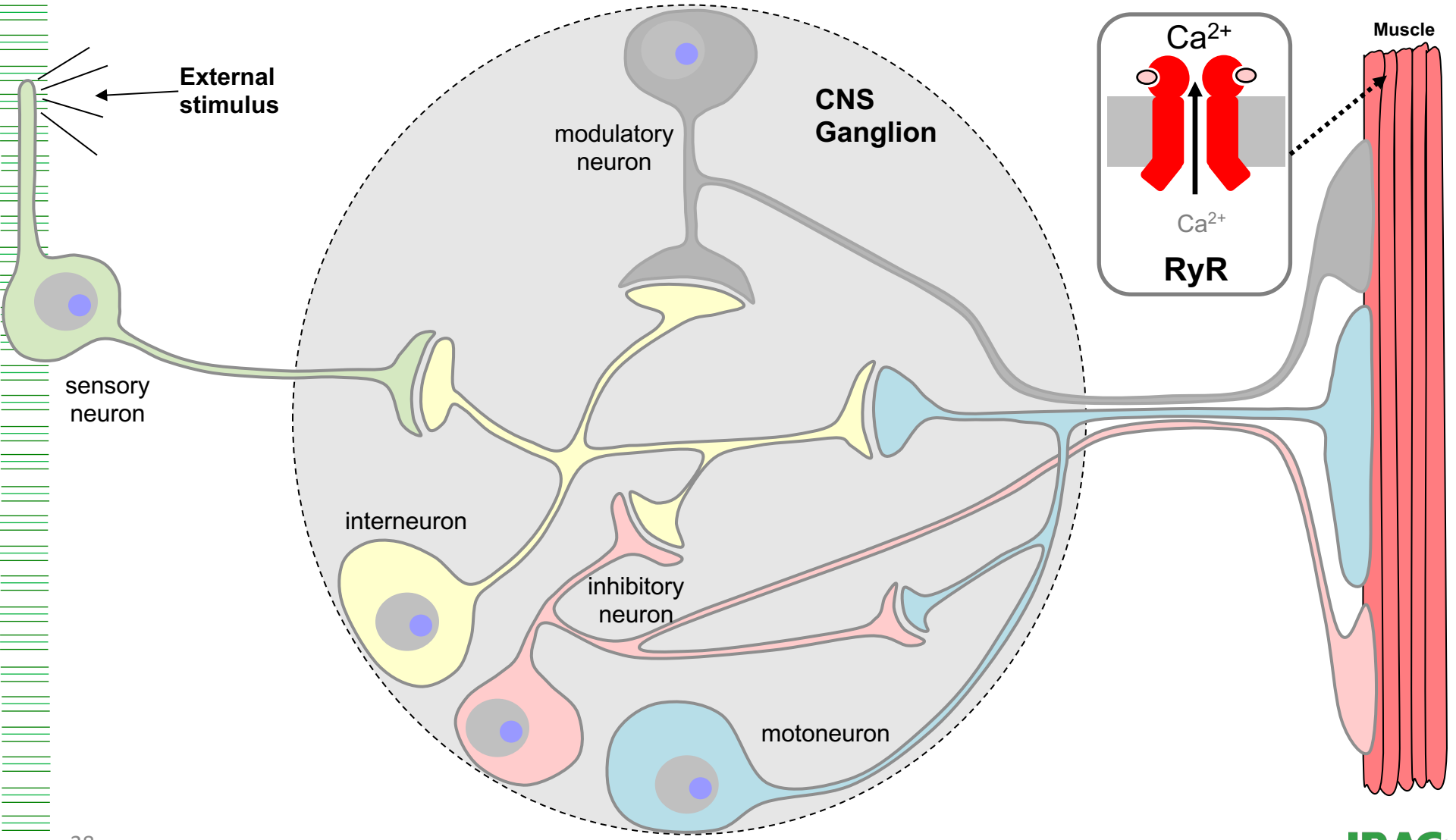


Overview of ion channels targeted by neuromuscular disruptors



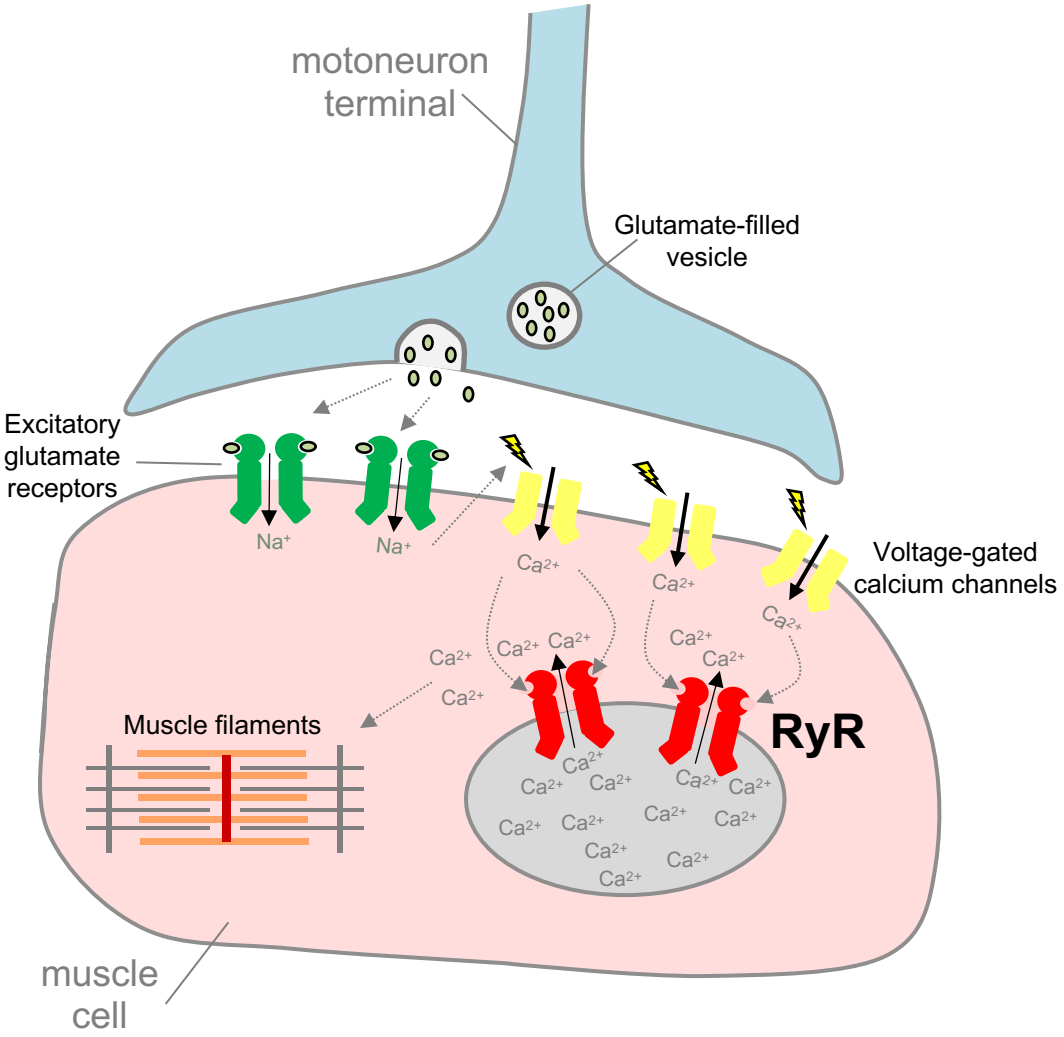
IRAC

Insecticides acting on the Ryanodine Receptor (RyR)



IRAC

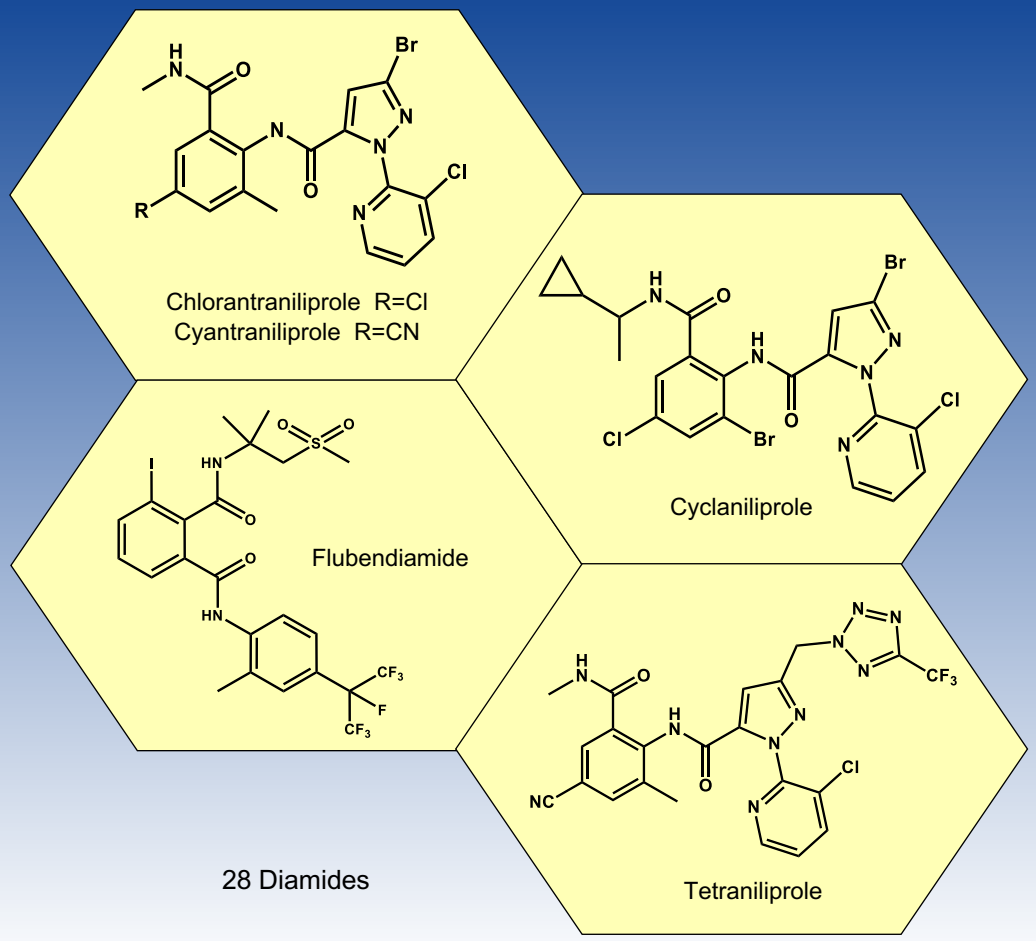
The Ryanodine receptor (RyR) plays a crucial role in insect muscle contraction



- Ca^{2+} ions entering the muscle cell activate RyR located on the muscle cell's intracellular Ca^{2+} store to release Ca^{2+} into the cytoplasm
- The rise in Ca^{2+} activates more RyRs, leading to massive Ca^{2+} release
- This in turn induces shortening of contractile filaments, leading to muscle cell contraction
- RyR modulators open the ryanodine receptor independent of cytoplasmic calcium levels causing uncontrolled muscle contraction, paralysis and death

