Insecticide Mode of Action Training Slide Deck

IRAC International MoA Working Group

Version 2.0, March 2026

IRAC

Insecticide Resistance Action Committee

Insecticide Resistance Action Committee – Mode of Action Training Slide Deck

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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 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 through rotation

The Insecticide Resistance Action Committee (IRAC) is a coordinated industry response to resistance management classifying insecticides by Mode of Action

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What is IRAC?

The Insecticide Resistance Action Committee (IRAC) is a coordinated industry response to resistance management classifying insecticides by Mode of Action.

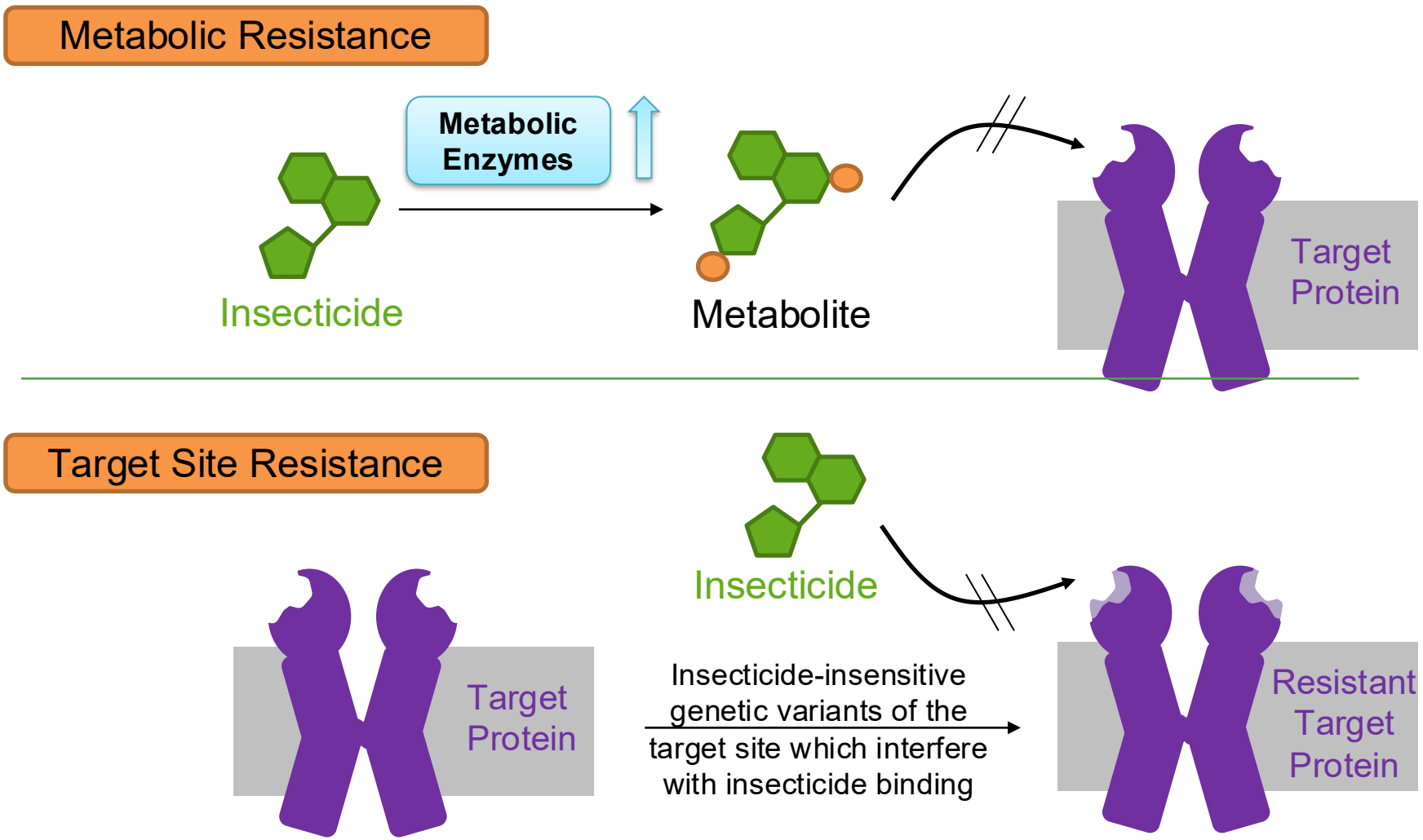
Our mission

- Facilitate communication and education on resistance to insecticides and insect-resistant traits.
- Promote and facilitate development and implementation of resistance management strategies to maintain efficacy and support sustainable agriculture and improved public health.

https://irac-online.org/

CONCEPT: Insecticide Resistance

Major mechanisms of insecticide resistance



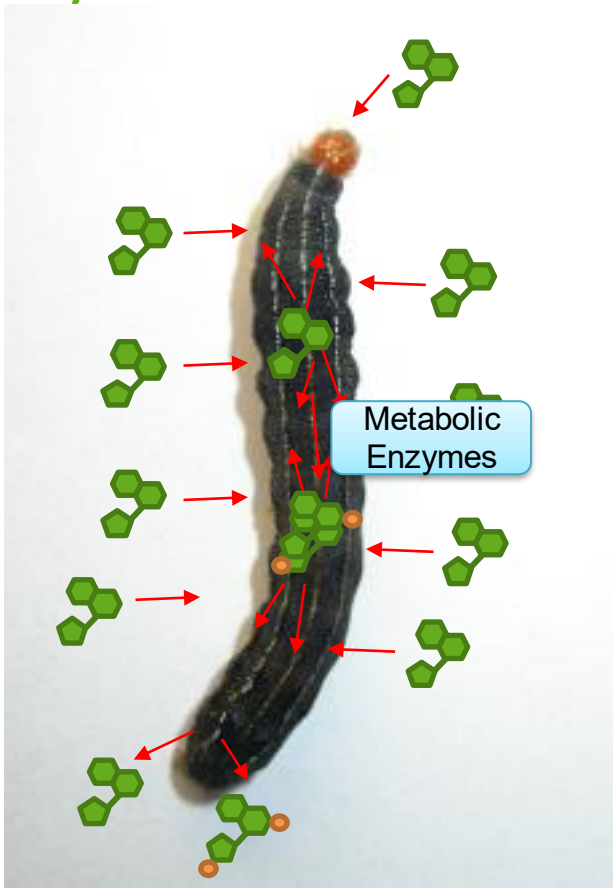
CONCEPT: Insecticide Bioavailability

What is insecticide's ADME?

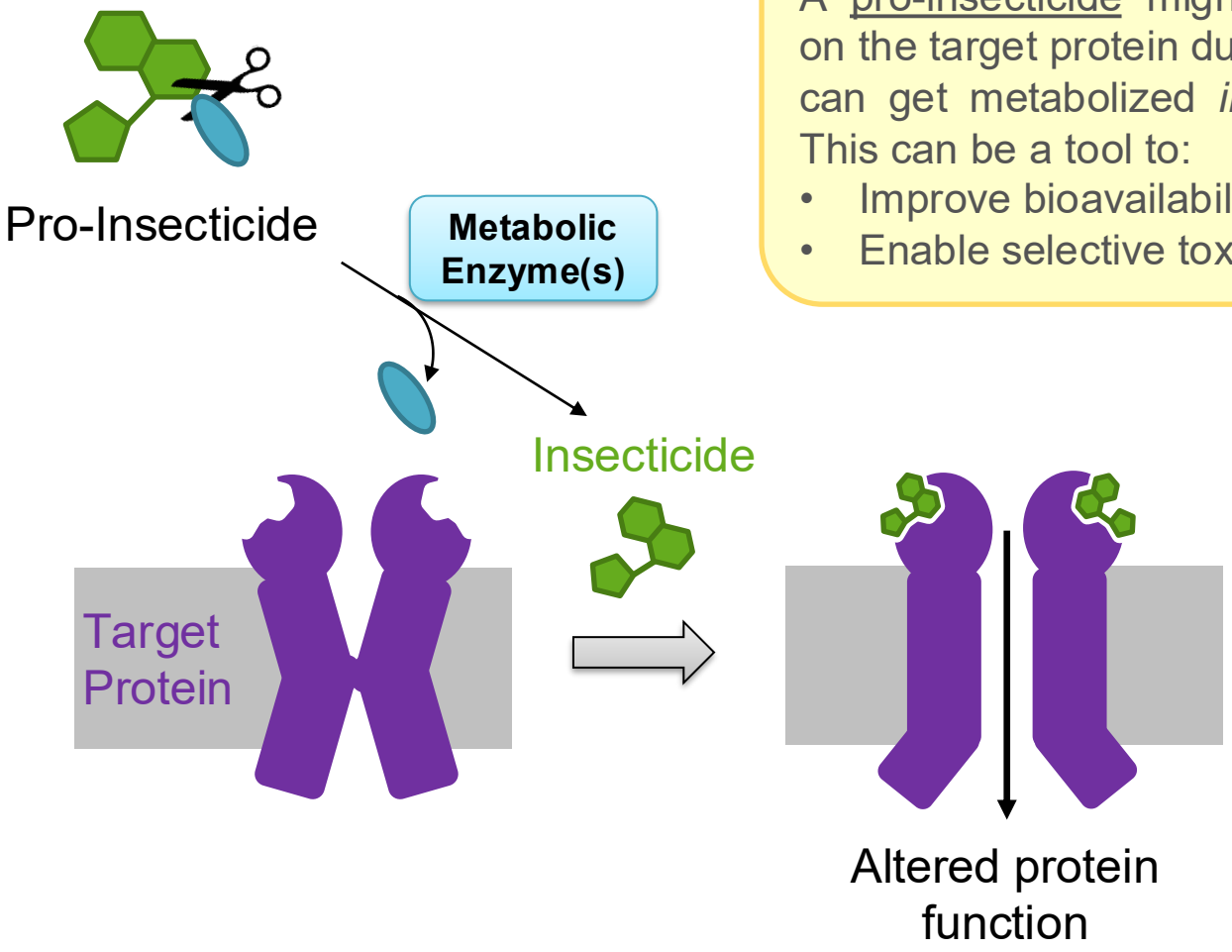
ADME = Absorption, Distribution, Metabolism (breakdown), Excretion

ADME is an important factor in an insecticide's bioavailability

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



The pro-insecticide concept

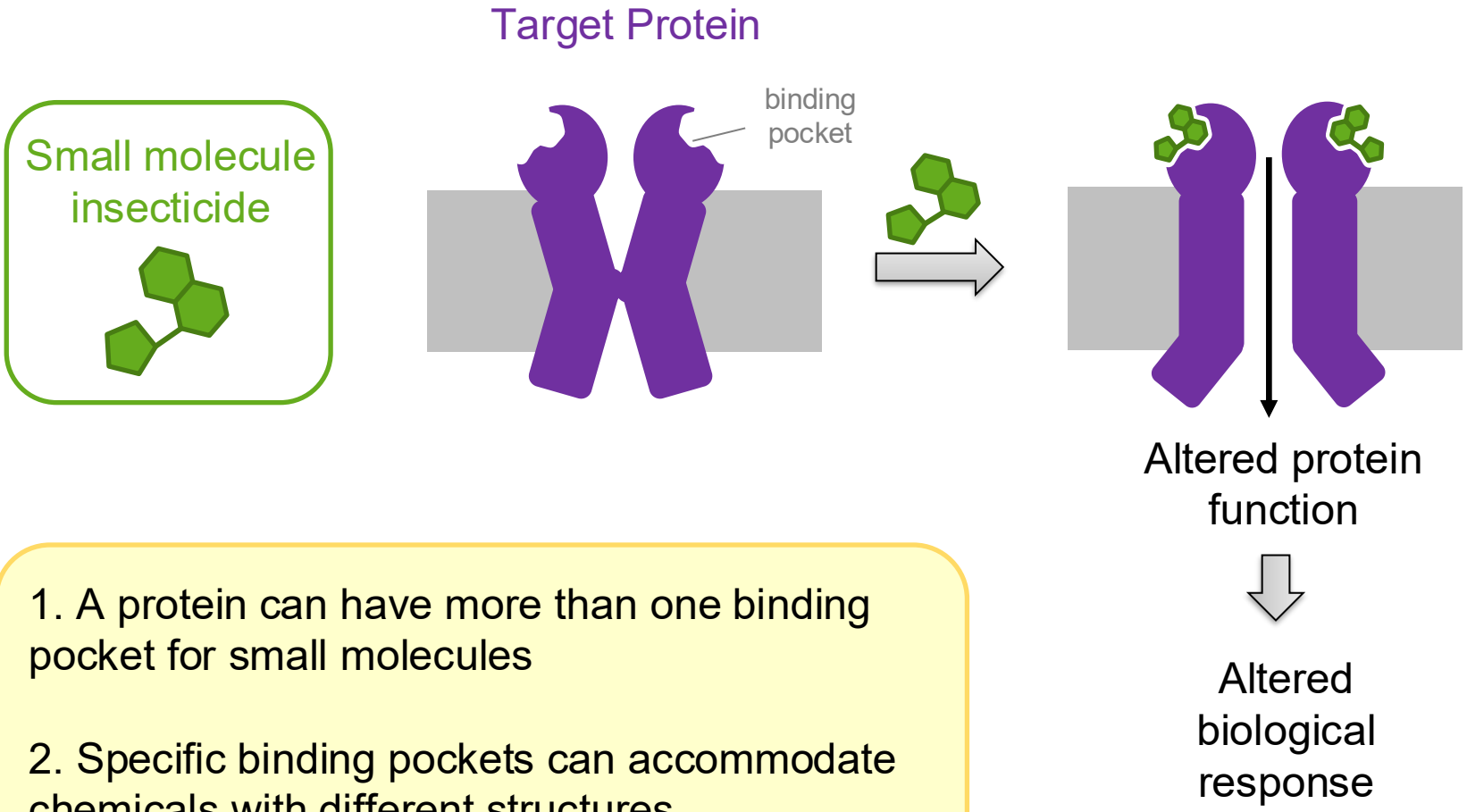


A pro-insecticide might have negligible activity on the target protein due to protecting groups but can get metabolized *in vivo* to its active form. This can be a tool to:

- Improve bioavailability
- Enable selective toxicity

CONCEPT: How insecticides work

Insecticides act on *key functional proteins* that regulate vital processes



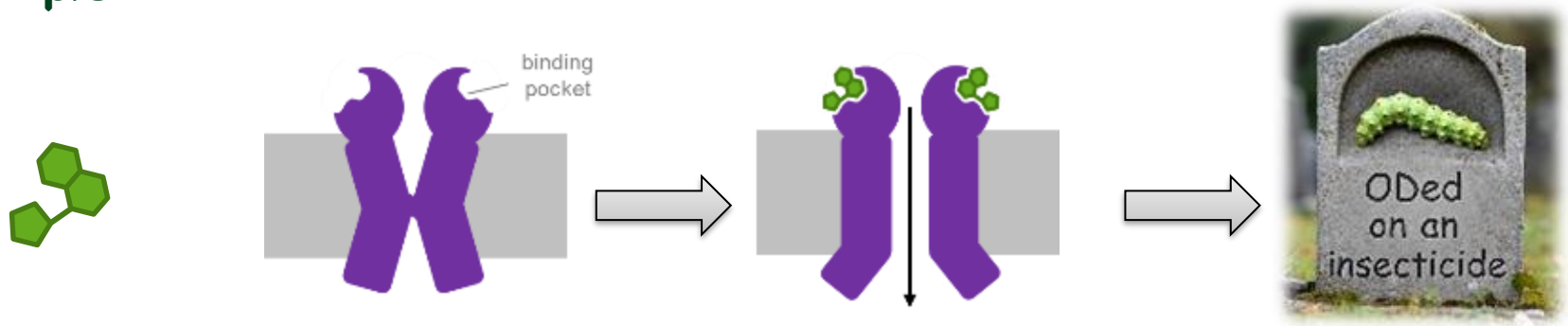
1. A protein can have more than one binding pocket for small molecules

2. Specific binding pockets can accommodate chemicals with different structures

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

The Mode of Action (MoA) defines the process of how an insecticide works on an insect at a molecular level resulting in a biological effect.

Example



Insecticide A binds to **Target Protein X** causing ***uncontrolled modulation*** leading to **Biological Effect**

Insecticides are currently grouped into 37 defined MoA groups or Unknown UN(X) MoA groups.

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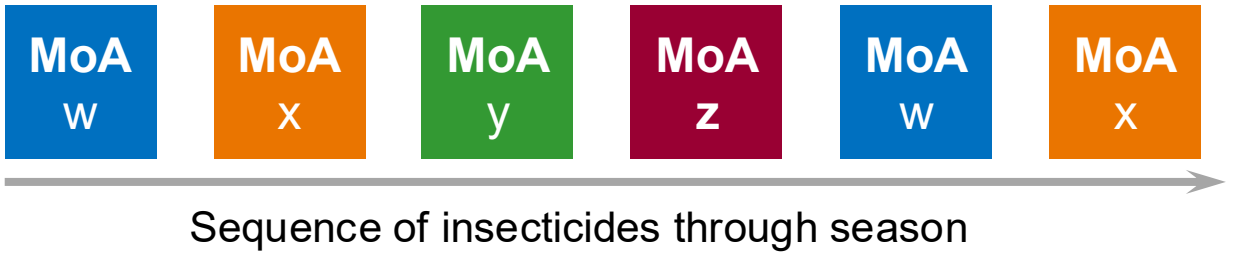
Why is it good to know the MoA of an Insecticide?

Knowing the mode of action of an insecticide is key to managing resistance through rotation.

Example



Alternations, sequences or rotations of insecticidal agents from different MoA groups provide sustainable and effective Insecticide Resistance Management (IRM)

Applications are often arranged into MoA spray windows or blocks that are defined by the stage of crop development and the biology of the pest species of concern. Local expert advice should always be followed with regards to spray windows and timing	Several sprays may be possible within each spray window, but it is generally essential that successive generations of the pest are not treated with compounds from the same MoA group	Metabolic resistance mechanisms may give cross-resistance between MoA groups; where this is known to occur, the above advice should be modified accordingly

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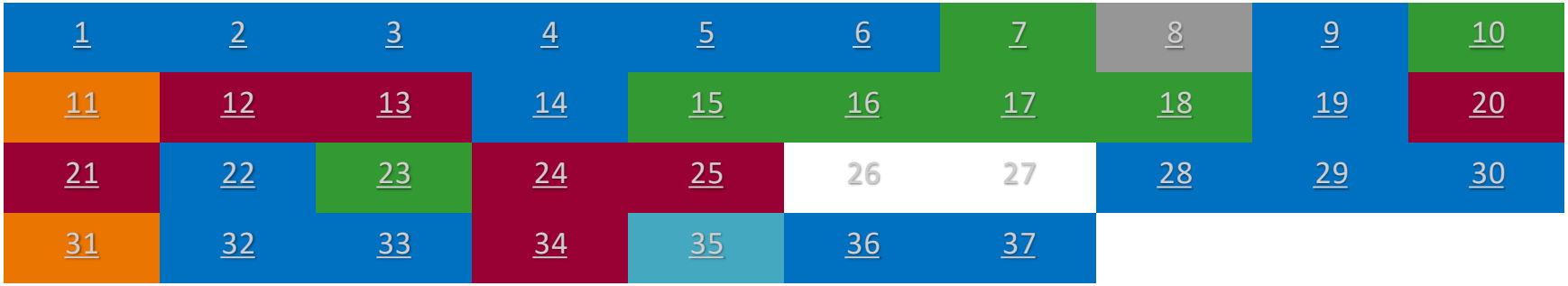
Classification of Mode of Action



UNF Fungal agents
UNB Bacterial agents (non-Bt)
UNM Non-specific mechanical and physical disruptors
UNE Botanical essence including synthetic, extracts & unrefined oils

Nerve & Muscle
Growth
Respiration
Midgut
Protein Suppressor
Unknown or Non-Specific
Unassigned MoA group

https://irac-online.org/mode-of-action/

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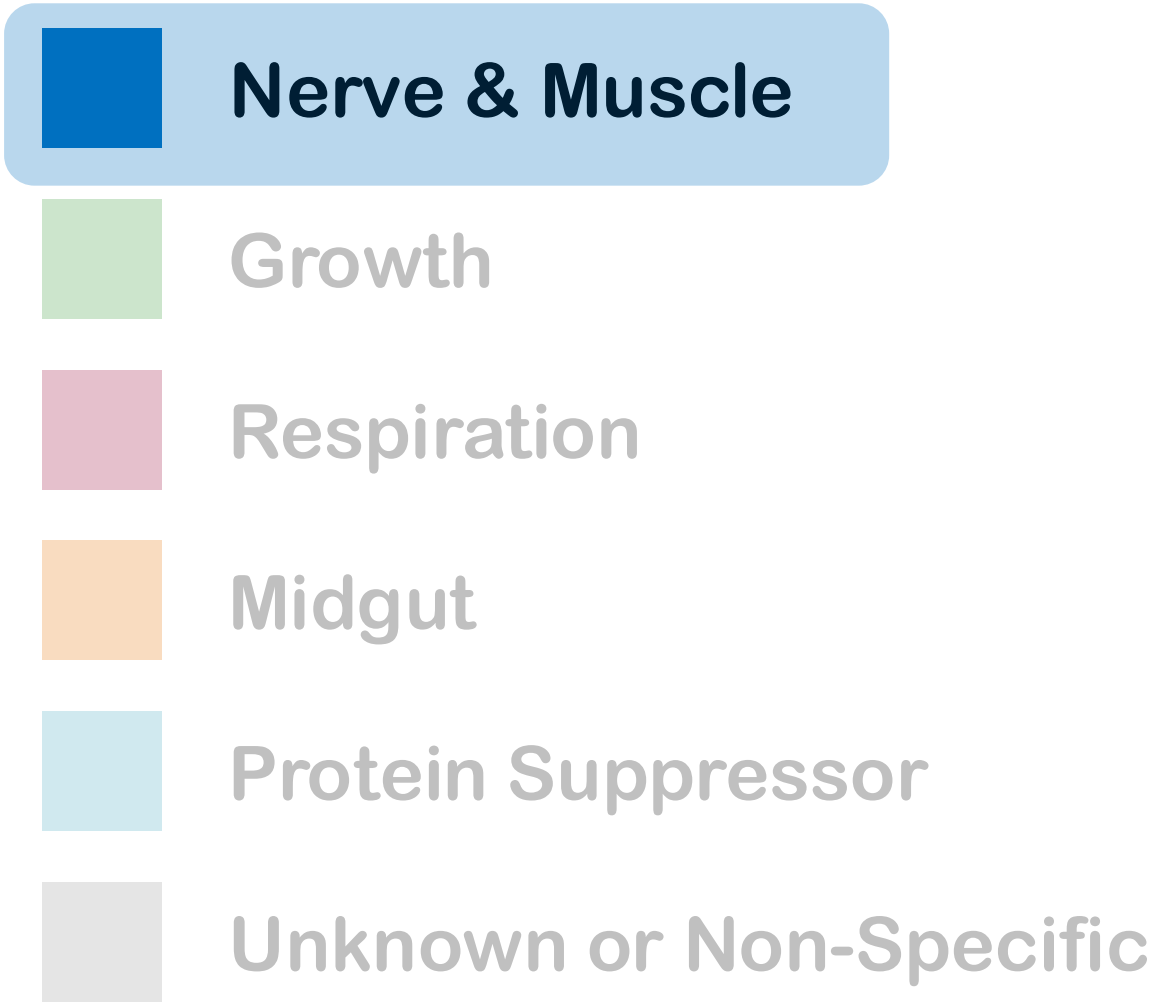
Insecticide Mode of Action: Major classes

Insecticide Mode of Action: Major classes



Key functional proteins that are targets for Nerve and Muscle Insecticides

Modulation of these targets can be generally grouped into disrupting the neuronal signalling pathways, either the excitatory pathway or the inhibitory pathway, ultimately resulting in insect paralysis.

Example: ***Interference with an excitatory pathway***

Group 3 insecticides bind to **voltage gated sodium channel** causing ***repetitive firing and hyperexcitation*** leading to **paralysis**

Example: ***Interference with an inhibitory pathway***

Group 30 insecticides bind to **GABA-gated chloride channel** causing ***negative modulation*** leading to **insect convulsions and death**

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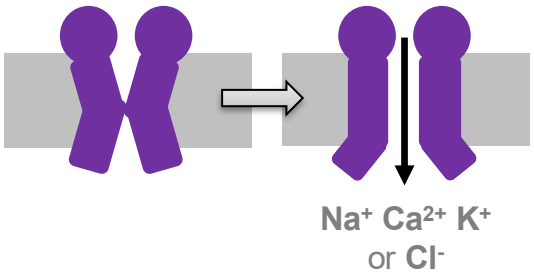
Key functional proteins that are targets for Nerve and Muscle Insecticides

Ion channels

essential for bioelectricity



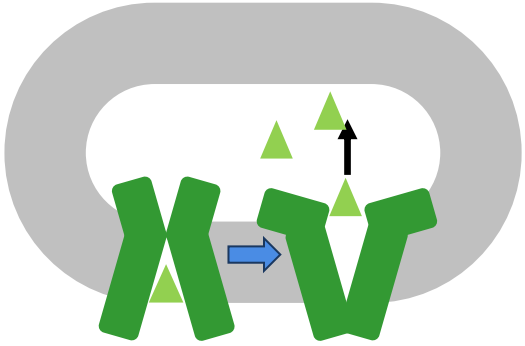
Enzymes

biocatalysts

Proteins accelerating chemical reactions

Transporters

storage of signalling molecules

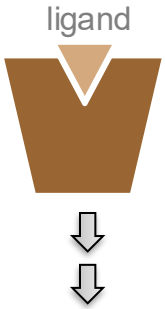


ACh

Signalling molecule

Receptors

signal transducer



Binding of a ligand triggers a response

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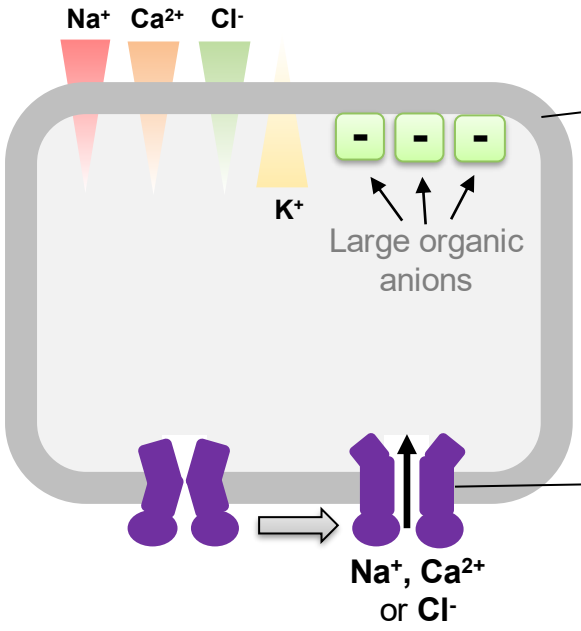
Ion channels are important targets of neuromuscular disruptors



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

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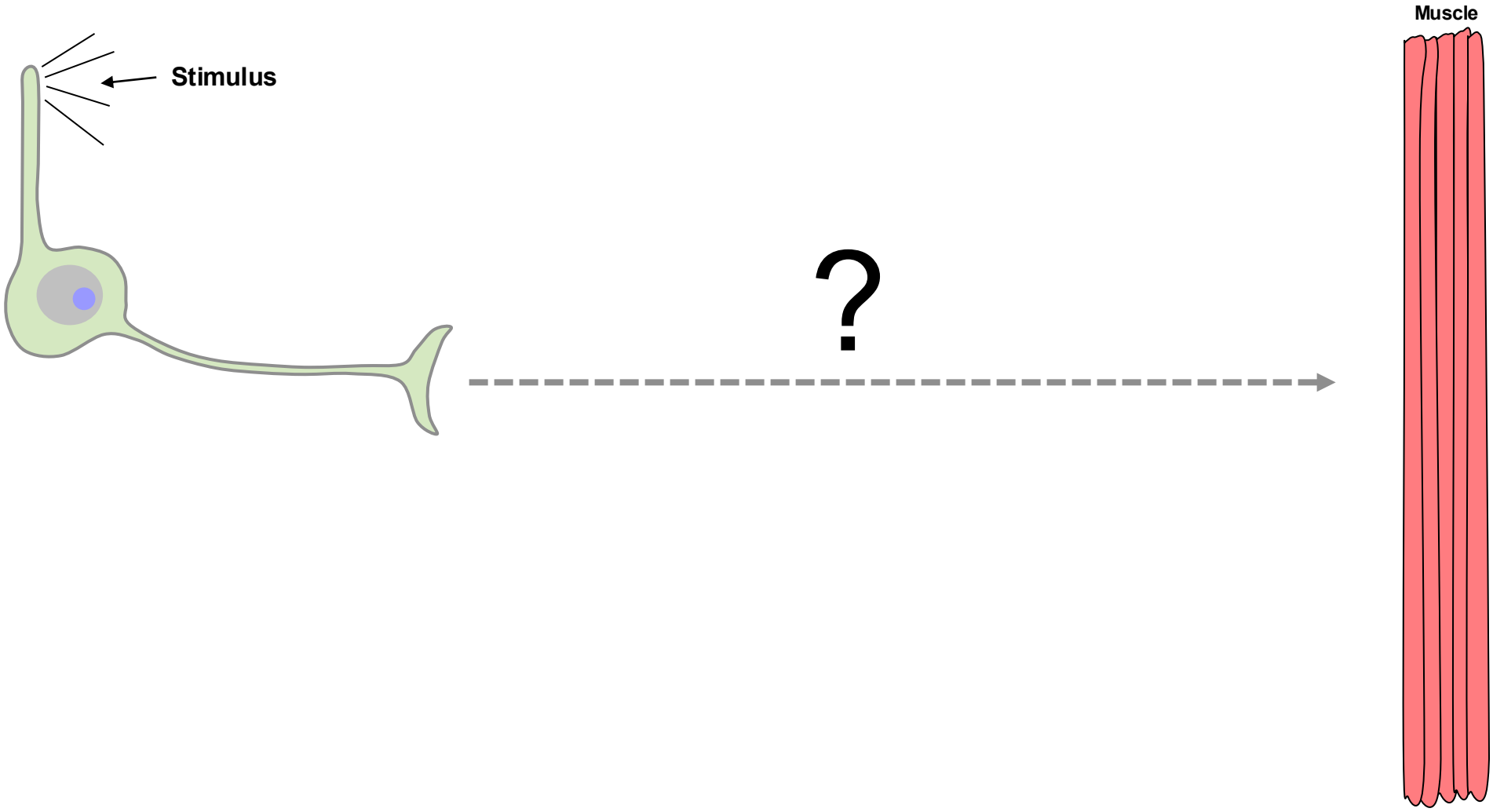
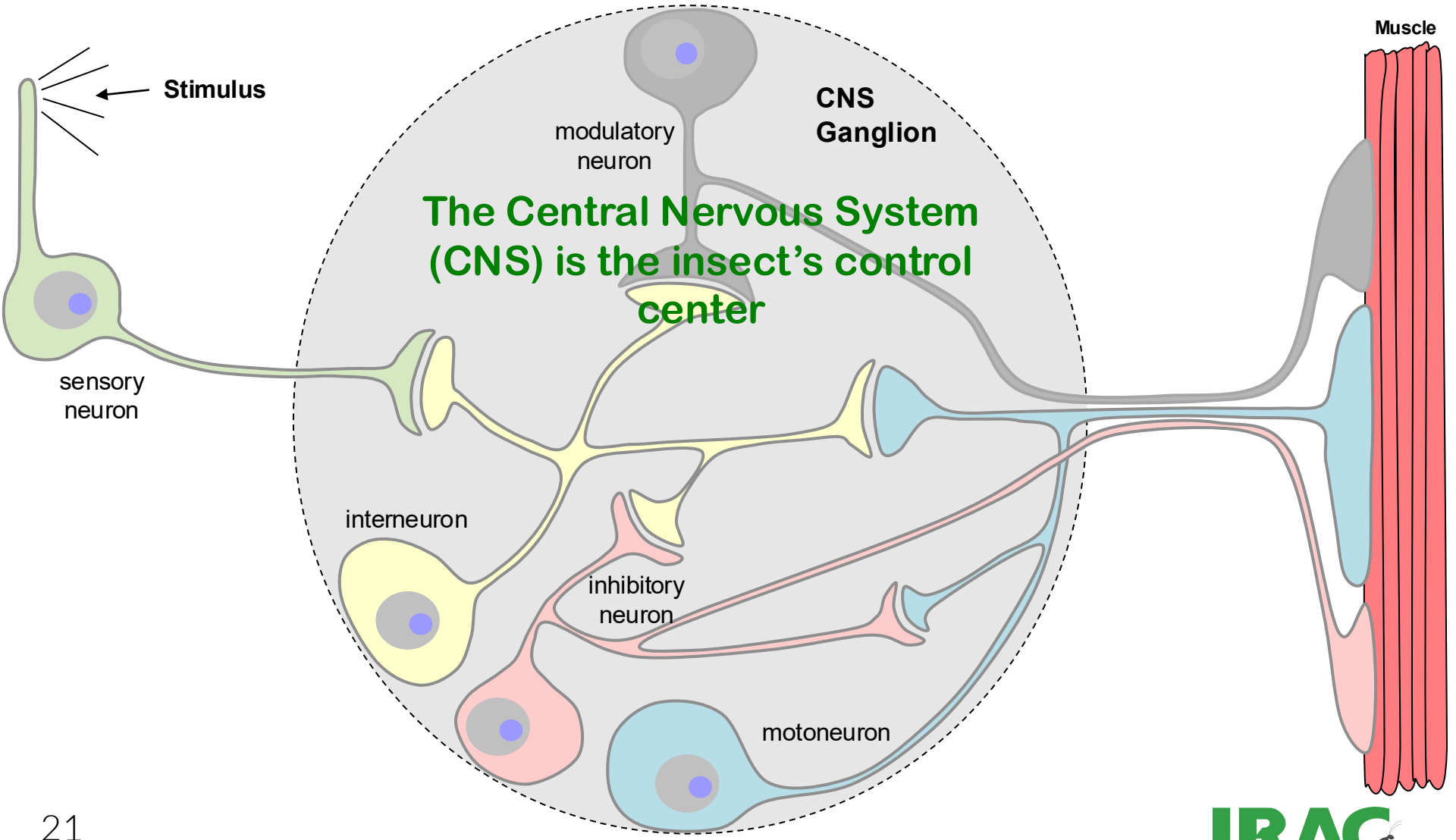
The insect neuromuscular system: Translating a stimulus into (muscle) action



