Pre-lecture Video

Glutamate activates NMDA + AMPA receptors.

Small presynaptic discharge causes glutamate release → influx of Na^+ to postsynaptic cell through AMPA receptors Depolarizes postsynaptic cells → small influx through NMDA

large presynaptic discharge causes glutamate release → influx of Na^+ to postsynaptic cell through AMPA receptors Depolarizes postsynaptic cell → Mg^{2+} block on NMDA receptor opens allowing influx of Ca^{2+} - a secondary messenger

↓

Ca^{2+} activates intracellular signaling cascades

CAMKII can adds AMPA receptors → response to a stimulus is 'greater'/enhanced

↓

underlies LTP

Lecture 16. Learning 1- NMDA Receptor Function

Professor Christiane Linster

Pre-lecture preparation

(1) Pre-lecture video on NMDA receptors
(2) Read pages 814-815; Figures 23.27, 23.28
(3) Read pages 827 – 828; Figures 24.2, 24.3
(4) Optional read Box 25.1 page 871-873
(5) Review lectures 7-11 (ion channels and synaptic communication)
(6) Review lecture 14 (Plasticity)

Learning Objectives

To understand the function and role of NMDA receptors in synaptic function and synaptic plasticity

(1) Be able to understand the role of plasticity for learning in a broad sense
(2) Understand the difference between non associative and associative learning in a broad sense and relate it to synaptic function
(3) Be able to describe the structure of NMDA receptors and compare it to other receptor types
(4) Understand how NMDA receptors can implement "AND" gates
(5) Be able to describe the mechanisms underlying NMDA receptor function
(6) Understand how NMDA receptor function is predictive of plasticity necessary for learning

Lecture Outline

1) Learning is the acquisition of new knowledge or skills and memory is the retention of this learned information. Learning generally involves changes in neural responses to a stimulus and changes in motor commands. These changes in return necessitate plasticity between neural pathways.
2) Most forms of learning need to associate events, stimuli or behavioral outcomes with other events or stimuli (Figures 24.2 and 24.3 and associated text). At the neural level, this type of association necessitates a mechanisms by which neural events can be associated with each other under certain conditions. One form of learning, habituation does not associate an event or stimulus with an outcome or stimulus, but rather functions in a "non-associative" manner. This type of learning can be related to short term synaptic plasticity (see Lecture 14).
3) Ion channels, voltage dependent channels and second messenger channels are all means to change communication between neurons or neuronal states as a function of context (other neurons' activities and states, sensory inputs ..) (Lectures 7-11). A special type of channel is the NMDA channel, which allows to associate pre and postsynaptic activity in a sense that this channel only opens to let ions flow in and out of the cell if both the postsynaptic and presynaptic neuron are active (Figures 23.27 and 23.28 and associated text).

4) An NMDA channel implements an "AND" gate for all practical purposes. Logical gates are comprised of "NOT", "OR", "AND" and "XOR". The table below shows how these gates work, with IN1 and IN2 being two logical inputs which can take on the values 0 (False) or 1 (True) and Out being one output also taking on the values 0 (False) or 1 (True) depending on the combination of inputs and the type of gate.

	IN1	**IN2**	**OUT**
NOT	0	-	1
	1	-	0
OR	0	0	0
	0	1	1
	1	0	1
	1	1	1
AND	0	0	0
	0	1	0
	1	0	0
	1	1	1
XOR	0	0	0
	0	1	1
	1	0	1
	1	1	0

5) NMDA channel function can be related to simple learning situations discussed in lecture.

Study Questions

1) How does the NMDA receptor function compare to other receptors you have studied?
2) How does the Mg+ block work?
3) In what sense does an NMDA channel act as an "AND" gate?

Lectures 16-21: Learning and memory

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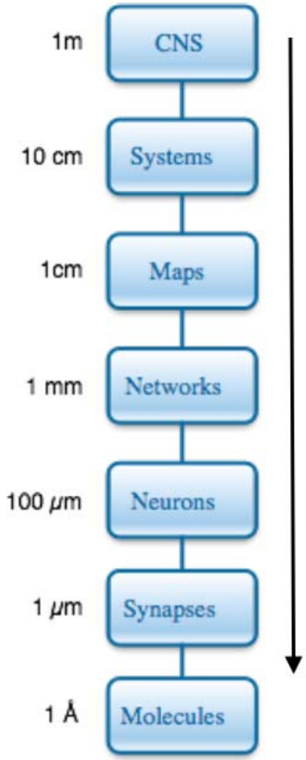
Office hours Wed. 1:30-2:30 or by appointment

Themes in this course



Neuroanatomy, structure and function
Prof. Andrew Bass

Learning and memory Prof. Christiane Linster

Foundations: Neurons and neural communication
Prof. Joseph Fetcho, Dr. Bruce Johnson and Dr. Shelby Dietz

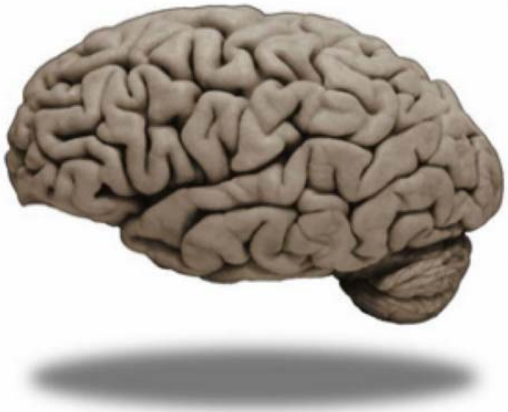
Neuroscience is the study of ...

Movement

Emotions

Sensation

Pattern recognition



Language

Object detection

Body regulation

Risk-reward assessment

Series of events?

Sensing the environment : Dr Yapici

Neurons, receptors, synapses

Creating an association between stimuli

Remembering an association

Acting on an association

Making a decision: Dr. Warden

Networks

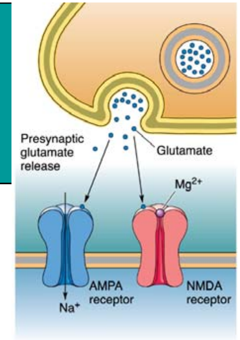
Giving a motor command : Dr Goldberg

Lectures 16-21: Learning and memory

Lecture 16	NMDA receptor allows to “associate” two events at the level of a synapse
Lecture 17	Learning at the synaptic level: LTP and LTD
Lecture 18	Learning at the network level: how are LTP and LTD involved in changing networks ?
Lecture 19	Learning while behaving: sequences of events and STDP
Lecture 20	Remembering: Consolidation of what has been learned
Lecture 21	What is a memory?