RyR modulators

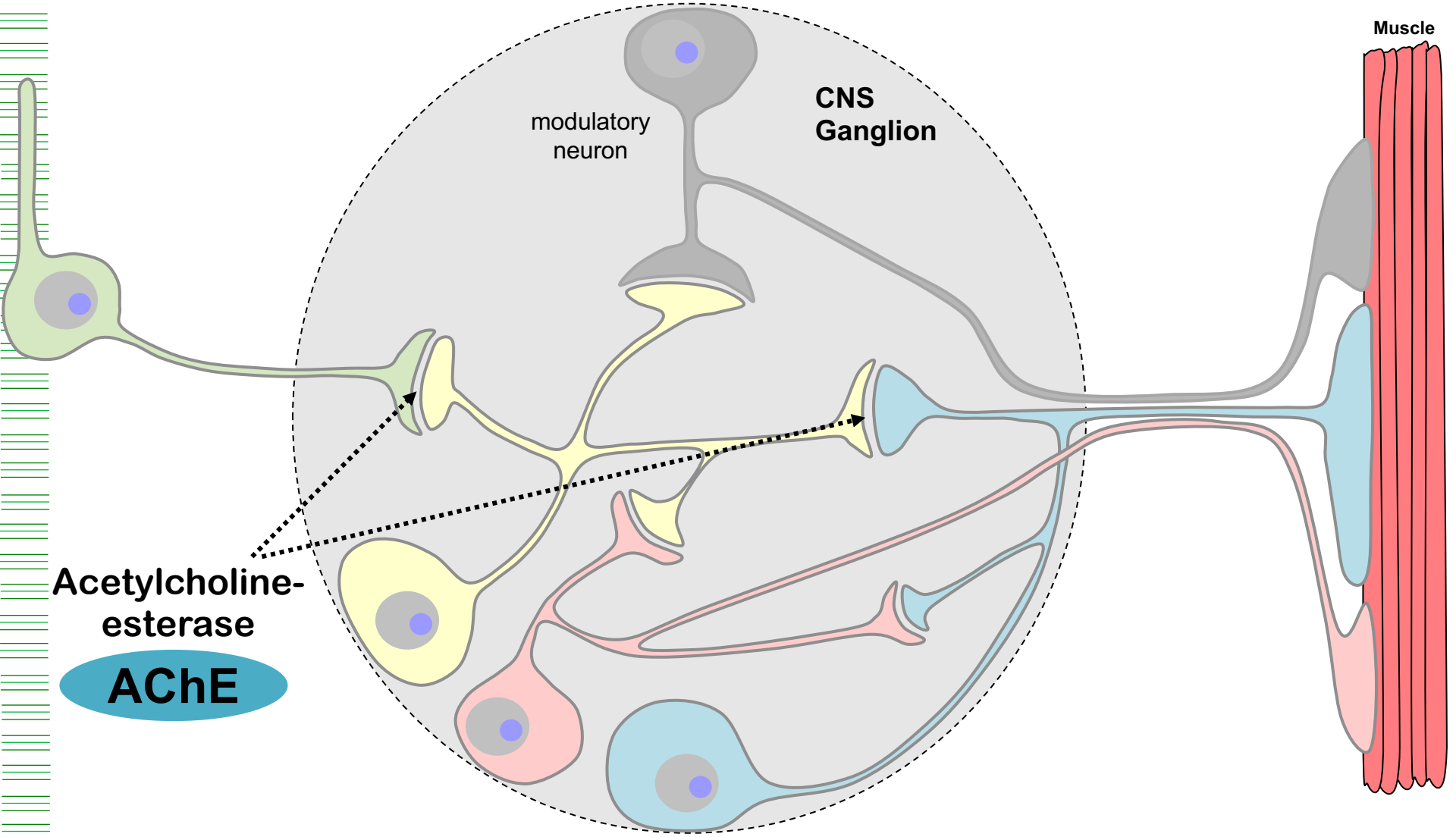
Group 28: Ryanodine receptor modulators



28 Diamides

IRAC

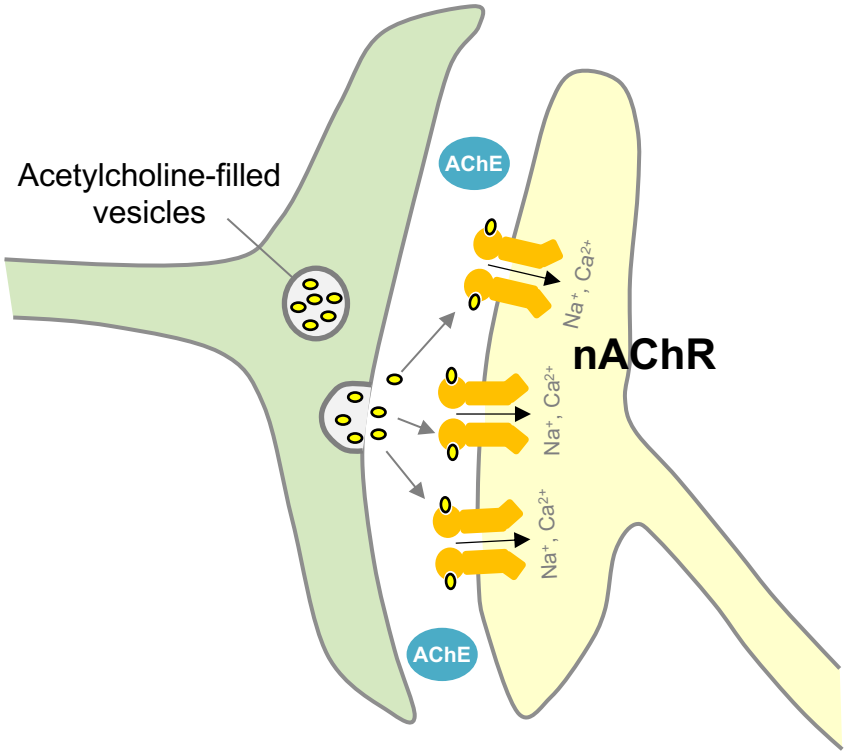
Enzymes targeted by neuromuscular disruptors

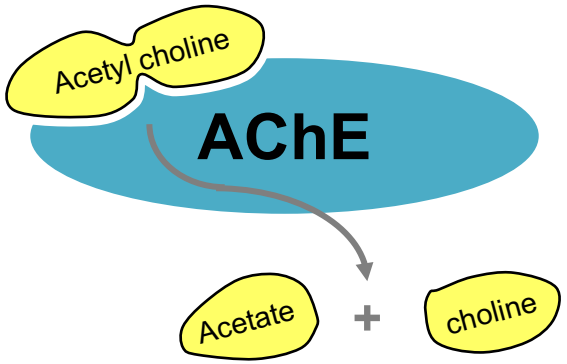


IRAC

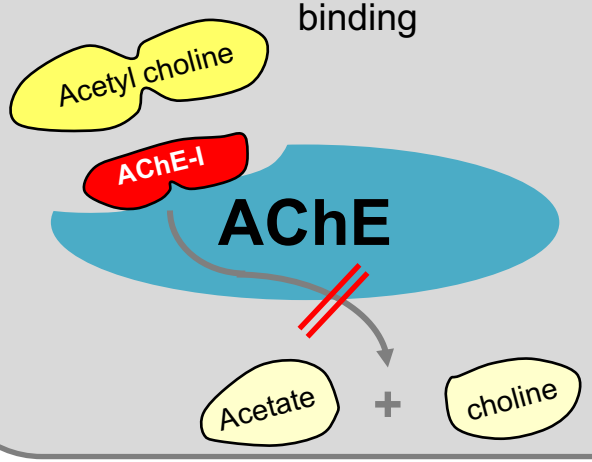
Acetylcholinesterase (AChE) degrades Acetylcholine in the synapse

Acetylcholinesterases degrade **Acetylcholine** in order to terminate the signal after it has been sent across the synapse



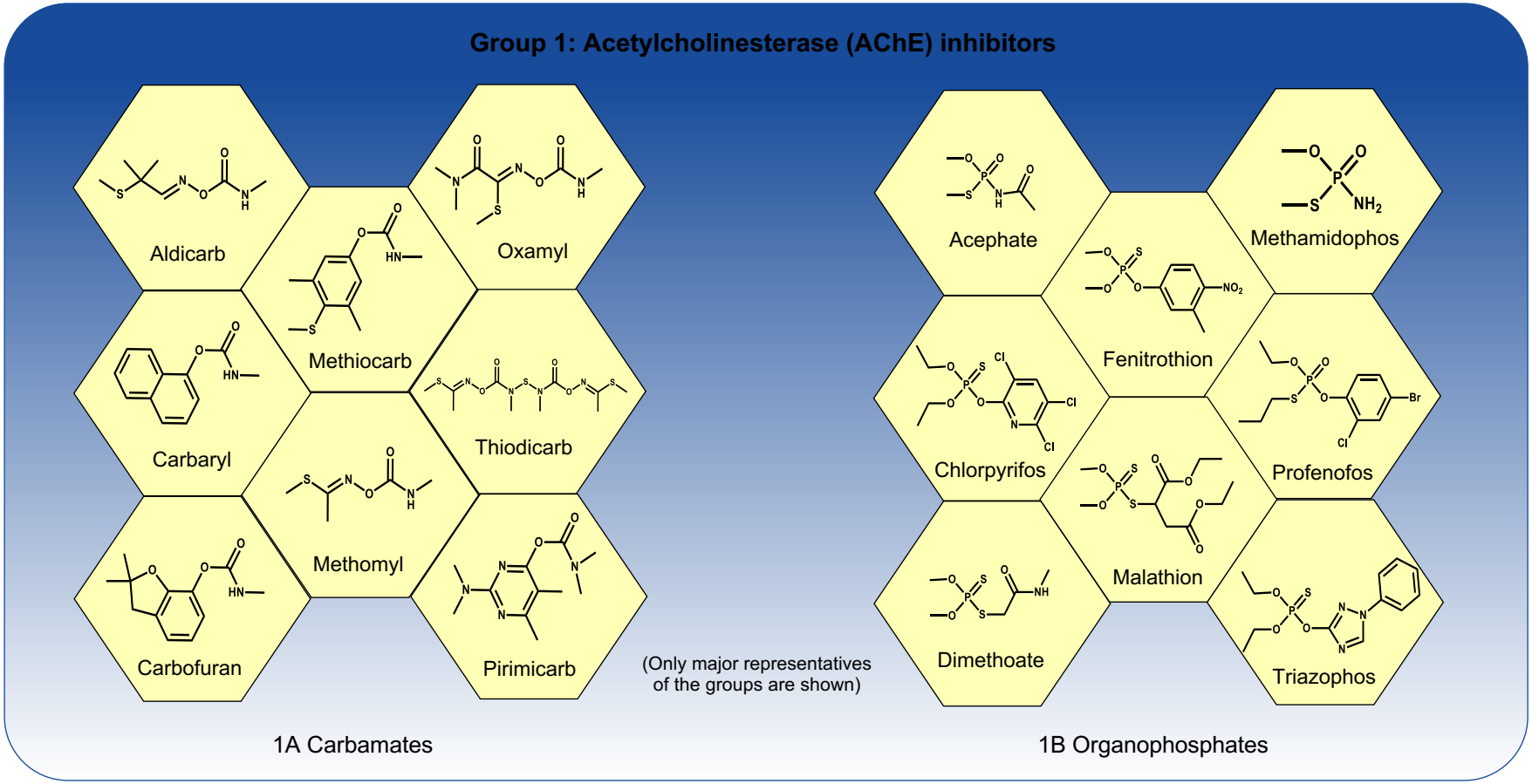


AChE inhibitors bind to the active site of the enzyme preventing Acetylcholine from binding