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



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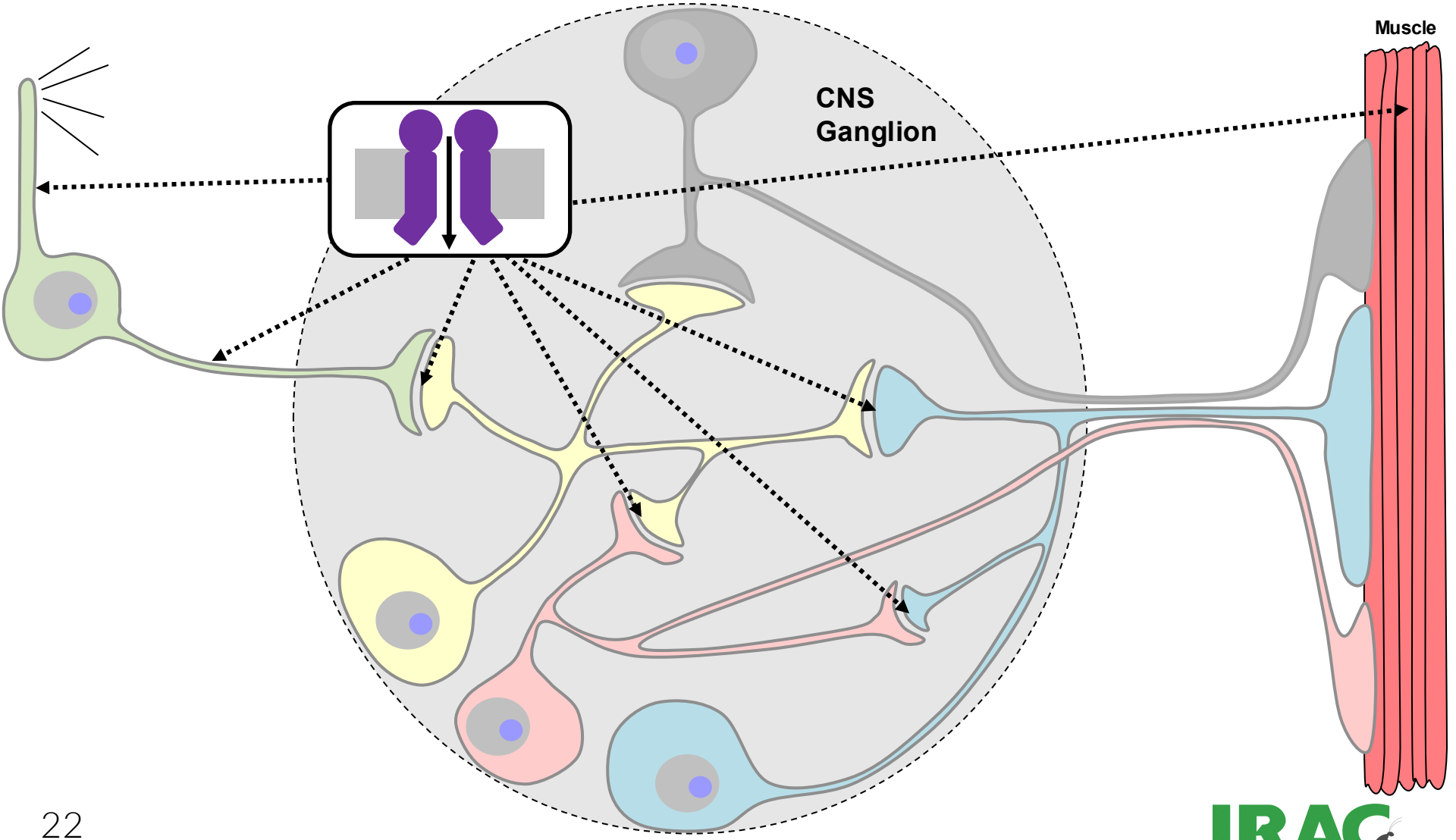
Ion channels play diverse roles within the neuromuscular system



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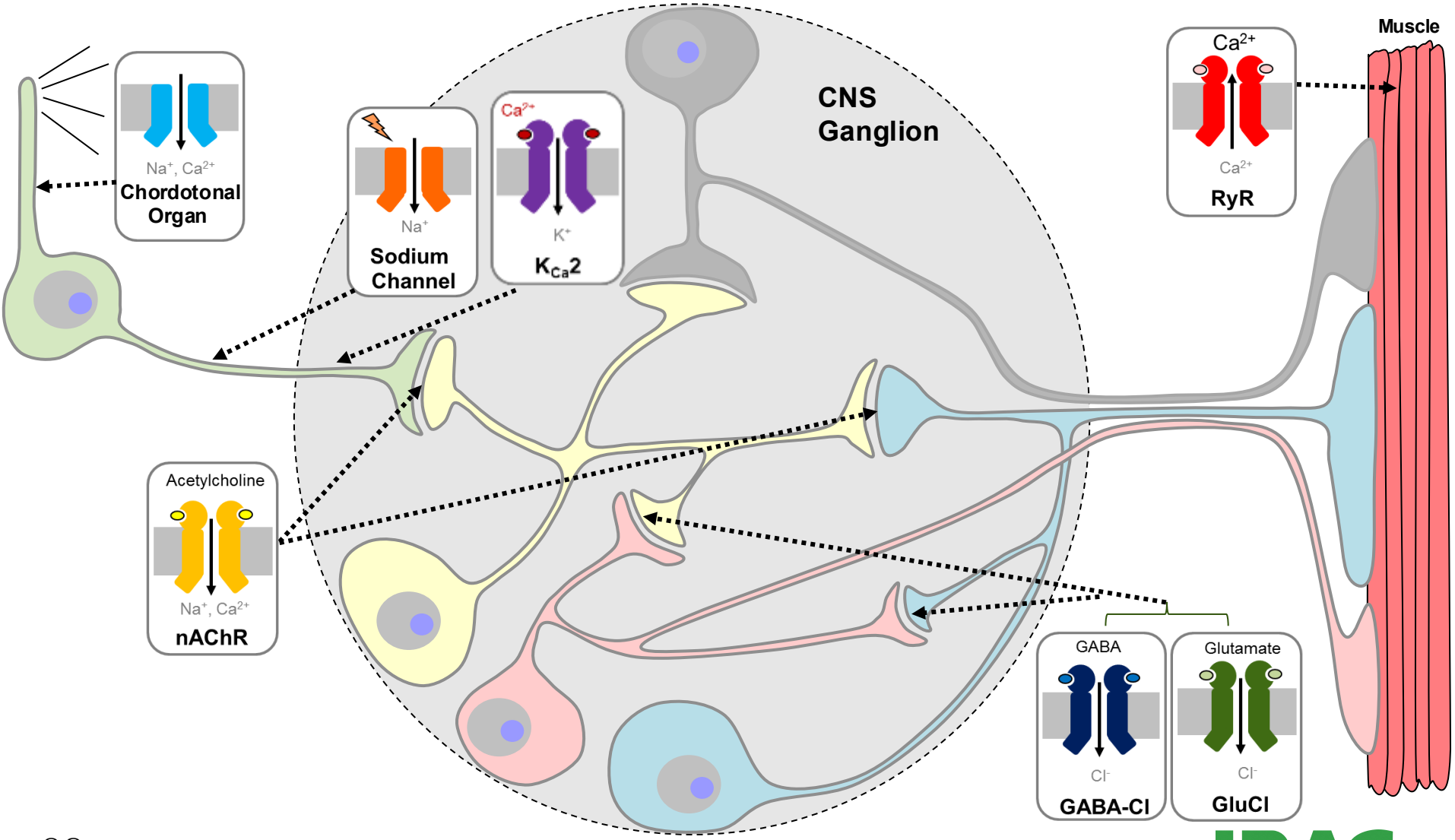
Overview of ion channels targeted by neuromuscular disruptors



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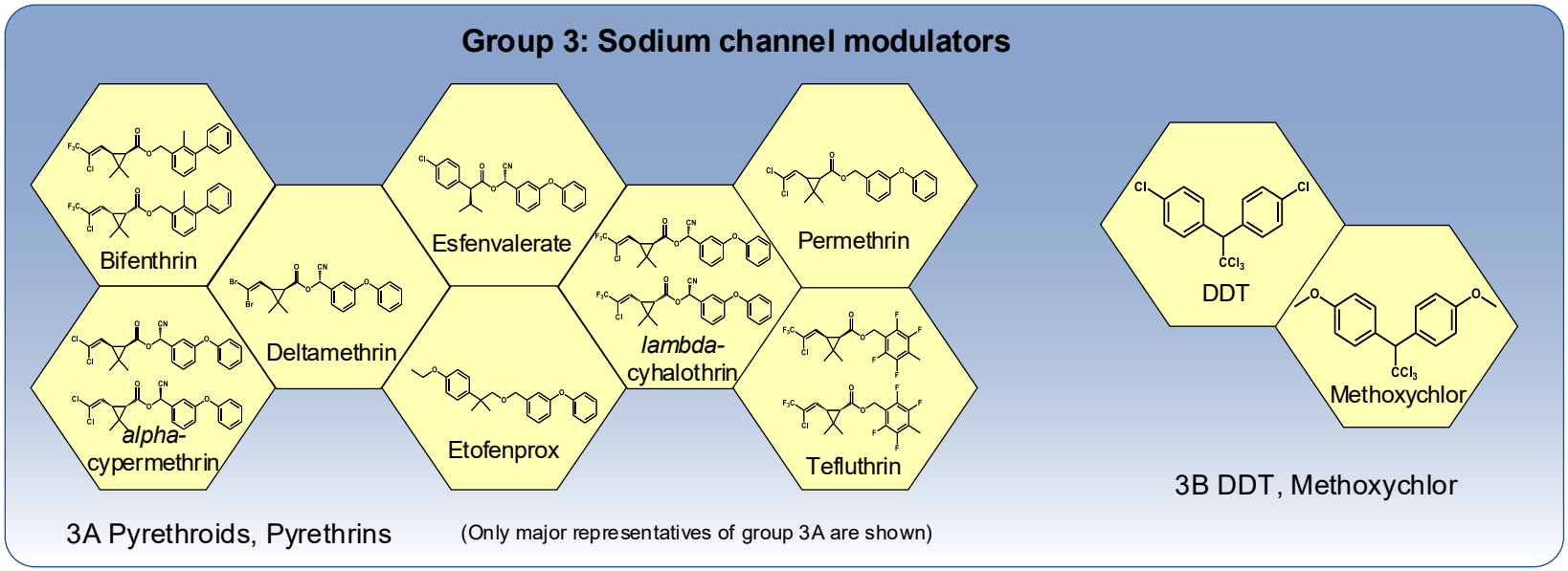
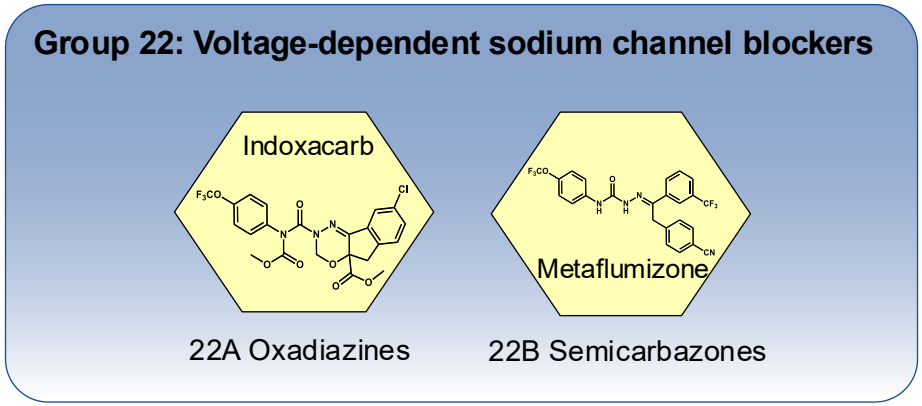
Insecticides acting on sodium channels





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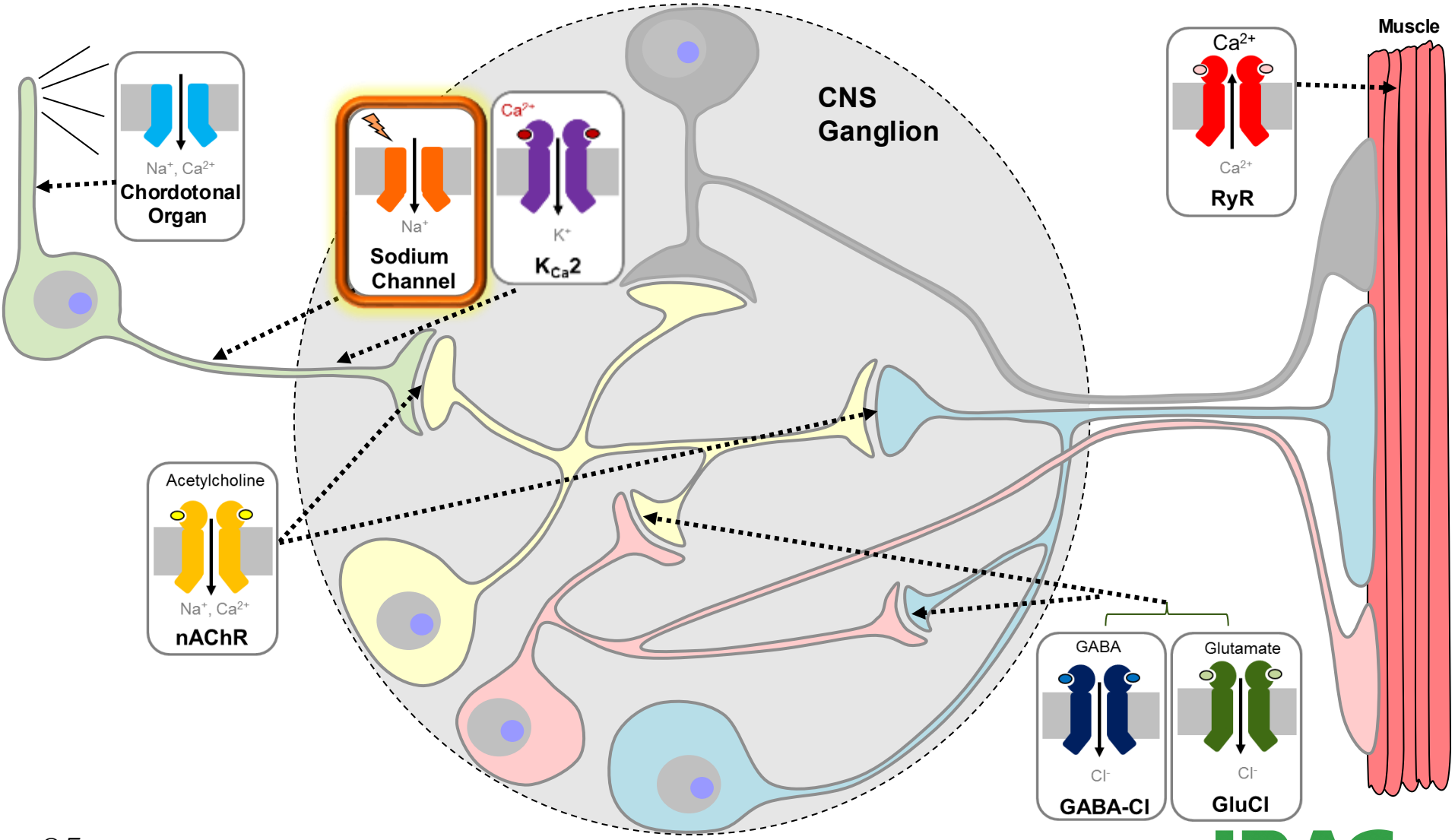

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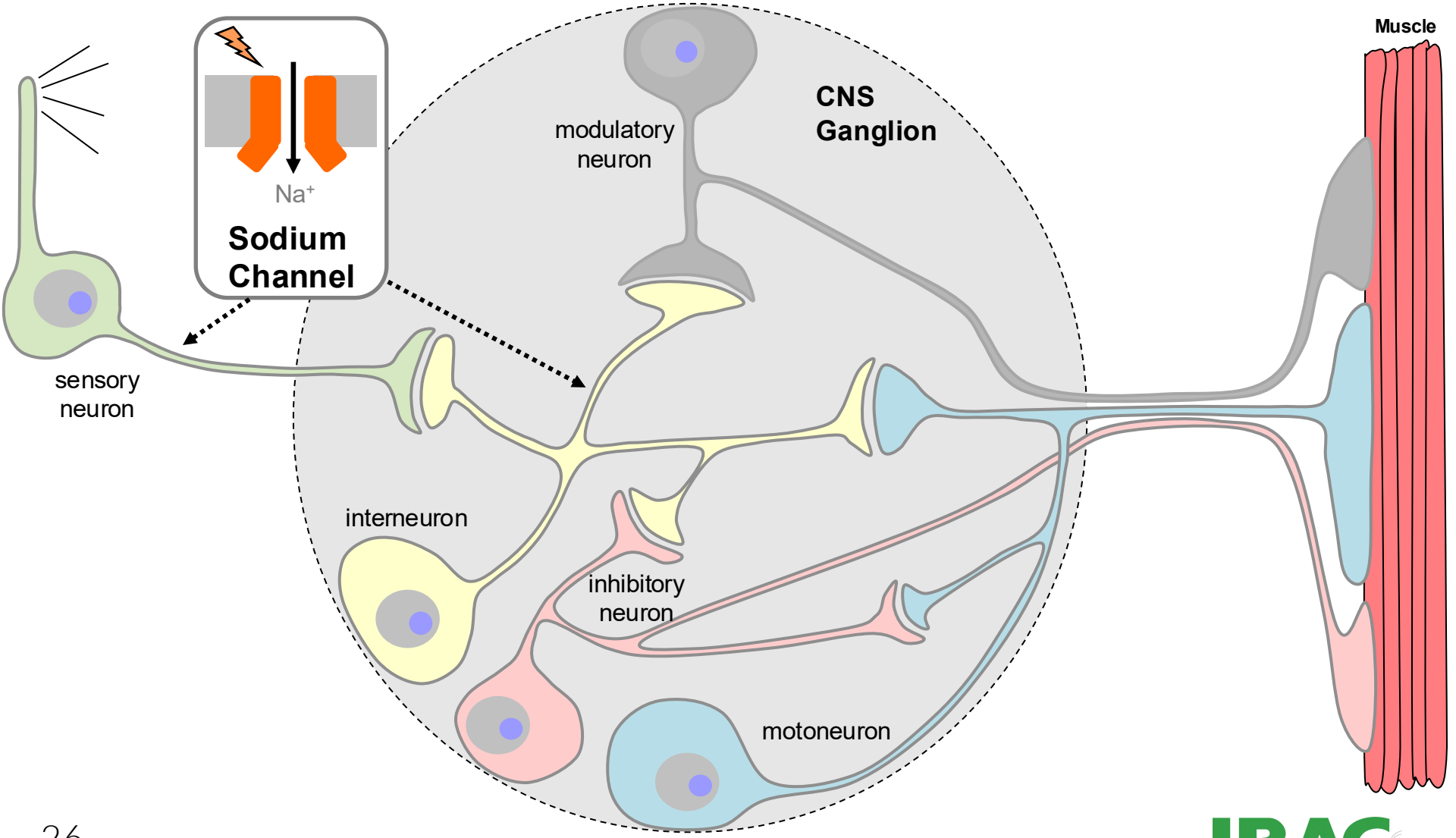
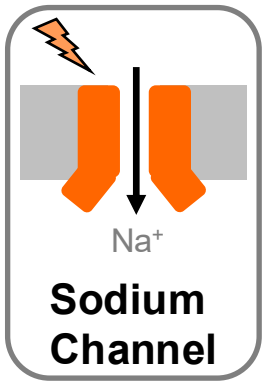
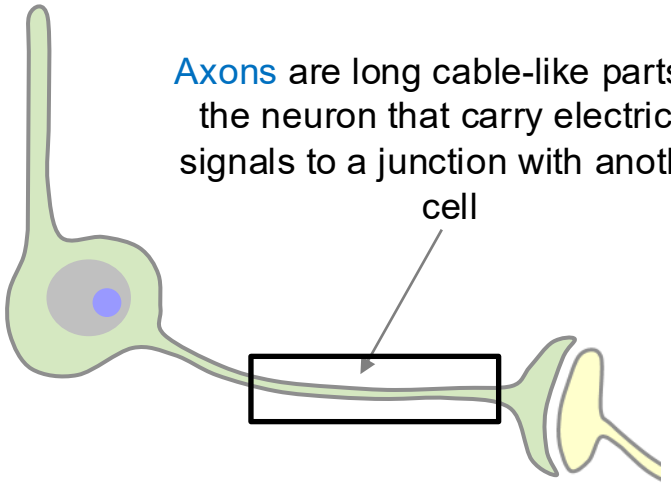
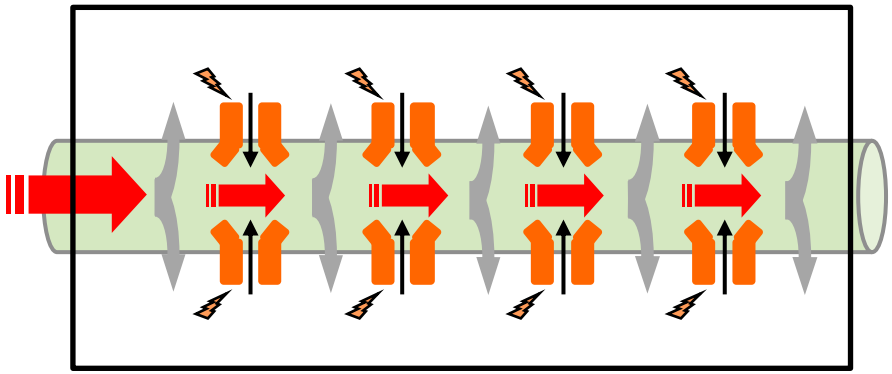
Insecticides acting on sodium channels



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

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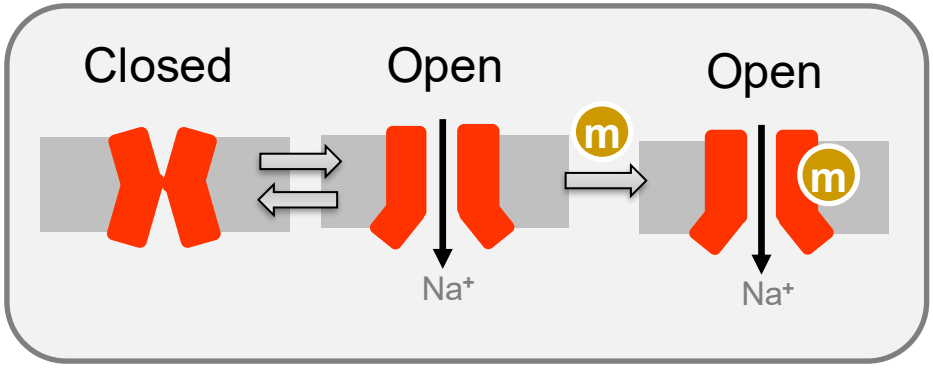
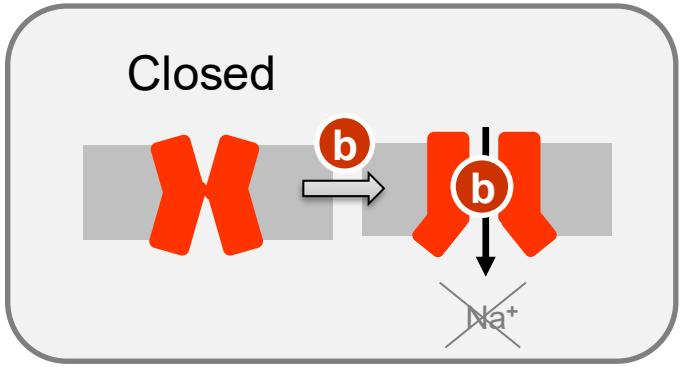
Sodium channel modulators & blockers

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

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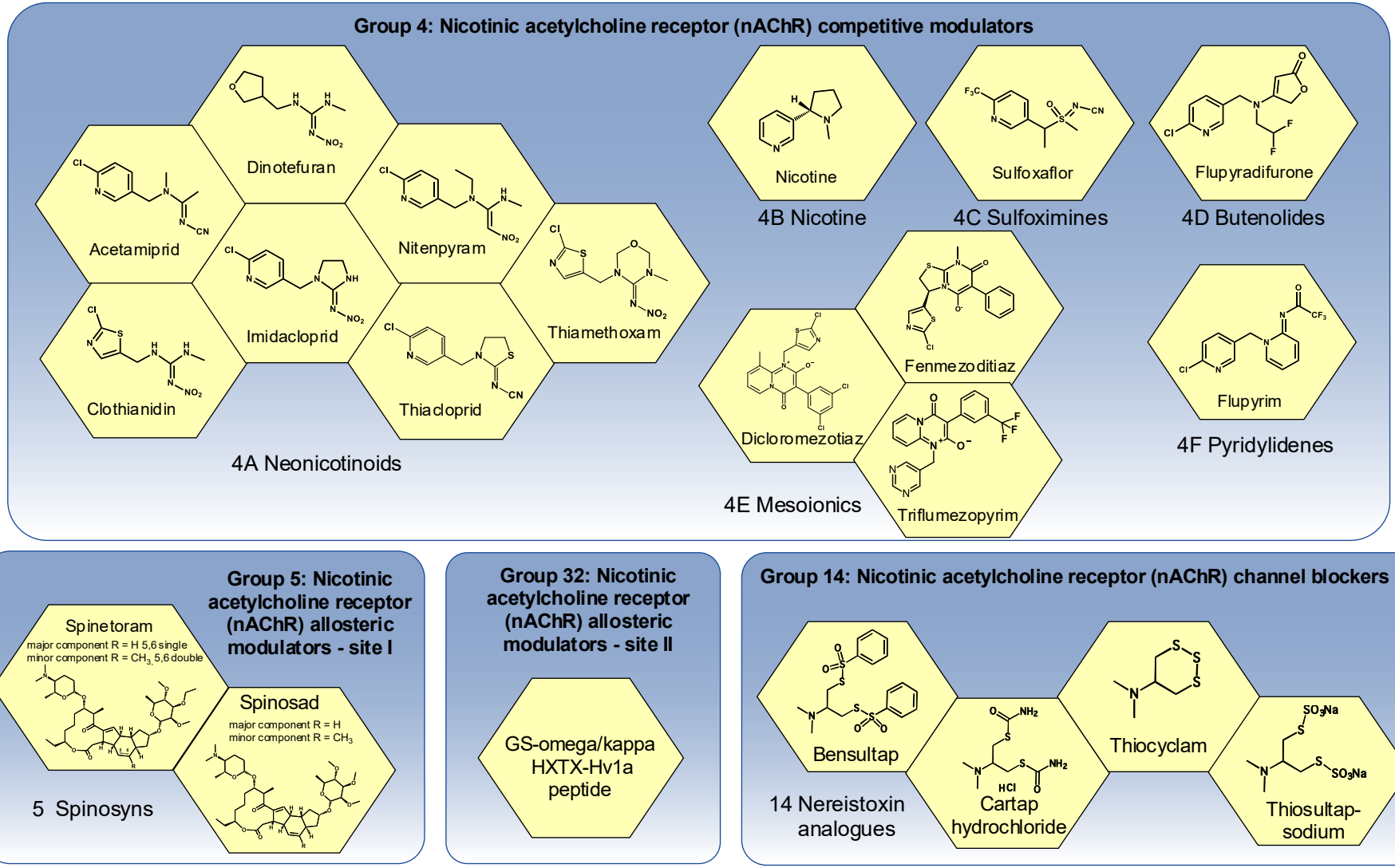
Summary of insecticides acting on nicotinic acetylcholine receptors (nAChR)



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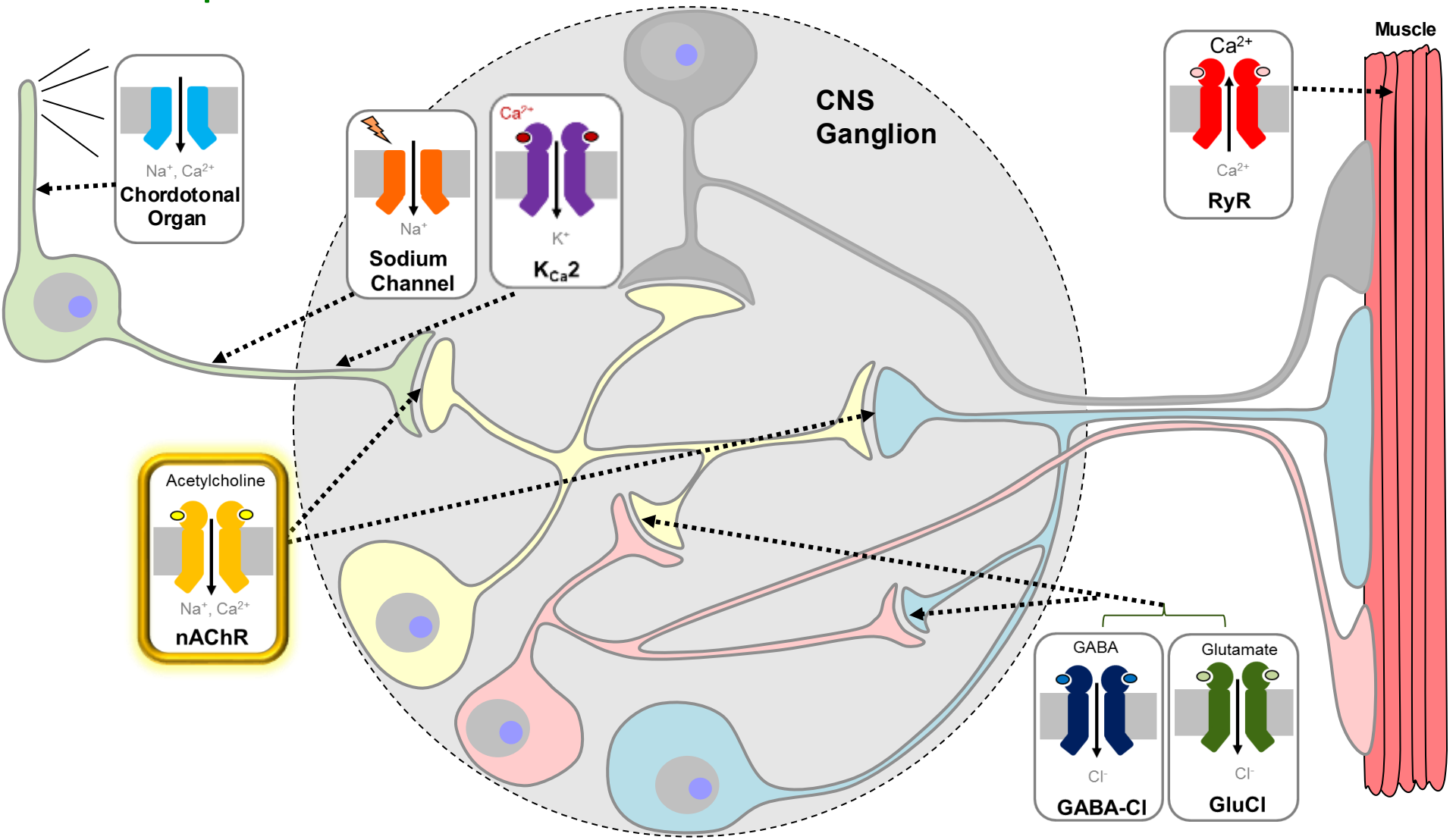
Overview of ion channels targeted by neuromuscular disruptors