Lecture 16: Learning 1

NMDA receptor function



(a) Postsynaptic membrane at **resting** potential

(1) To understand the function and role of NMDA receptors in synaptic function and synaptic plasticity

(2) Be able to understand the role of plasticity for learning in a broad sense

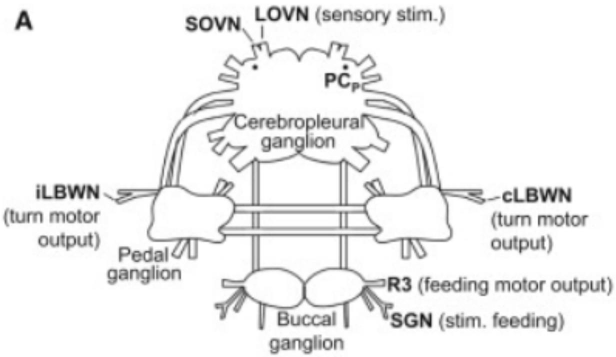
(3) Be able to describe the structure of NMDA receptors and compare it to other receptor types

(4) Understand how NMDA receptors can implement "AND" gates

(5) Be able to describe the mechanisms underlying NMDA receptor function

(6) Understand how NMDA receptor function is predictive of plasticity necessary for learning

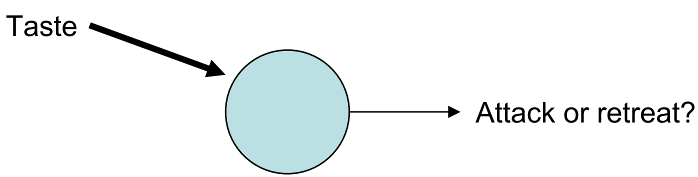
Pleurobranchaea californica



A Neuronal Network Switch for Approach/Avoidance Toggled by Appetitive State. Current Biology, 2011; DOI: 10.1016/j.cub.2011.10.055 http://www.cell.com/current-biology/r...

Pleurobranchaea californica

Remember from Dr. Dietz: SOME actions want to be hardwired and not submitted to learning!



Pleurobranchaea californica

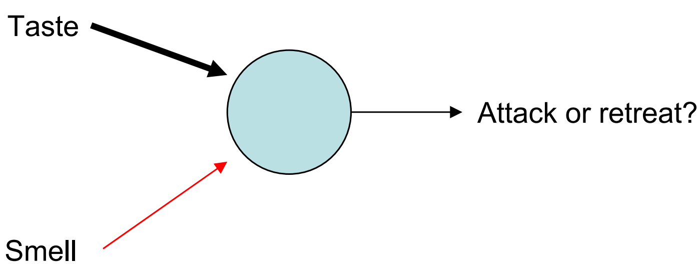
Taste

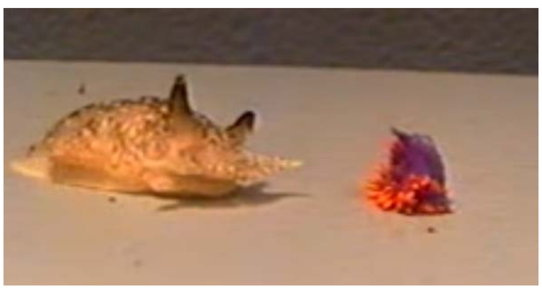
Attack or retreat?

Remember from Dr. Dietz: SOME actions want to be hardwired and not submitted to learning!

Pleurobranchaea californica

Remember from Dr. Dietz: SOME actions want to be hardwired and not submitted to learning!



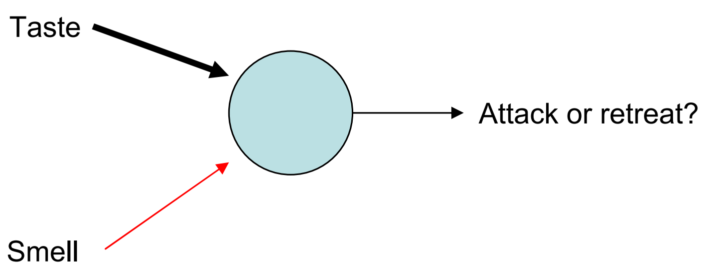


The association between smell and taste has to be learned and retrieved to prevent future bad tastes

Clicker question

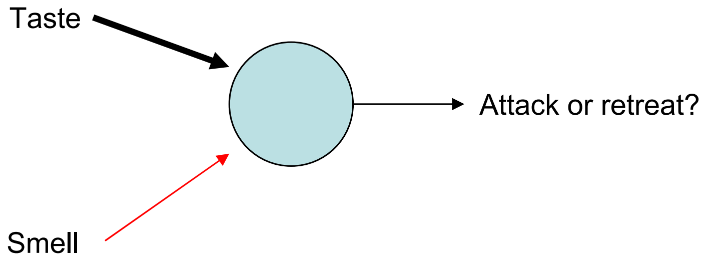
Which of the following statements are true to ensure proper learning in this situation:

A. You want to increase the effect of smell on motor command in the absence of bad taste
B. You want to keep the effect of bad taste on motor command constant
C. You want to increase the effect of smell on motor command in the presence of bad taste
D. A&B
E. B&C



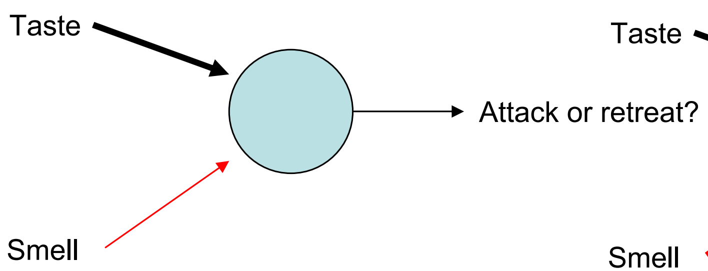
(1) Before learning the association, bad taste has to trigger motor command

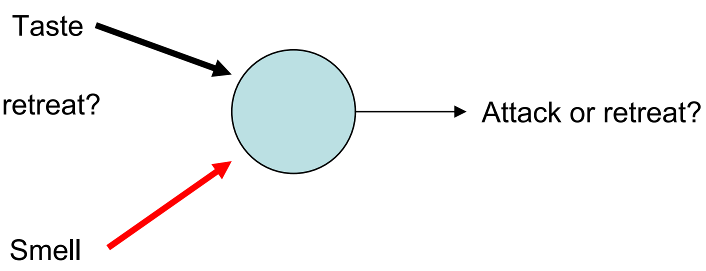
What are the steps necessary ? What ingredients do you need?



(1) Before learning the association, bad taste has to trigger motor command
(2) Before learning the association, smell should NOT trigger motor command
(3) After learning, smell SHOULD trigger motor command BEFORE taste stimulus

What are the steps necessary ? What ingredients do you need? What mechanisms do you know of to make this happen? What can change in the synapses to create this new way to trigger motor command?

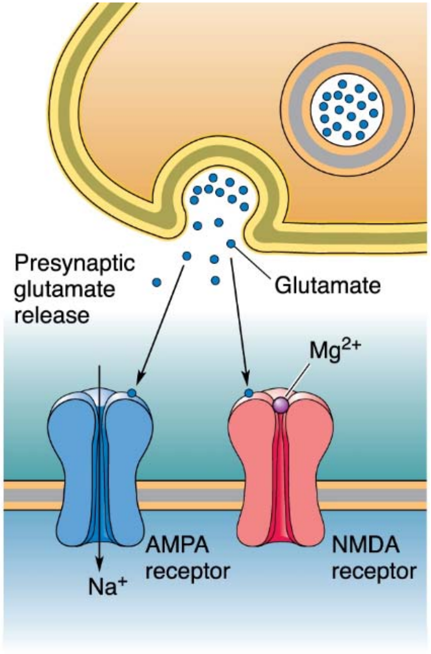




Clicker question

Which are the permissive factors for Ca+ to enter the postsynaptic cell?