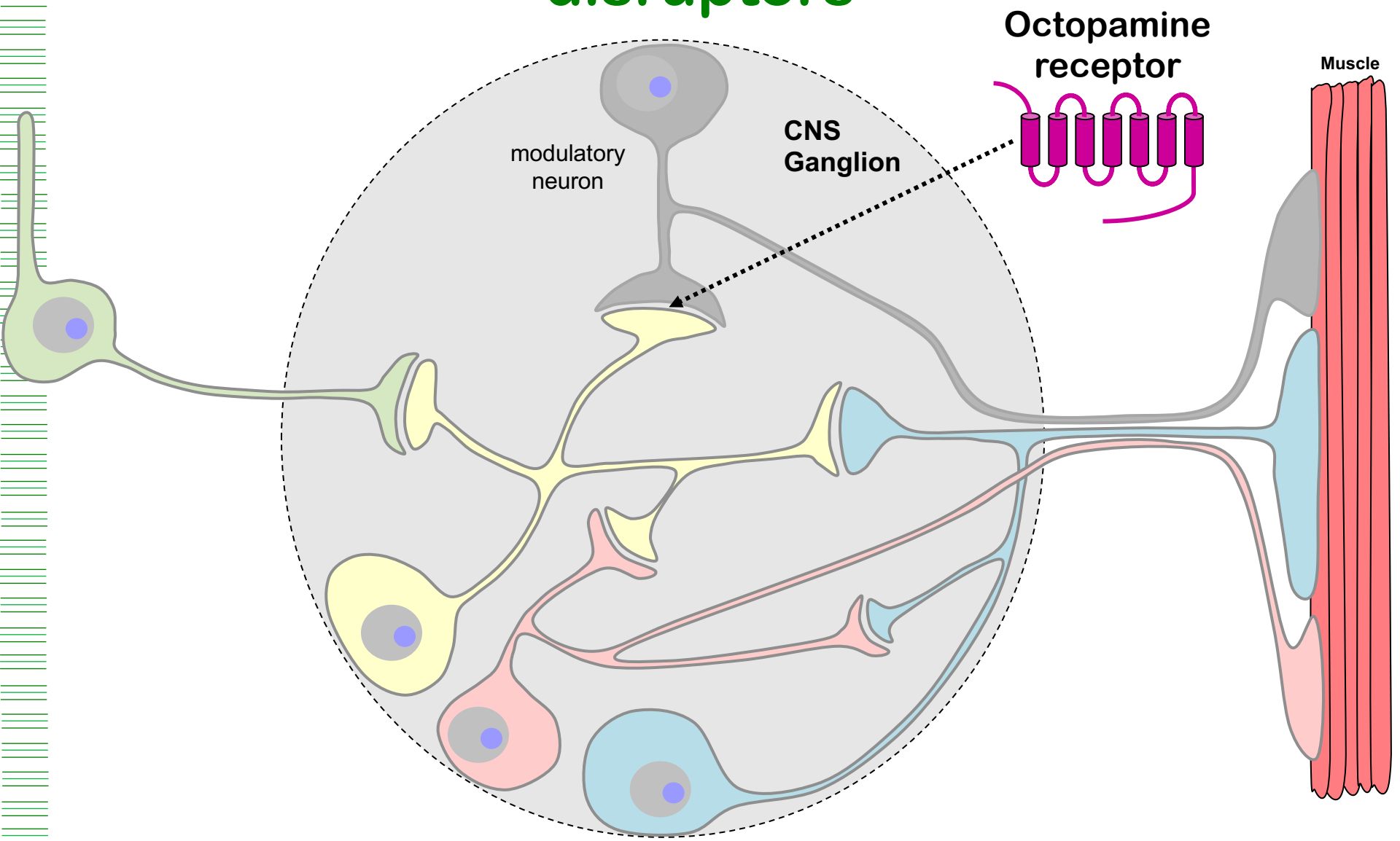
IRAC

Acetylcholinesterase (AChE) inhibitors



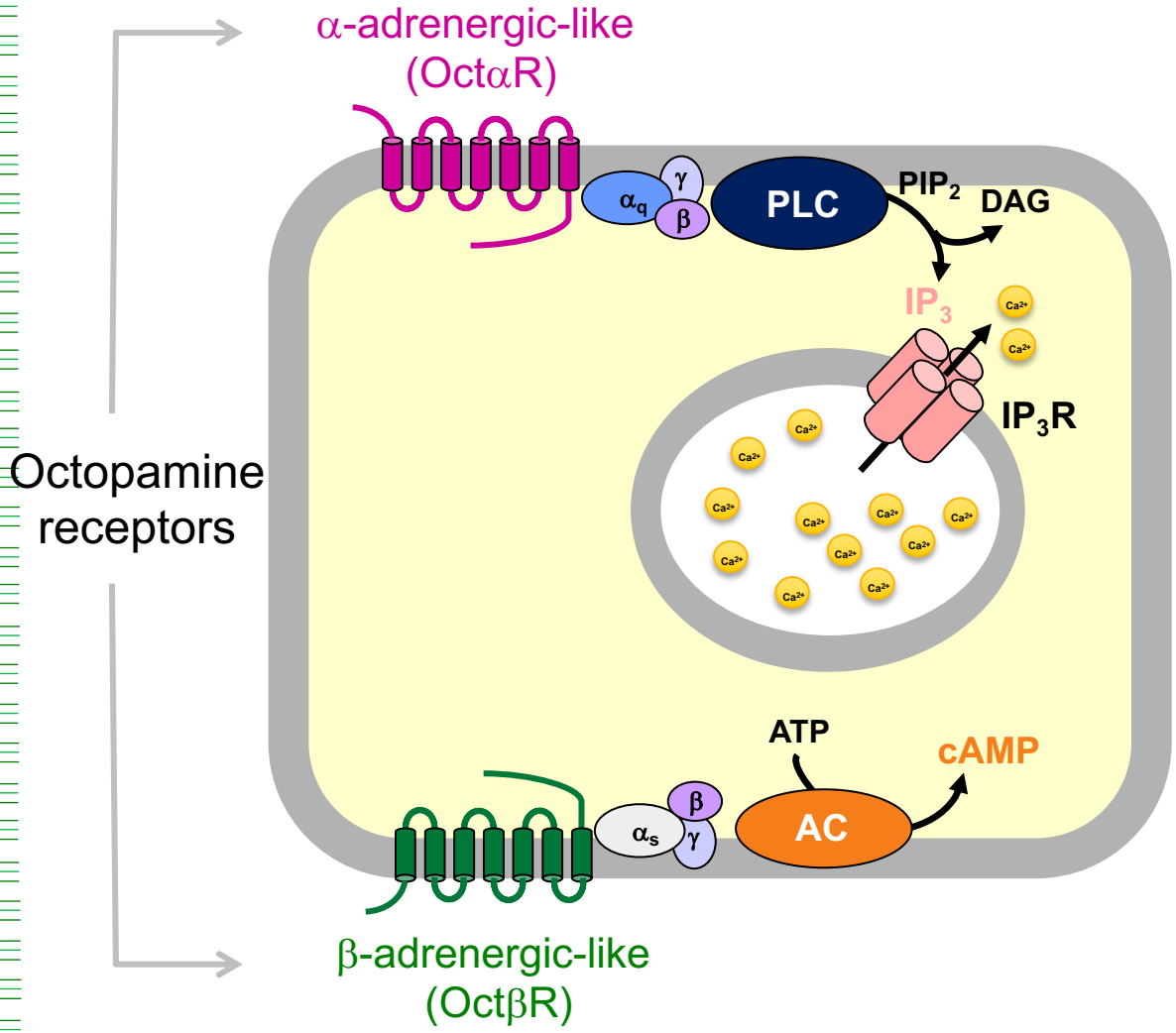
IRAC

Receptors targeted by neuromuscular disruptors



IRAC

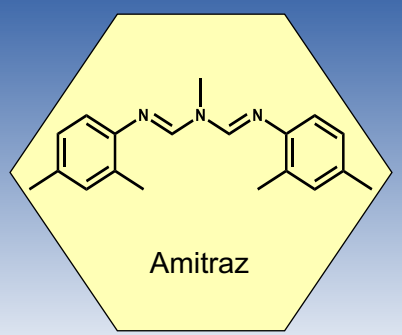
Octopamine receptor signalling



- Octopamine is the major modulatory neurotransmitter in insects; it can increase the general level of arousal like adrenaline does in mammals
- Upon release, Octopamine binds to G-protein-coupled Receptors (GPCRs) on the postsynaptic membrane, which can be coupled via G-proteins ($\alpha\beta\gamma$) to Phospholipase C (PLC), an enzyme catalyzing the formation of IP_3, which in turn can activate intracellular Ca^{2+} release channels. Other octopamine receptors are coupled to adenylyl cyclase (AC) to stimulate cAMP production
- Octopamine receptor agonists can mimic the action of this neurotransmitter

Octopamine receptor agonists

Group 19: Octopamine receptor agonists



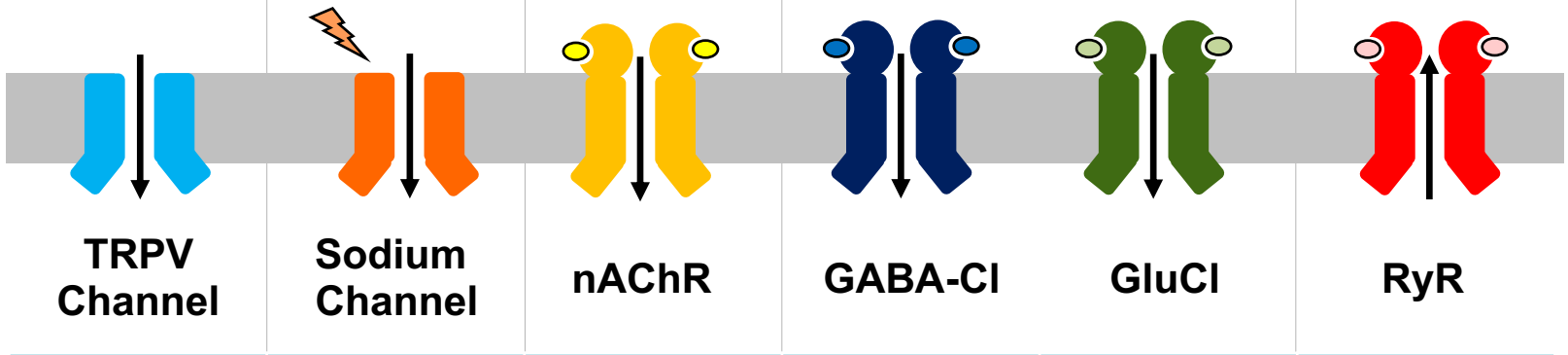
Amitraz

19 Amitraz

IRAC

Targets of Neuromuscular Disruptors & Their key Physiological Roles

Ion Channels

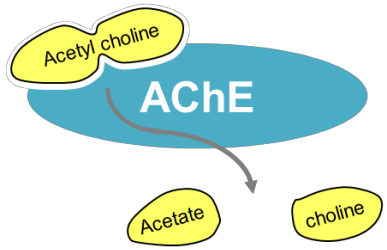


TRPV Channel	Sodium Channel	nAChR	GABA-Cl	GluCl	RyR
Proprioception	Action potential propagation	Excitatory neuro-transmission	Inhibitory neuro-transmission	Inhibitory neuro-transmission	Muscle contraction

Enzymes

Acetylcholin-esterase

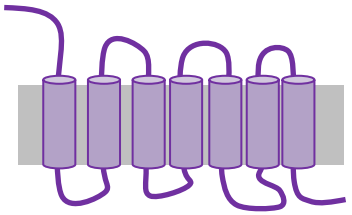
Excitatory neurotransmission



Receptors

Octopamine Receptor

Excitatory neurotransmission



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Insecticide Mode of Action
Major classes

Nerve & Muscle

Growth

Respiration

Midgut

Unknown or Non-Specific

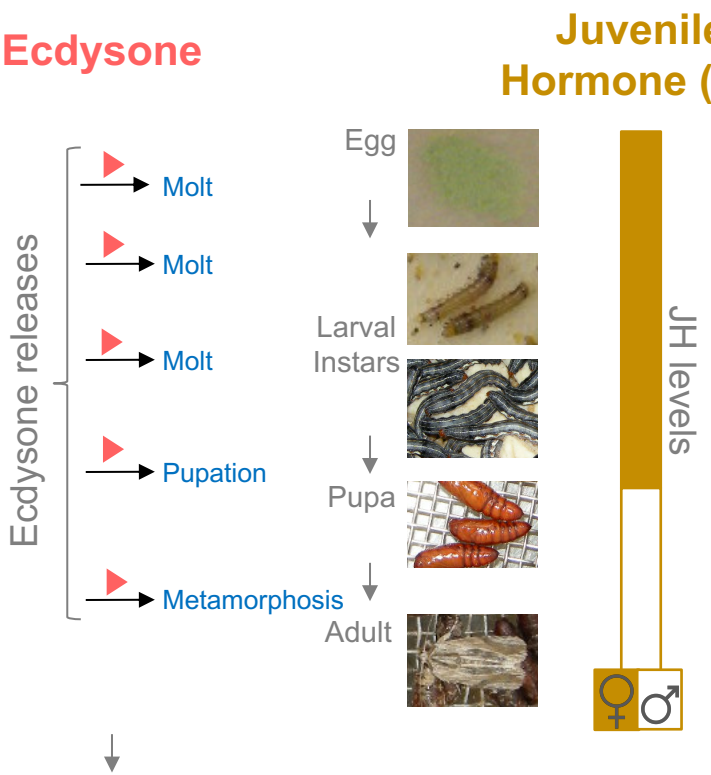
IRAC

Growth & Development Disruptors Background

The insect's skeleton is external (**exoskeleton)** and contains chitin. Since the exoskeleton cannot expand, it must be replaced with a larger one by the process of molting as the insect grows, requiring **chitin synthesis**. Molting is under strict hormonal control:

Ecdysone is released by the prothoracic gland in the thorax

Pulses of Ecdysone induce molting



JH prevents molting to a more mature stage

JH production stops during metamorphosis

Targets of Growth & Development Disruptors

1. Nuclear Hormone Receptors (NHR)

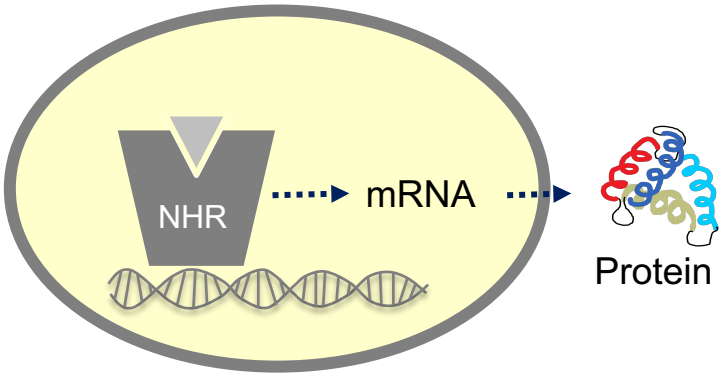
Ecdysone Receptor

Ecdysone

EcR

Pulses of Ecdysone induce molting

NHRs alter the expression of genes needed for ecdysis (**EcR**) or to form adult structures (**JHR**)