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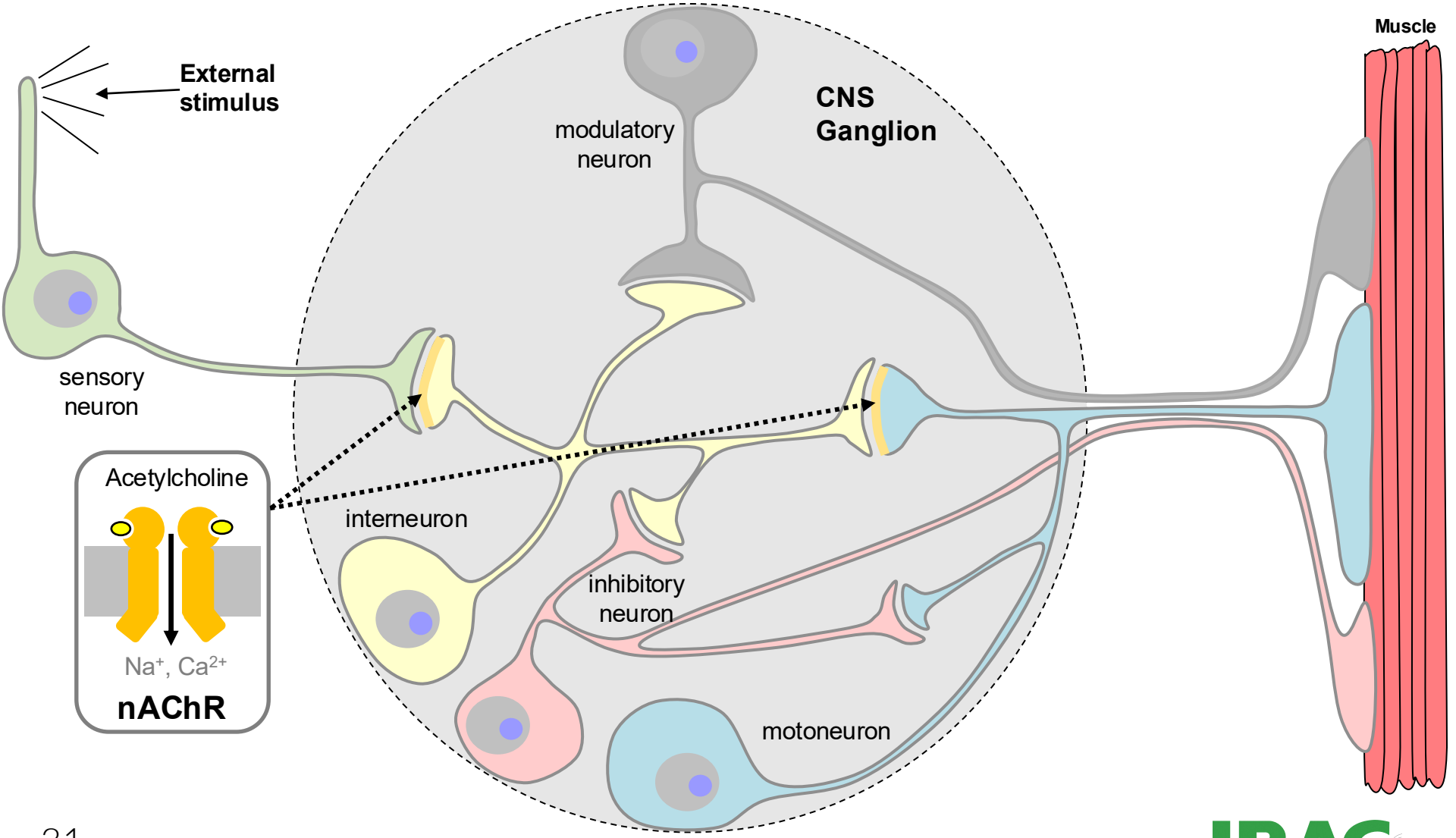

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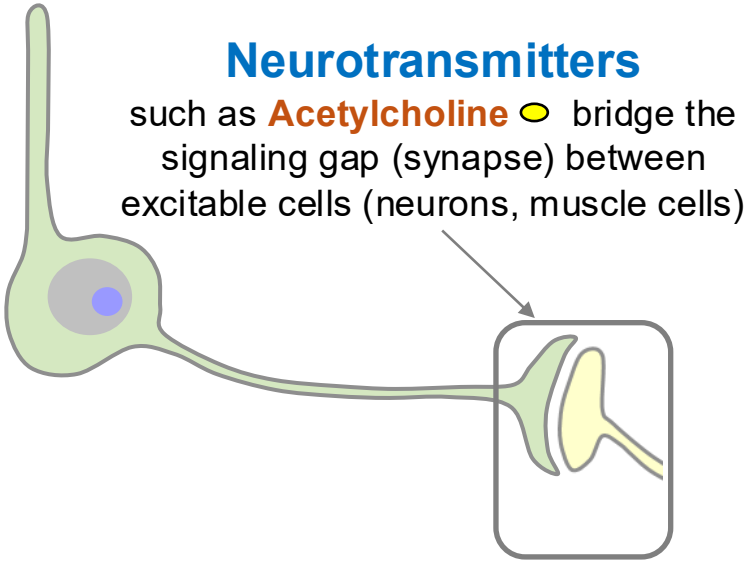

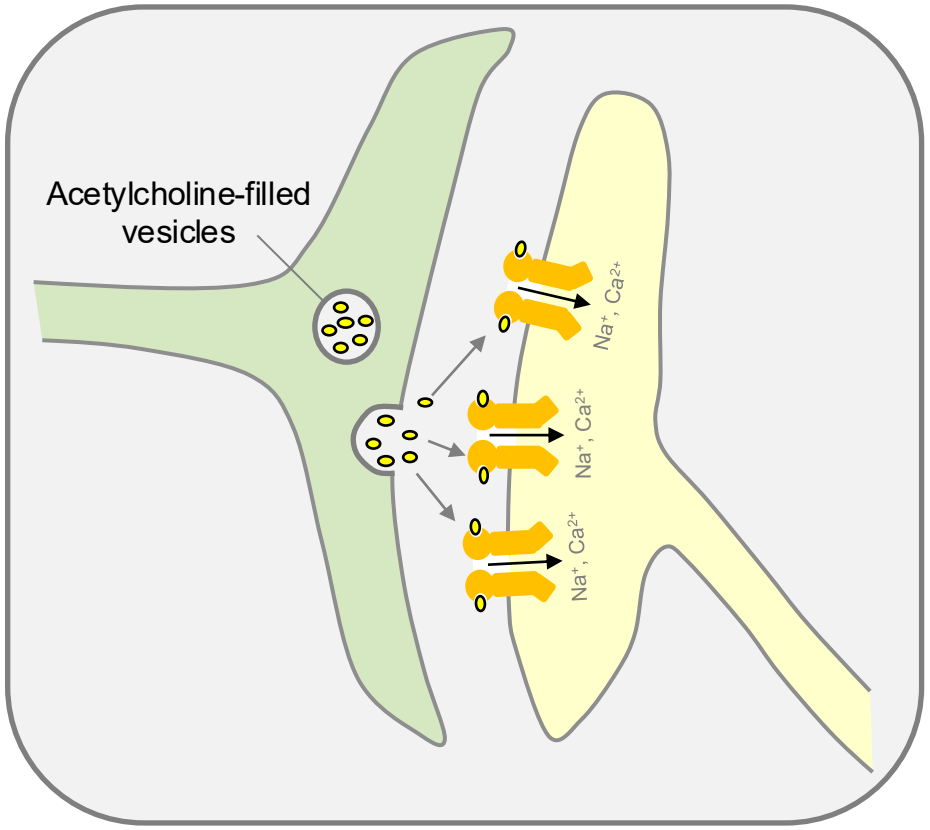

- Most fast excitatory synapses in the insect CNS use **Acetylcholine** as the neurotransmitter
- Synaptic vesicles store **Acetylcholine** that can be released into the synapse in response to nerve impulses and in turn activate postsynaptic nAChRs

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Insecticides acting on nicotinic acetylcholine receptors (nAChR)

nAChR competitive modulators

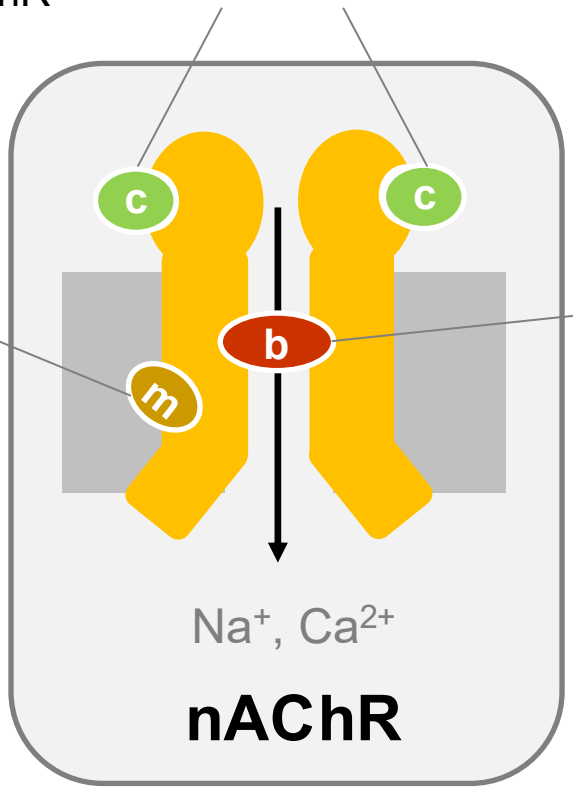
- Bind to the same site as acetylcholine
- desensitize nAChR

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

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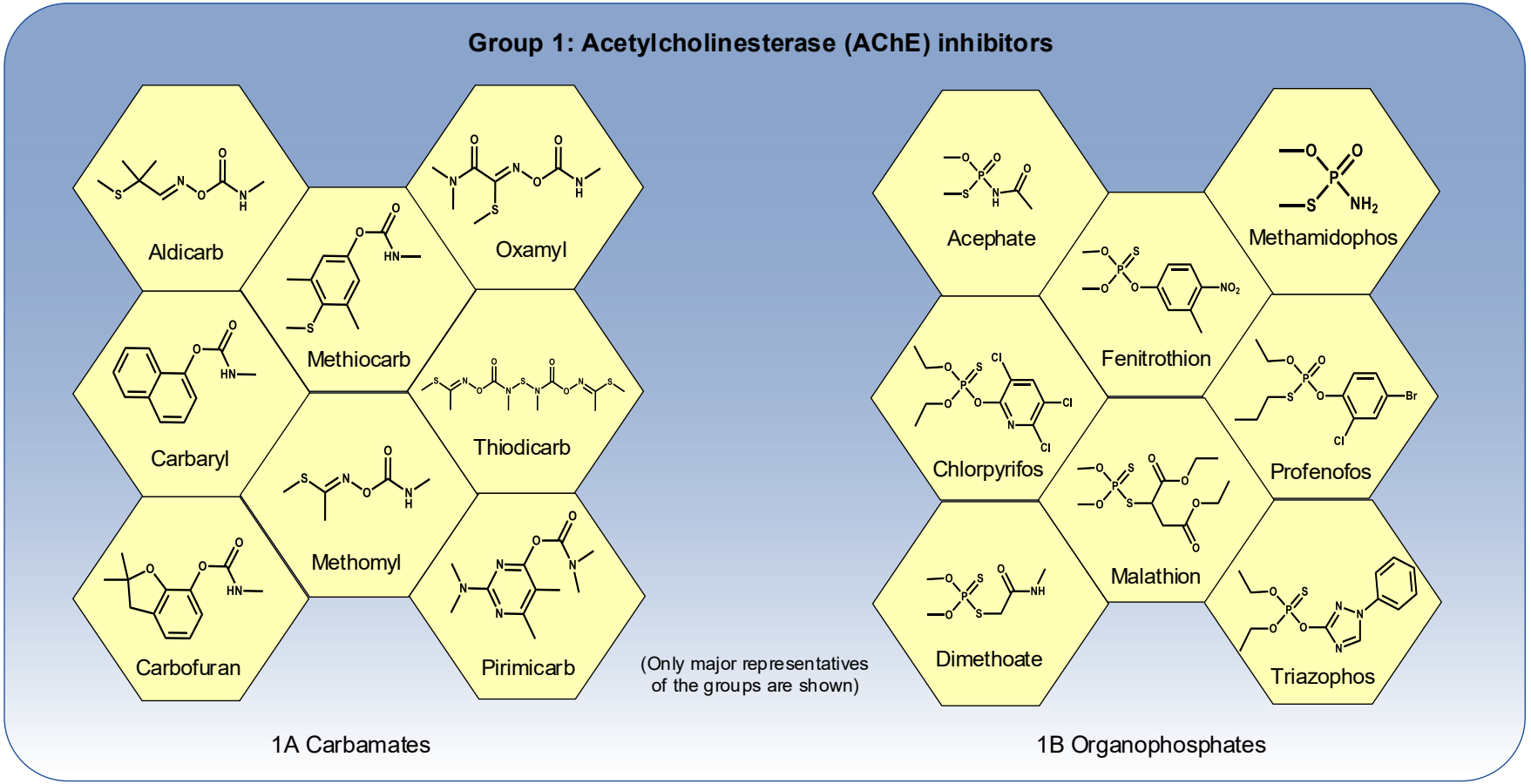
Acetylcholinesterase (AChE) inhibitors



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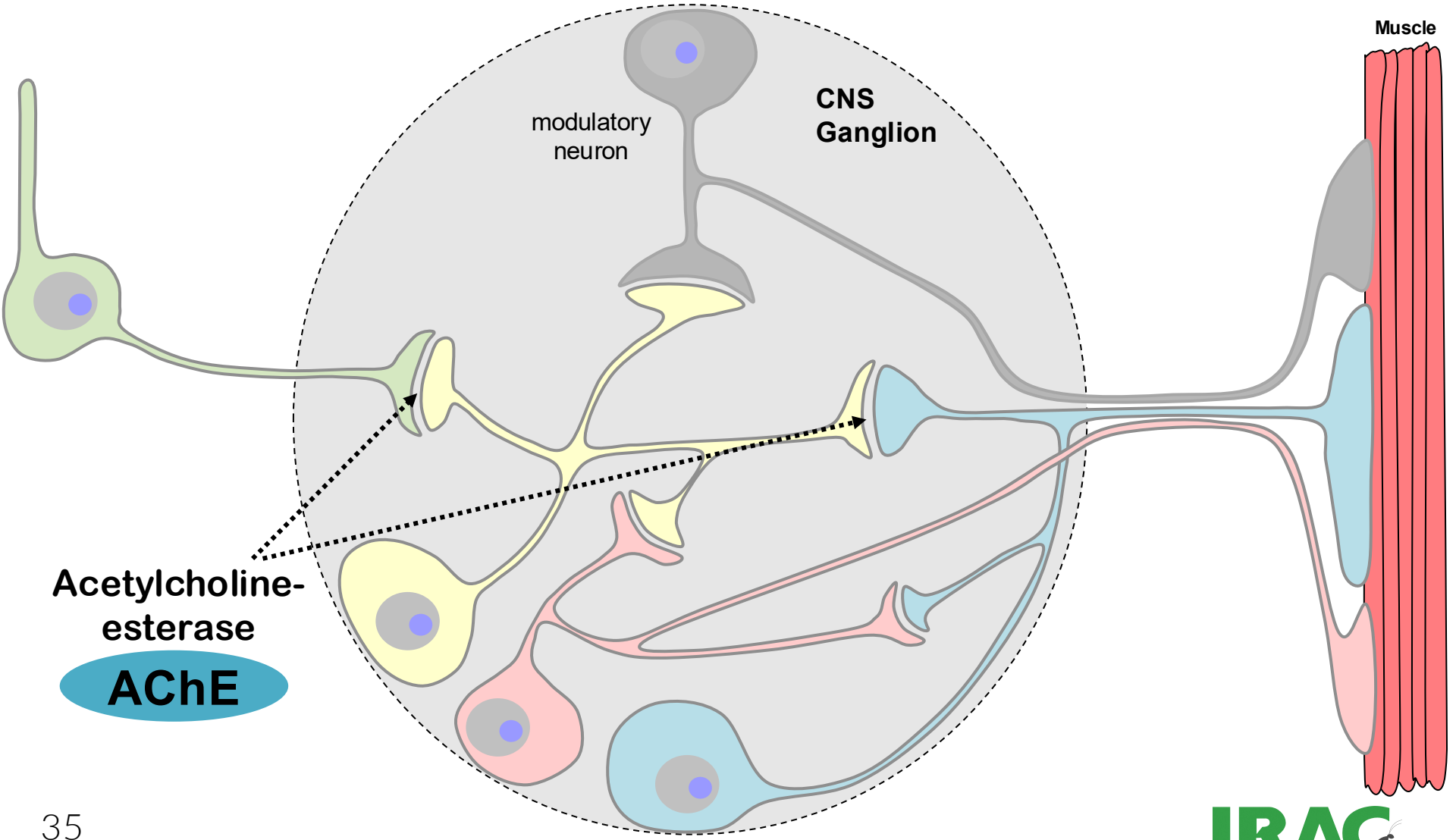
Enzymes targeted by neuromuscular disruptors



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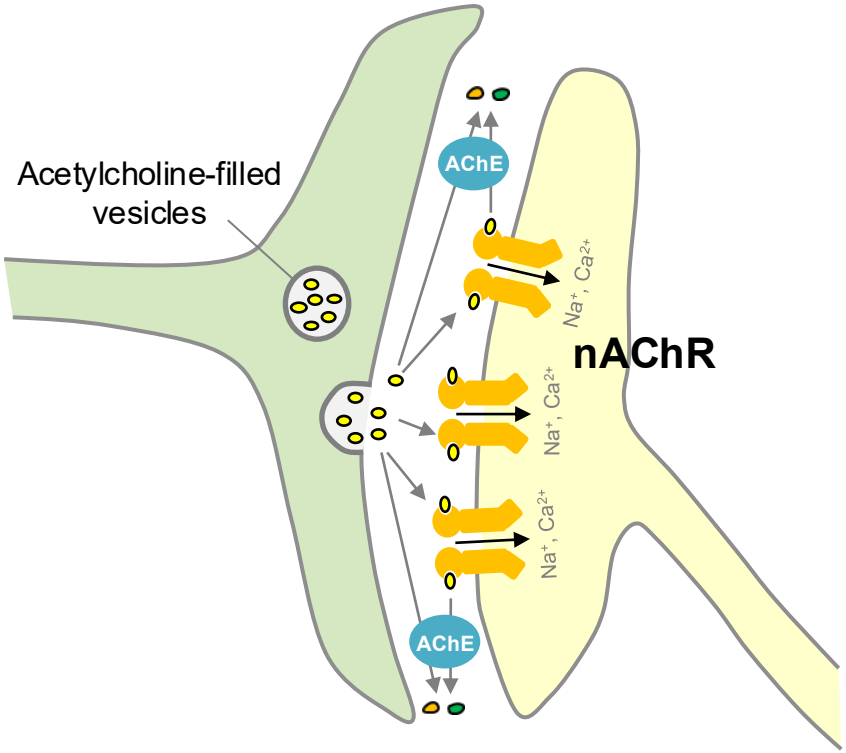
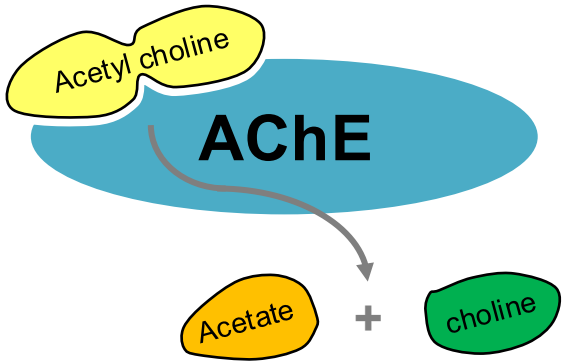
Acetylcholinesterase (AChE) degrades acetylcholine in the synapse



Acetylcholinesterase degrades **Acetylcholine** in order to terminate the signal after it has been sent across the synapse



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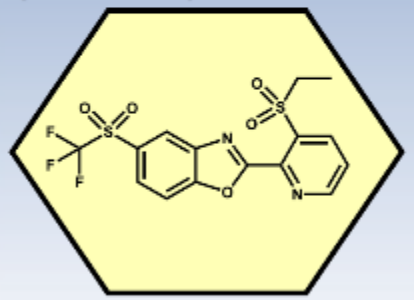
Summary of Insecticides acting on vesicular acetylcholine transporter (vAChT)

Group 37:
Vesicular acetylcholine transporter (VAChT) inhibitor



37 Oxazosulfyl

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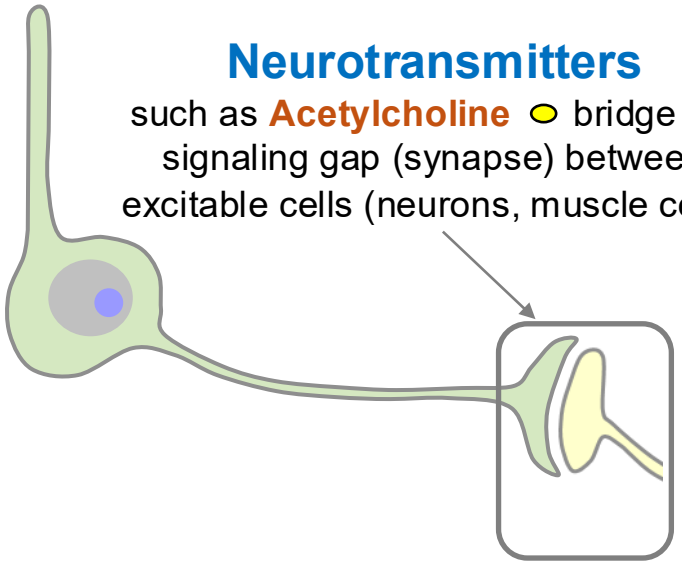
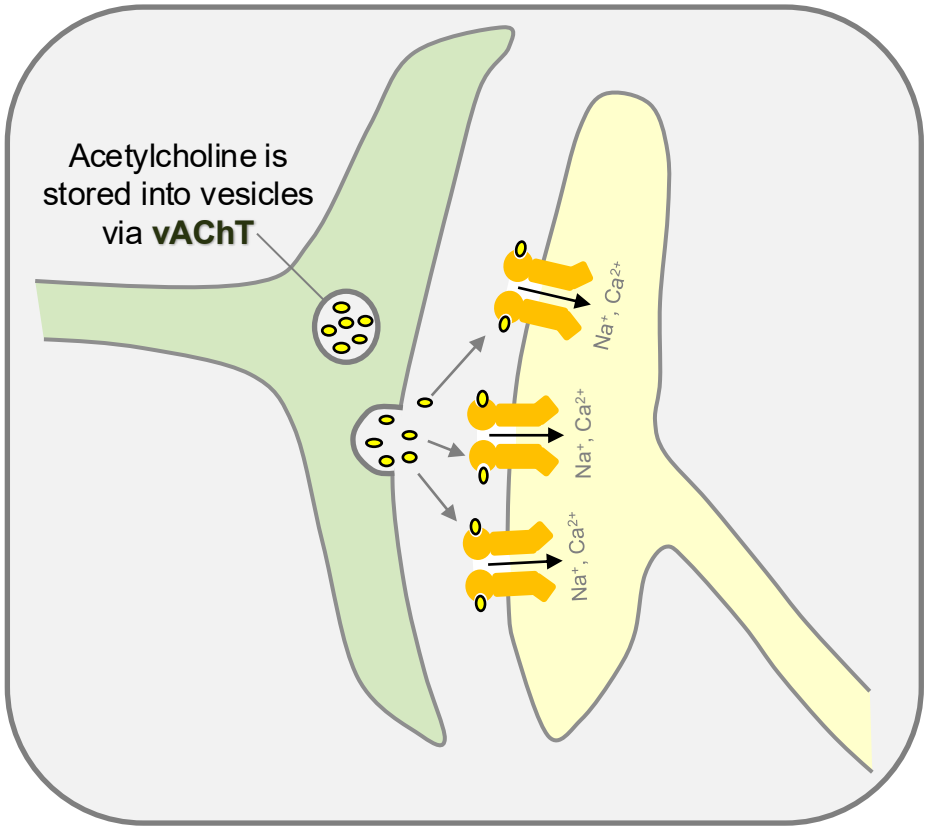
Insecticides acting on vesicular acetylcholine transporter (vAChT)





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

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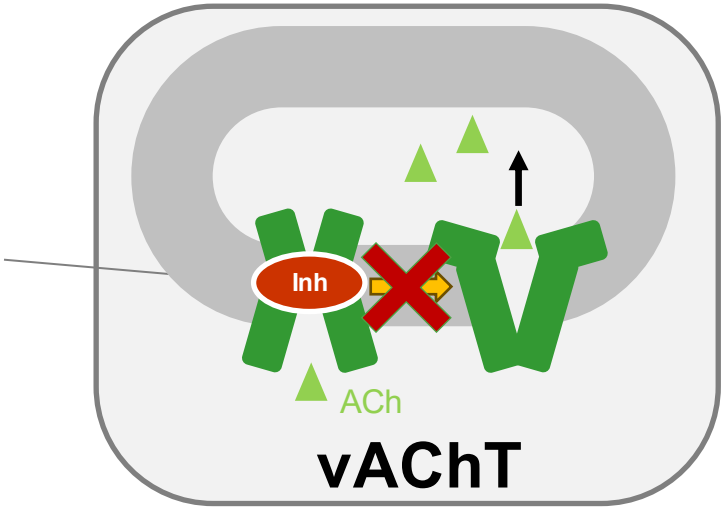
Insecticides acting on vesicular acetylcholine transporter (vAChT)

vAChT inhibitor

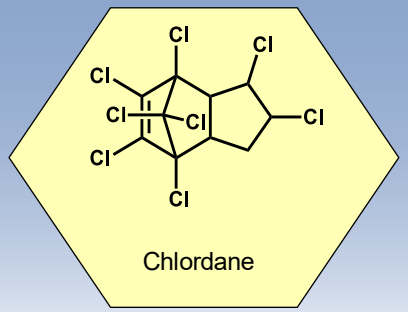
- Inhibits the transporter resulting in depletion of pre-synaptic storage of ACh.
- Downregulate acetylcholine signal transduction

Reduces
neuronal excitation
leading to paralysis

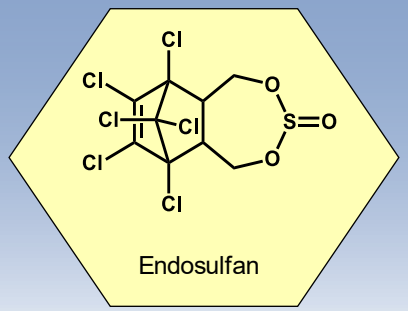


Summary of insecticides acting on GABA-gated chloride channels (GABA-Cl)

Group 2: GABA-gated chloride channel antagonists

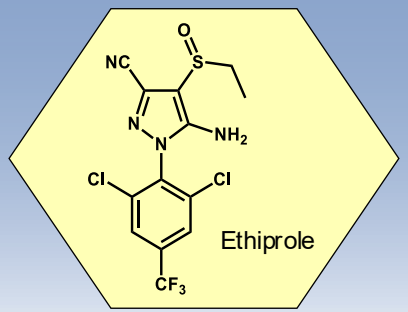


Chlordane

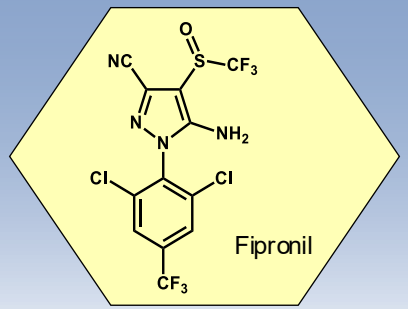


Endosulfan

2A Cyclodiene Organochlorines



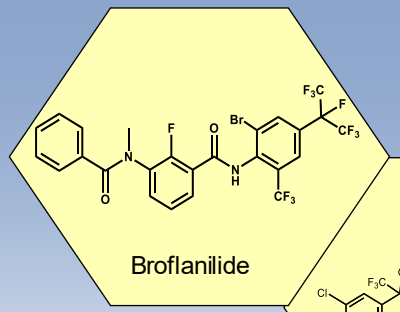
Ethiprole



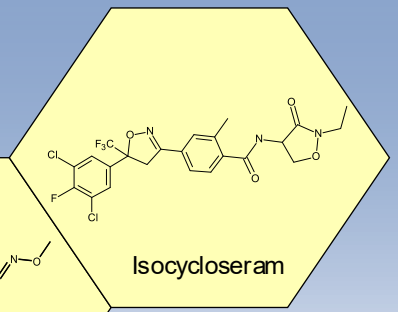
Fipronil

2B Phenylpyrazoles (Fiproles)

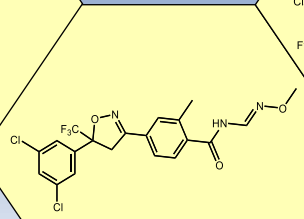
Group 30: GABA-gated chloride channel allosteric modulators



Broflanilide



Isocycloseram

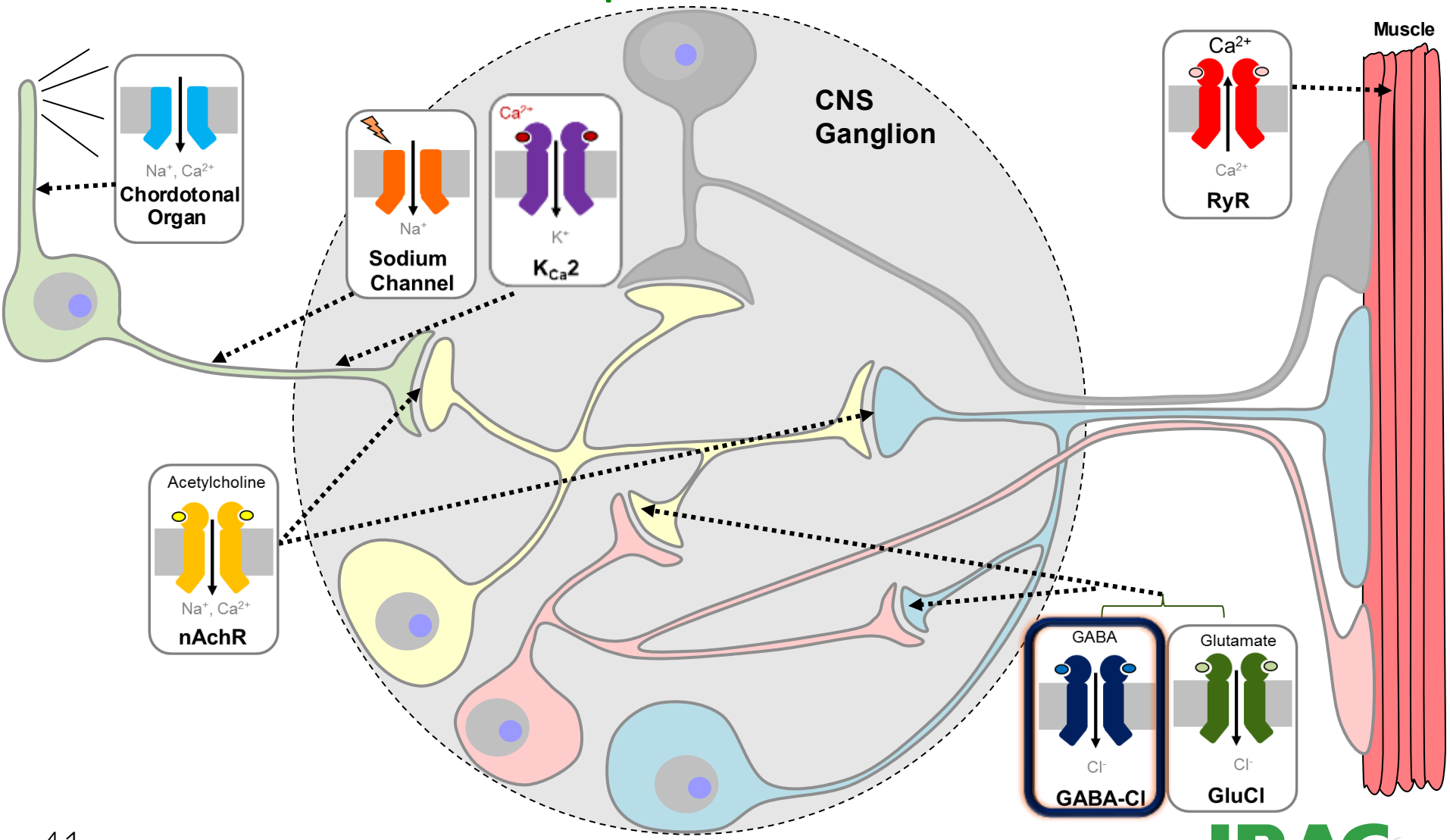


Fluxametamide

Meta-diamides &
Isoxazolines

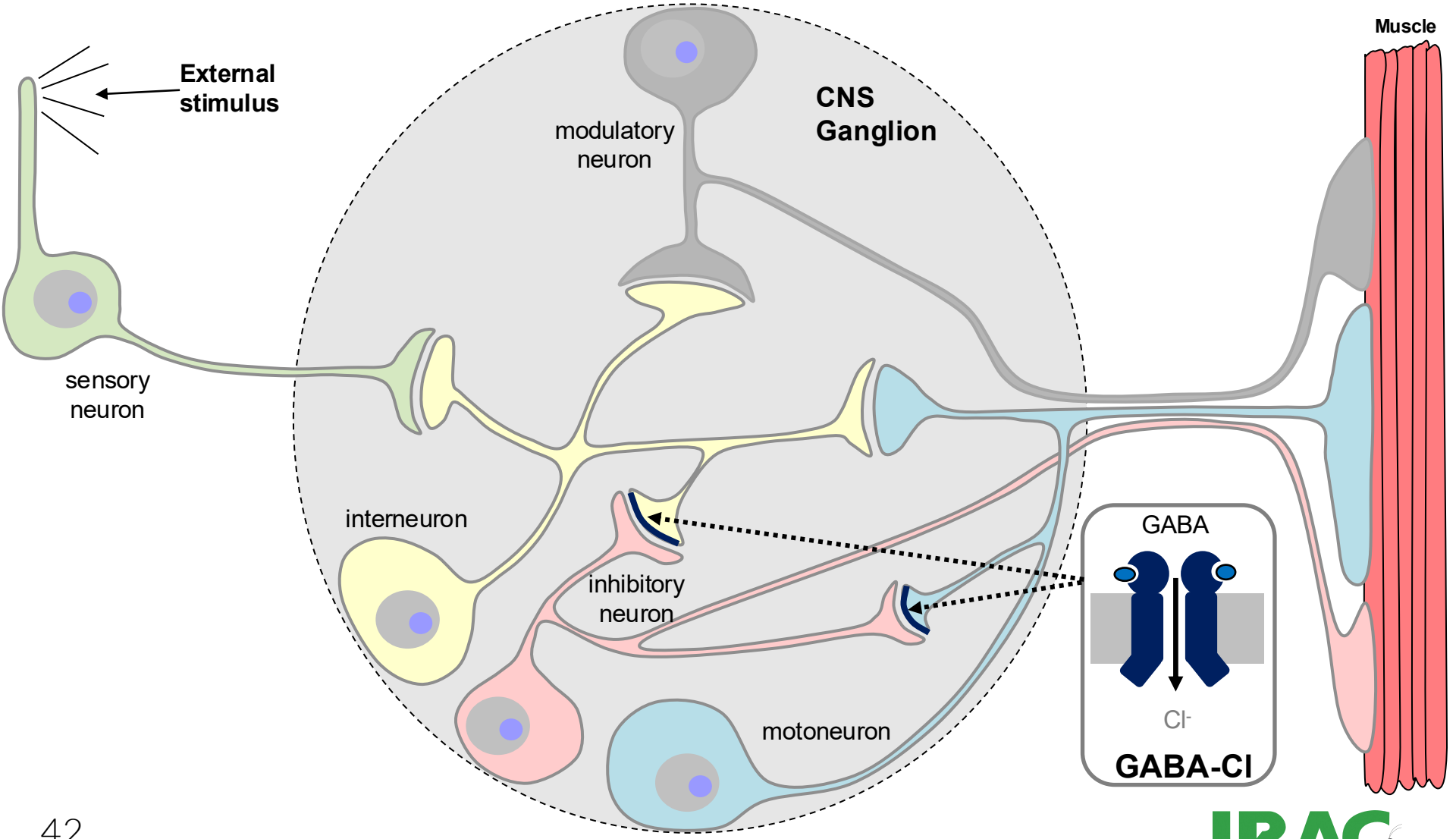
IRAC

Overview of ion channels targeted by neuromuscular disruptors



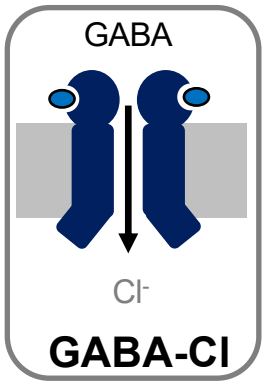
IRAC

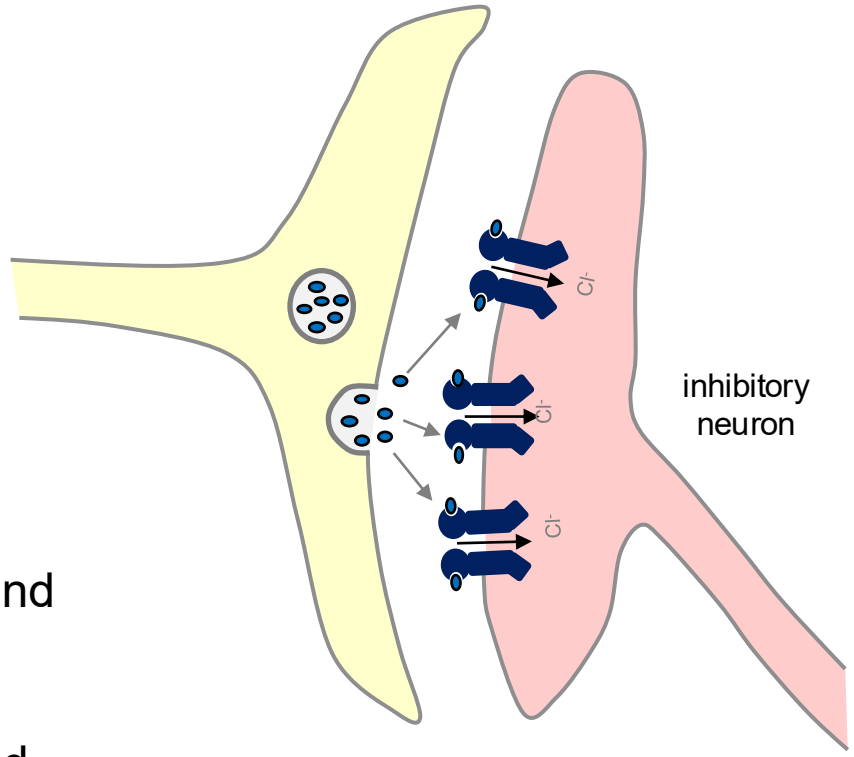
Insecticides acting on GABA-gated chloride channels (GABA-Cl)