A. Mg+ release and postsynaptic depolarization
B. MG+ release and presence of glutamate
C. Presence of glutamate and depolarization
D. Presynaptic action potential and presence of glutamate

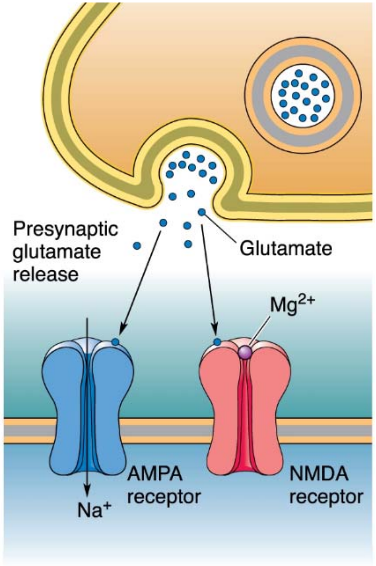


(a) Postsynaptic membrane at **resting** potential

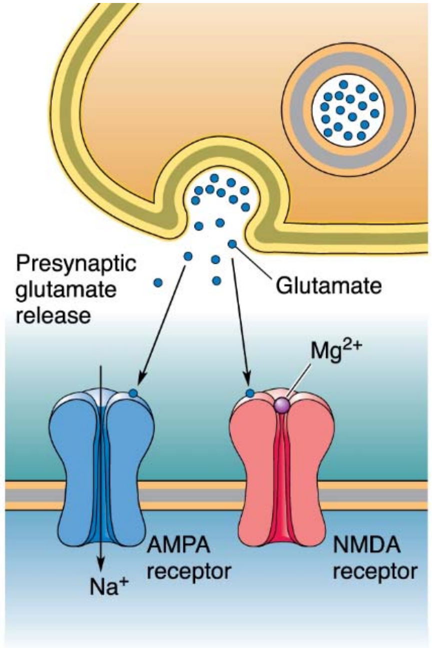
Clicker question

What is the correct sequence of actions to allow Ca+ to enter the postsynaptic cell?

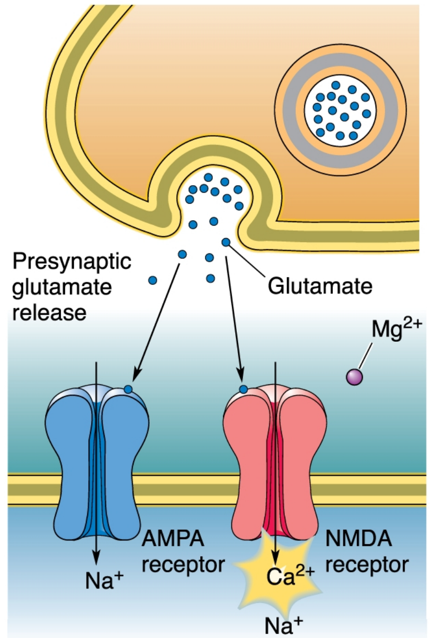
A. Postsynaptic cell depolarizes, Mg+ is released, presynaptic cell release glutamate, glutamate binds
B. Mg+ is released, postsynaptic cell depolarizes, glutamate binds
C. Glutamate is released, Na+ enters through AMPA receptor, postsynaptic cell depolarizes, Mg+ is released
D. All of the above
E. None of the above



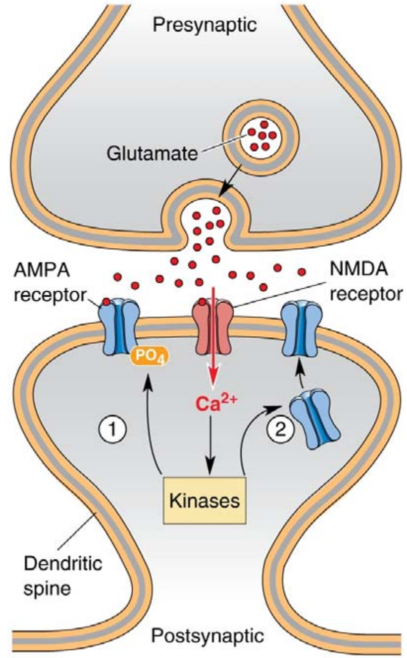
(a) Postsynaptic membrane at **resting** potential



(a) Postsynaptic membrane at **resting** potential



(b) Postsynaptic membrane at **depolarized** potential



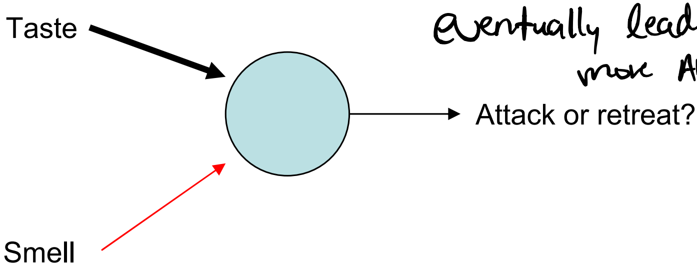
Clicker question

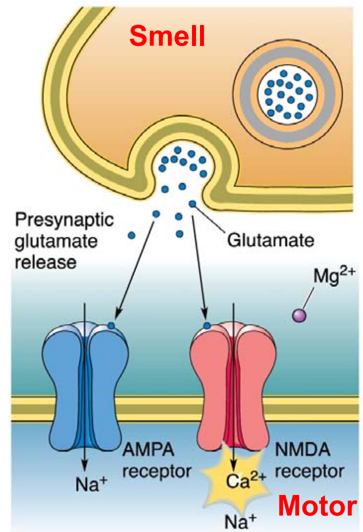
During learning, the goal is to strengthen smell – motor association in the presence of taste!

The “synaptic” goal is therefore to

~~A.~~ Let Mg+ block the NMDA receptor when smell is present
B. Let Ca+ into the cell when taste and smell are present at the same time
~~C.~~ Let Na+ into the cell when taste is detected
~~D.~~ Hyperpolarize the cell when smell is detected
~~E.~~ All of the above

eventually leads to more AMPA receptors



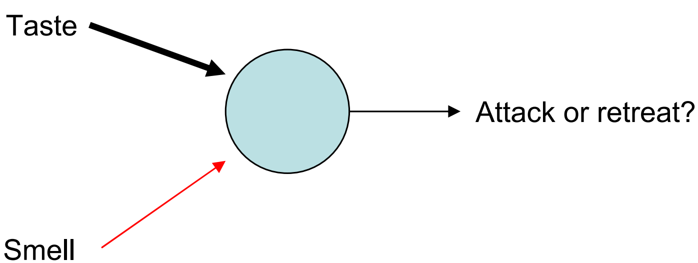


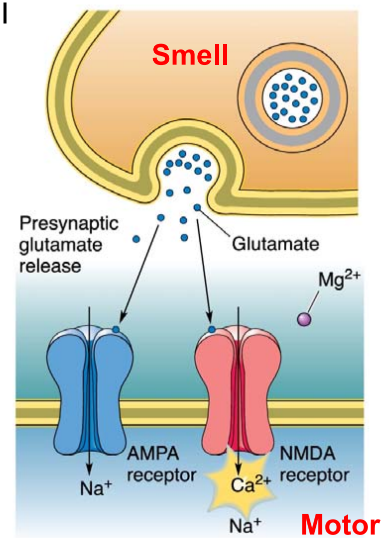
(b) Postsynaptic membrane at **depolarized** potential