Juvenile Hormone Receptor

JH

JHR

JH prevents molting to a more mature stage

EcR agonists directly and persistently activate Ecdysone receptors causing the insect to go into a precocious, incomplete molt, leading eventually to death

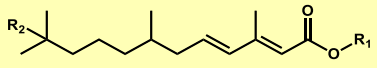
JH mimics activate the JH receptor and strongly suppress the development of adult characteristics keeping the insect in an 'immature' state

IRAC

Juvenile hormone mimics

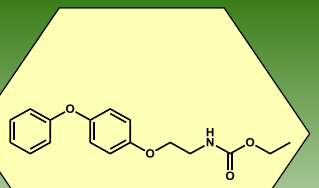
Group 7: Juvenile hormone mimics

Hydroprene R1 = ethyl, R2 = H
Methoprene R1 = isopropyl, R2 – OCH_3



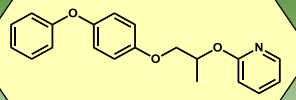
Kinoprene R1 = propargyl, R2 = H

7A Juvenile hormone analogues



Fenoxycarb

7B Fenoxycarb

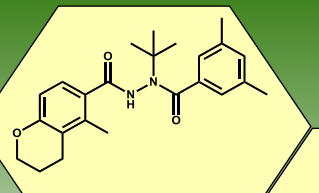


Pyriproxyfen

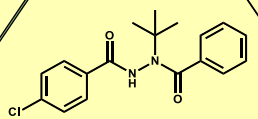
7C Pyriproxyfen

Ecdysone receptor agonists

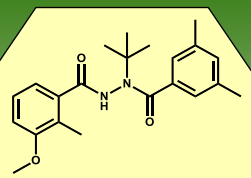
Group 18: Ecdysone receptor agonists



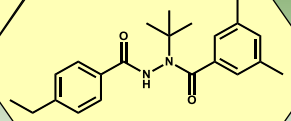
Chromafenozide



Halofenozide



Methoxyfenozide

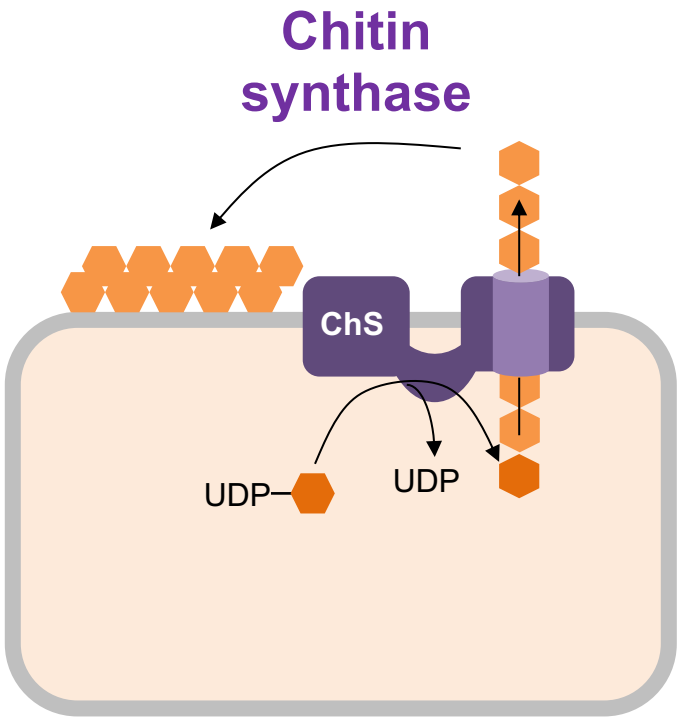


Tebufenozide

18 Diacylhydrazines

Targets of Growth & Development Disruptors

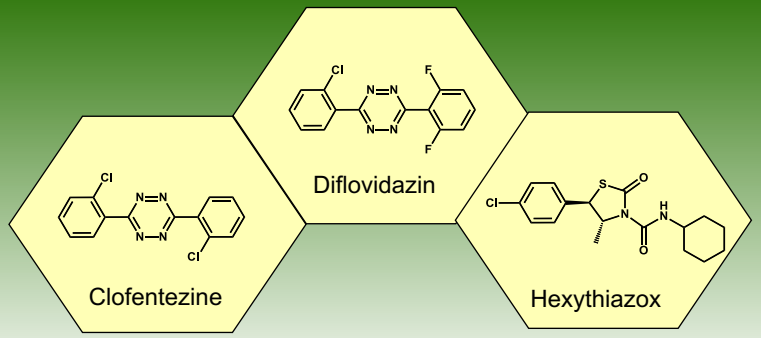
2. Chitin Synthesis Inhibitors



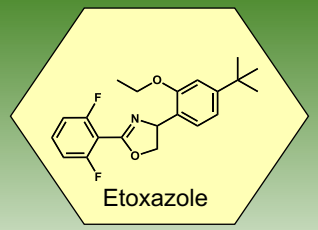
- Chitin is a polymer of N-Acetyl glucosamine (NAcGlc; ⬢)
- Chitin synthase uses activated NAcGlc (UDP-NAcGlc; UDP–⬢) to extend the growing chitin chain
- The nascent chain is released into the extracellular space
- Interfering with chitin synthesis results in a weak and soft exoskeleton as well as deformed appendages and sexual organs

Chitin synthesis inhibitors

Group 10: Mite growth inhibitors affecting CHS1

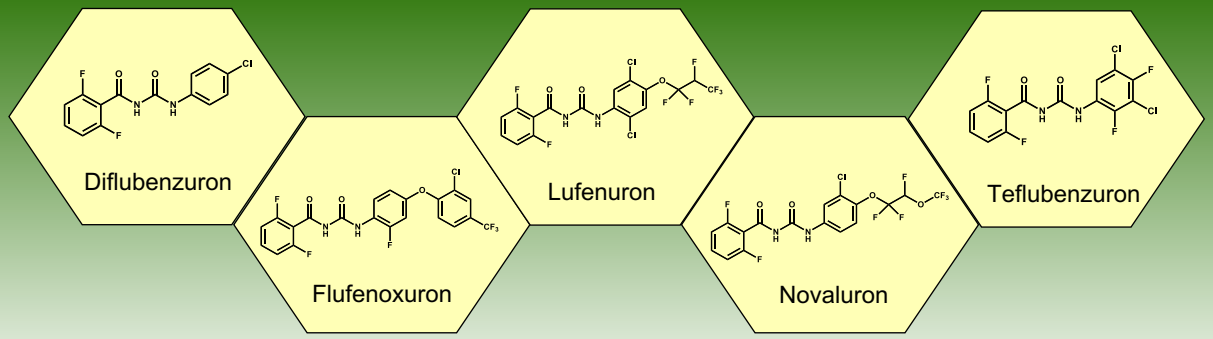


10A Clofentezine, Diflovidazin, Hexythiazox



10B Etoxazole

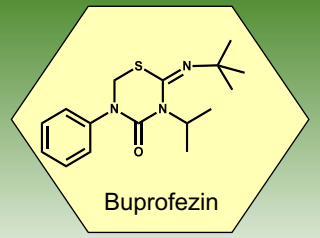
Group 15: Inhibitors of chitin biosynthesis affecting CHS1



15 Benzoylureas

(Only major representatives of group are shown)

Group 16: Inhibitors of chitin biosynthesis, type 1

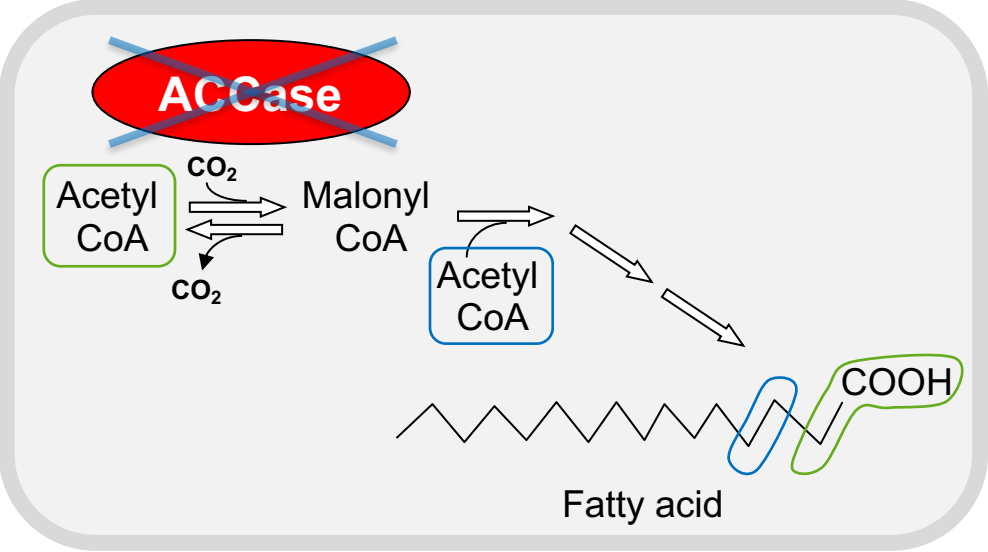


16 Buprofezin

IRAC

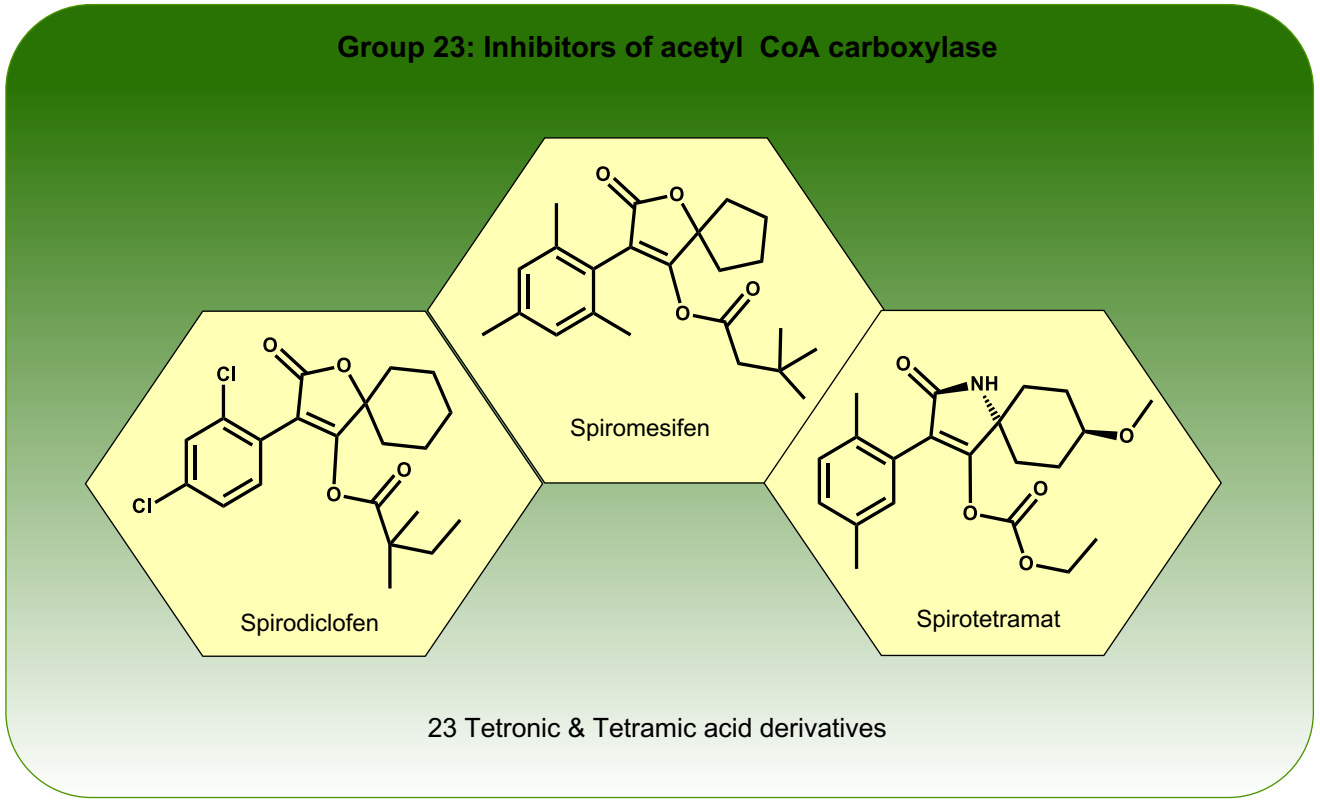
Targets of Growth & Development Disruptors