IRAC

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





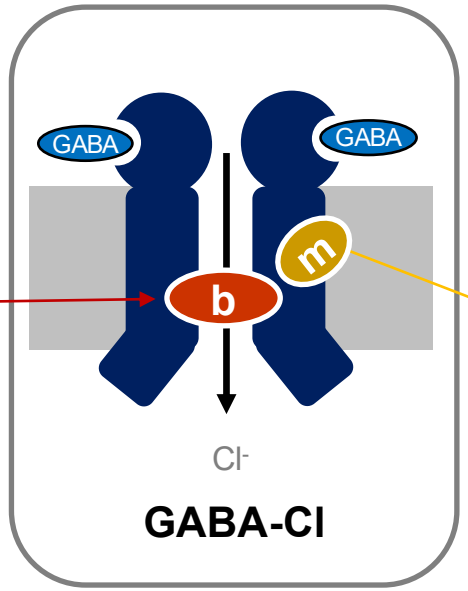
- GABA is a major inhibitory neurotransmitter in the CNS and neuromuscular synapses
- Influx of the negatively charged Cl- ions has an inhibitory effect, counteracting excitatory signals

IRAC

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

GABA-Cl antagonists

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



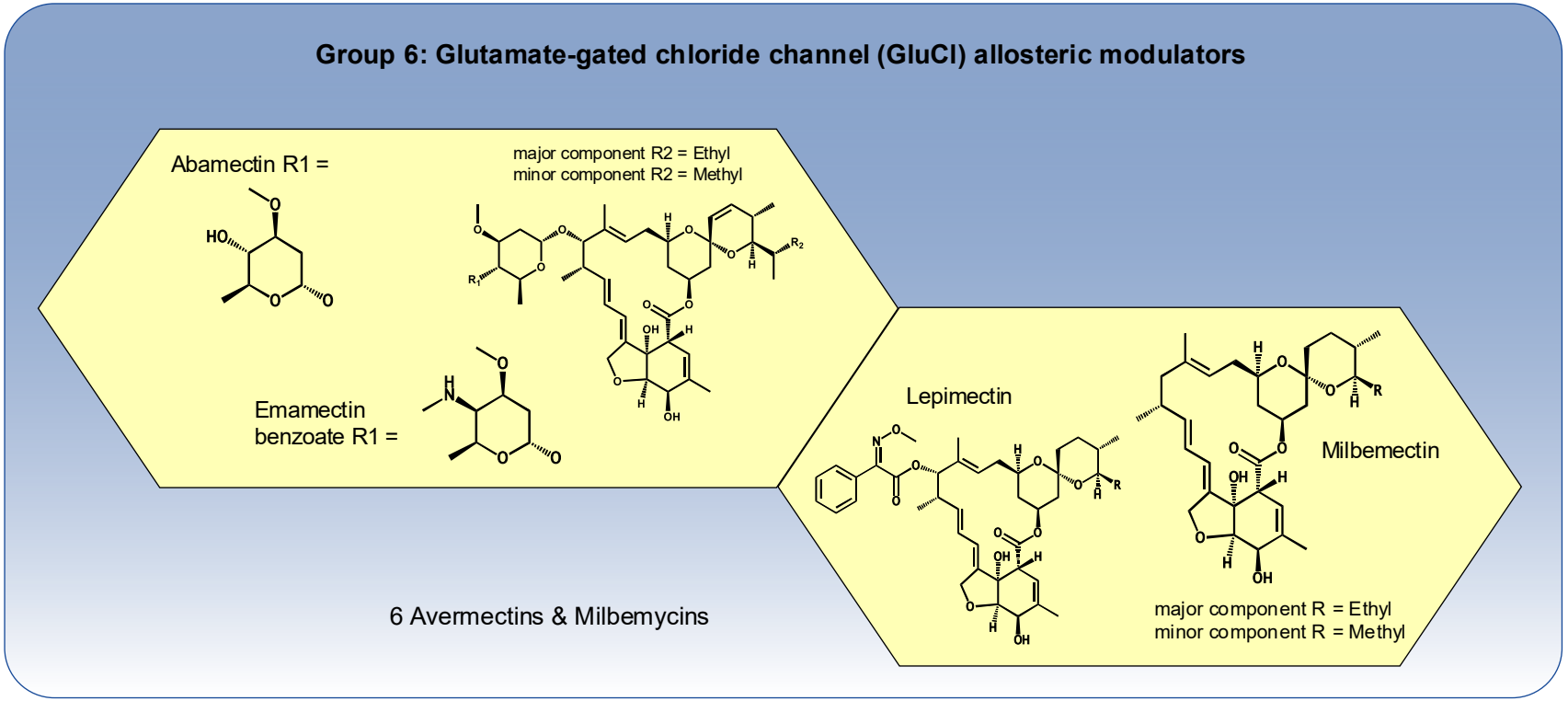
GABA-Cl allosteric modulators

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

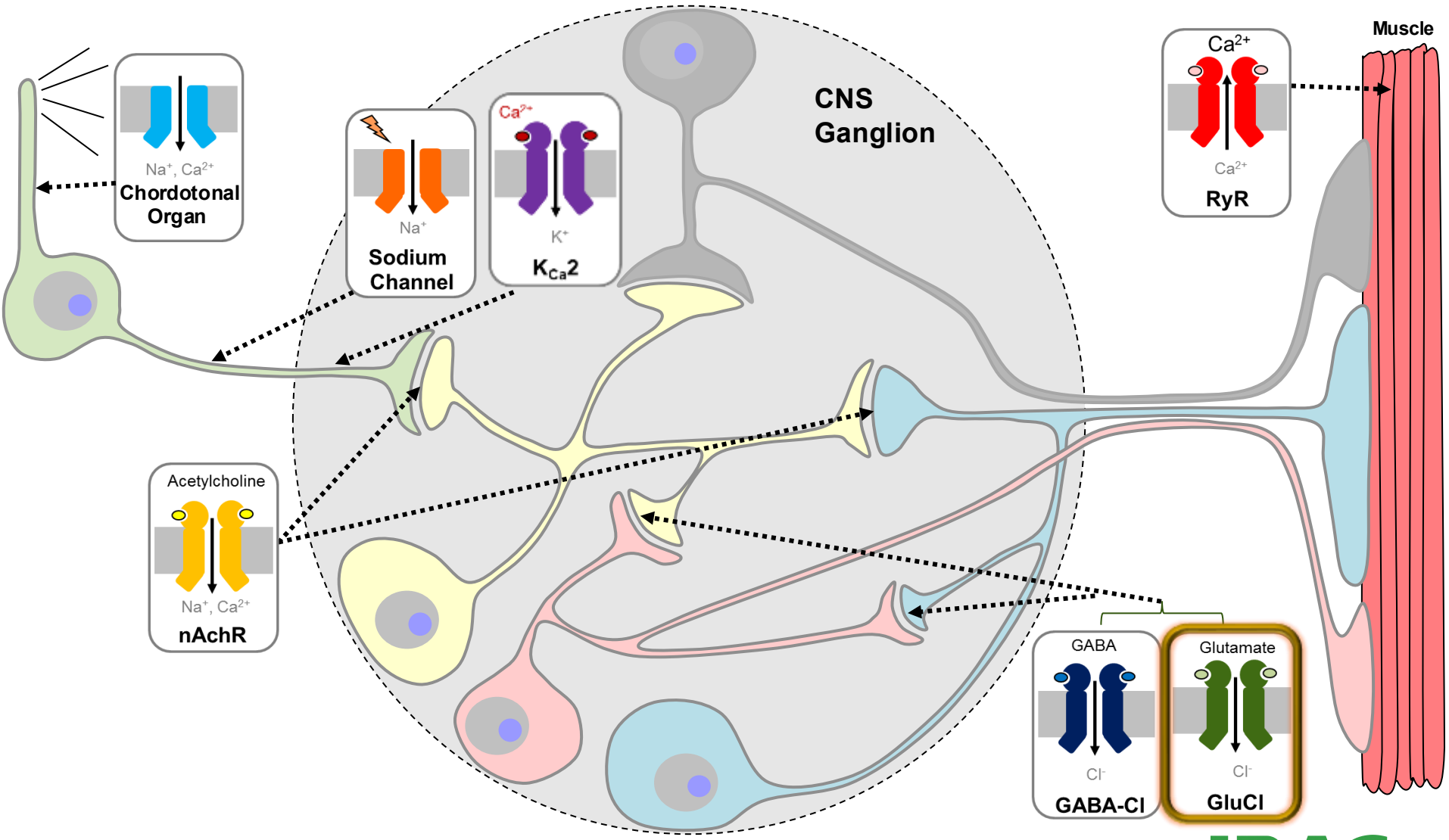
Pore blockers and negative modulators both cause convulsions and death

IRAC

Allosteric modulators of glutamate-gated chloride channels (GluCl)

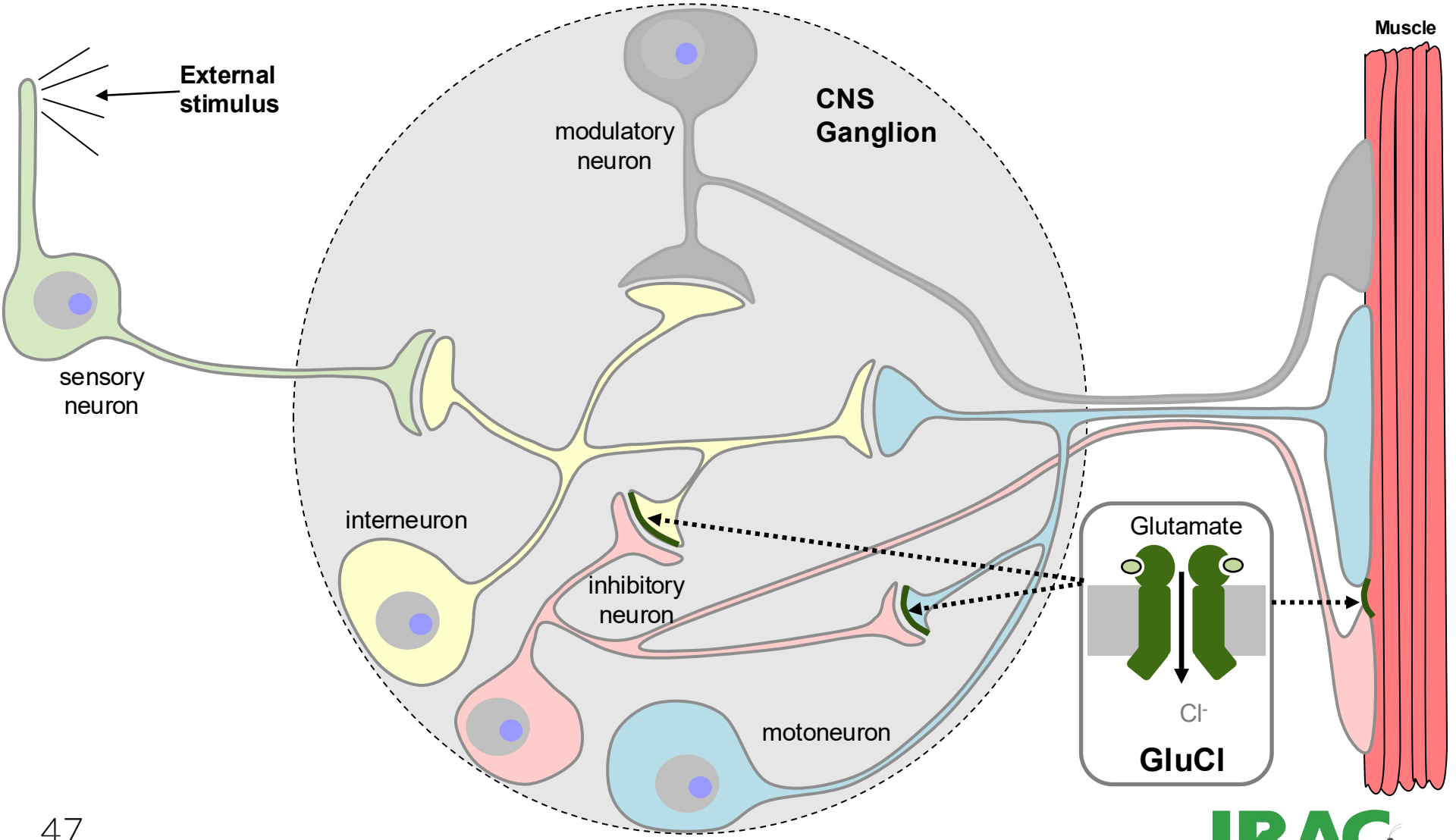


Overview of ion channels targeted by neuromuscular disruptors



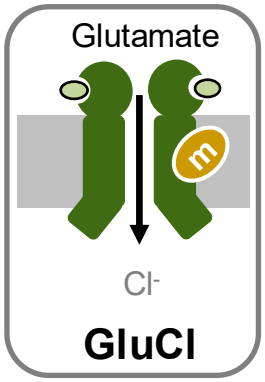
IRAC

Insecticides acting on glutamate-gated chloride channels (GluCl)



IRAC

Allosteric modulators of glutamate-gated chloride channels (GluCl)

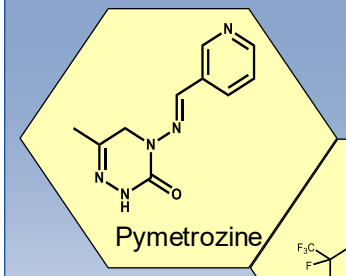


- Inhibitory glutamate-gated chloride channels (GluCl) are widespread on insect nerve and muscle cells and likely function in inhibitory neurotransmission
- GluCl modulators activate chloride influx, causing flaccid paralysis

IRAC

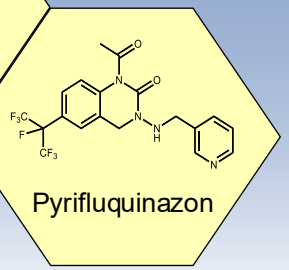
TRPV channel and chordotonal organ modulators

Group 9: Chordotonal organ TRPV channel modulators

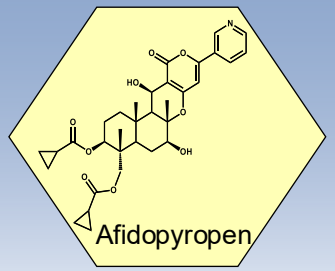


Pymetrozine

9B Pyridine azomethine derivatives



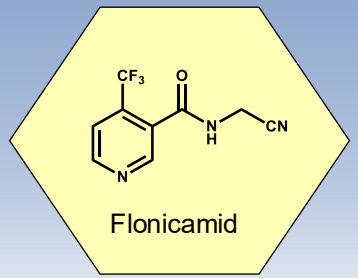
Pyrifluquinazon



Afidopyropen

9D Pyropenes

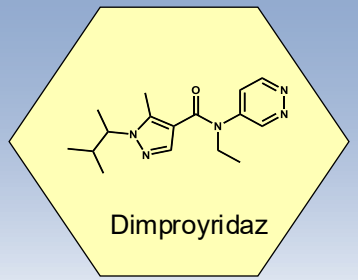
Group 29: Chordotonal organ nicotinamidase inhibitors



Flonicamid

29 Flonicamid

Group 36: Chordotonal organ modulators – undefined target site

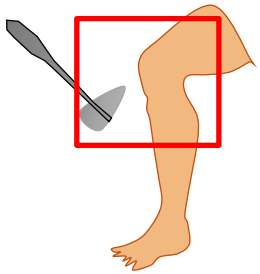


Dimproyridaz

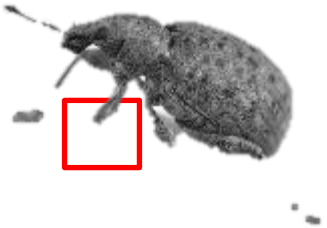
36 Dimpropyridaz

IRAC

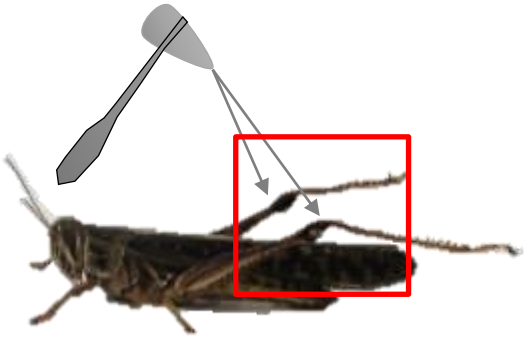
Chordotonal organs detect stretch in insects



Doctors test knee jerk reflex by activating stretch receptors that signal to the spinal cord to activate and inhibit specific muscles resulting in a kick.



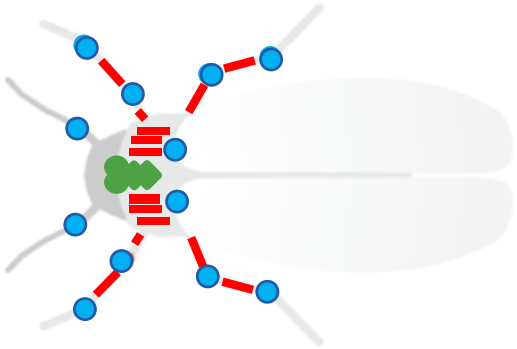
Insect chordotonal organs also detect joint bending to help coordinate muscle activity



Some chordotonal organ modulating insecticides act as a “molecular hammer” continuously triggering stretch receptors, whereas others inhibit chordotonal organ activity and interfere with stretch receptor feedback

IRAC

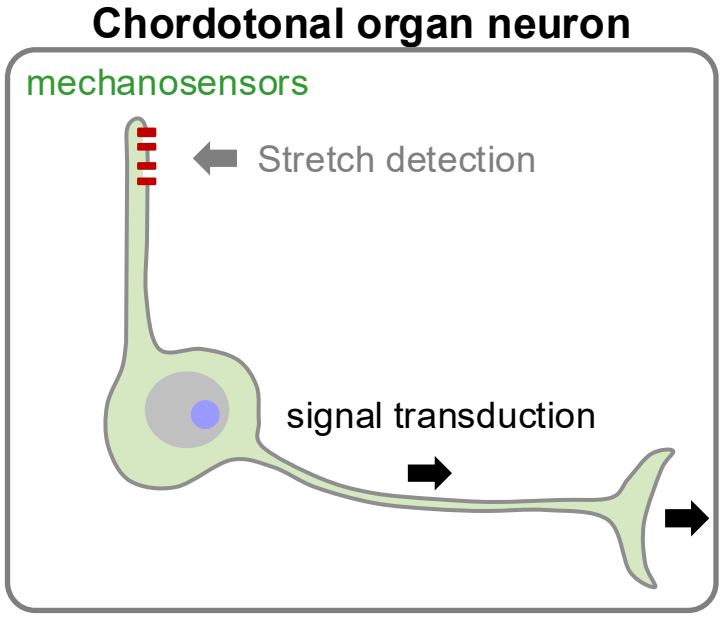
Chordotonal organs are essential for insect behavior



Central nervous system

Muscles

Chordotonal organs



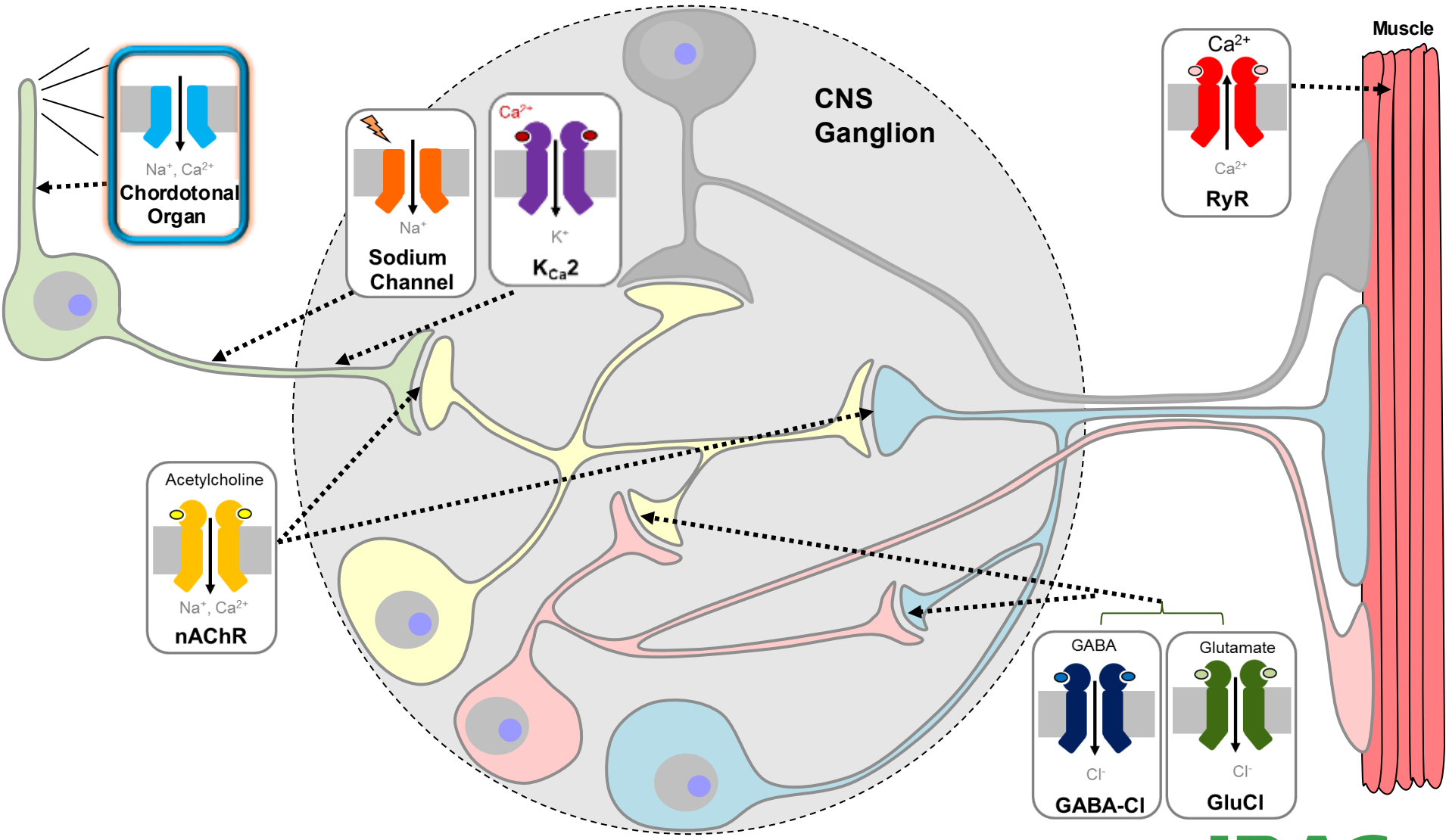
Chordotonal organ stretch detection is used for:

- Hearing (antenna)
- Gravity (antenna)
- Body position sensing (joints)

Interfering with insect chordotonal organ function can cause:

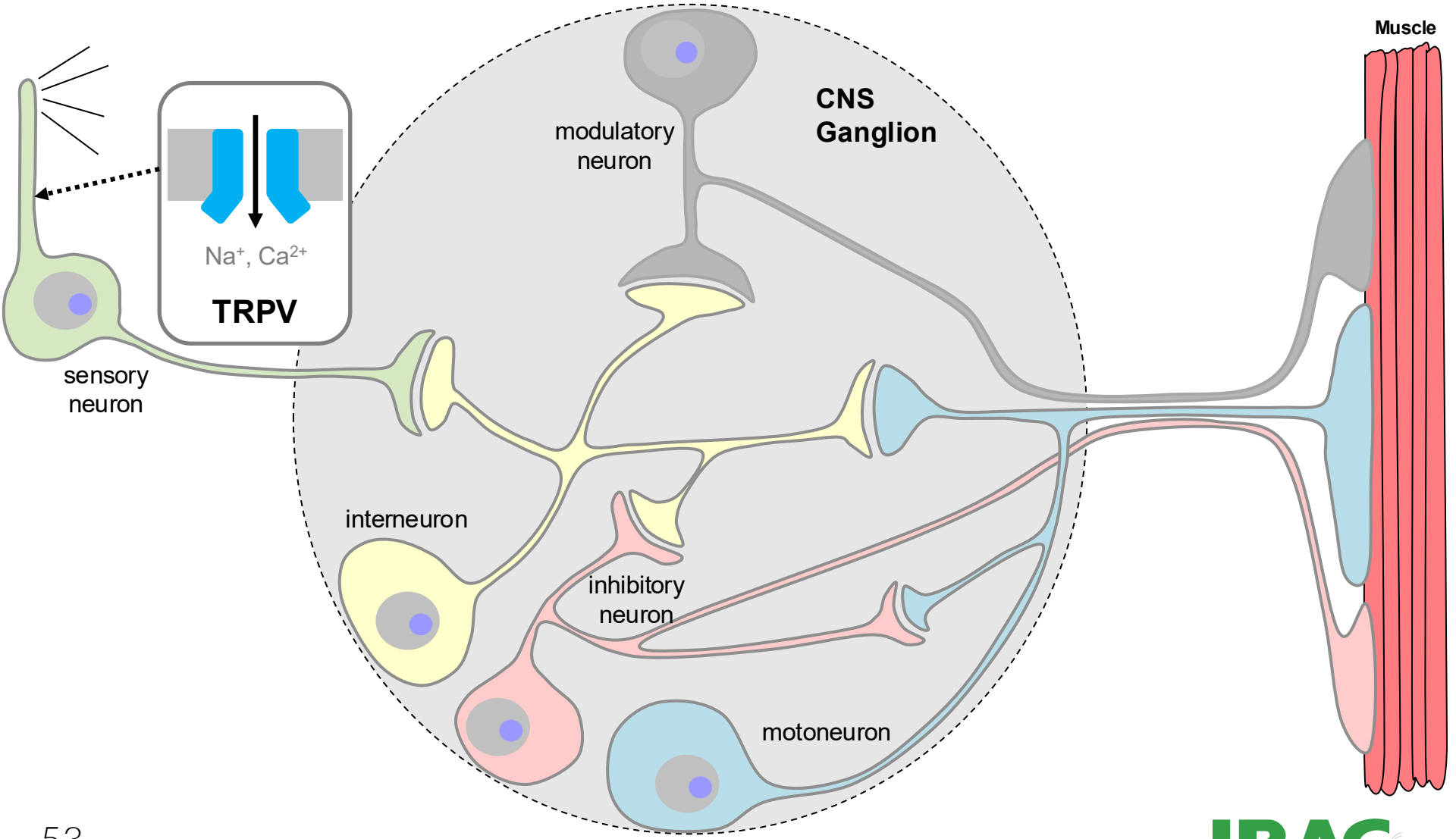
- Uncoordinated movement
- Feeding cessation
- Starvation
- Death