Clicker question

After learning, the strength of action between smell and motor output could be modulated by

A. Weakening the Mg+ block of the NMDA receptor
B. Increasing the number of NMDA receptors
C. Rendering the presynaptic cell more excitable
D. Increasing the number of AMPA receptors on the postsynaptic cell
E. None of the above





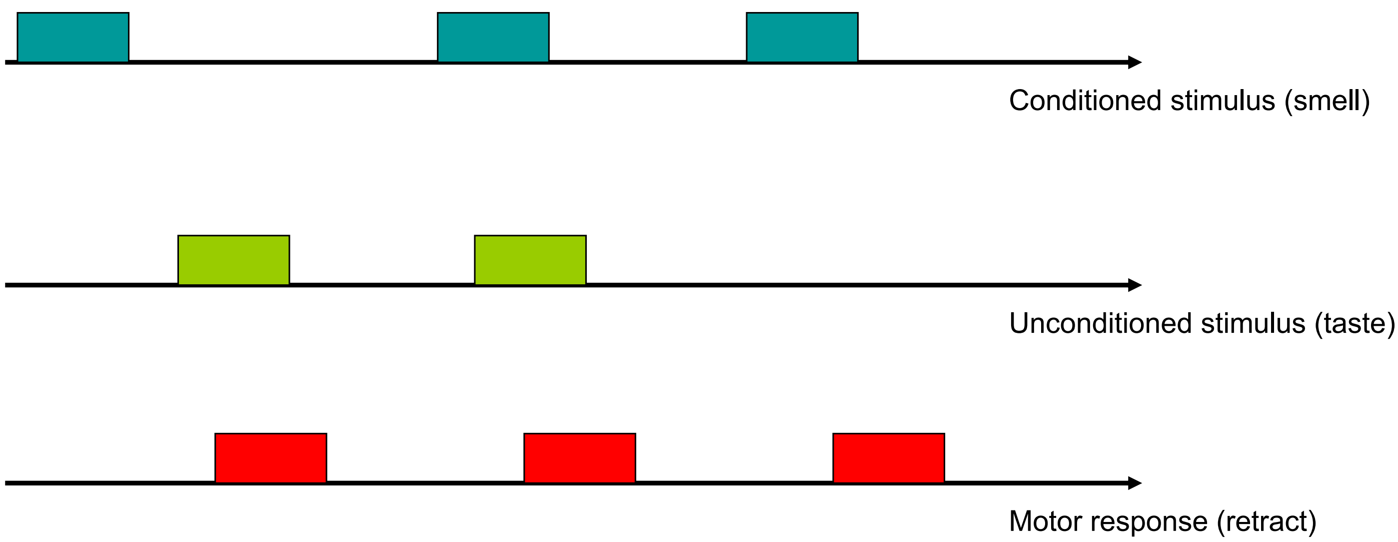
(b) Postsynaptic membrane at **depolarized** potential

Clicker question

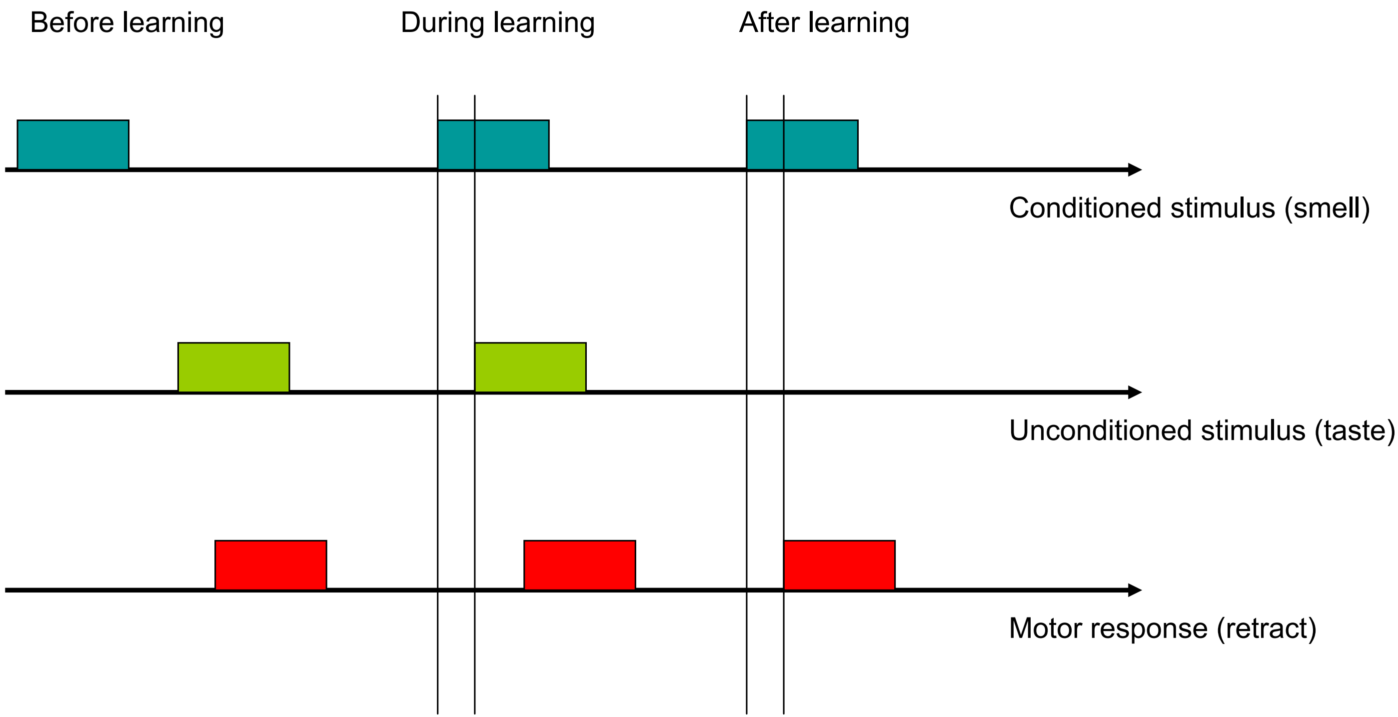
An NMDA receptor acts like an “AND” gate because

A. ~~It opens only when either pre or postynaptic cell are “active”~~
B. ~~It opens only when the postsynaptic cell is “active”~~
C. It opens only when both pre and postsynaptic cells are “active”
D. ~~It is always open~~
E. ~~It is always closed~~