3. ACCase Inhibitors



- ACCase (acetyl CoA carboxylase) catalyzes the first and rate-limiting step of fatty acid biosynthesis
- ACCase inhibitors prevent biosynthesis of fats needed for growth and development resulting in incomplete molts and desiccation of the insect

Inhibitors of acetyl CoA carboxylase



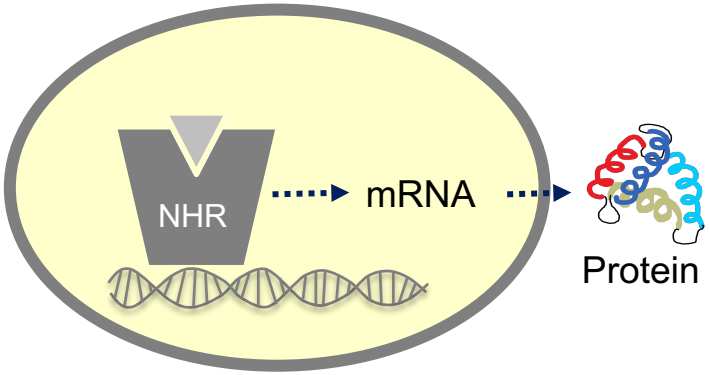
Overview Growth & Development Targets

Nuclear Hormone Receptors

Ecdysone Receptor

Ecdysone

Pulses of Ecdysone induce molting



NHRs alter the expression of genes needed for ecdysis (EcR) or to form adult structures (JHR)

Juvenile Hormone Receptor

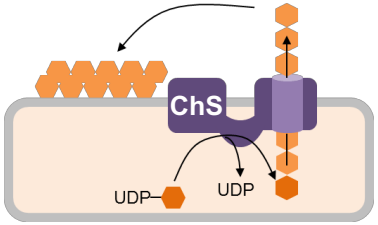
JH

JH prevents molting to a more mature stage

Enzymes

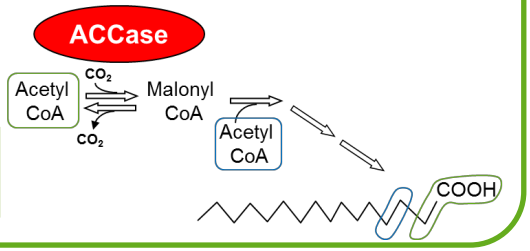
Chitin synthase

Chitin synthesis



Acetyl CoA carboxylase

Fatty acid synthesis



IRAC

Insecticide Mode of Action
Major classes

Nerve & Muscle

Growth

Respiration

Midgut

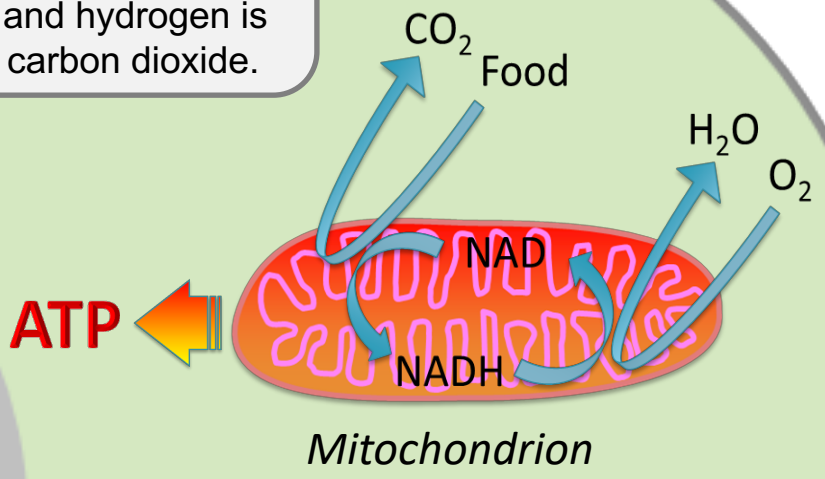
Unknown or Non-Specific

IRAC

Respiration and Energy Conservation
Background

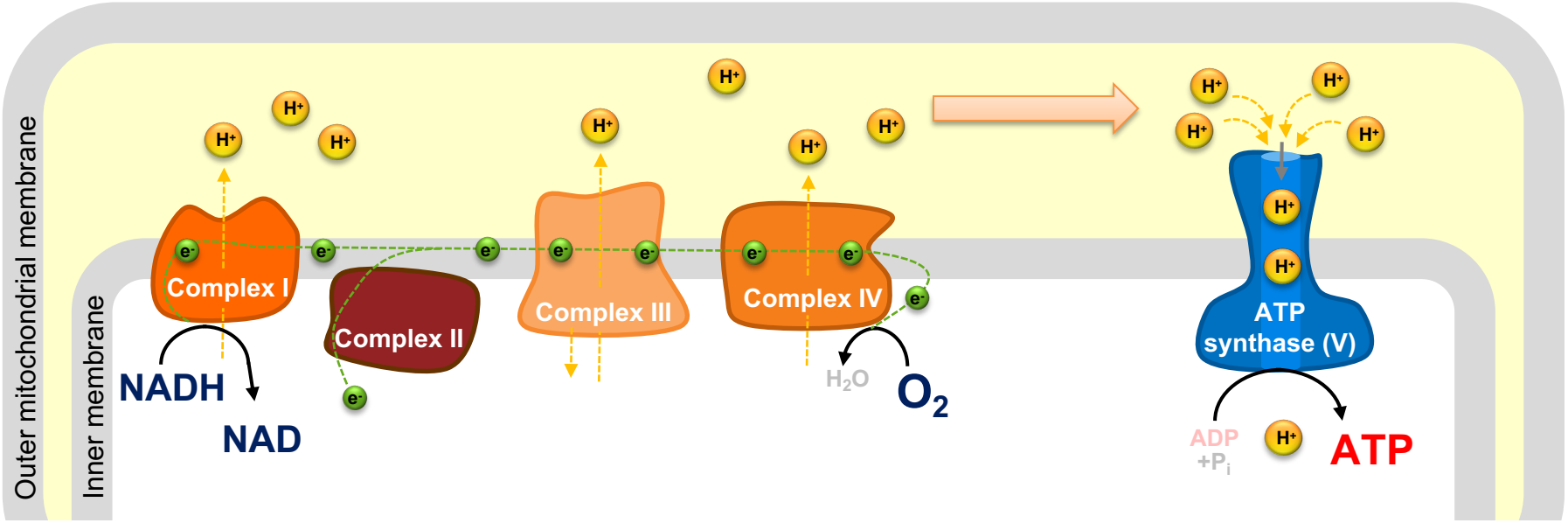
Cells get the energy they need by "oxidizing" food such as fat and sugars to produce carbon dioxide and water. In the cell this process is conducted in many steps in which oxygen is added to the fuel (from water) and hydrogen is removed so that the fuel is converted to carbon dioxide.

The hydrogen is removed by adding it to NAD (a form of vitamin B3) forming NADH. The regeneration of NAD requires oxygen, produces water and releases a lot of energy.



Most of these steps are contained in a special part of the cell called the mitochondrion. The mitochondrion has a closed membrane system that allows the energy released to be captured by generating ATP which fuels many cellular processes.

A number of complex proteins are needed to conserve the energy available



NADH oxidation at **Complex I** is dependent on an **electron transfer chain** mostly contained within **Complex I**, **Complex III** and **Complex IV**

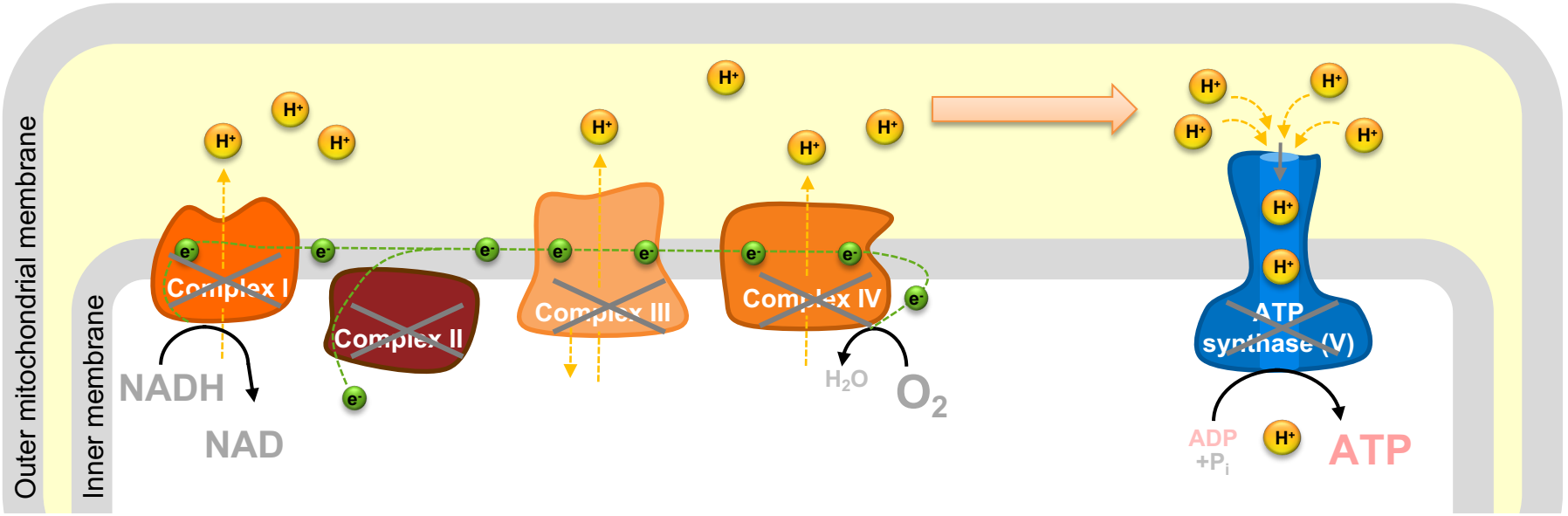
Electron flow ---e⁻--- initiated by NADH oxidation drives consumption of oxygen at **Complex IV** and the pumping of protons H⁺ across the membrane

The enzyme **ATP synthase** (Complex V) is driven by the proton gradient and catalyzes the formation of **ATP**

The enzyme **succinate dehydrogenase** (**Complex II**) feeds electrons into the chain and is also required for the overall process of food oxidation.