Overview of ion channels targeted by neuromuscular disruptors

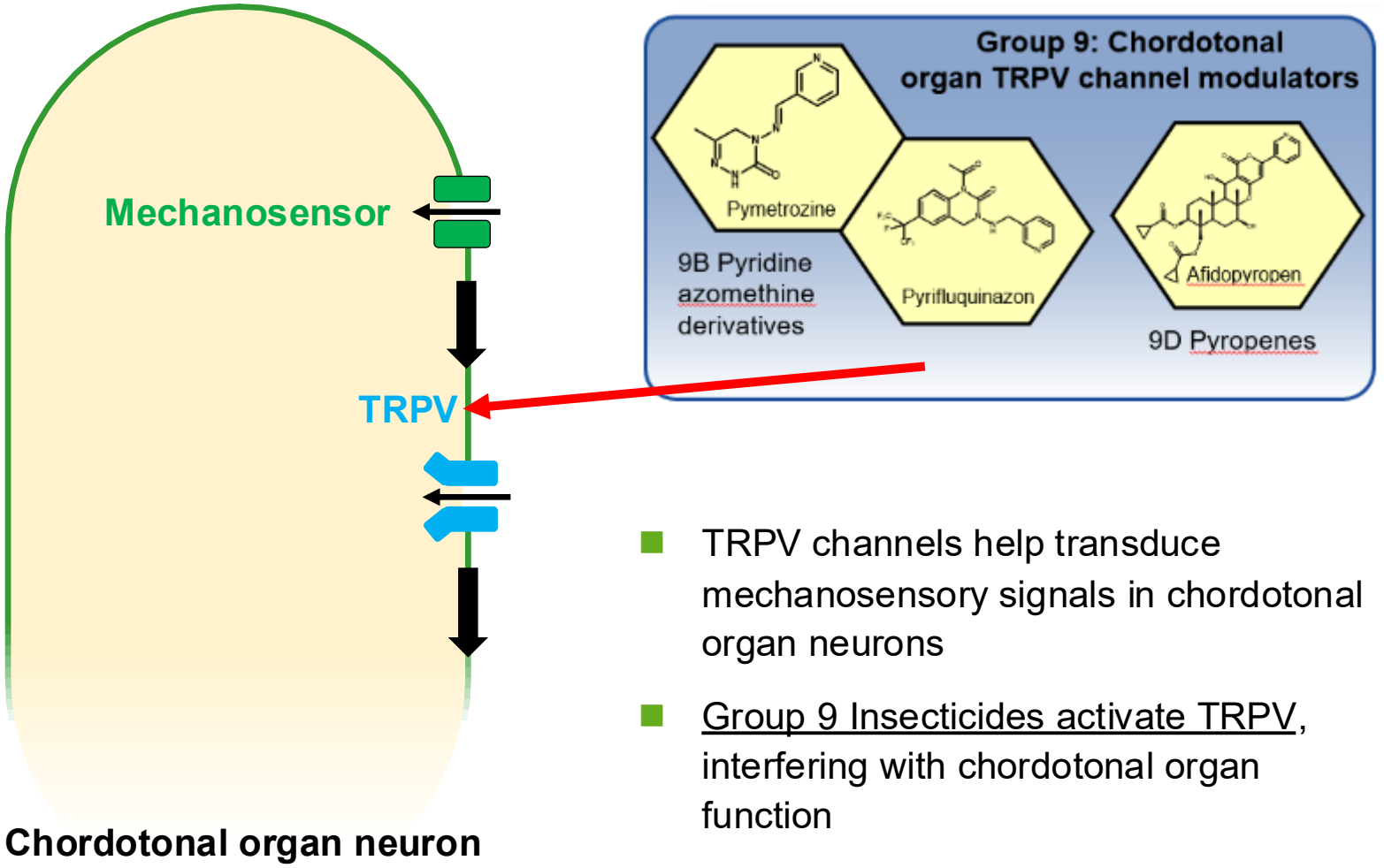


IRAC

The TRPV channels exist in specialized sensory neurons that detect stretch



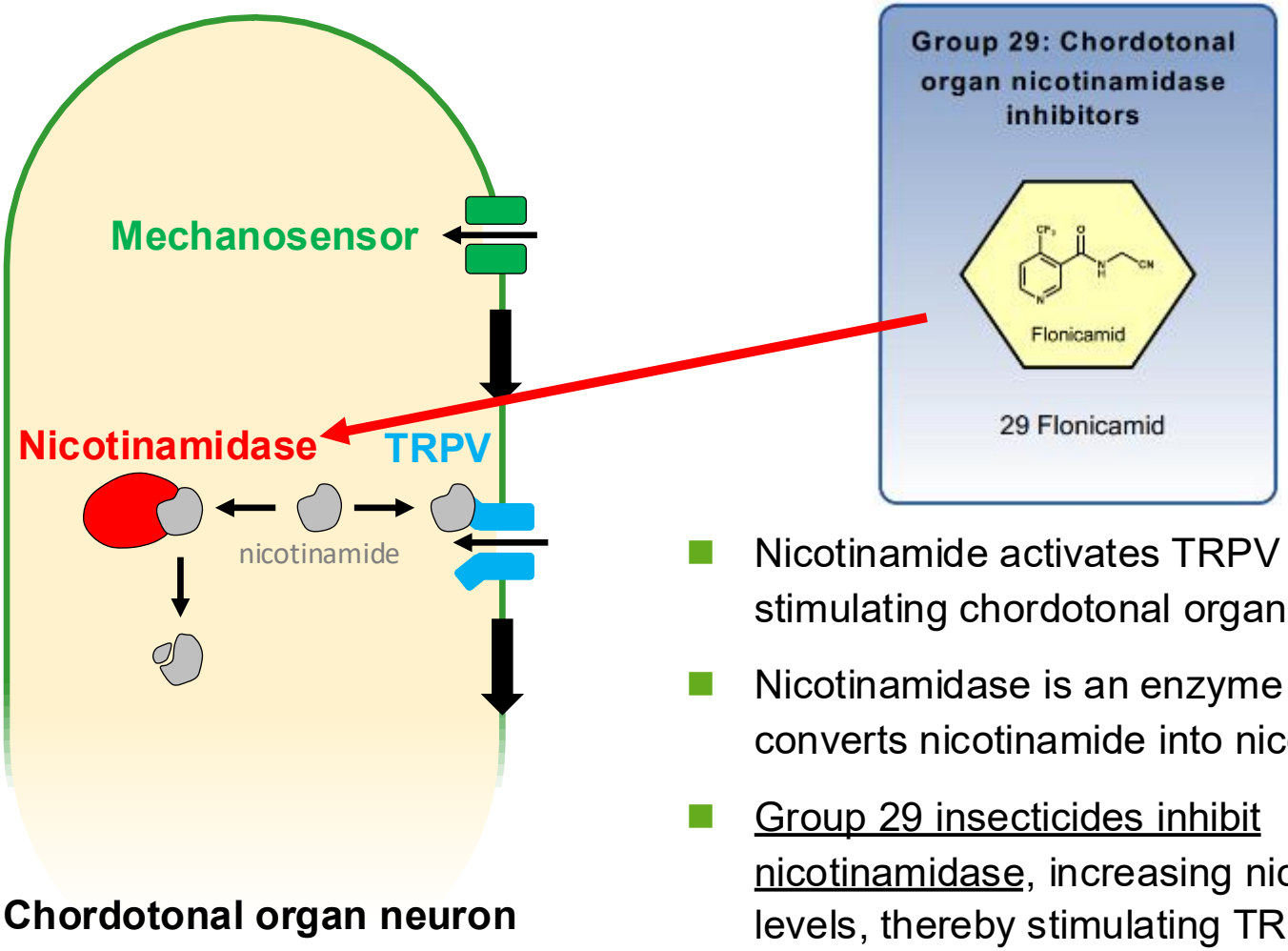
Chordotonal organ TRPV channel modulators



- TRPV channels help transduce mechanosensory signals in chordotonal organ neurons
- Group 9 Insecticides activate TRPV, interfering with chordotonal organ function

IRAC

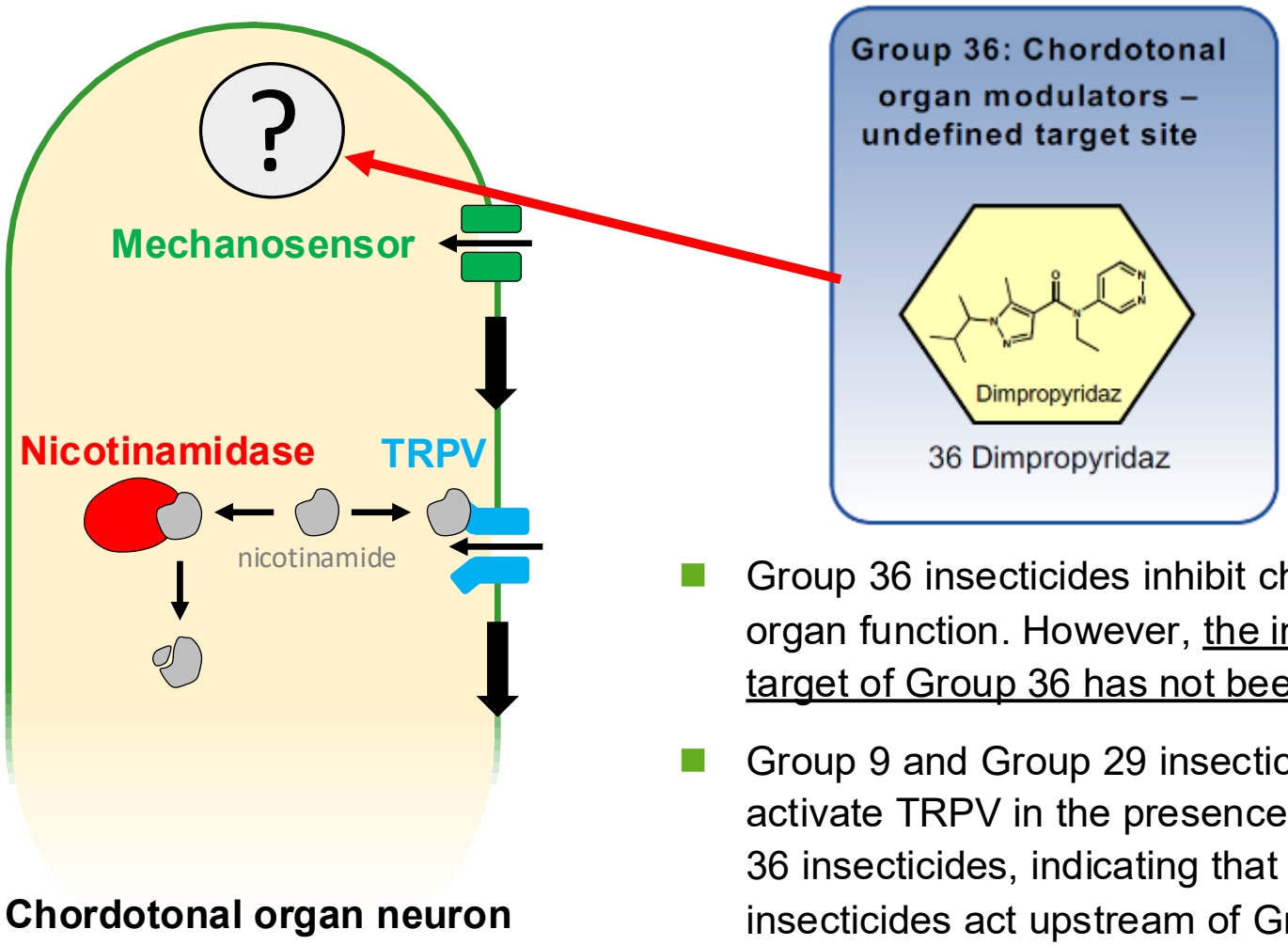
Chordotonal organ nicotinamidase inhibitors



- Nicotinamide activates TRPV receptors, stimulating chordotonal organ signaling
- Nicotinamidase is an enzyme that converts nicotinic acid into nicotinic acid
- Group 29 insecticides inhibit nicotinamidase, increasing nicotinamide levels, thereby stimulating TRPV

IRAC

Chordotonal organ modulators – undefined target site

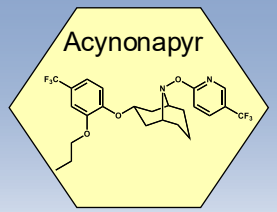


- Group 36 insecticides inhibit chordotonal organ function. However, <u>the insecticidal target of Group 36 has not been defined</u>
- Group 9 and Group 29 insecticides activate TRPV in the presence of Group 36 insecticides, indicating that such insecticides act upstream of Group 9 and 29 insecticides

IRAC

Insecticides acting on calcium-activated potassium channels

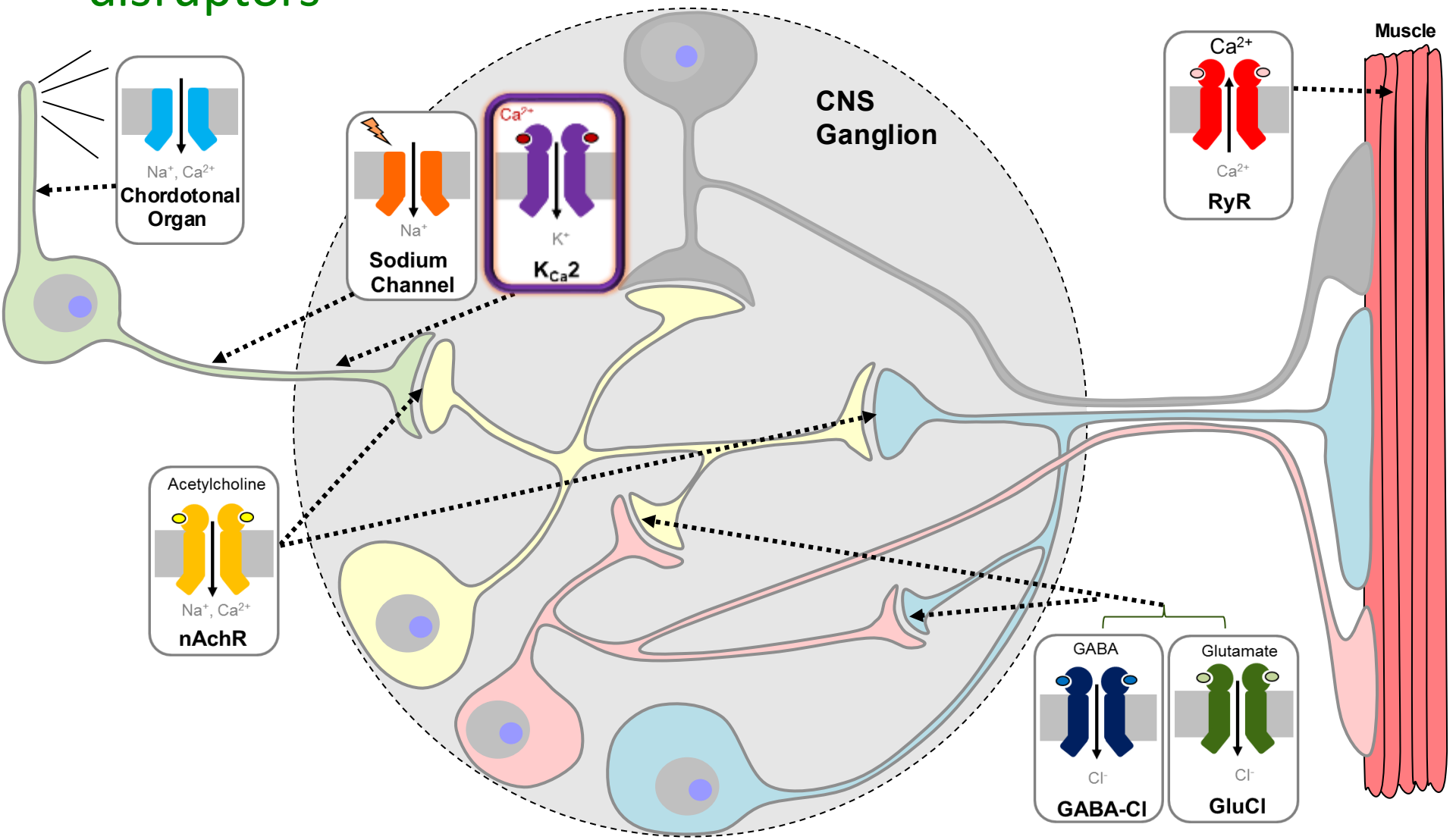
Group 33: Calcium-activated potassium channel (K_{Ca2}) modulators



33 Acynonapyr

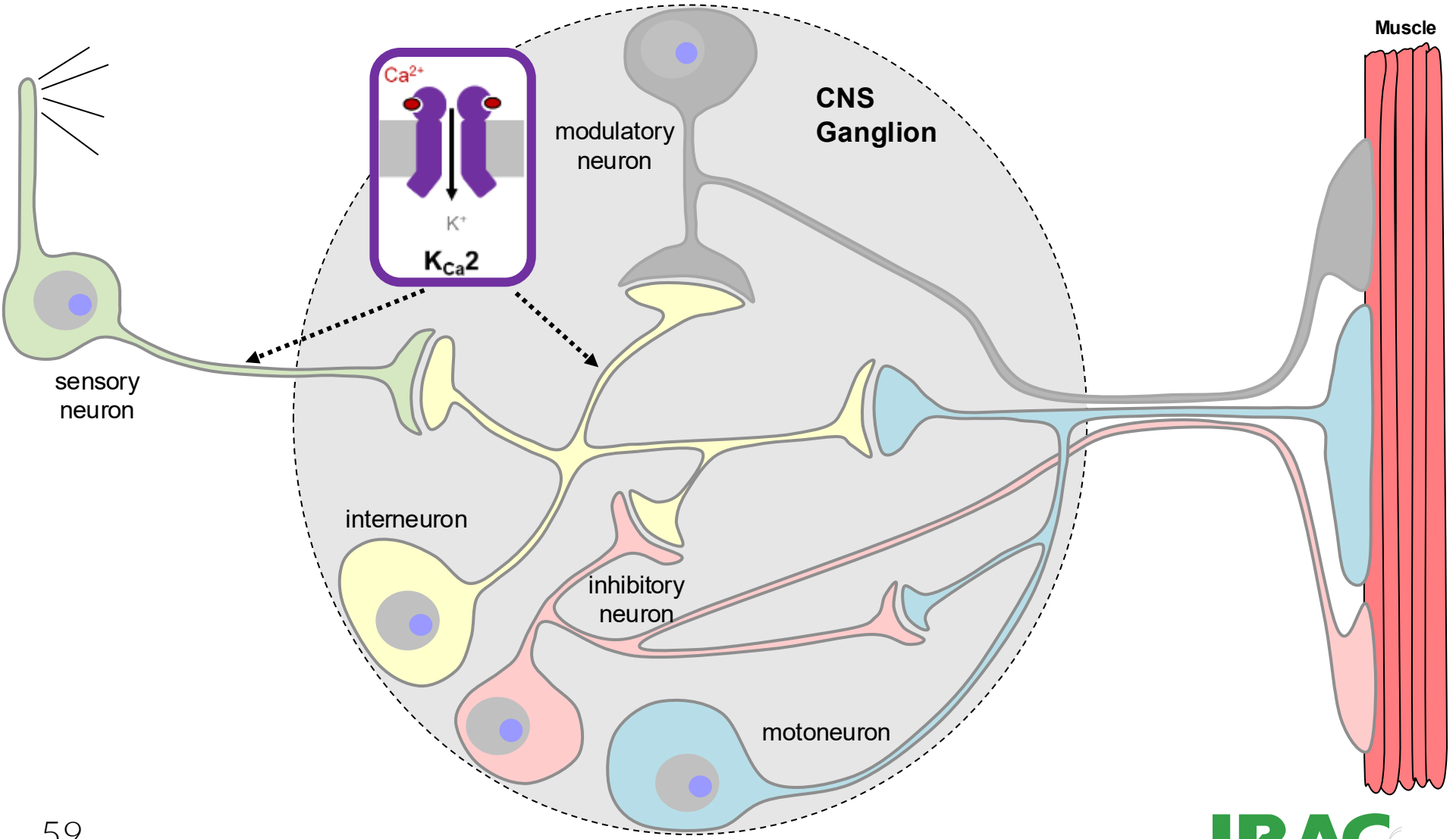
IRAC

Overview of ion channels targeted by neuromuscular disruptors



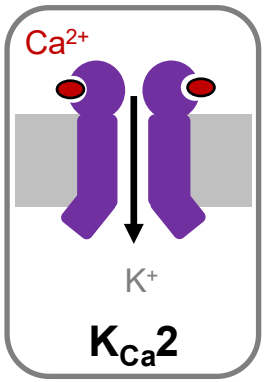
IRAC

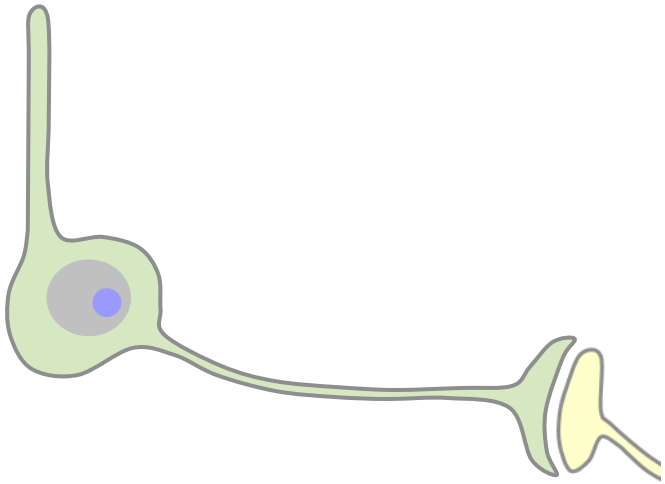
Insecticides acting on calcium-activated potassium channels



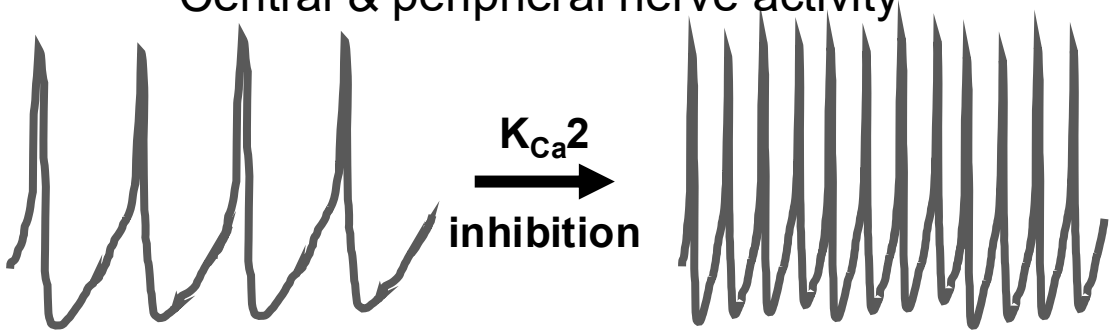
IRAC

Calcium-activated potassium channels play a role in signal propagation of excitable cells





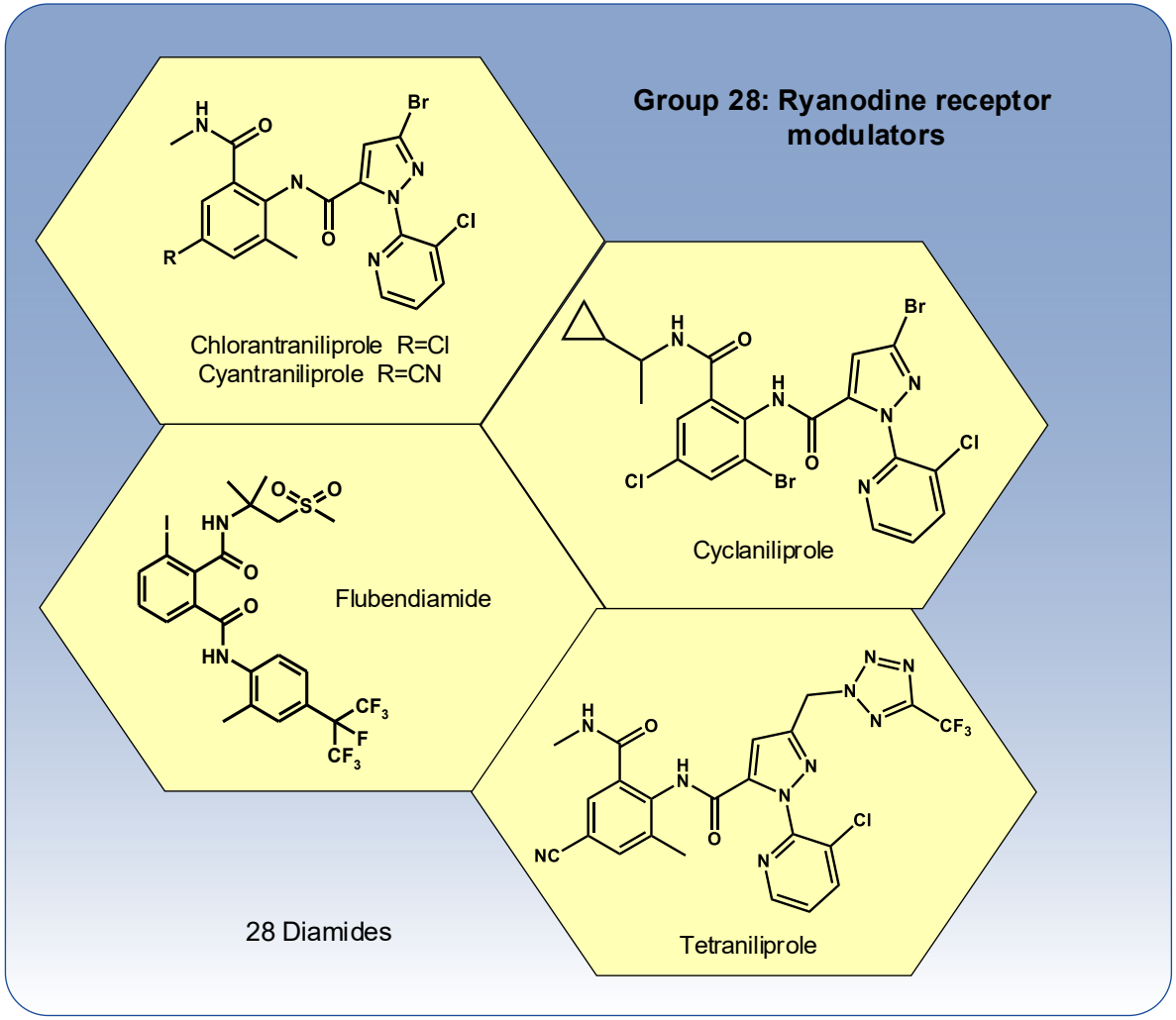
Central & peripheral nerve activity



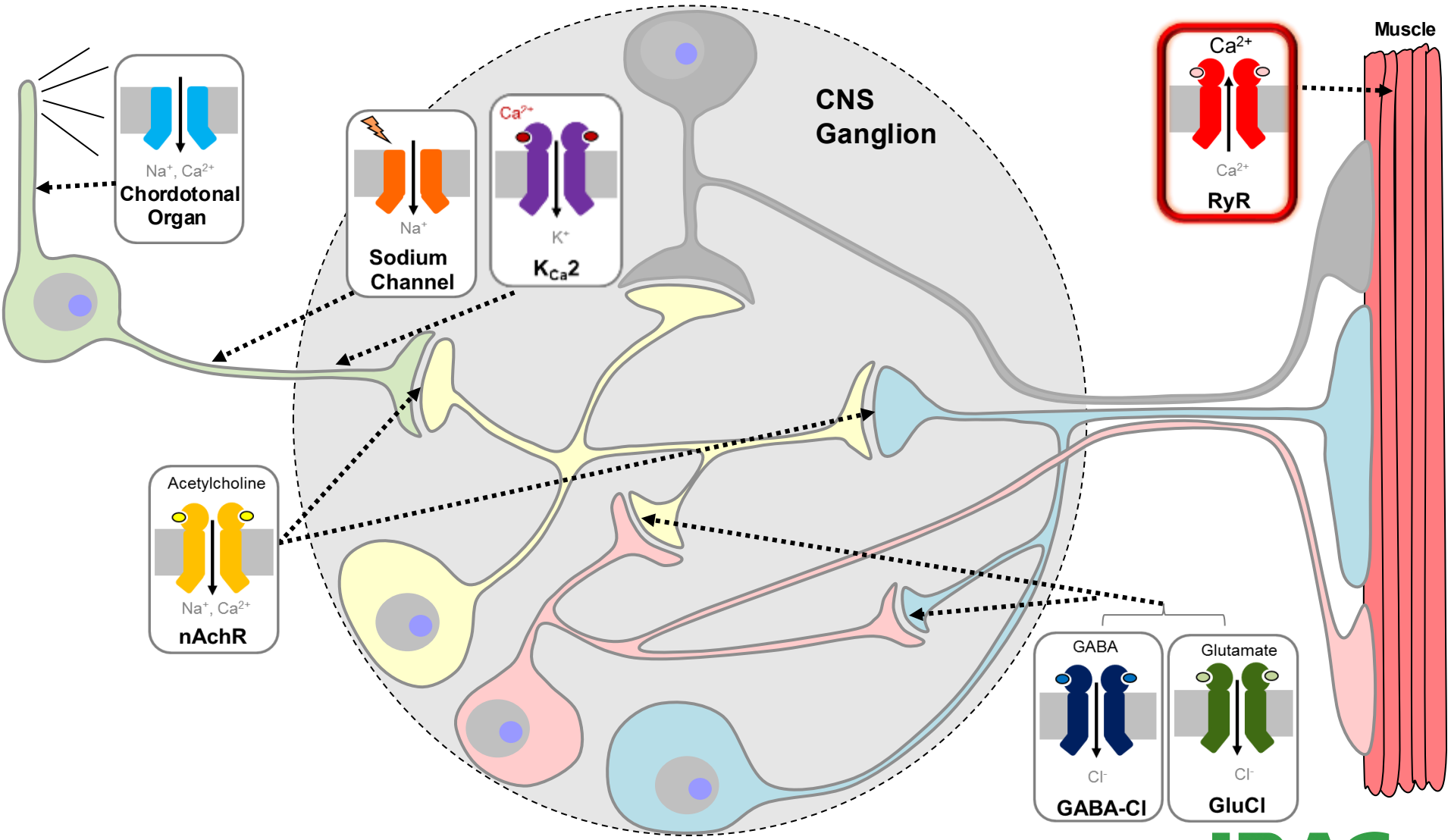
Potassium channels are critical in regulating cellular volume, membrane potential and nerve firing frequency. Calcium-activated potassium ($K_{Ca}2$) channels are voltage-independent channels that are gated exclusively by Ca^{2+} binding to proteins such a calmodulin. $K_{Ca}2$ channels are ubiquitous in the central and peripheral nervous system and regulate intrinsic excitability and nerve firing rates.

IRAC

RyR modulators

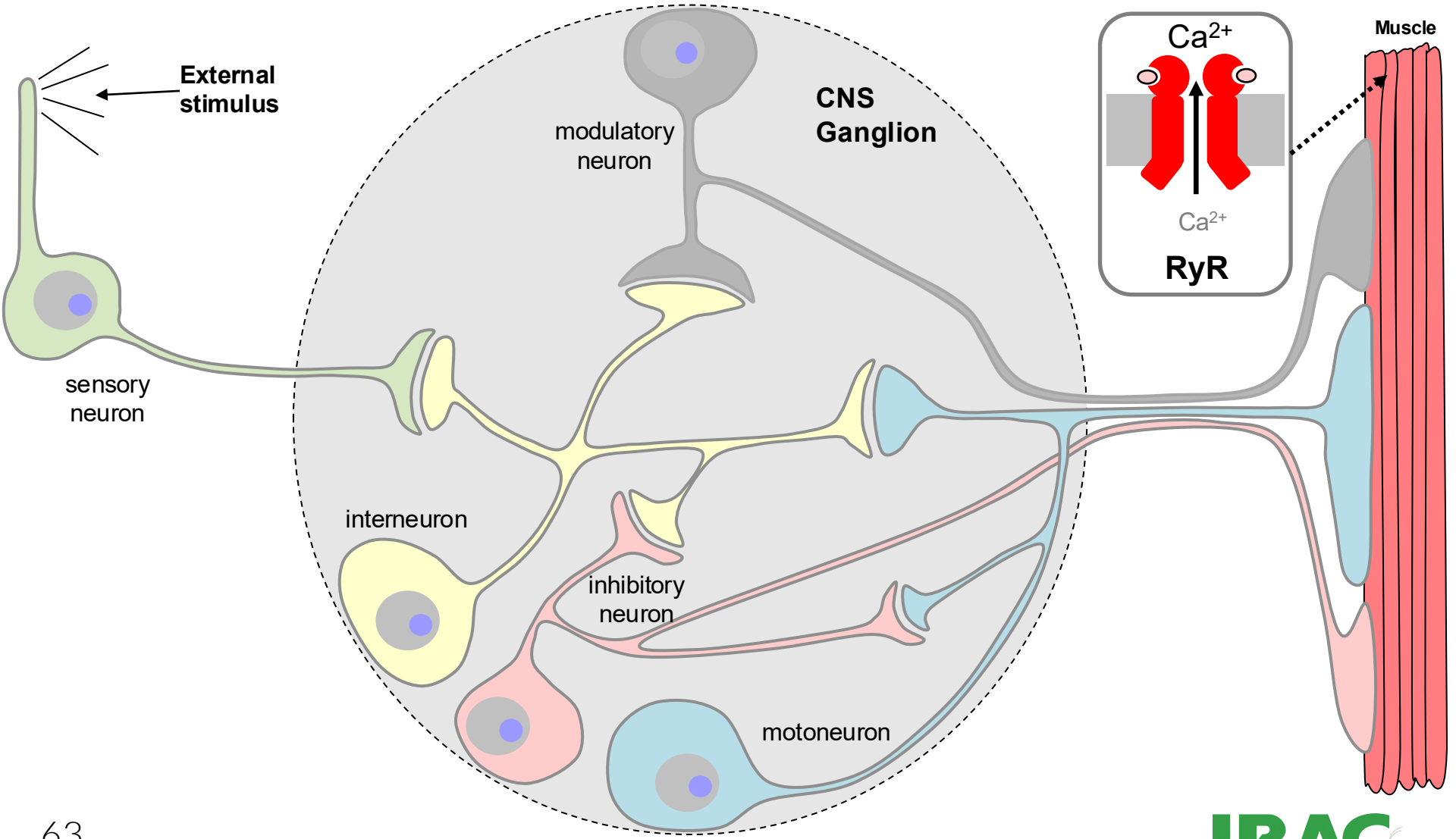


Overview of ion channels targeted by neuromuscular disruptors



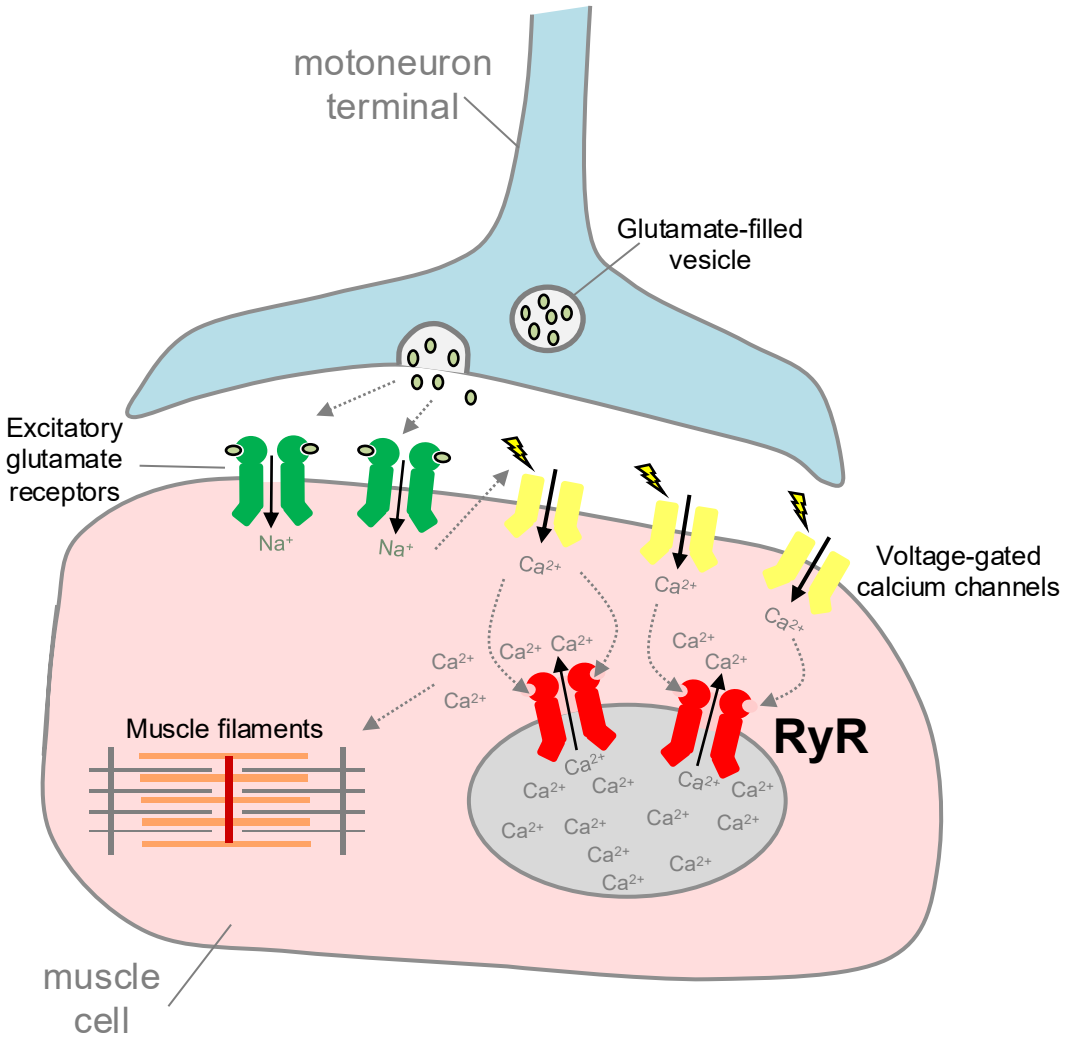
IRAC

Insecticides acting on the ryanodine receptor (RyR)