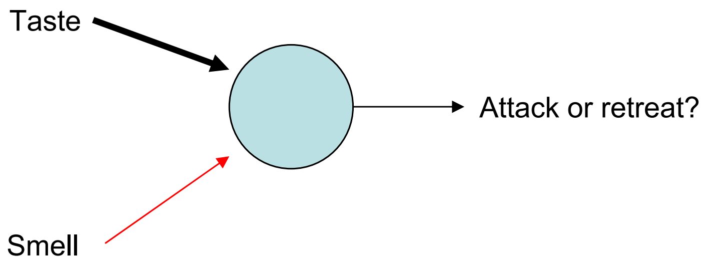
Time course of classical conditioning



Time course of classical conditioning

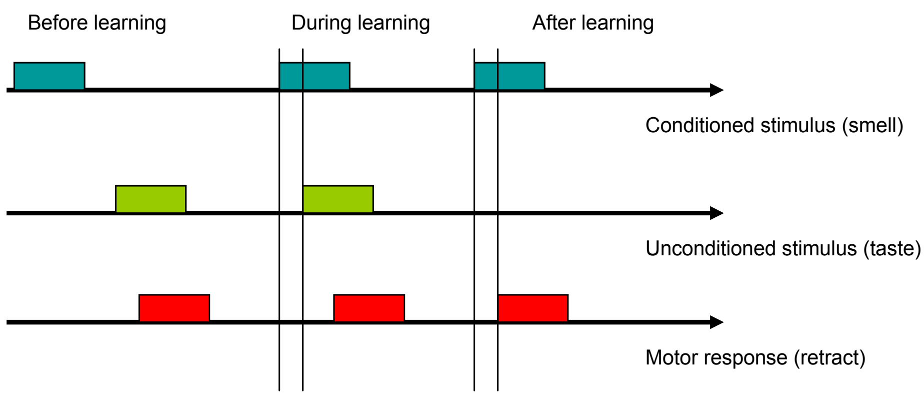


Clicker question:



Which synapse needs AMPA receptors?

A. Taste-motor
B. Smell-motor
C. Both
D. Neither



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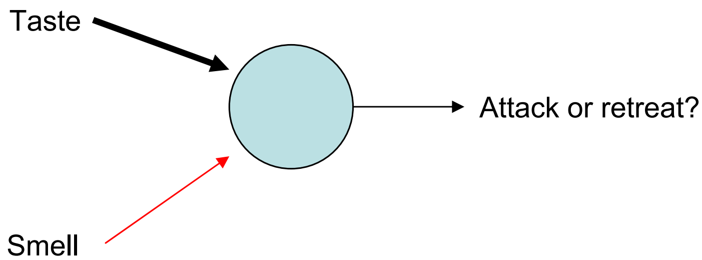
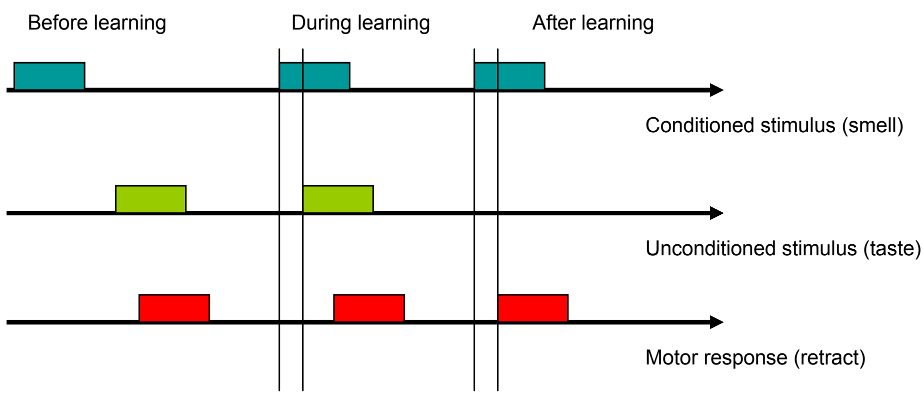


Which synapse needs NMDA receptors?

A. Taste-motor
B. Smell-motor
C. Both
D. Neither

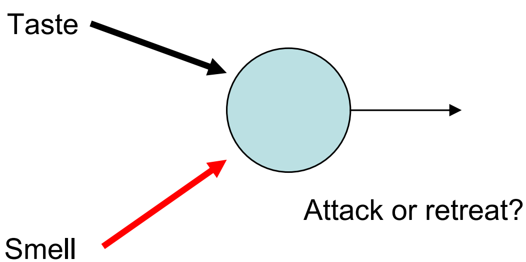


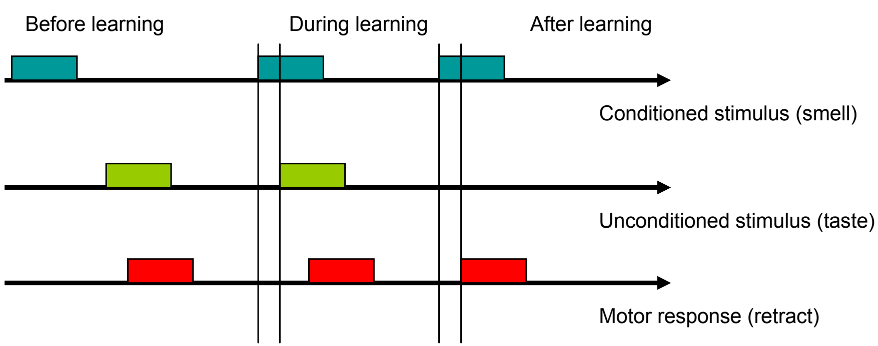
Clicker question:

Which neural time course matches the behavioral time course?

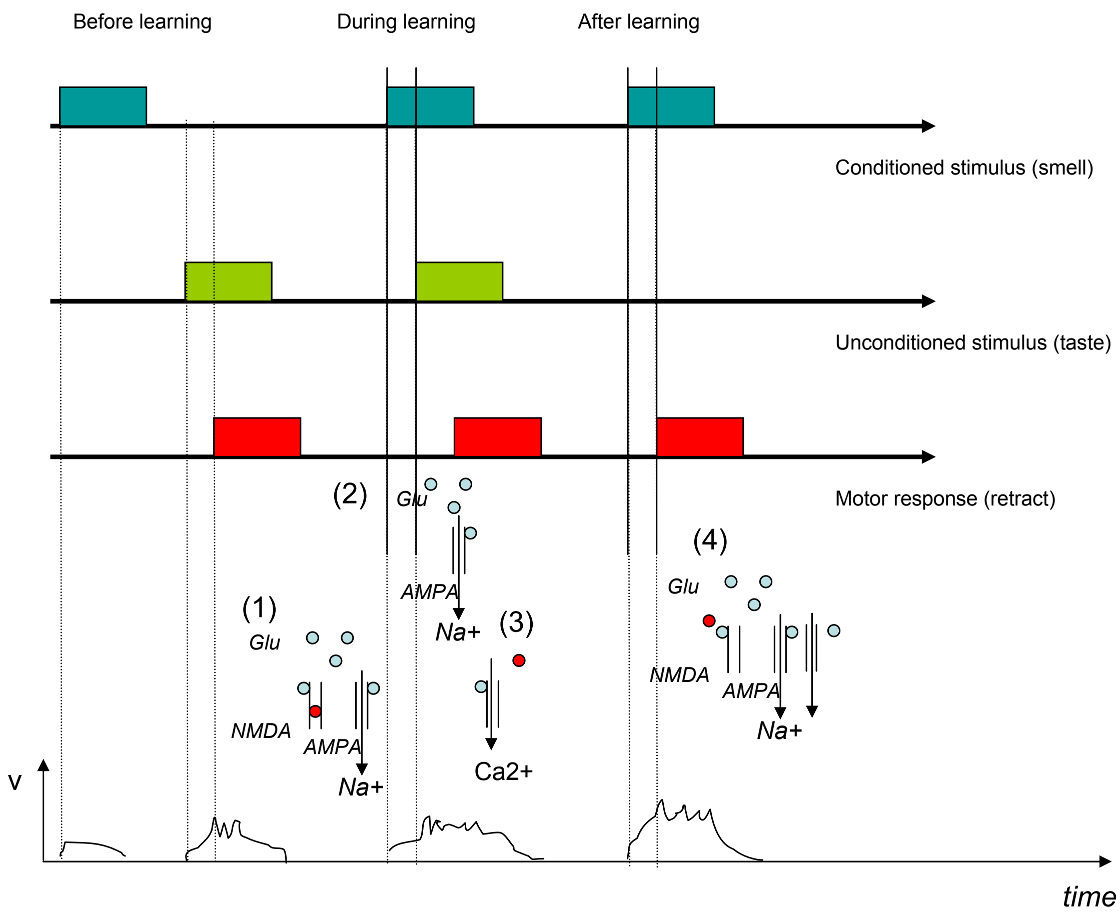
A. (1) Glu released into smell synapse binds to AMPA and NMDA, Na+ enters cells
(2) Glu released into taste synapse binds to AMPA, Na+ enters cell and depolarizes cell
(3) Mg+ block is released
(4) Ca+ enters cell through NMDA receptors
(5) Smell synapse is strengthened