How insecticides interfere with cellular respiration:

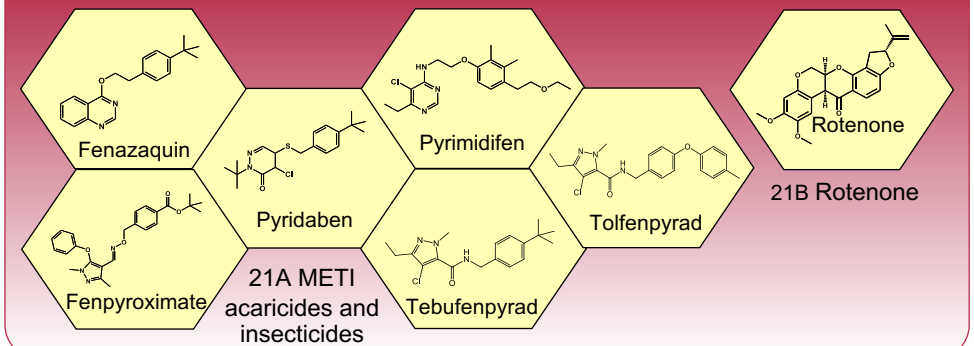
1. Inhibition of Complexes I-V



Inhibitors of one of the electron transport complexes I-IV or the mitochondrial ATP synthase (Complex V) starve cells of energy by preventing ATP formation, resulting in paralysis

Inhibitors of Complexes I-V

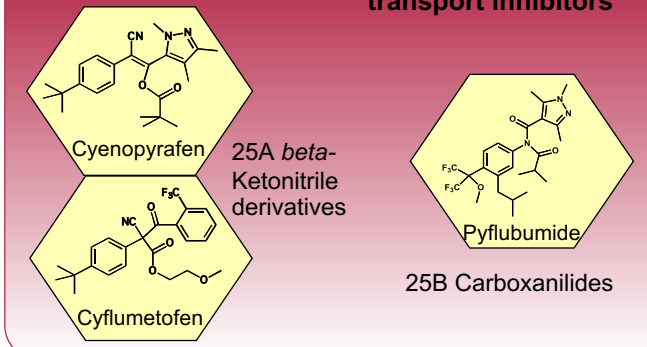
Group 21: Mitochondrial complex I electron transport inhibitors



21A METI acaricides and insecticides

21B Rotenone

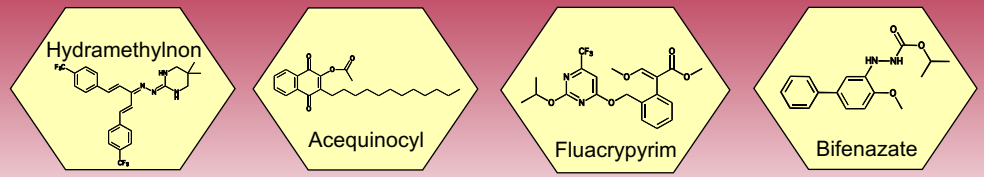
Group 25: Mitochondrial complex II electron transport inhibitors



25A *beta*-Ketonitrile derivatives

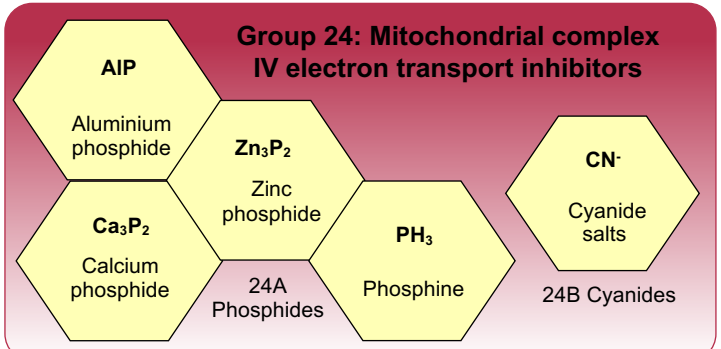
25B Carboxanilides

Group 20: Mitochondrial complex III electron transport inhibitors



20A Hydramethylnon | 20B Acequinocyl | 20C Fluacrypyrim | 20D Bifenazate

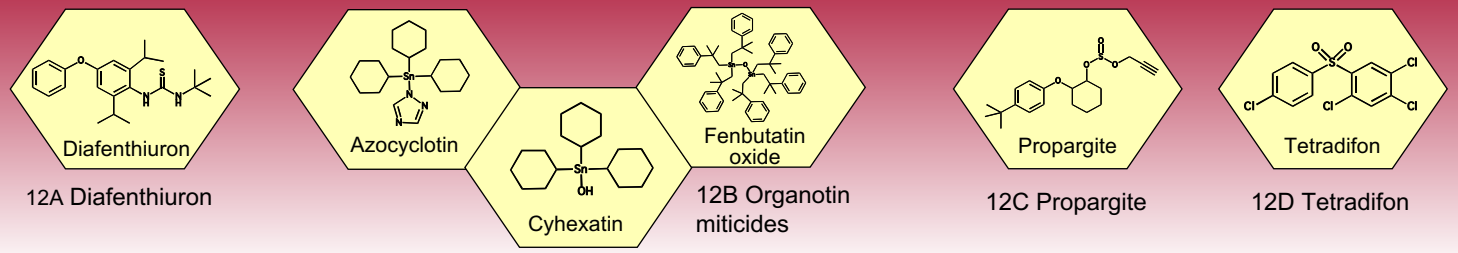
Group 24: Mitochondrial complex IV electron transport inhibitors



24A Phosphides

24B Cyanides

Group 12: Inhibitors of mitochondrial ATP synthase



12A Diafenthiuron

12B Organotin miticides

12C Propargite

12D Tetradifon

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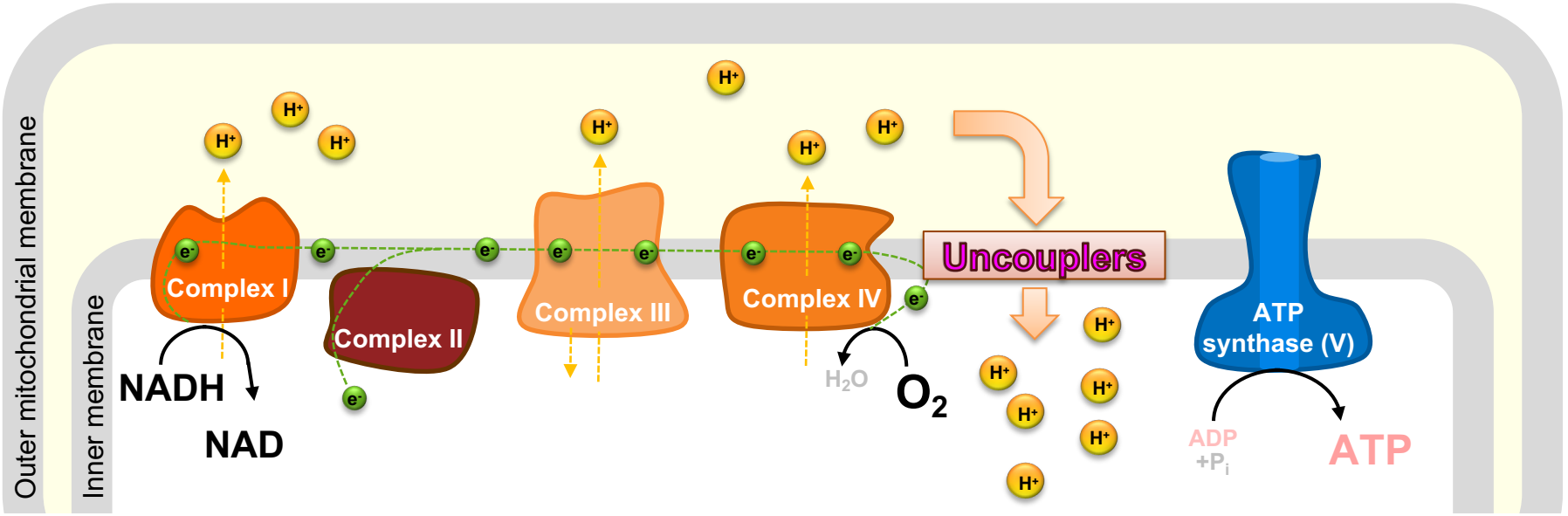
How insecticides interfere with cellular respiration:

2. Uncoupling



Uncouplers have the ability to carry protons across the inner mitochondrial membrane, thus removing the proton gradient

➔ ATP synthase is no longer able to provide cellular ATP
➔ O_2 consumption is accelerated

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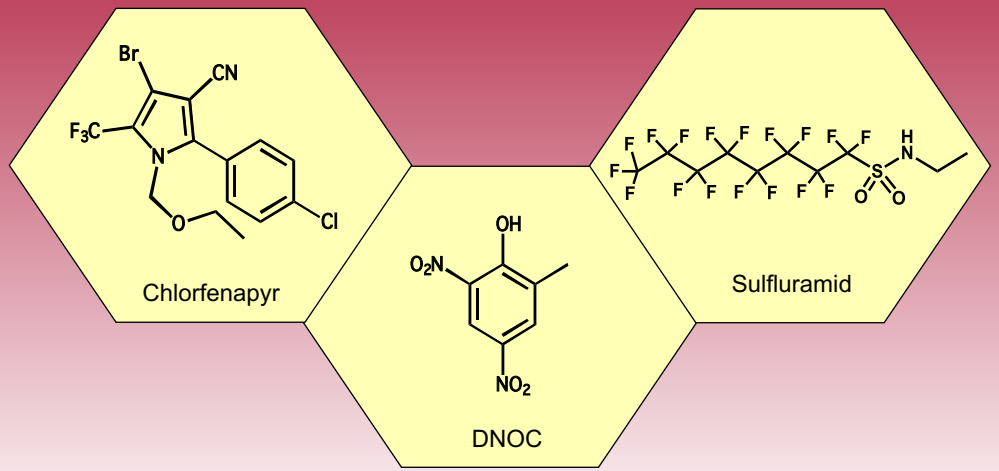
Uncouplers

Group 13: Uncouplers of oxidative phos-phorylation via disruption of proton gradient



13 Pyrroles, Dinitrophenols, Sulfluramid

Insecticide Mode of Action
Major classes

Nerve & Muscle

Growth

Respiration

Midgut

Unknown or Non-Specific

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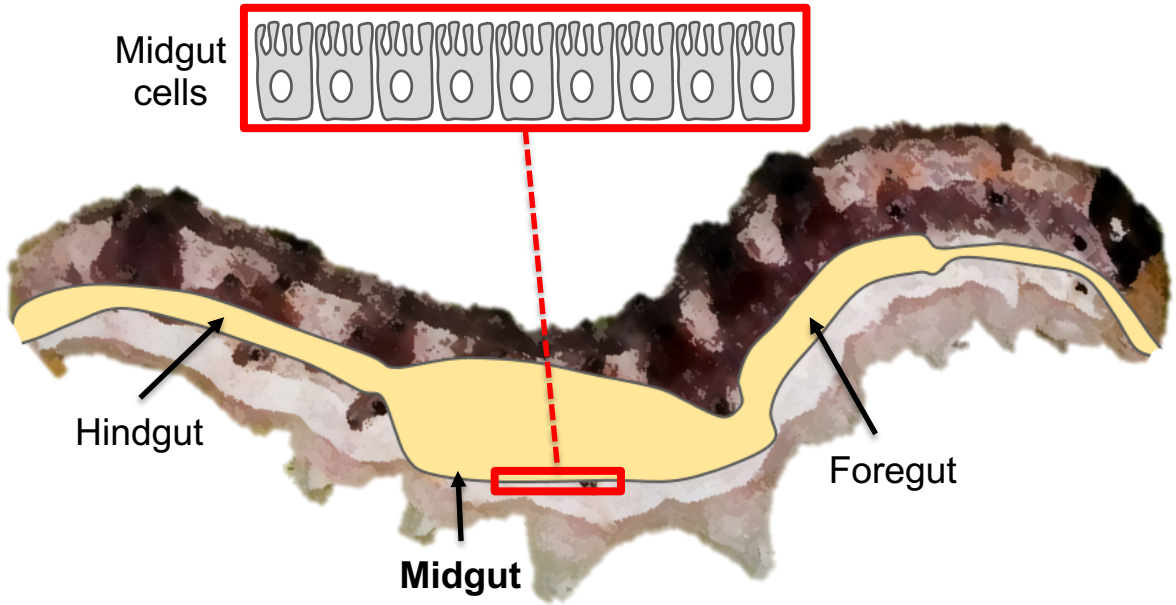
The insect midgut as a target for insecticidal agents

Bacillus thuringensis **derived toxins**

- Released in the insect midgut upon ingestion of 'packaged forms'
- Cause lysis of midgut epithelial cells via different mechanisms
- Result in loss of midgut integrity and ultimately death of the pest insect