IRAC

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

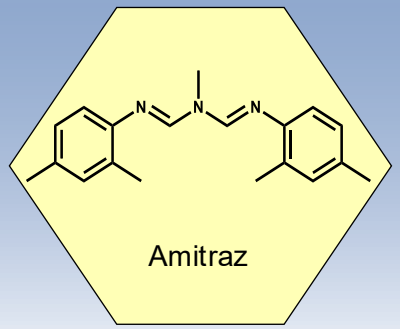


- Ca^{2+} ions entering the muscle cell activate RyRs located on the muscle cell's intracellular Ca^{2+} store to release Ca^{2+} into the cytoplasm
- The rise in Ca^{2+} activates more RyRs, leading to massive Ca^{2+} release
- This in turn induces shortening of contractile filaments, leading to muscle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

IRAC

Octopamine receptor agonists

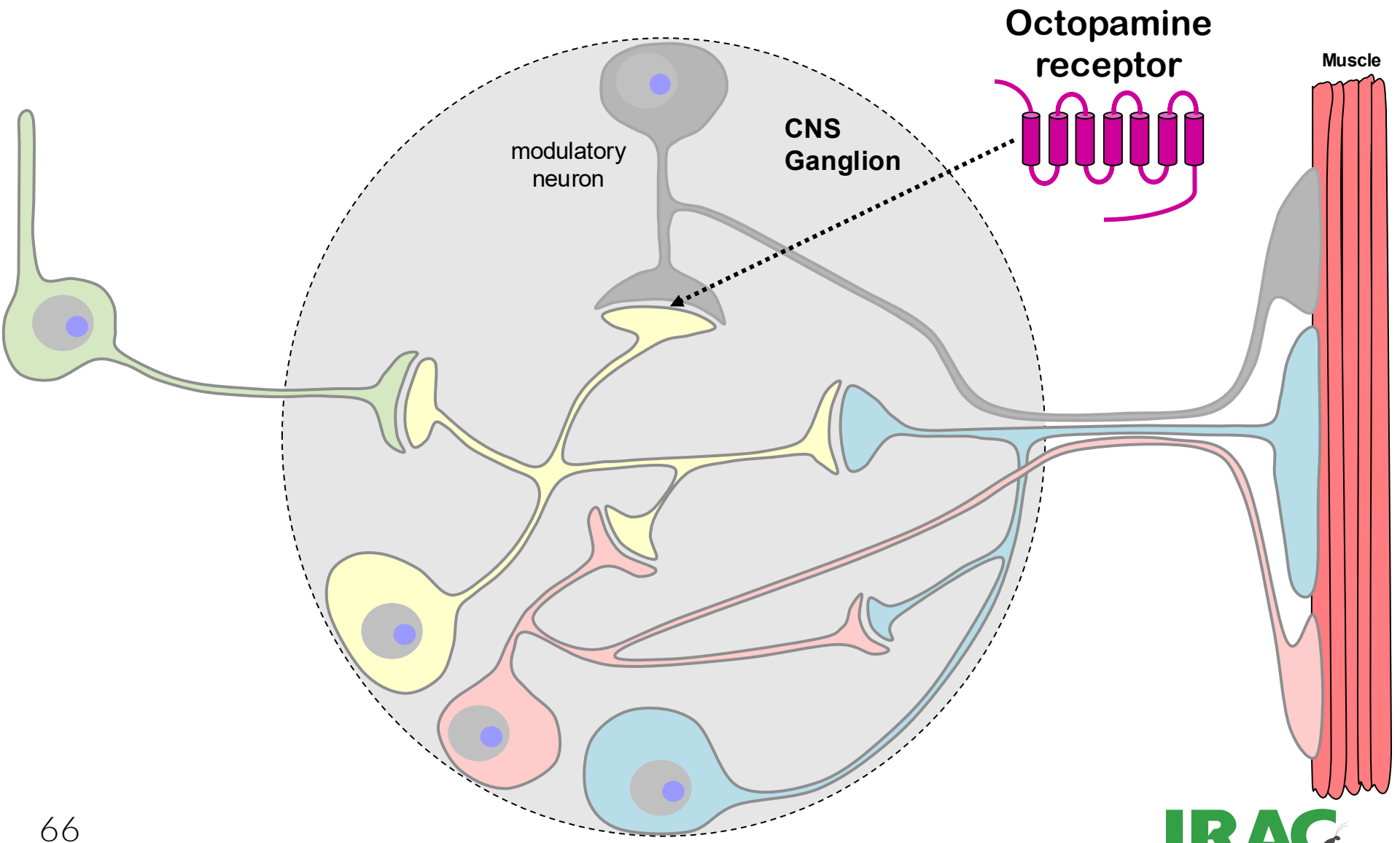
Group 19: Octopamine receptor agonists



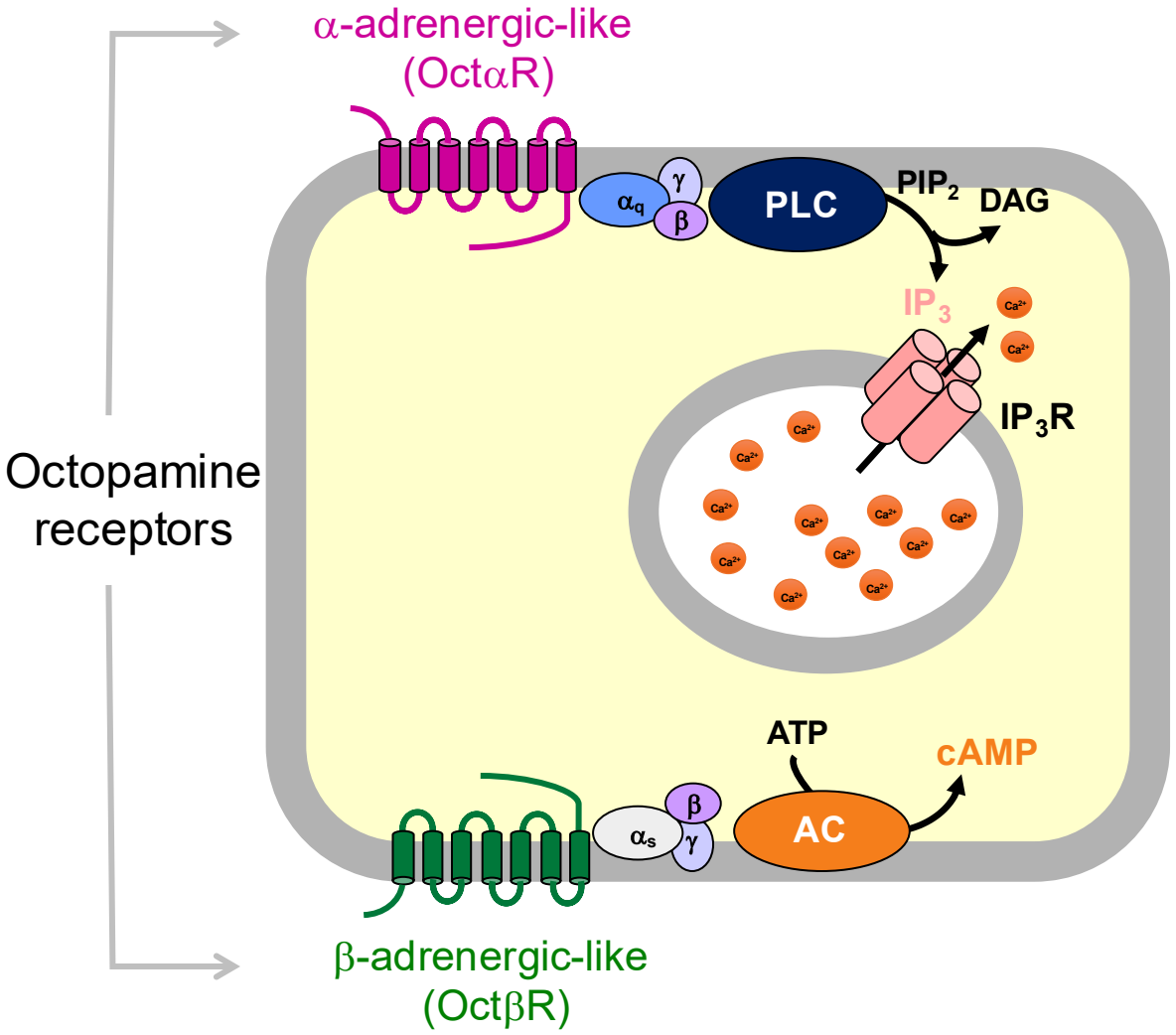
Amitraz

19 Amitraz

Receptors targeted by neuromuscular disruptors



Octopamine receptor signalling

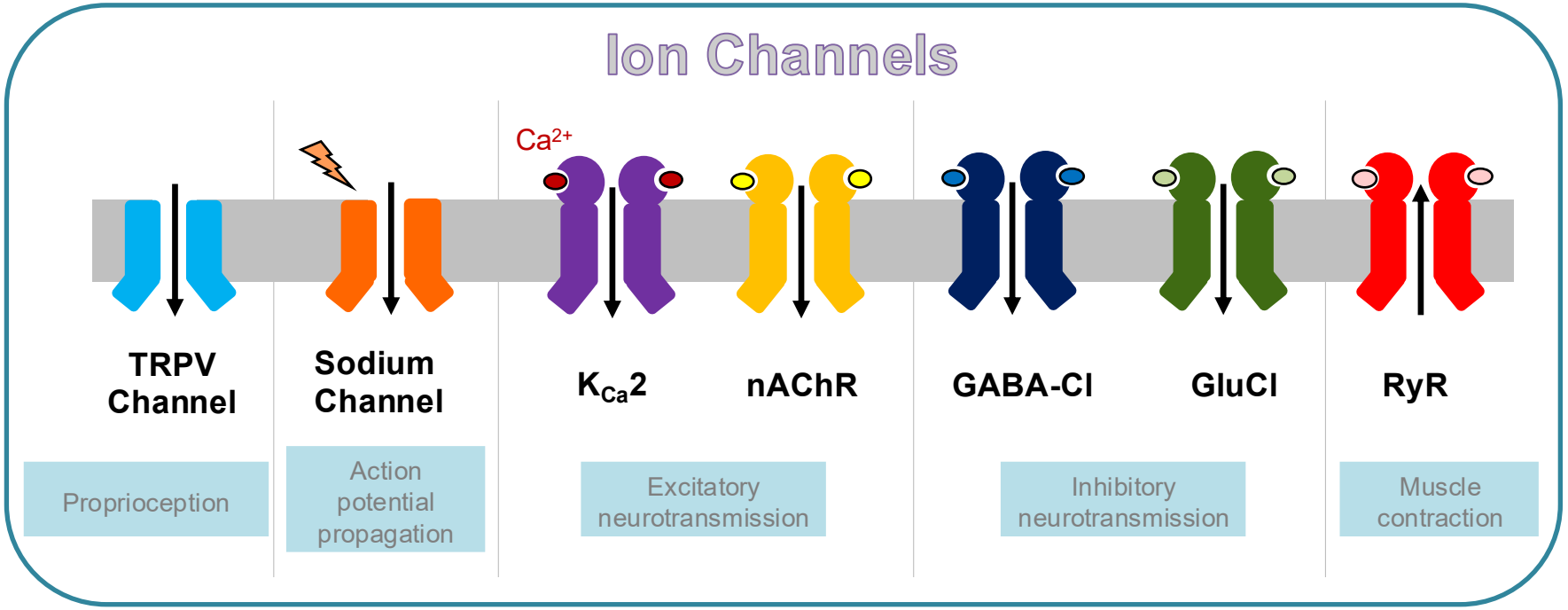


- Octopamine is the major modulatory neurotransmitter in insects; it can increase the general level of arousal like adrenaline does in mammals

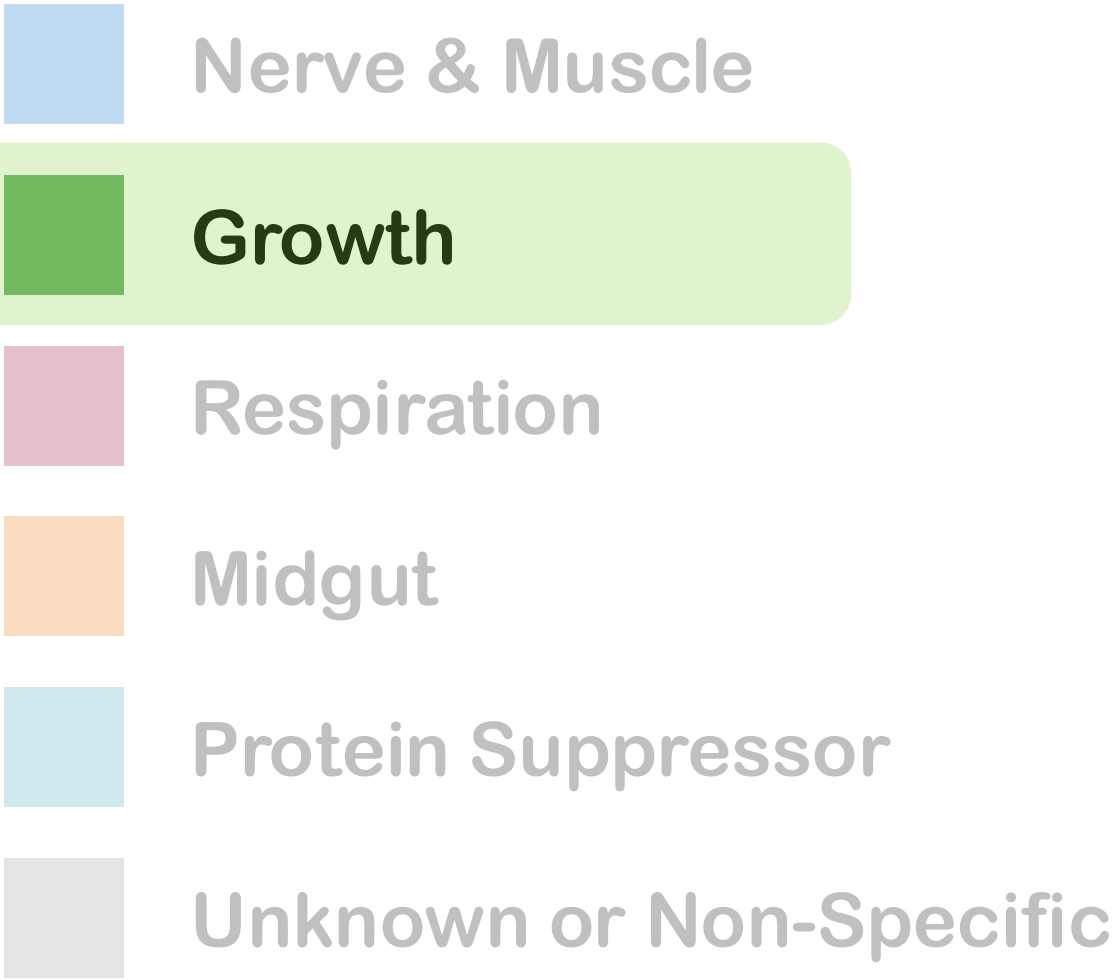
- Upon release, Octopamine binds to G-Protein-Coupled Receptors (GPCRs) on the postsynaptic membrane, which can be coupled via G-proteins ($\alpha\beta\gamma$) to Phospholipase C (PLC), an enzyme catalyzing the formation of IP_3. This in turn can activate intracellular Ca^{2+} release channels. Other octopamine receptors are coupled to adenylyl cyclase (AC) to stimulate cAMP production

- Octopamine receptor agonists can mimic the action of this neurotransmitter

Targets of neuromuscular disruptors & their key physiological roles



Insecticide Mode of Action: Major classes



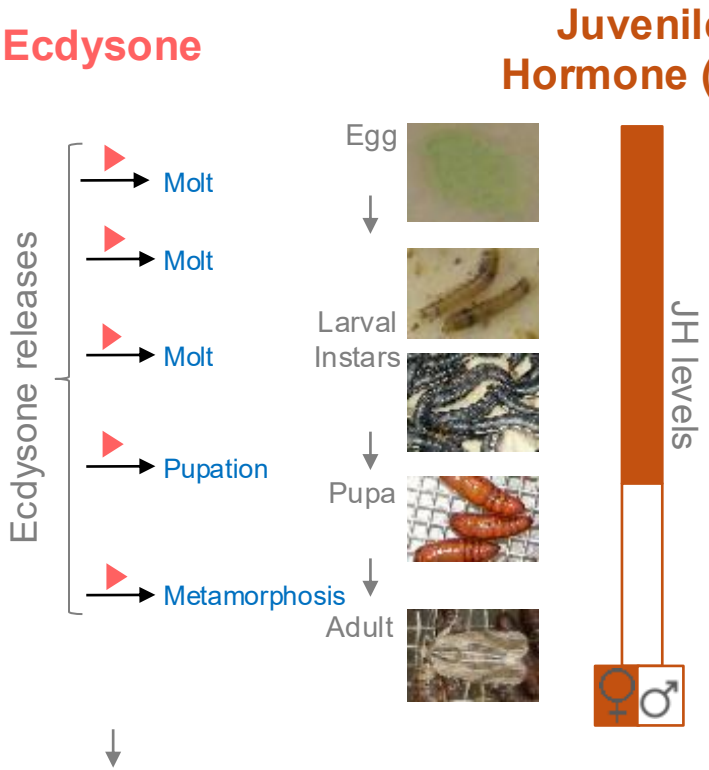
IRAC

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

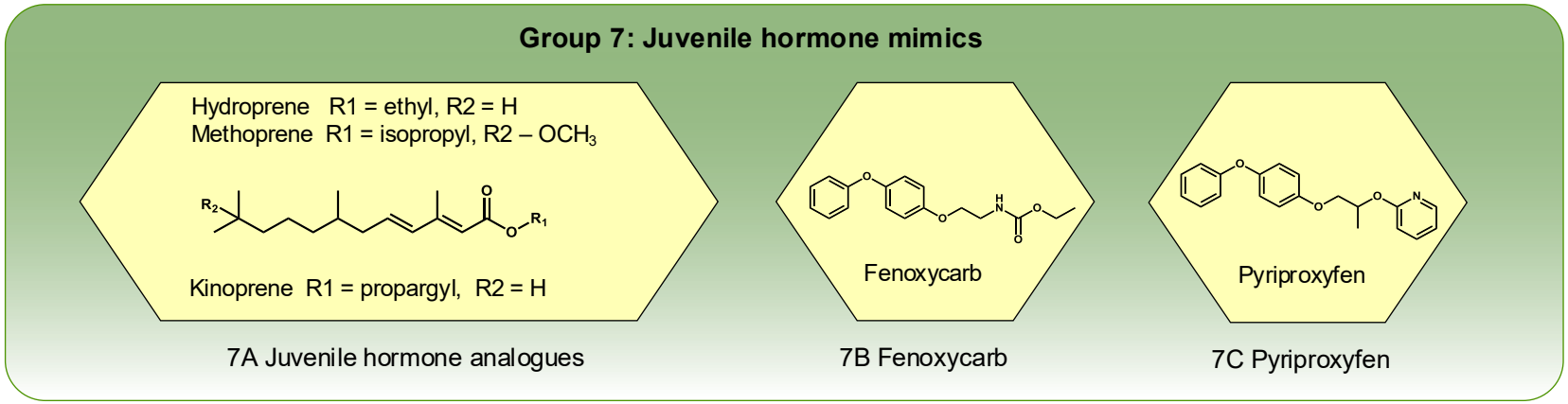


JH prevents molting to a more mature stage

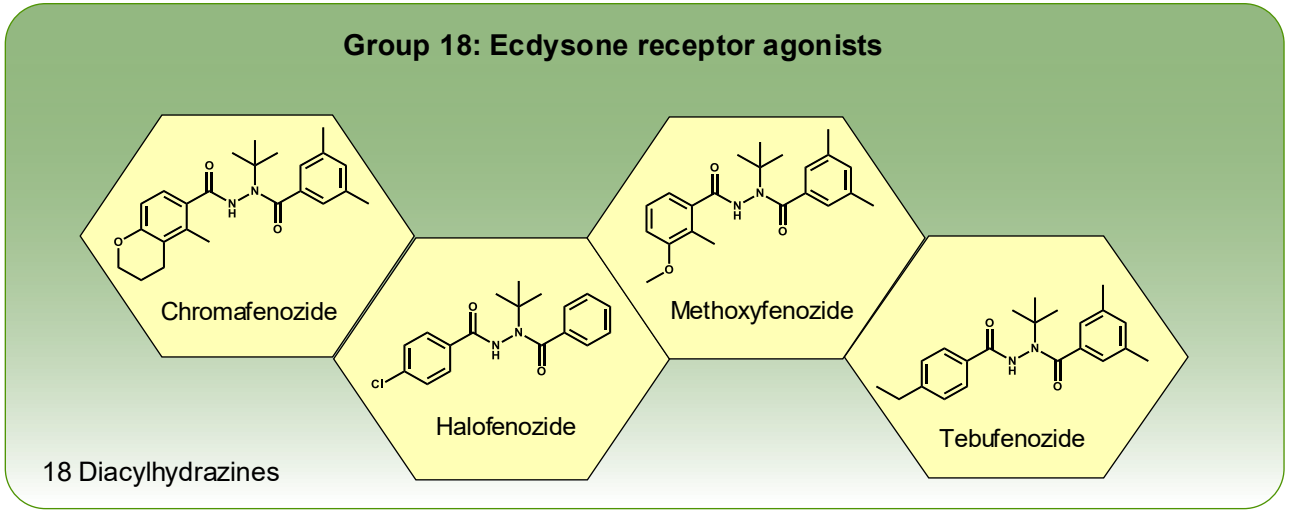
JH production stops during metamorphosis

IRAC

Juvenile hormone mimics



Ecdysone receptor agonists



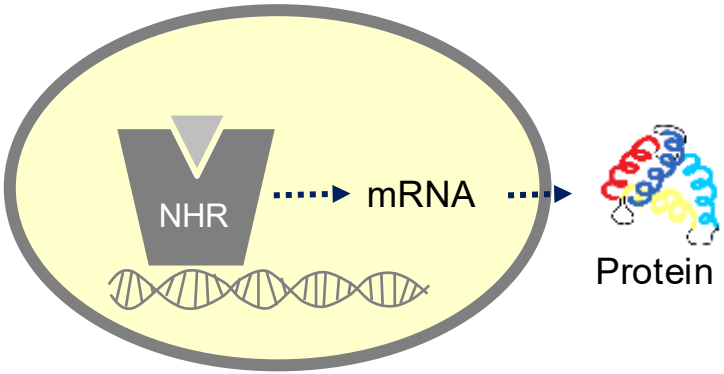
Targets of growth & development disruptors

1. Nuclear Hormone Receptors (NHR)

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

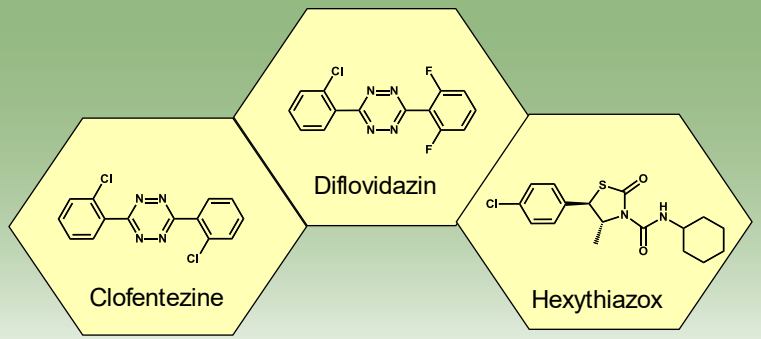
JH

JH prevents molting to a more mature stage

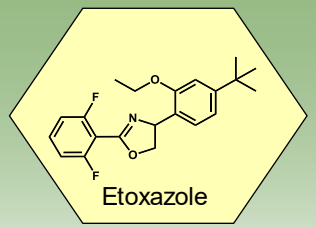
IRAC

Chitin synthesis inhibitors

Group 10: Mite growth inhibitors affecting CHS1

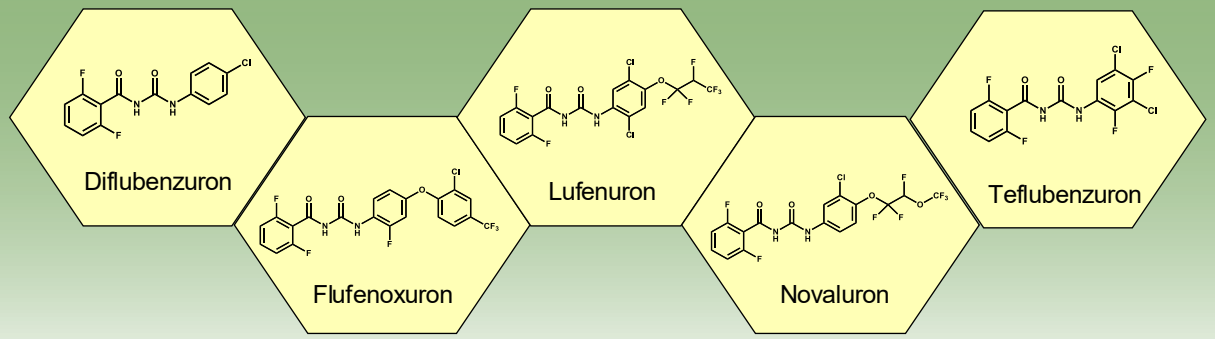


10A Clofentezine, Diflovidazin, Hexythiazox



10B Etoxazole

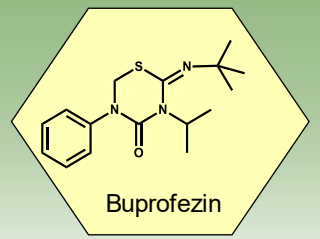
Group 15: Inhibitors of chitin biosynthesis affecting CHS1



15 Benzoylureas

(Only major representatives of group are shown)

Group 16: Inhibitors of chitin biosynthesis, type 1

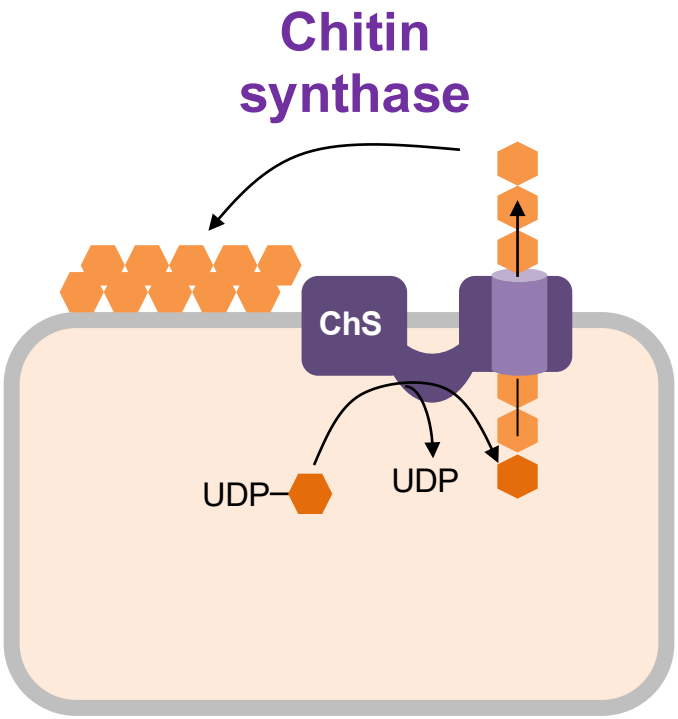


16 Buprofezin

IRAC

Targets of growth & development disruptors

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

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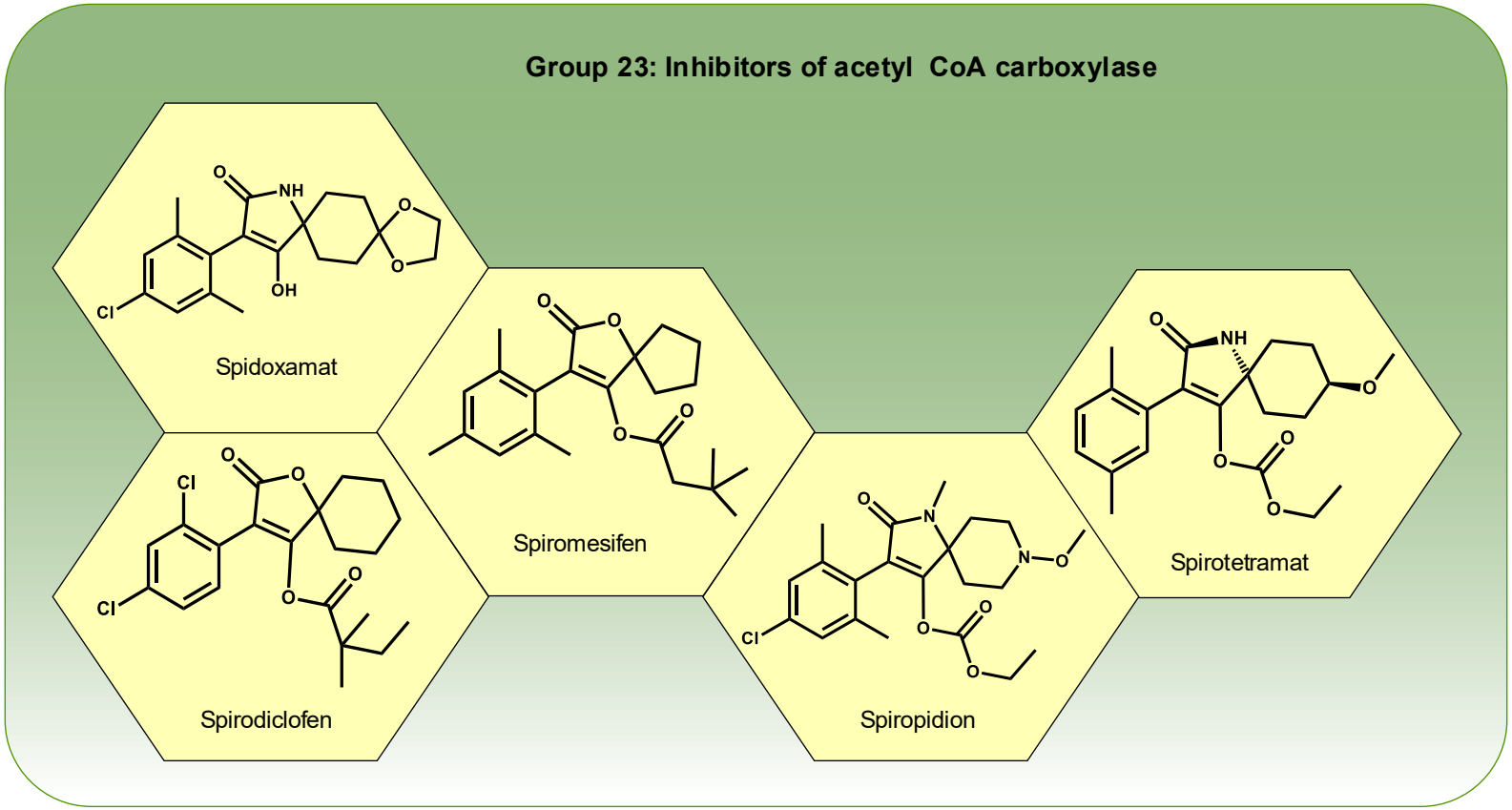
Inhibitors of acetyl CoA carboxylase