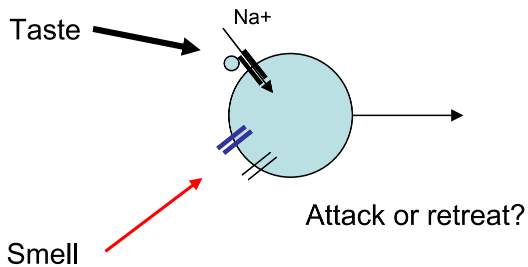
B. (1) Glu released into taste synapse binds to AMPA and depolarizes cell
(2) Glu released into smell synapse binds to NMDA and lets Na+ into cell
(3) Mg+ block released
(4) Synapse strengthened.

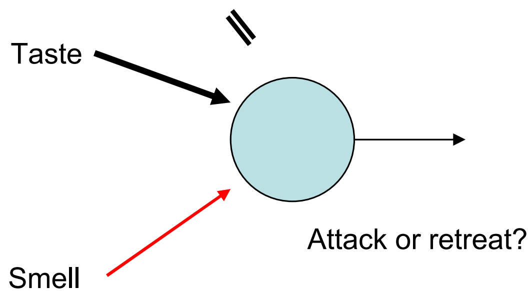




Time course of classical conditioning



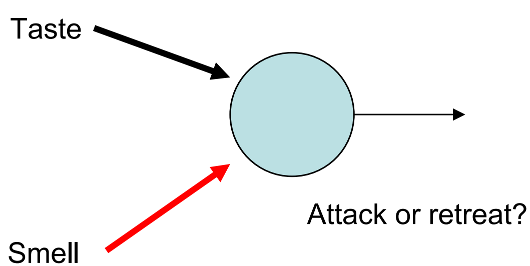


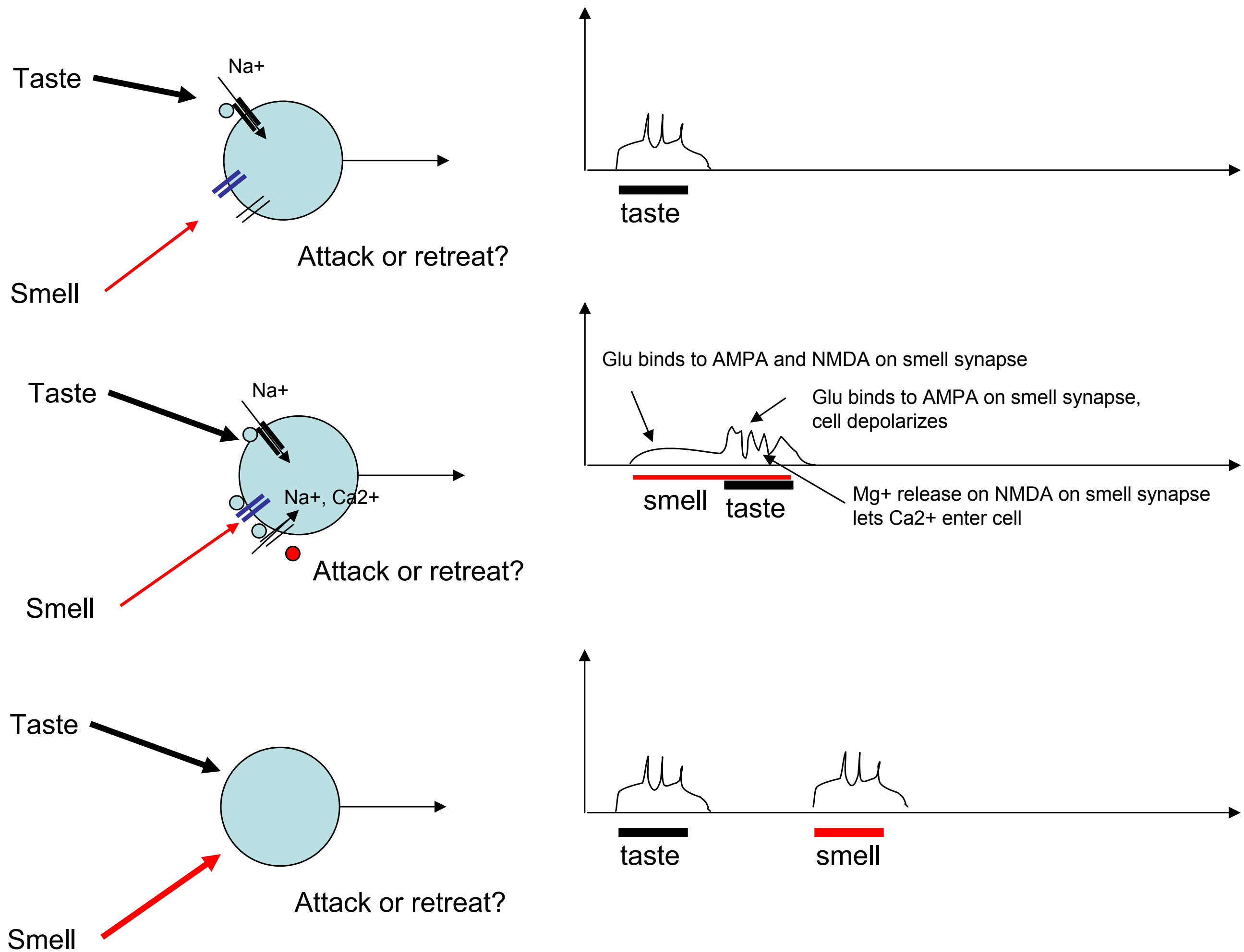


Clicker question:

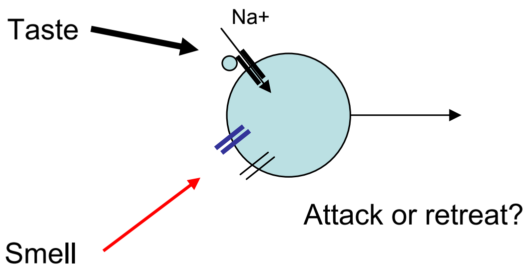
Depolarization by taste stimulus has to reach --- to create the motor response:

A. Threshold for action potential
B. Voltage for Mg+ release
C. Nernst potential for Na+





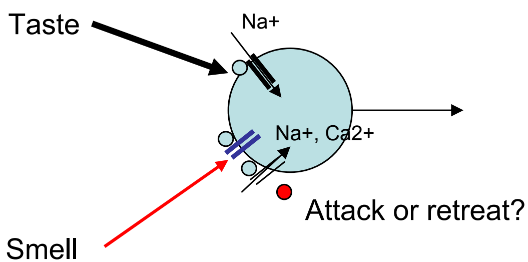
Taste
Na+
Smell
Attack or retreat?
taste
Taste
Na+
Na+, Ca2+
Smell
Attack or retreat?
Glu binds to AMPA and NMDA on smell synapse
Glu binds to AMPA on smell synapse, cell depolarizes
smell
taste
Mg+ release on NMDA on smell synapse lets Ca2+ enter cell
Taste
Smell
Attack or retreat?
taste
smell

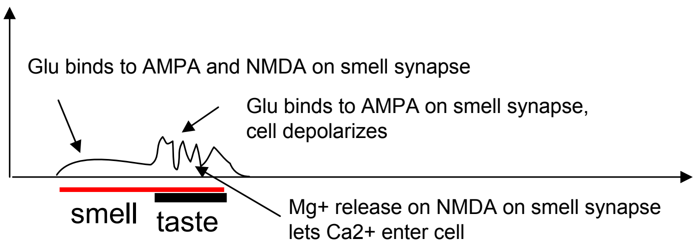


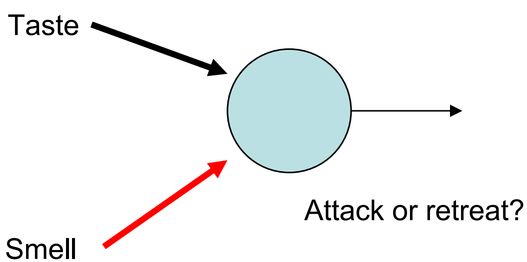
Clicker question:

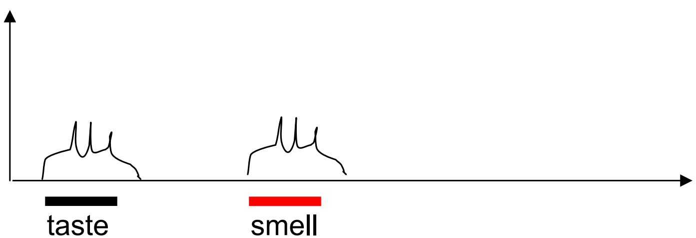
Are NMDA receptors needed for smell to trigger retreat AFTER learning:

A. Yes
B. No









Clicker question

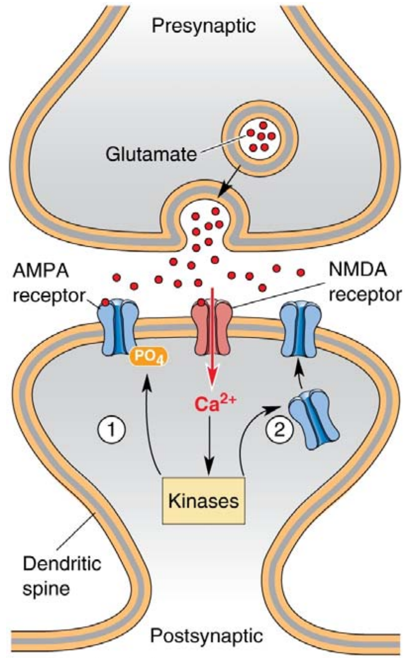
What happens to the plasticity induced by NMDA receptor activation if extracellular Ca2+ is reduced?

A. Nothing
B. It decreases
C. It increases

Clicker question

In brain slice experiments, the bath solution often contains NO Mg+.
In these experiments :

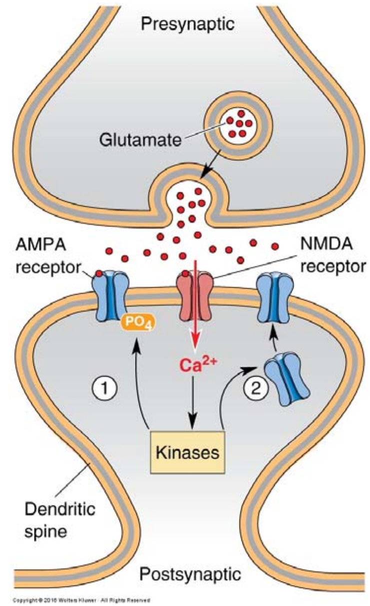
A. NMDA receptors can never opne
B. NMDA receptors are always open
C. NMDA receptors open when glut binds independent of voltage
D. NMDA receptors only open when Glu binds and cell is hyperpolarized
E. None of the above



Clicker question

The NMDA receptor creates an AND gate in which :

A. Presynaptic activity is signaled by Ca+ and postsynaptic activity by Na+
B. Presynaptic activity is signaled by Glu release and postsynaptic activity by Na+
C. Presynaptic activity is signaled by Na+ release and postsynaptic activity by Glu
D. Presynaptic activity is signaled by Glu release and postsynaptic activity Mg+ block release
E. Presynaptic activity is signaled by Mg+ release and postsynaptic activity by Na+



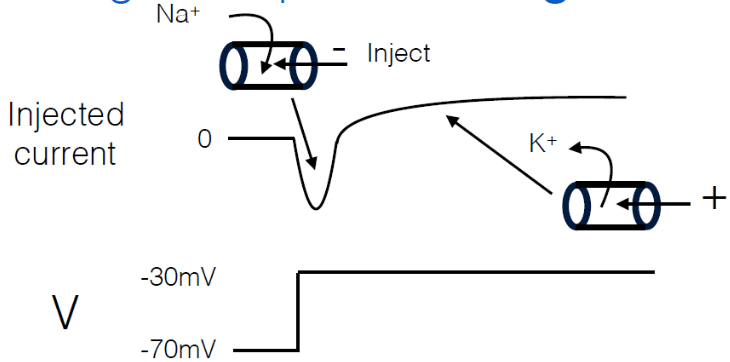
Clicker question

Can you study the “AND” gate function of the NMDA receptor in a voltage-clamp experiment?