Baculoviruses



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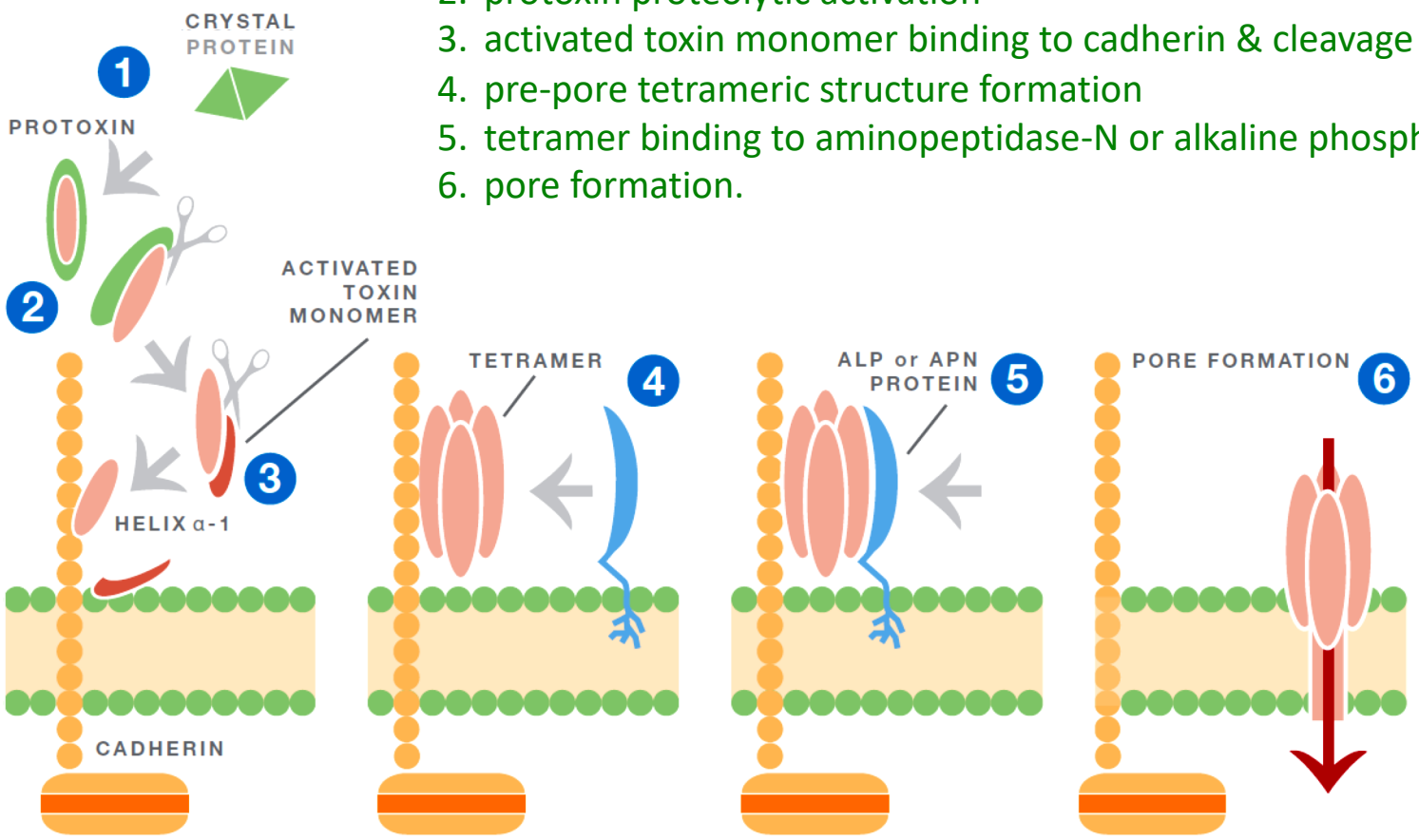
Mode of Action of *Bacillus thuringiensis* Cry Toxins on Midgut Epithelium

1. crystal solubilization
2. protoxin proteolytic activation
3. activated toxin monomer binding to cadherin & cleavage of helix α-1
4. pre-pore tetrameric structure formation
5. tetramer binding to aminopeptidase-N or alkaline phosphatase
6. pore formation.



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Microbial disruptors of insect midgut

Group 11: Microbial disruptors of insect midgut membranes

Includes transgenic crops expressing *Bacillus thuringiensis* toxins (however, specific guidance for resistance management of transgenic crops is not based on rotation of modes of action)

Bacillus thuringiensis
and the insecticidal proteins produced

B.t. israelensis, B.t. aitzawai, B.t. kurstaki, B.t. tenebrionis
Bt crop proteins*
Cry1Ab, Cry1Ac, Cry1Fa, Cry1A.105, Cry2Ab, Vip3A, mCry3A, Cry3Ab, Cry 3Bb, Cry34Ab1/Cry35Ab1

11A *Bacillus thuringiensis*

Bacillus sphaericus

11B *Bacillus sphaericus*

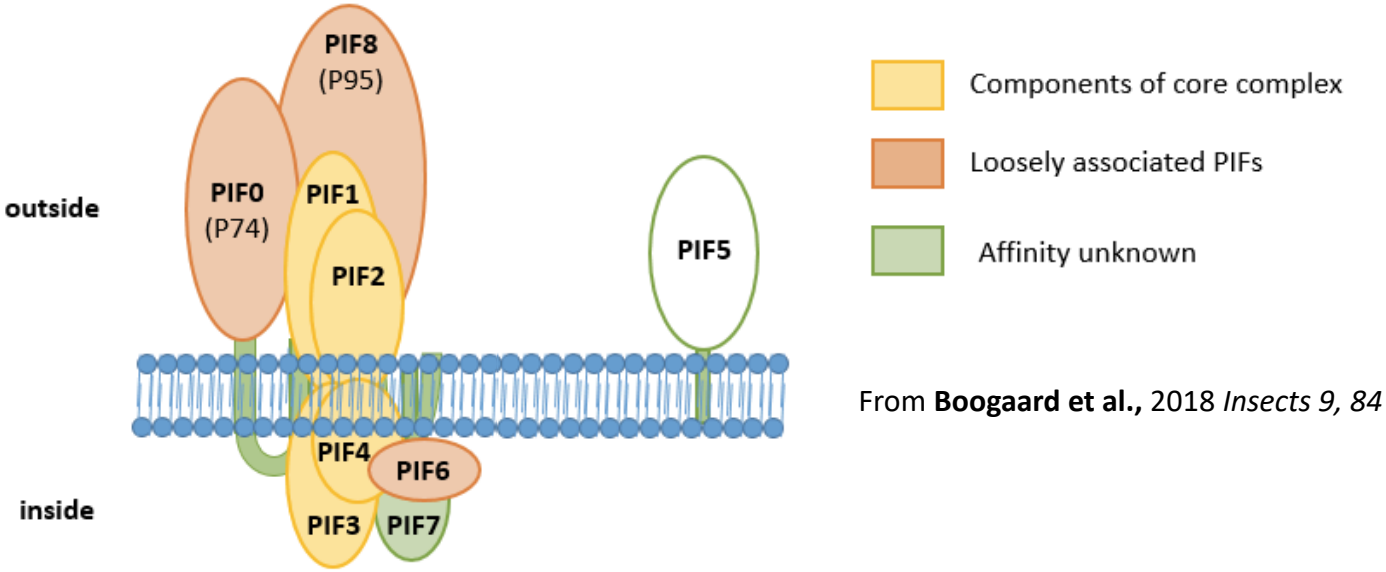
Different *B.t.* products that target different insect orders may be used together without compromising their resistance management.

Rotation between certain specific *B.t.* microbial products may provide resistance management benefits for some pests. Consult product-specific recommendations.

* Where there are differences among the specific receptors within the midguts of target insects, transgenic crops containing certain combinations of these proteins provide resistance management benefits.

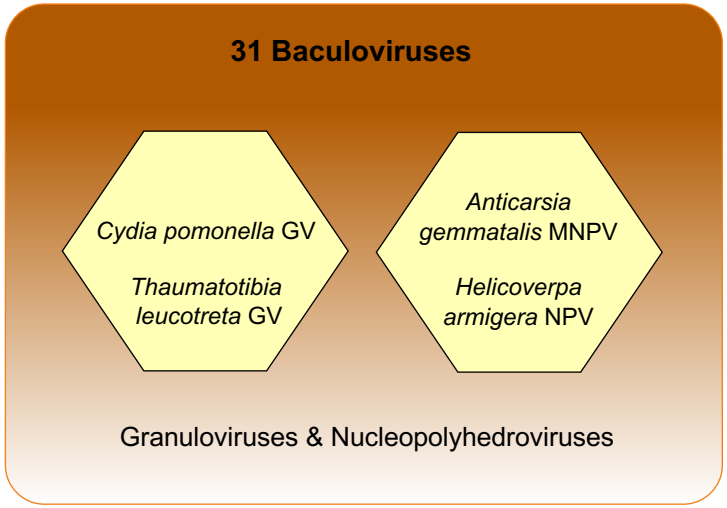
Mode of Action of Baculoviruses on Midgut Epithelium

1. Viral occlusion body disintegrates in alkaline midgut
2. Released occlusion derived virus passes through the peritrophic membrane to bind to species-specific receptors on the microvilli of midgut columnar epithelial cells
3. Viral envelope fuses with cell membrane releasing nucleocapsids in the cells
4. Entry mediated by viral proteins called *per os* infection factors (PIF 0-8)



From **Boogaard et al.,** 2018 *Insects 9, 84*

Baculoviruses acting on insect midgut



Insecticide Mode of Action
Major classes

Nerve & Muscle

Growth

Respiration

Midgut

Unknown or Non-Specific

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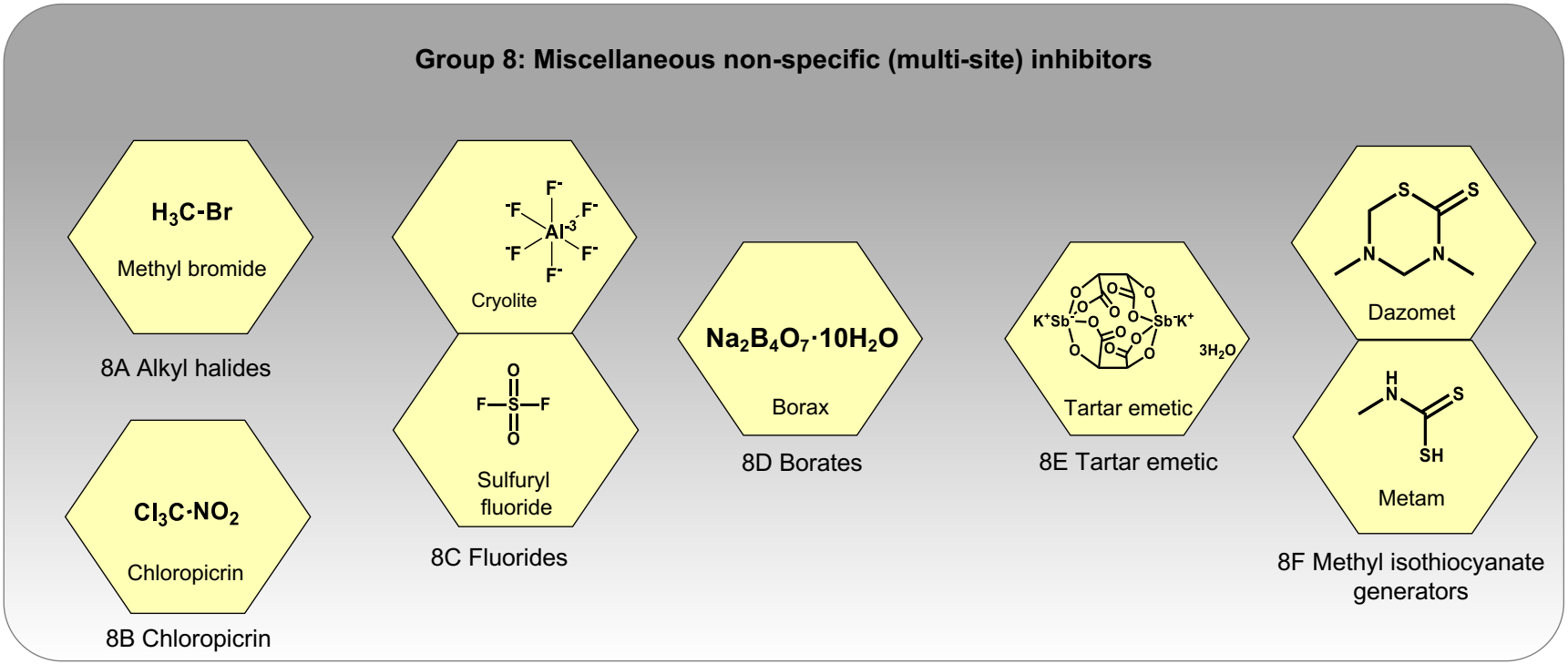
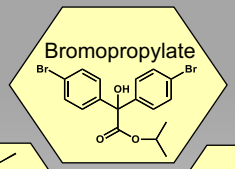
Non-specific (multi-site inhibitors)

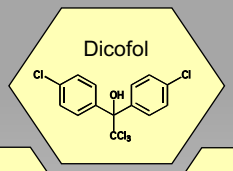


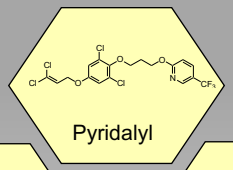
Unlike many other insecticides and miticides, non-specific or multi-site inhibitors do not act on a distinct target site but likely disrupt a variety of important physiological functions.