23 Tetronic & Tetramic acid derivatives

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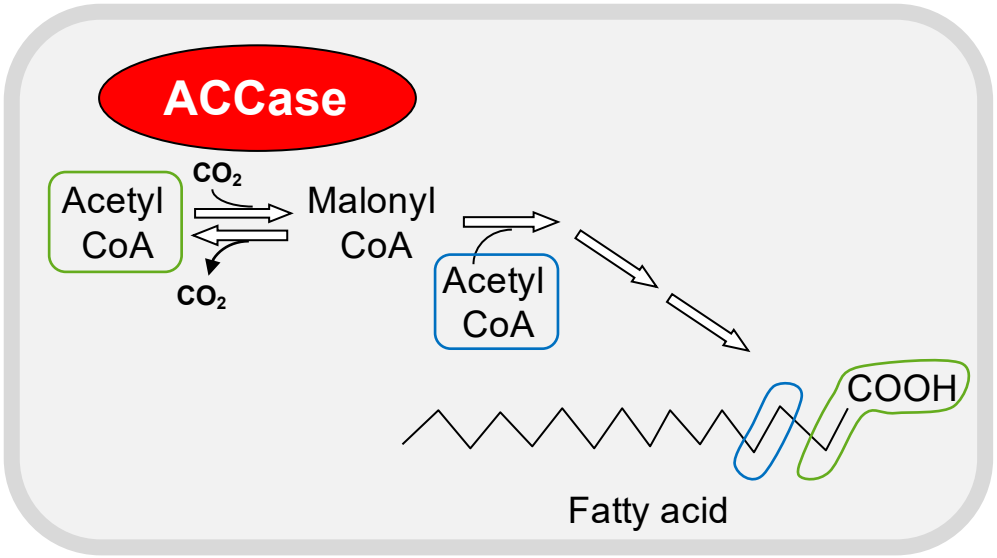
Targets of growth & development disruptors

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

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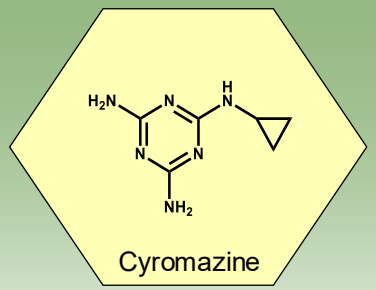
Others: Moulting disruptors (dipteran)

Group 17: Moulting disruptors, Dipteran



Cyromazine

17 Cyromazine

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Overview growth & development targets

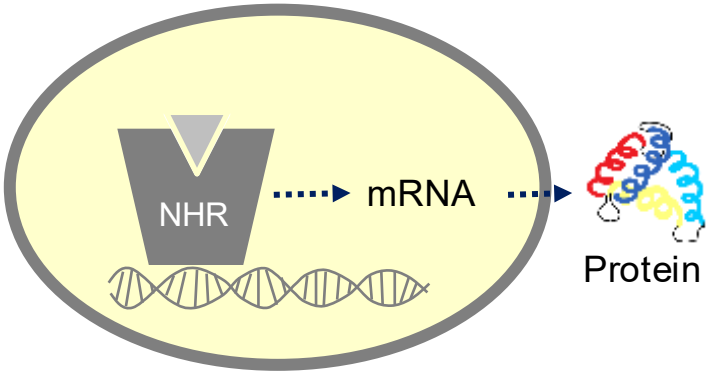
Nuclear Hormone Receptors

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

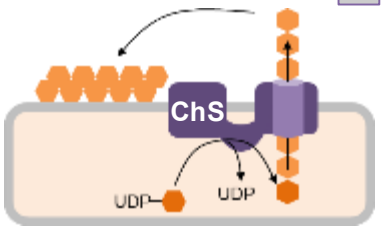
JHR

JH prevents molting to a more mature stage

Enzymes

Chitin synthase

Chitin synthesis



Acetyl CoA carboxylase

Fatty acid synthesis

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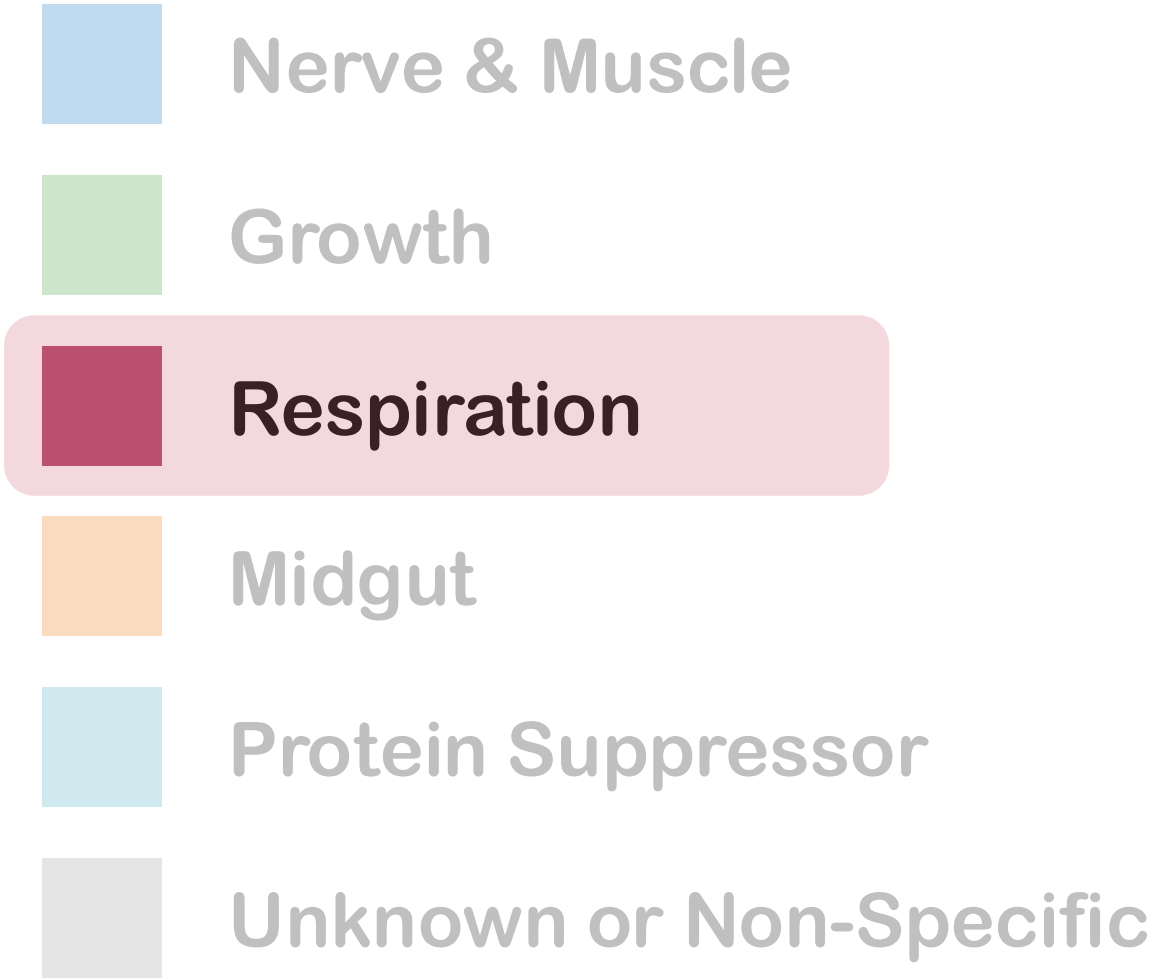
Insecticide Mode of Action: Major classes



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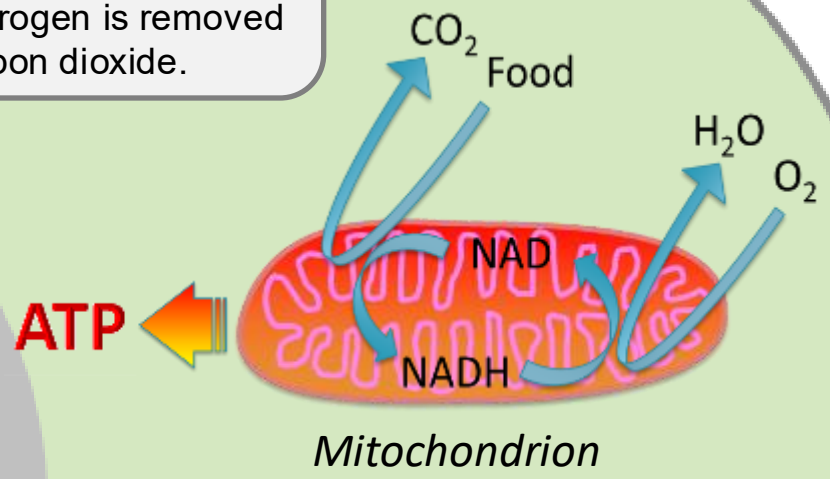
Respiration and energy conservation Background

Cells obtain the energy they need by "oxidizing" fats 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.



Mitochondrion

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.

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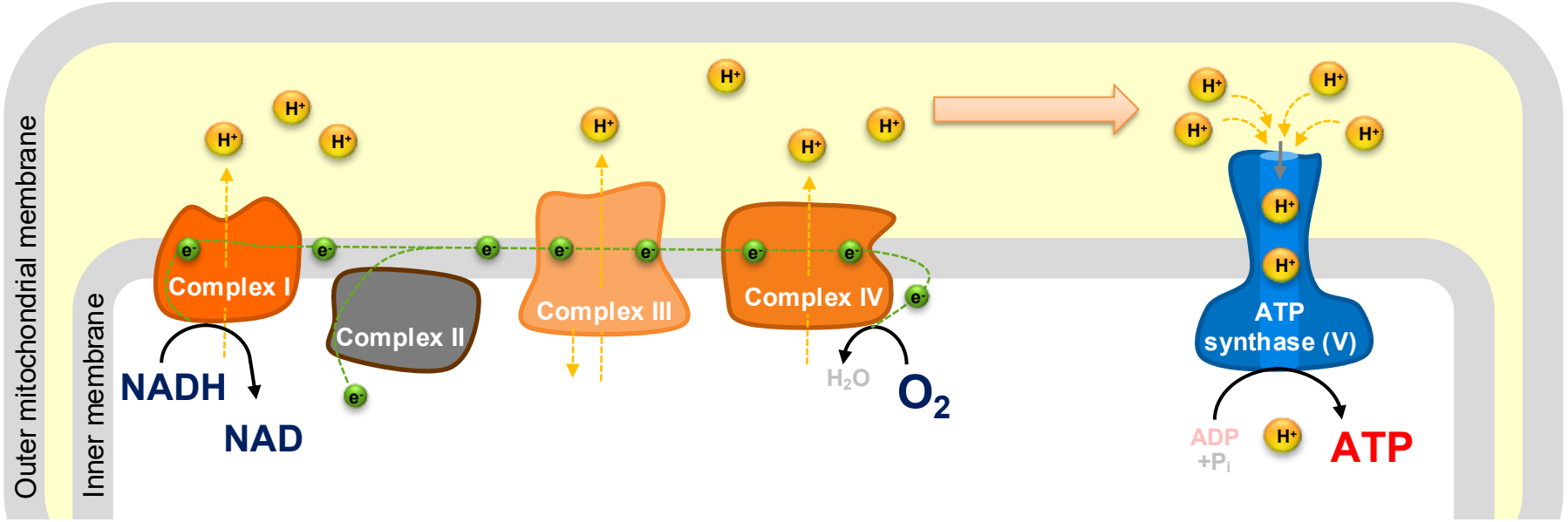
A number of complex proteins are needed to conserve the energy available



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.

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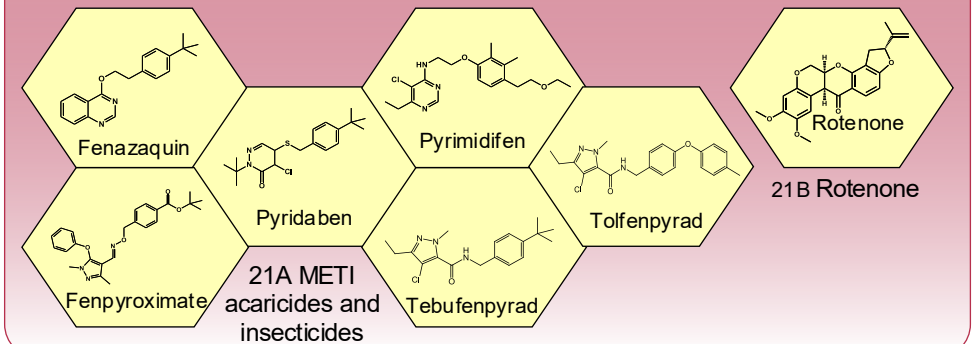
Inhibitors of Complexes I-V

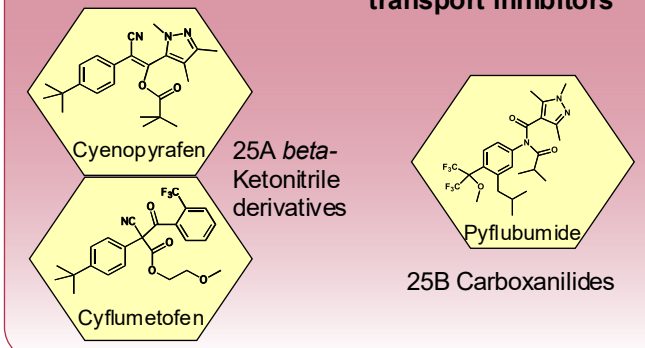
Group 21: Mitochondrial complex I electron transport inhibitors



21A METI acaricides and insecticides

21B Rotenone

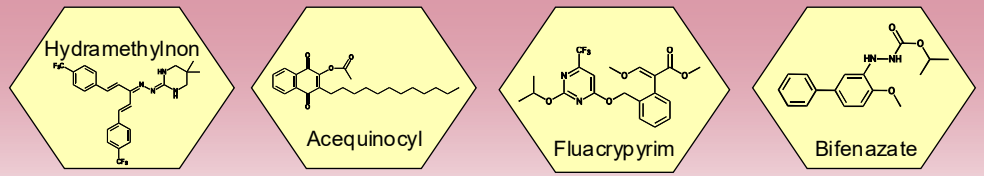
Group 25: Mitochondrial complex II electron transport inhibitors



25A *beta*-Ketonitrile derivatives

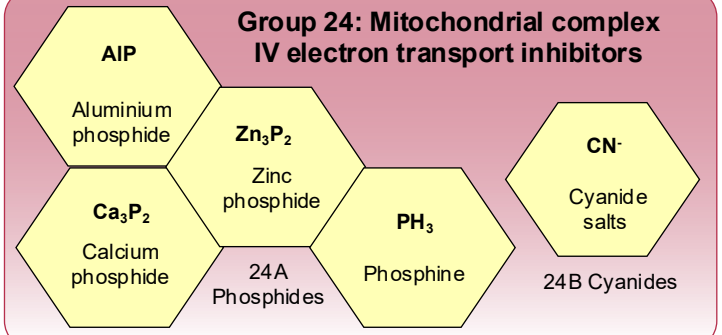
25B Carboxanilides

Group 20: Mitochondrial complex III electron transport inhibitors



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

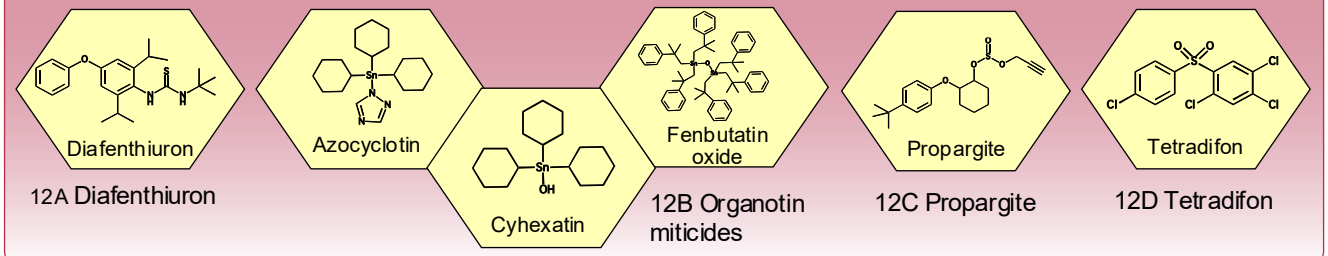
Group 24: Mitochondrial complex IV electron transport inhibitors



24A Phosphides

24B Cyanides

Group 12: Inhibitors of mitochondrial ATP synthase



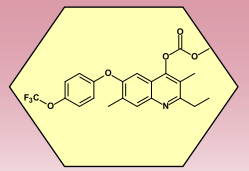
12A Diafenthiuron

12B Organotin miticides

12C Propargite

12D Tetradifon

Group 34: Mitochondrial complex III inhibitors (Qi site)

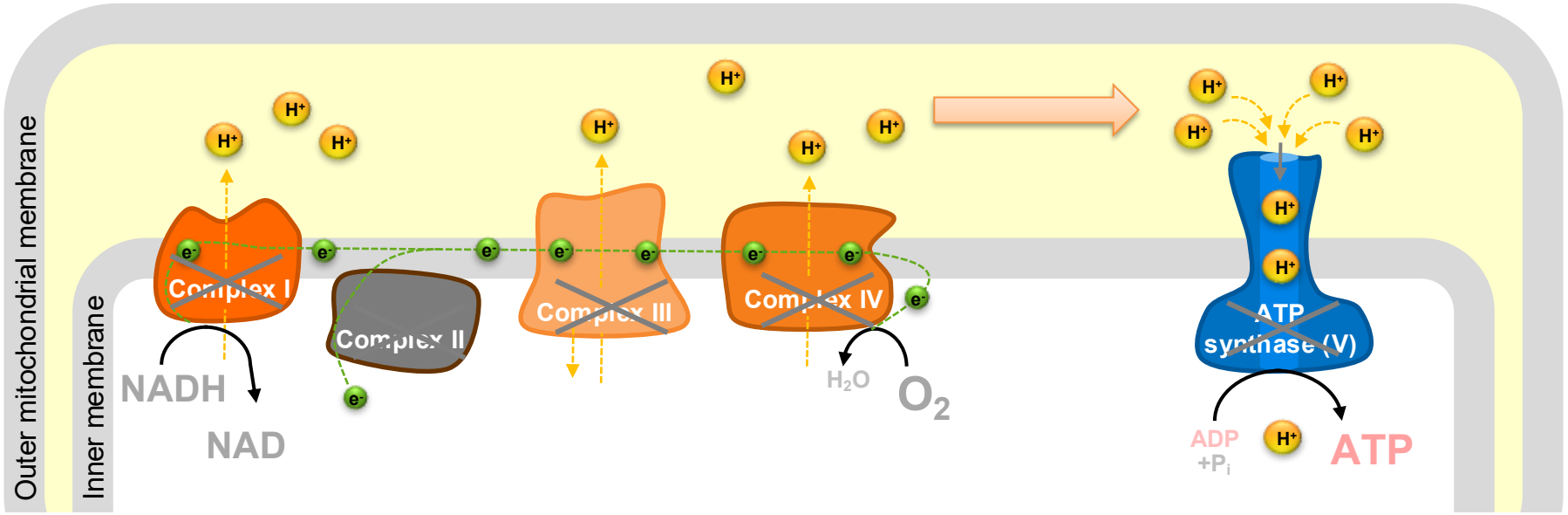


34 Flometoquin

IRAC

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

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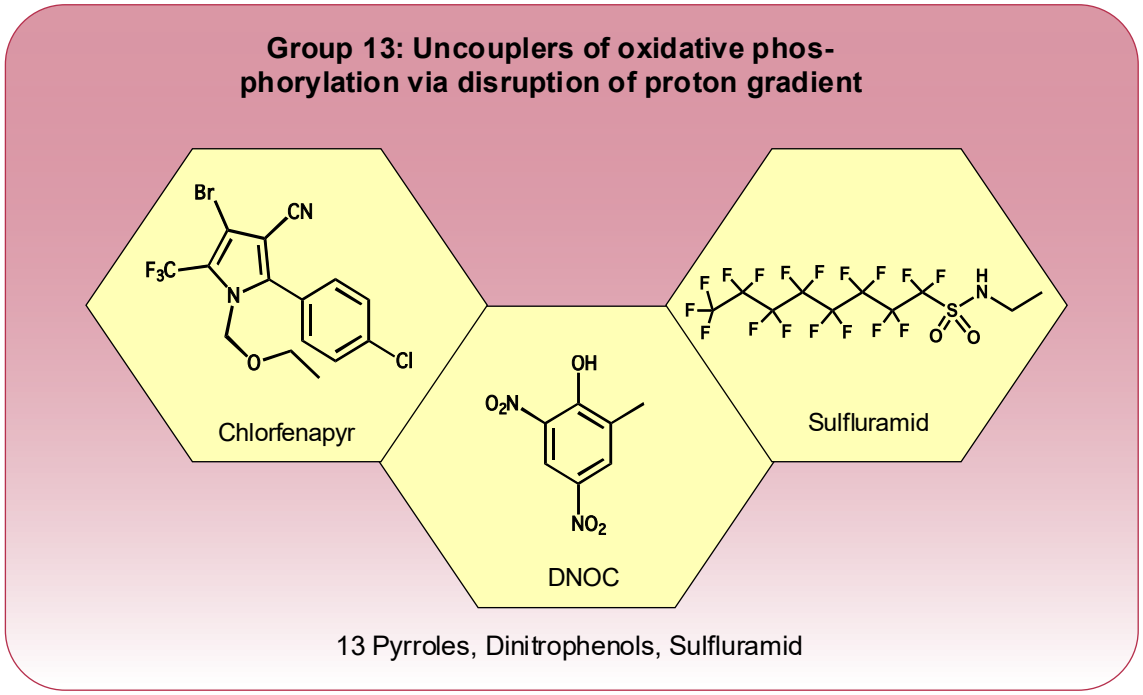
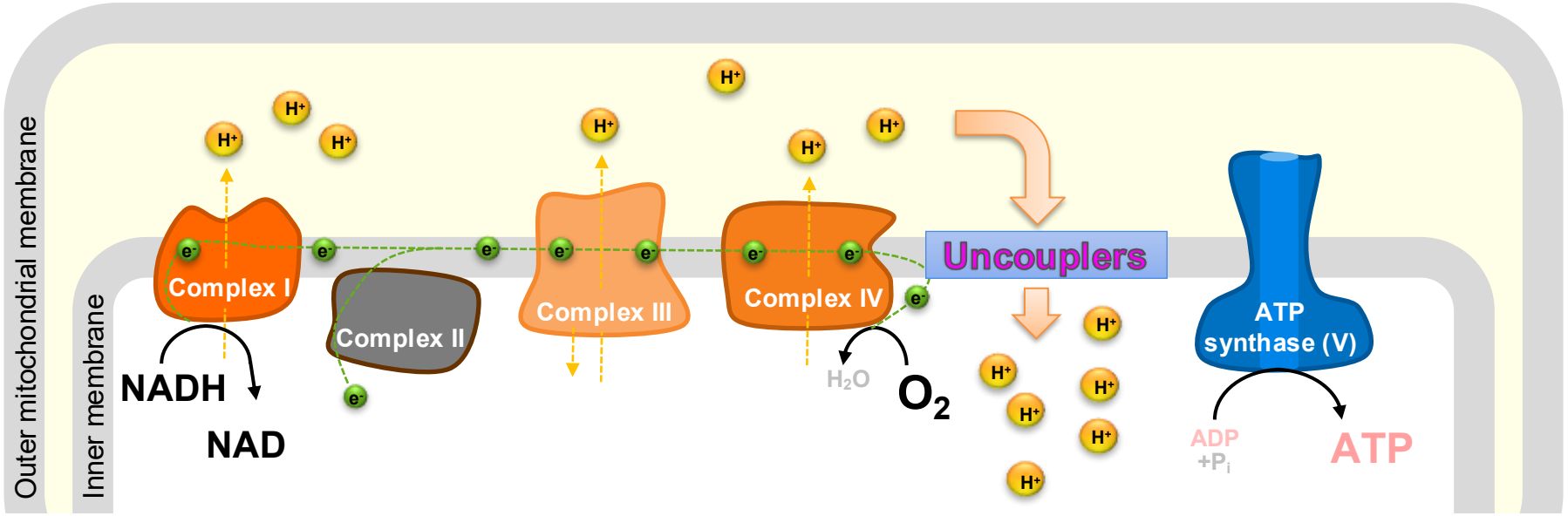
Uncouplers


Group 13: Uncouplers of oxidative phos-
phorylation via disruption of proton gradient
Chlorfenapyr
DNOC
Sulfluramid
13 Pyrroles, Dinitrophenols, Sulfluramid

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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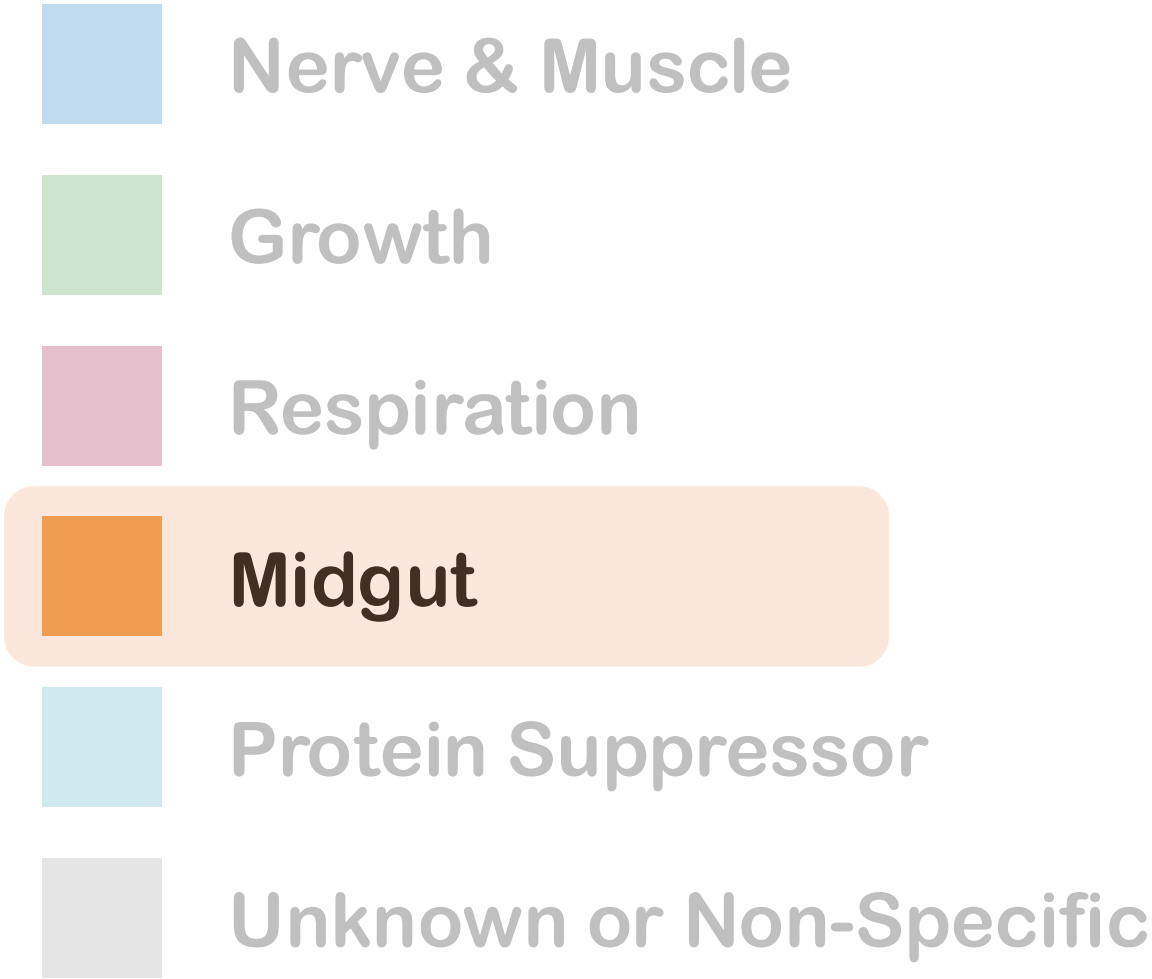
Insecticide Mode of Action: Major classes



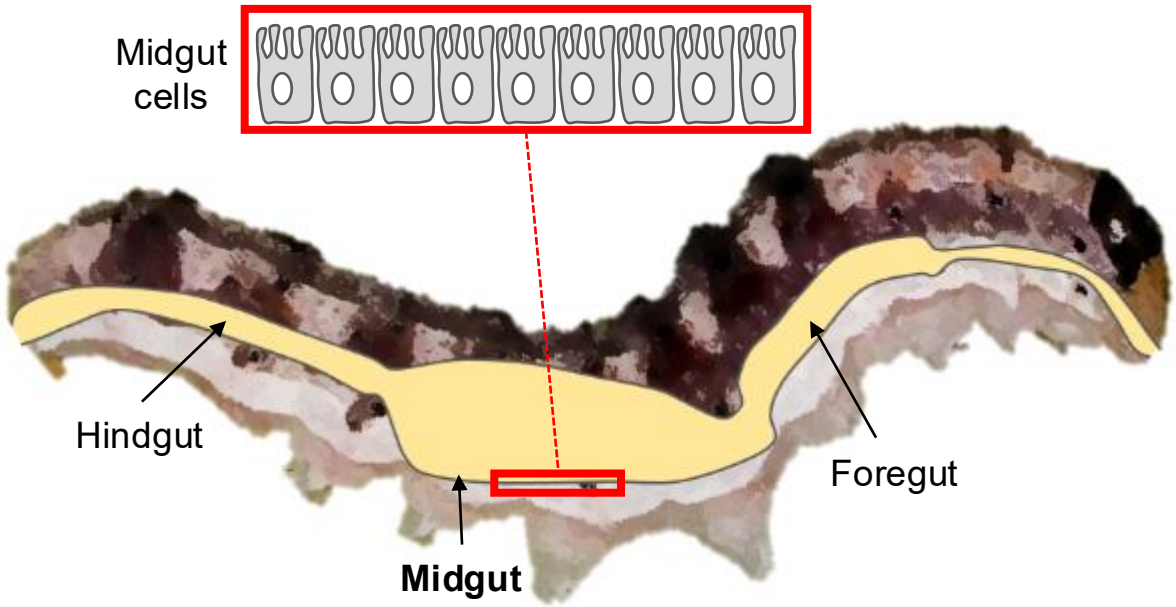
IRAC

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



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.