A. Yes
B. No

Reminder:

Voltage clamp: **measuring current, control voltage**



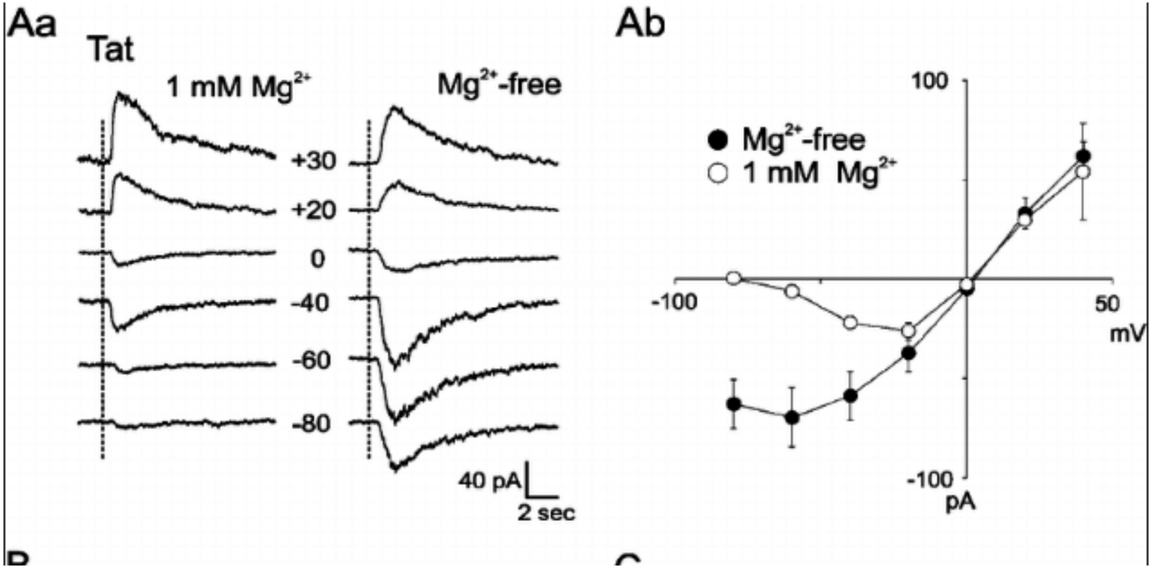
Clicker question

Can you study the “AND” gate function of the NMDA receptor in a voltage-clamp experiment?

A. Yes
B. No

In a voltage clamp experiment, where would you clamp the voltage while stimulating presynaptic transmitter release to see the “AND” function

A. At rest
B. At the reversal potential for Na+
C. At the voltage that triggers Mg+ release
D. At the reversal potential for Ca2+
E. None of the above

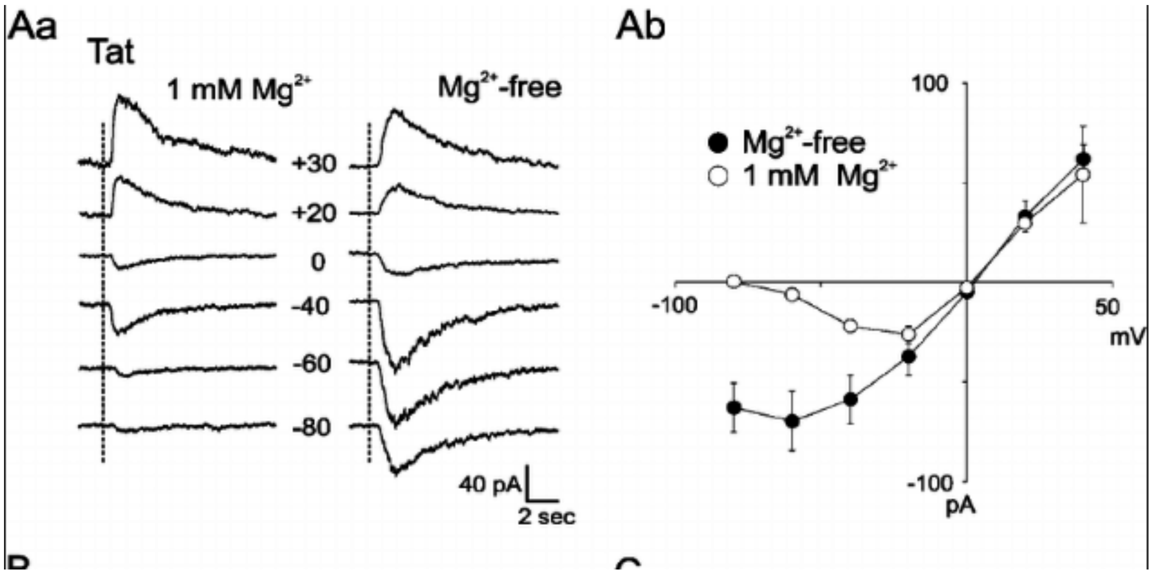


Journal of NeuroVirology 9(3):399-403 · July 2003 *with* 143 Reads
DOI: 10.1080/13550280390201704 · Source: PubMed

Clicker question

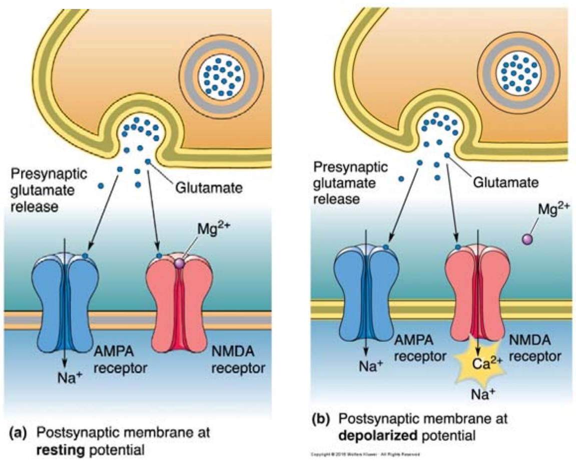
Knowing the average values for reversal (Nernst) potentials for ions, what can you conclude from these traces?

A Mainly Cl- ions flow
B. Mainly K+ ions flow
C. Mainly Na+ ions flow



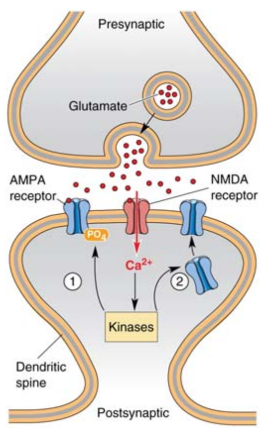
What you should take away from this lecture and remember

(1) NMDA receptors are both ligand (Glu) and voltage gated
(2) NMDA receptors when open are permeable to Na+ and Ca2+
(3) At resting membrane potential, NMDA receptors are blocked by Mg+
(4) At resting membrane potential, Glu can bind to the receptor but not open it
(5) Mg+ block can be released via depolarization of the cell
(6) Once Mg+ block is released, Na+ and Ca2+ enter cell via NMDA receptor
(7) Ca2+ entry into cell sets in motion synaptic plasticity
(8) NMDA and AMPA receptors are often co-localized, one regulates synaptic strength (AMPA), the other plasticity (NMDA)
(9) The time course of interactions between synaptic events that leads to plasticity can match the time course of behavioral plasticity



(a) Postsynaptic membrane at **resting** potential

(b) Postsynaptic membrane at **depolarized** potential



(10) The NMDA receptors implements an AND gate in that it opens only when both pre and postsynaptic cells are active