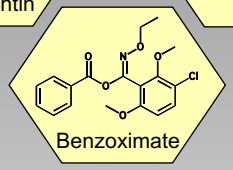
Insecticidal agents of unknown MoA

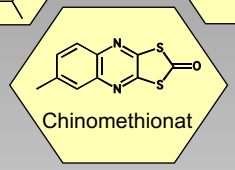
Group UN: Compounds of unknown or uncertain MoA

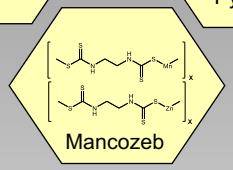












S
CaSX
(Lime sulfur)
Sulfurs

Group UNB: Bacterial agents (non-Bt) of unknown or uncertain MoA

Burkholderia spp,
Wolbachia pipientis (Zap)

Group UNE: Botanical essence including synthetic, extracts and unrefined oils with unknown or uncertain MoA

Chenopodium ambrosioides near ambrosioides extract
Fatty acid monoesters with glycerol or propanediol
Neem oil

Group UNF: Fungal agents of unknown or uncertain MoA

Beauveria bassiana strains
Metarhizium anisopliae strain F52
Paecilomyces fumosoroseus Apopka strain 97

Group UNM: Non-specific mechanical disruptors

Diatomaceous earth

Compounds with the unknown designation may act on a distinct target site, but the mechanism of action has not been conclusively determined. Because of their non-specific or unknown MoA, active ingredients in IRAC MoA groups 8 (non-specific, multi-site inhibitors), 13 (uncouplers of oxidative phosphorylation), and all UN groups (UN, UNB, UNE, UNF, UNM) are thought not to share a common target site and therefore may be freely rotated with each other unless there is a reason to expect cross-resistance.

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Insecticide Resistance Action Committee

Mode of Action Classification

Group 1: Acetylcholinesterase (AChE) inhibitors (Only major representatives of the groups are shown)

1A Carbamates: Aldicarb, Oxamyl, Methiocarb, Thiodicarb, Carbaryl, Methomyl, Carbofuran, Pirimicarb

1B Organophosphates: Acephate, Methamidophos, Fenitrothion, Profenofos, Chlorpyrifos, Malathion, Dimethoate, Triazophos

Group 2: GABA-gated chloride channel antagonists

2A Cyclodiene Organochlorines: Chlordane, Endosulfan

2B Phenylpyrazoles (Fiproles): Ethiprole, Fipronil

Group 3: Sodium channel modulators (Only major representatives of group 3A are shown)

3A Pyrethroids Pyrethrins: Bifenthrin, Deltamethrin, Esfenvalerate, lambda-cyhalothrin, Permethrin, Tefluthrin, Etofenprox, alpha-cypermethrin

3B DDT, Methoxychlor: DDT, Methoxychlor

Group 4: Nicotinic acetylcholine receptor (nAChR) competitive modulators

4A Neonicotinoids: Acetamiprid, Clothianidin, Dinotefuran, Imidacloprid, Nitenpyram, Thiacloprid, Thiamethoxam

4B Nicotine: Nicotine

4C Sulfoximines: Sulfoxaflor

4D Butenolides: Flupyradifurone

4E Mesoionics: Triflumezopyrim

Group 5: Nicotinic acetylcholine receptor (nAChR) allosteric modulators site I

5 Spinosyns: Spinetoram, Spinosad

Group 6: Glutamate-gated chloride channel (GluCl) allosteric modulators

6 Avermectins & Milbemycins: Abamectin, Emamectin benzoate, Lepimectin, Milbemectin

Group 7: Juvenile hormone mimics

7A Juvenile hormone analogues: Hydroprene, Methoprene, Kinoprene

7B Fenoxycarb: Fenoxycarb

7C Pyriproxyfen: Pyriproxyfen

Use of Groups and Sub-Groups:

- Alternations, sequences or rotations of compounds between MoA groups reduce selection for target site resistance.
- Applications are arranged into MoA spray windows defined by crop growth stage and pest biology.
- Several sprays of a compound may be possible within each spray window, but successive generations of a pest should not be treated with compounds from the same MoA group.
- Local expert advice should always be followed with regard to spray windows and timing.
- Groups in the classification whose members do not act at a common target site are exempt from the proscription against rotation within the group. These are, Group 8, Group 13 and all the UN groups: UN, UNB, UNE, UNF, UNM, UNP & UNV.
- Sub-groups represent distinct structural classes which are believed to have the same mode of action.
- Sub-groups provide differentiation between compounds that may bind at the same target site but are structurally different enough that risk of metabolic cross-resistance is lower than for close chemical analogs.
- Cross-resistance potential between sub-groups is higher than between groups, so rotation between sub-groups should be considered only when there are no alternatives, and only if cross-resistance does not exist, following consultation with local expert advice. These exceptions are not sustainable, and alternative options should be sought.
- Sub-group 3B: DDT is no longer used in agriculture and therefore this is only applicable for the control of insect vectors of human disease, such as mosquitoes, because of a lack of alternatives.
- Sub-group 10A: Hexythiazox is grouped with clofentezine because they exhibit cross-resistance even though they are structurally distinct. Diflovidazin has been added to this group because it is a close analogue of clofentezine and is expected to have the same mode of action.

Group 8: Miscellaneous non-specific (multi-site) inhibitors

8A Alkyl halides: Methyl bromide, Chloropicrin

8B Chloropicrin

8C Fluorides: Cryolite, Sulfuryl fluoride

8D Borates: Borax

8E Tartar emetic: Tartar emetic

8F Methyl isothiocyanate generators: Dazomet, Metam

Group 9: Chordotonal organ TRPV channel modulators

9B Pyridine azomethine derivatives: Pymetrozine, Pyrifluquinazon

9D Pyropenes: Afidopyropen

Group 10: Mite growth inhibitors affecting CHS1

10A Clofentezine, Diflovidazin, Hexythiazox: Clofentezine, Diflovidazin, Hexythiazox

10B Etoxazole: Etoxazole

Group 11: Microbial disruptors of insect midgut membranes

(includes transgenic crops expressing *Bacillus thuringiensis* toxins (however, specific guidance for resistance management of transgenic crops is not based on rotation of modes of action))

Different *B.t.* products that target different insect orders may be used together without compromising their resistance management. Rotation between certain specific *B.t.* microbial products may provide resistance management benefits for some pests. Consult product-specific recommendations.

* Where there are differences among the specific receptors within the midguts of target insects, transgenic crops containing certain combinations of these proteins provide resistance management benefits.

11A *Bacillus thuringiensis*: *Bacillus thuringiensis* and the insecticidal proteins produced: *B.t. aizawai*, *B.t. kurstaki*, *B.t. tenebrionis*, Bt crop proteins *: Cry1Ab, Cry1Ac, Cry1Fa, Cry1A.105, Cry2Ab, Vip3A, mCry3A, Cry3Ab, Cry 3Bb, Cry34Ab1/Cry35Ab1

11B *Bacillus sphaericus*: *Bacillus sphaericus*

Group 12: Inhibitors of mitochondrial ATP synthase

12A Diafenthiuron: Diafenthiuron

12B Organotin miticides: Azocyclotin, Cyhexatin, Fenbutatin oxide

12C Propargite: Propargite

12D Tetradifon: Tetradifon

Group 13: Uncouplers of oxidative phosphorylation via disruption of proton gradient

13 Pyrroles, Dinitrophenols, Sulfluramid: Chlorfenapyr, DNOC, Sulfluramid

Group 14: Nicotinic acetylcholine receptor (nAChR) channel blockers

14 Nereistoxin analogues: Bensultap, Cartap hydrochloride, Thiocyclam, Thiosultap-sodium

Group 15: Inhibitors of chitin biosynthesis affecting CHS1

(Only major representatives of group are shown)

15 Benzoylureas: Diflubenzuron, Flufenoxuron, Lufenuron, Novaluron, Teflubenzuron

Group 16: Inhibitors of chitin biosynthesis, type 1

16 Buprofezin: Buprofezin

Group 17: Moulting disruptors, Dipteran

17 Cyromazine: Cyromazine

Group 18: Ecdysone receptor agonists

18 Diacylhydrazines: Chromafenozide, Halofenozide, Methoxyfenozide, Tebufenozide

Group 19: Octopamine receptor agonists

19 Amitraz: Amitraz

Group 20: Mitochondrial complex III electron transport inhibitors

20A Hydramethylnon: Hydramethylnon

20B Acequinocyl: Acequinocyl

20C Fluacrypyrim: Fluacrypyrim

20D Bifenazate: Bifenazate

Group 21: Mitochondrial complex I electron transport inhibitors

21A METI acaricides and insecticides: Fenazaquin, Fenpyroximate, Pyridaben, Pyrimidifen, Tebufenpyrad, Tolfenpyrad

21B Rotenone: Rotenone

Group 22: Voltage-dependent sodium channel blockers

22A Oxadiazines: Indoxacarb

22B Semicarbazones: Metaflumizone

Group 23: Inhibitors of acetyl CoA carboxylase

23 Tetronic & Tetramic acid derivatives: Spirodiclofen, Spiromesifen, Spirotetramat

Group 24: Mitochondrial complex IV electron transport inhibitors

24A Phosphides: Aluminium phosphide, Zinc phosphide, Calcium phosphide

24B Cyanides: Cyanide salts

Phosphine

Group 25: Mitochondrial complex II electron transport inhibitors

25A beta-Ketonitrile derivatives: Cyenopyrafen, Cyflumetofen

25B Carboxanilides: Pyflubumide

Group 28: Ryanodine receptor modulators

28 Diamides: Chlorantraniliprole, Cyantraniliprole, Flubendiamide, Cyclaniliprole

29: Chordotonal organ modulators – undefined target site

29 Flonicamid: Flonicamid

30 GABA-gated chloride channel allosteric modulators

Meta-diamides & Isoxazolines: Broflanilide, Fluxametamide

31 Baculoviruses

Granuloviruses & Nucleopolyhedroviruses: Cydia pomonella GV, Thaumatotibia leucotreta GV, Anticarsia gemmatalis MNPV, Helicoverpa armigera NPV

32 Nicotinic Acetylcholine Receptor (nAChR) Allosteric Modulators - Site II

GS-omega/kappa HXTX-Hv1a peptide

Group UN: Compounds of unknown or uncertain mode of action

Azadirachtin, Benzoximate, Bromopropylate, Chinomethionat, Dicofol, Mancozeb, Pyridalyl, S CaS_x (Lime sulfur) Sulfura

UNB Bacterial agents (non-Bt) of unknown or uncertain MoA

Burkholderia spp. Wolbachia pipientis (Zap)

UNE Botanical essence including synthetic, extracts and unrefined oils with unknown or uncertain MoA

Chenopodium ambrosioides near ambrosioides extract; Fatty acid monoesters with glycerol or propylenediol; Neem oil

UNF Fungal agents of unknown or uncertain MoA

Beauveria bassiana strains; Metarhizium anisopliae strain F52; Paecilomyces fumosoroseus Apopka strain 97

UNM Non-specific mechanical disruptors

Diatomaceous earth

Key to Targeted Physiology

Nerve & Muscle | Growth & Development | Respiration | Midgut | Unknown or Non-specific

Poster Notes:

- Groups 26 and 27 are unassigned.
- The poster is for educational purposes only. Information presented is accurate to the best of our knowledge at the time of publication, but IRAC or its member companies cannot accept responsibility for how this information is used or interpreted. Advice should always be sought from local experts or advisors, and health and safety recommendations followed.
- In some cases only representative compounds in Groups are shown where indicated.
- Please visit www.irac-online.org for the complete IRAC classification.

CropLife

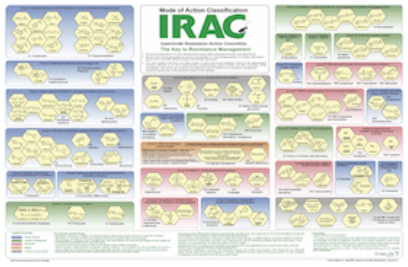
Poster Edition 7, December 2018. Based on the MoA Classification Version 9.1

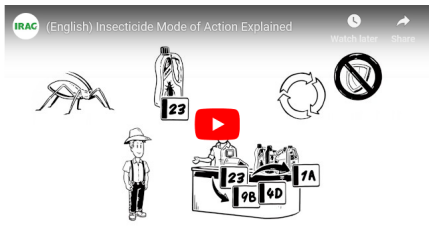
IRAC

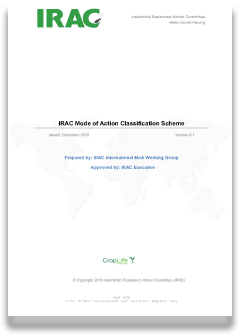
Important links

https://www.irac-online.org/

Modes of Action







Pests

Crops

Teams

Test Methods

News