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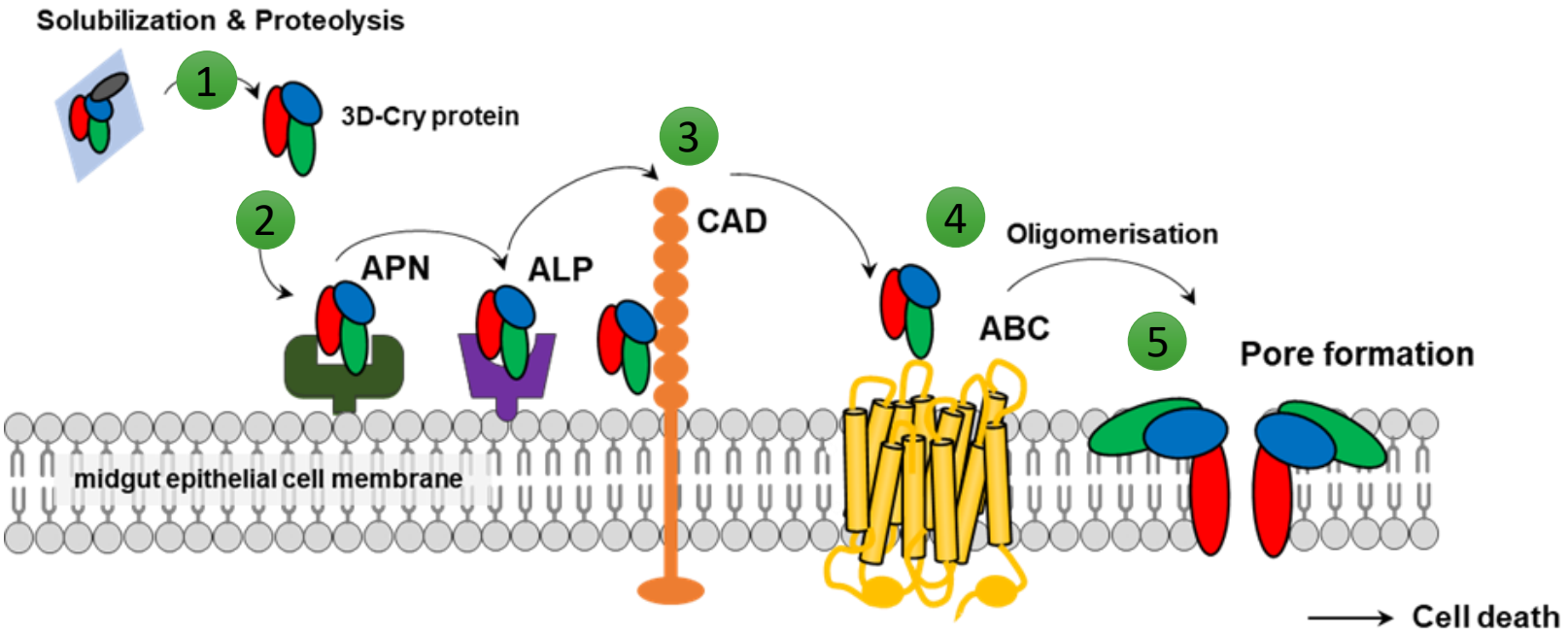
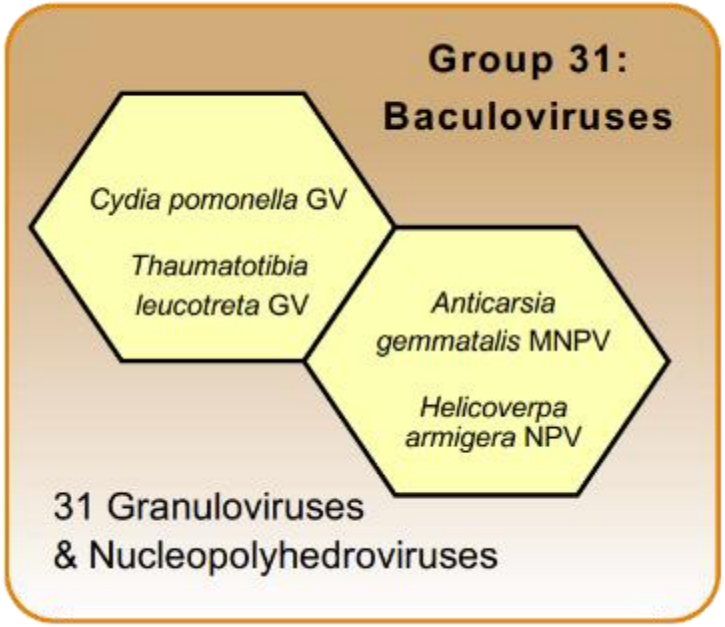
Mode of Action of *Bacillus thuringiensis* (Bt) Cry toxins on midgut epithelium

1. Crystal solubilization
2. Protoxin proteolytic activation of 3-domain Cry protein
3. Activated toxin monomer binding to receptors, e.g. cadherin and ABC transporters such as ABCC2
4. Conformational change and oligomerization
5. Membrane insertion and pore formation

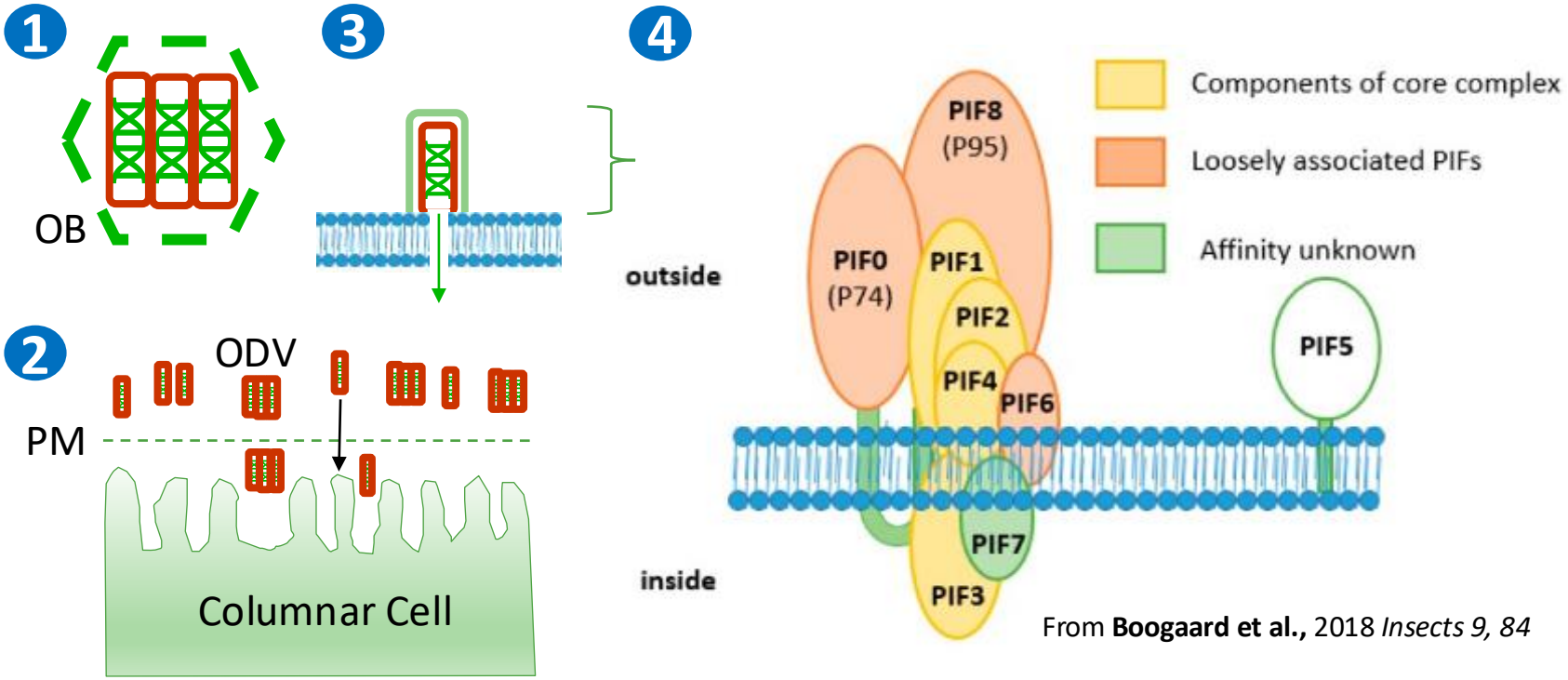


Baculoviruses acting on insect midgut



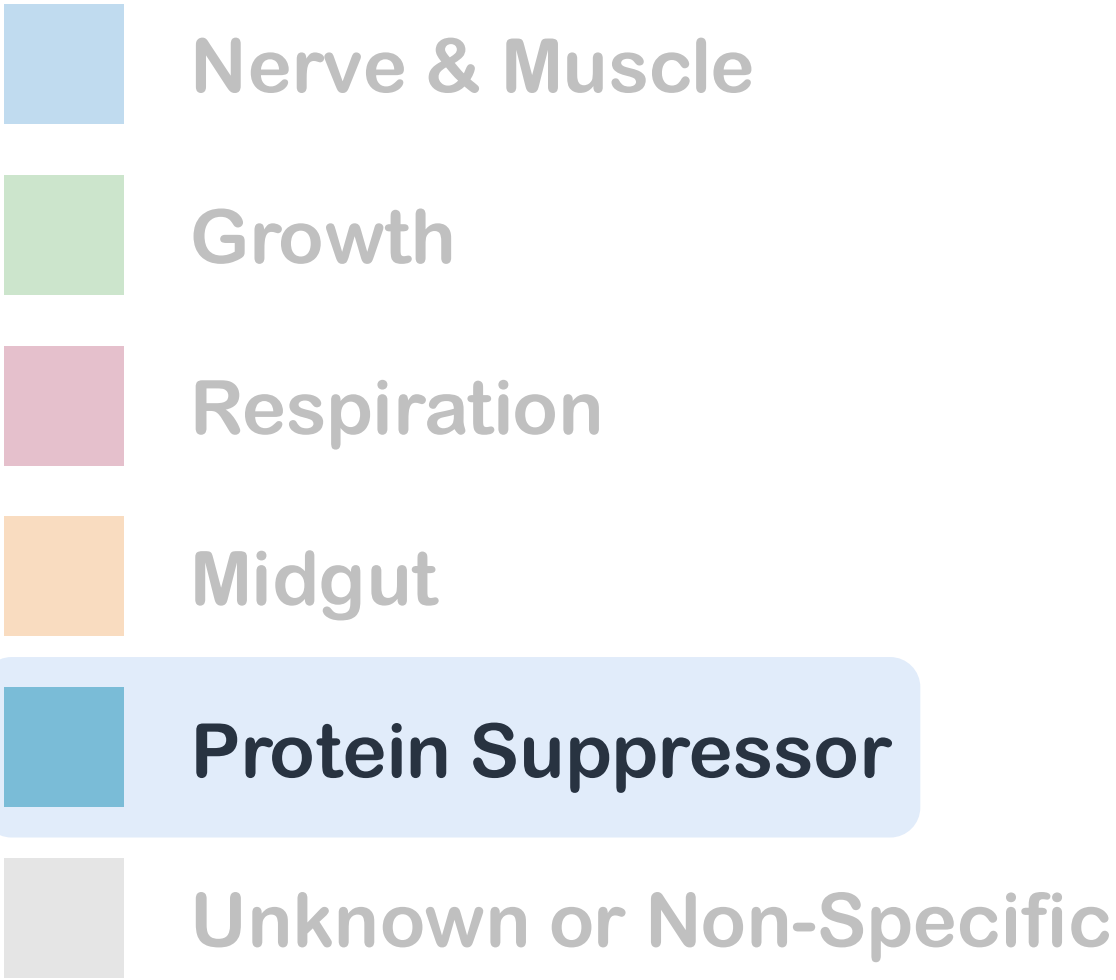
Mode of action of baculoviruses on midgut epithelium

1. Viral occlusion body (OB) disintegrates in alkaline midgut
2. Released occlusion derived virus (ODV) passes through the peritrophic membrane (PM) 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)



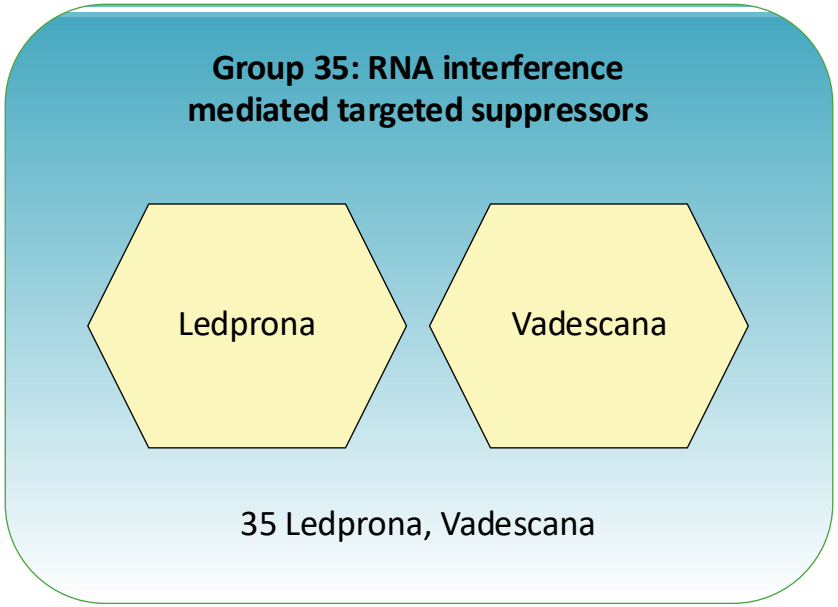
From **Boogaard et al.,** 2018 *Insects 9, 84*

Insecticide Mode of Action: Major classes



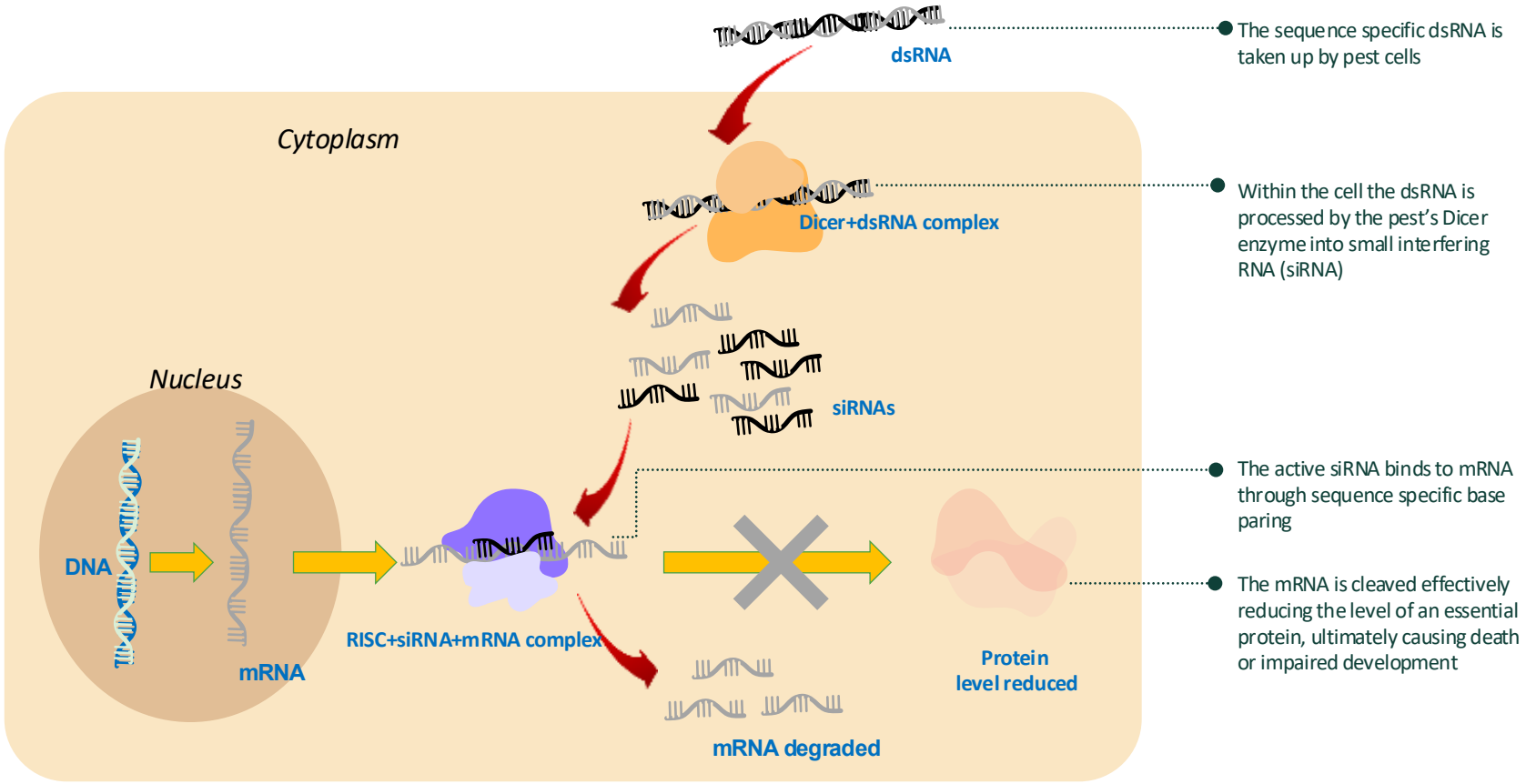
IRAC

RNA interference suppresses translation of target proteins

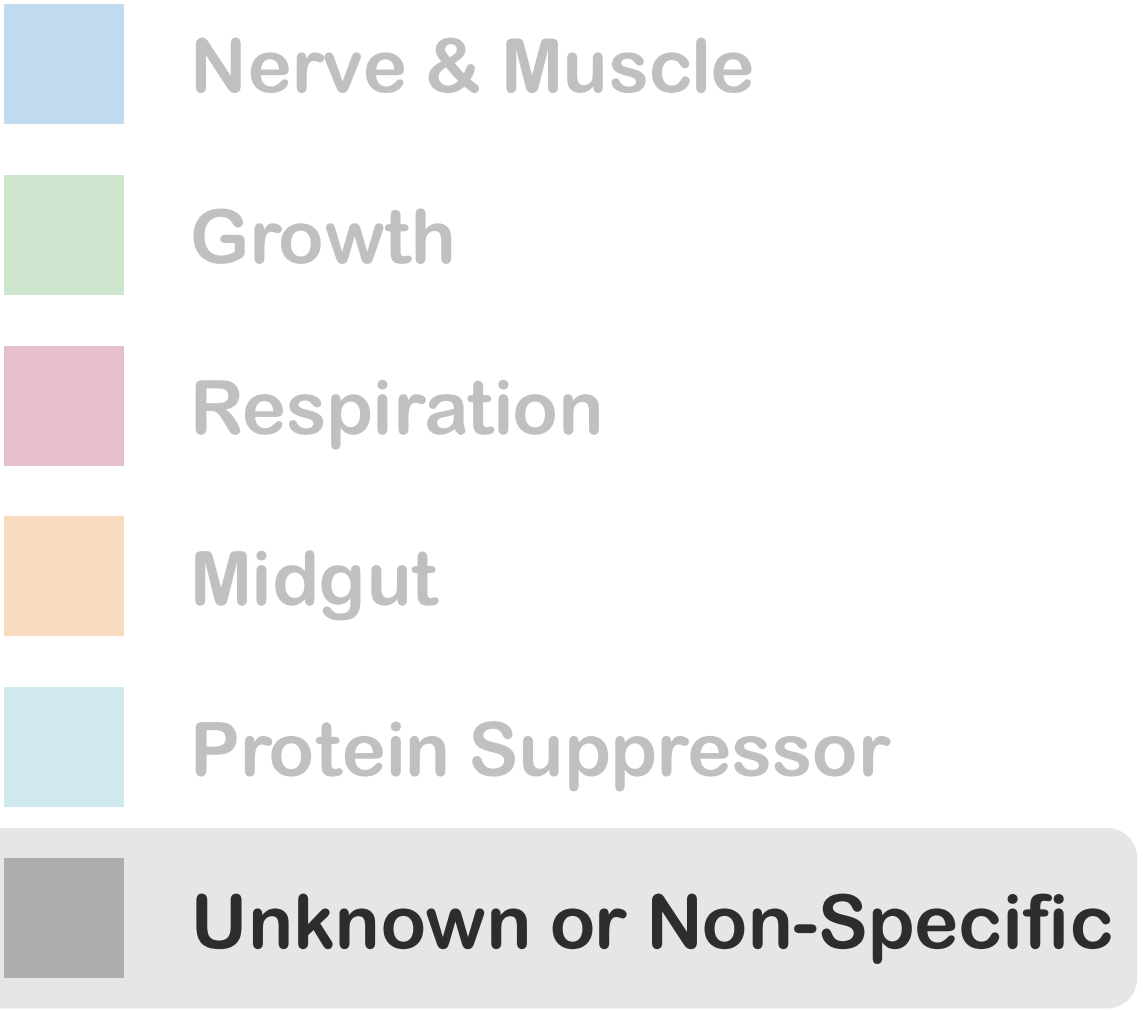


- RNA interference (RNAi) is a natural cellular mechanism that regulates gene expression; it acts as a silencing system for specific messenger RNAs (mRNAs), preventing the production of specific proteins
- dsRNA insecticides act by mimicking this natural gene-silencing process, offering high species specificity which reduces the risk of non-target effects
- In RNAi-based insecticides, double-stranded RNA (dsRNA) molecules are taken up by insect cells. Inside the cells, the dsRNAs are processed by the enzyme, Dicer, into small interfering RNAs (siRNAs), which interact with RNA-induced silencing complex (RISC) proteins to bind to its complementary mRNA sequences, targeting the mRNA for cleavage and degradation
- By destroying these mRNAs, RNAi suppresses the expression of essential genes in the target pest, ultimately causing death or impaired development

RNA interference suppresses translation of target proteins

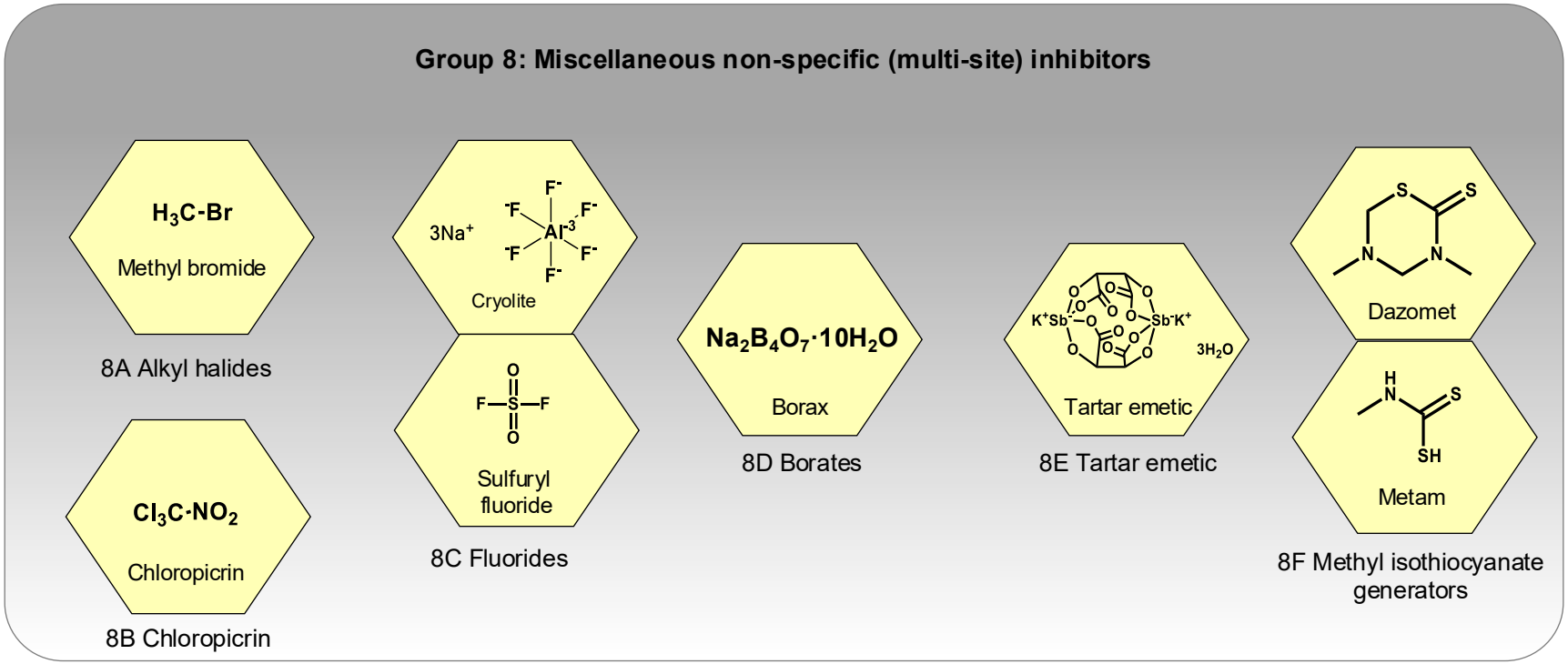


Insecticide Mode of Action: Major classes



IRAC

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.

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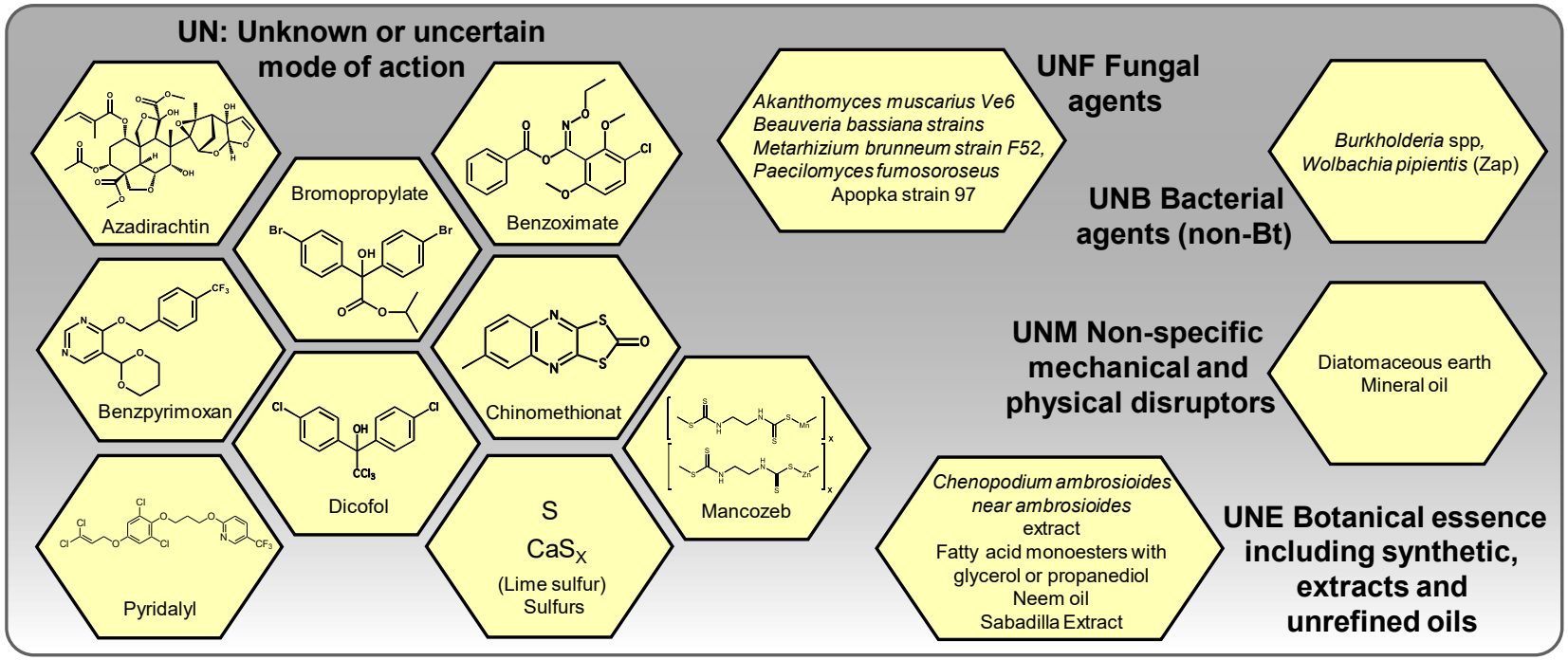
Insecticidal agents of unknown MoA



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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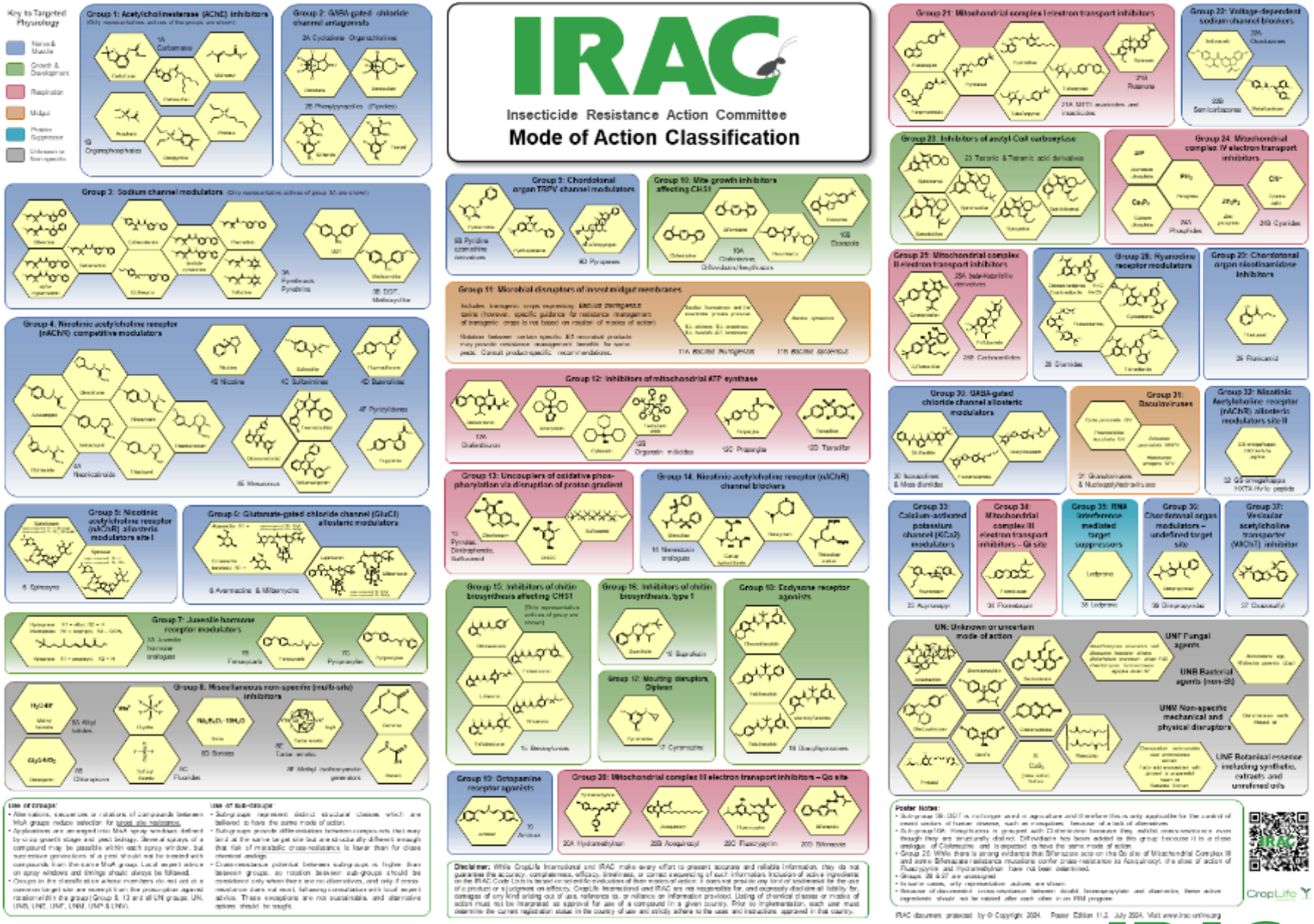
IRAC
Insecticide Resistance Action Committee
Mode of Action Classification
Key to Targeted Physiology
Nerve & Muscle
Growth & Development
Respiration
Midgut
Protein Suppressor
Unknown or Non-specific
Group 1: Acetylcholinesterase (AChE) inhibitors
1A Carbamates
1B Organophosphates
Group 2: GABA-gated chloride channel antagonists
2A Cyclodiene Organochlorines
2B Phenylpyrazoles (Fiproles)
Group 3: Sodium channel modulators
3A Pyrethroids, Pyrethrins
3B DDT, Methoxychlor
Group 4: Nicotinic acetylcholine receptor (nAChR) competitive modulators
4A Neonicotinoids
4B Nicotine
4C Sulfoximines
4D Butenolides
4E Mesoionics
4F Pyridylidenes
Group 5: Nicotinic acetylcholine receptor (nAChR) allosteric modulators site I
5 Spinosyns
Group 6: Glutamate-gated chloride channel (GluCl) allosteric modulators
6 Avermectins & Milbemycins
Group 7: Juvenile hormone receptor modulators
7A Juvenile hormone analogues
7B Fenoxycarb
7C Pyriproxyfen
Group 8: Miscellaneous non-specific (multi-site) inhibitors
8A Alkyl halides
8B Chloropicrin
8C Fluorides
8D Borates
8E Tartar emetic
8F Methyl isothiocyanate generators
Group 9: Chordotonal organ TRPV channel modulators
9B Pyridine azomethine derivatives
9D Pyropenes
Group 10: Mite growth inhibitors affecting CHS1
10A Clofentezine, Diflovidazin, Hexythiazox
10B Etoxazole
Group 11: Microbial disruptors of insect midgut membranes
11A Bacillus thuringiensis
11B Bacillus sphaericus
Group 12: Inhibitors of mitochondrial ATP synthase
12A Diafenthiuron
12B Organotin miticides
12C Propargite
12D Tetradifon
Group 13: Uncouplers of oxidative phosphorylation via disruption of proton gradient
13 Pyrroles, Dinitrophenols, Sulfluramid
Group 14: Nicotinic acetylcholine receptor (nAChR) channel blockers
14 Nereistoxin analogues
Group 15: Inhibitors of chitin biosynthesis affecting CHS1
15 Benzoylureas
Group 16: Inhibitors of chitin biosynthesis, type 1
16 Buprofezin
Group 17: Moulting disruptor, Dipteran
17 Cyromazine
Group 18: Ecdysone receptor agonists
18 Diacylhydrazines
Group 19: Octopamine receptor agonists
19 Amitraz
Group 20: Mitochondrial complex III electron transport inhibitors – Qo site
20A Hydramethylnon
20B Acequinocyl
20C Fluacrypyrim
20D Bifenazate
Group 21: Mitochondrial complex I electron transport inhibitors
21A METI acaricides and insecticides
21B Rotenone
Group 22: Voltage-dependent sodium channel blockers
22A Oxadiazines
22B Semicarbazones
Group 23: Inhibitors of acetyl CoA carboxylase
23 Tetronic & Tetramic acid derivatives
Group 24: Mitochondrial complex IV electron transport inhibitors
24A Phosphides
24B Cyanides
Group 25: Mitochondrial complex II electron transport inhibitors
25A Beta-ketonitrile derivatives
25B Carboxanilides
Group 28: Ryanodine receptor modulators
28 Diamides
Group 29: Chordotonal organ nisoxinamidine inhibitors
29 Flonicamid
Group 30: GABA-gated chloride channel allosteric modulators
30 Isoxazolines & Meta-diamides
Group 31: Baculoviruses
31 Granuloviruses & Nucleopolyhedroviruses
Group 32: Nicotinic Acetylcholine receptor (nAChR) allosteric modulators site II
32 GS omega/kappa HXTX-Hv1a peptide
Group 33: Calcium-activated potassium channel (KCa3) modulators
33 Aryl pyrroles
Group 34: Mitochondrial complex III electron transport inhibitors – Qi site
34 Flometoquin
Group 35: RNA interference-mediated target suppressors
35 Lotilaner
Group 36: Chordotonal organ modulators – undefined target site
36 Dicloromezotiaz
Group 37: Vesicular acetylcholine transporter (VAChT) inhibitor
37 Dicloromezotiaz
UN: Unknown or uncertain mode of action
UNF Fungal agents
UNB Bacterial agents (non-Bt)
UNN Non-specific mechanical and physical disruptors
UNE Botanical essence including synthetic, extracts and unrefined oils
Use of groups:
Use of sub-groups:
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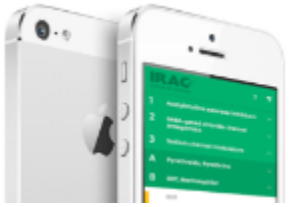
Modes of Action



Pests

Crops

Teams

Test Methods

News

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