Bioassay of Antiepileptic Activity

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Epilepsy Definition

- Epilepsy is a common chronic neurological disorder characterized by seizures.

- An epileptic SEIZURE (convulsion; fit) is the transient abnormal
  1. excessive or
  2. synchronous (simultaneous)

  neuronal activity in the brain.

Anticonvulsant

- The goal of an anticonvulsant is to suppress the rapid and excessive firing of neurons that start a seizure.

Antiepileptic

- Antiepileptic drugs are medicines that reduce the frequency of epileptic seizures.

Methods

A. Anticonvulsant Models

1. Chemical-induced Convulsions
2. Maximal Electroshock (MES) in Mice

B. Antiepileptic Models

1. Electrical Stimulation
2. Chemical-induced Kindling
3. Genetic epilepsy models

A. Anticonvulsant Models

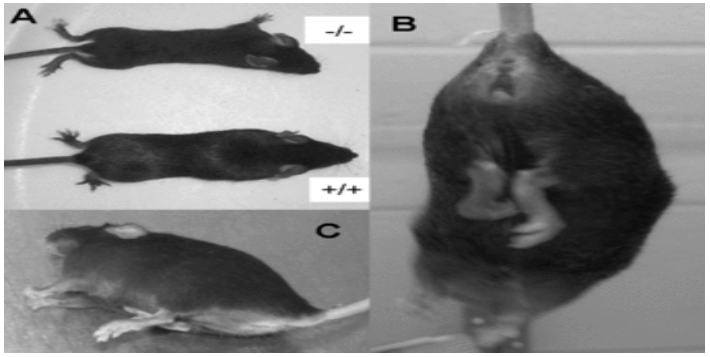
1. Chemical-induced Convulsions

Principle

convulsion is reduced by

anticonvulsants

anxiolytic agents



Convulsive response

act on **similar targets** of anticonvulsants

A. Anticonvulsant Models

1. Chemical-induced Convulsions

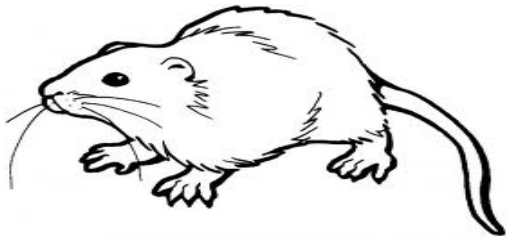
Procedure

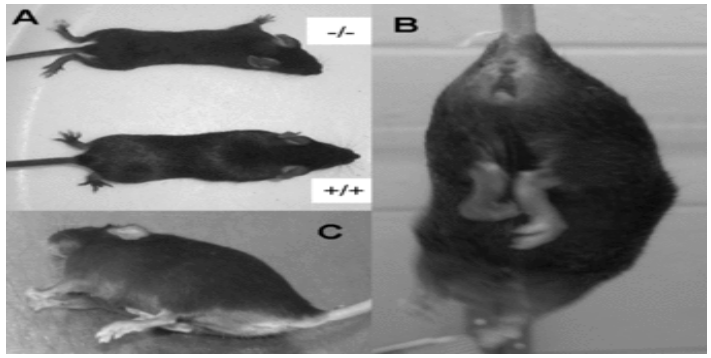
Administration

before

Regimen

Standard Test





Convulsive response

Animal Species

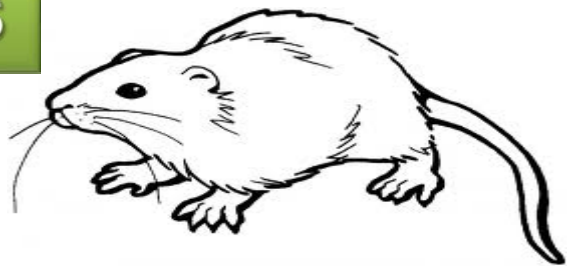
1. Mice
2. rats
3. Male Swiss-Webster mice

→ **Yohimbine-induced convulsions**

The administered convulsant is observed for a period lasting 0.5-1 hours

A. Anticonvulsant Models

1. Chemical-induced Convulsions



male Swiss-Webster mice

Convulsant

Pentylenetetrazole	Strychnine	Picrotoxin	Isoniazid	Yohimbine
$GABA_A$ antagonist (non-competitive)	competitive glycine receptor antagonist	Non-competitive $GABA_A$ antagonist	GABA-synthesis inhibitor	clonic-tonic seizures

A. Anticonvulsant Models

1. Chemical-induced Convulsions

N.B. Model validity

Convulsion should be produced in 80% of the animals in the model group

Response [observation period]

- Seizures latency
- Number of
  - tonic/clonic convulsions
  - dead animals
  - protected animals

A. Anticonvulsant Models

2. Maximal Electroshock (MES) in Mice

Principle

male mice

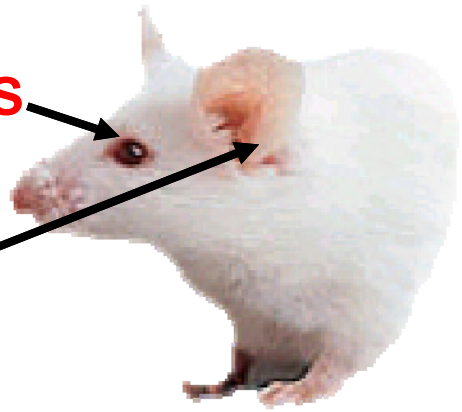
↓

electric stimuli

using corneal electrodes

or

ear electrodes



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observed closely for 2 min

A. Anticonvulsant Models

2. Maximal Electroshock (MES) in Mice

It is a **model** for Grand Mal Epilepsy

because **electrical stimulation** causes
Tonic Hind limb Extensions

Tonic convulsion is reduced by

- anticonvulsants
- other centrally active drugs e.g. anxiolytics

A. Anticonvulsant Models

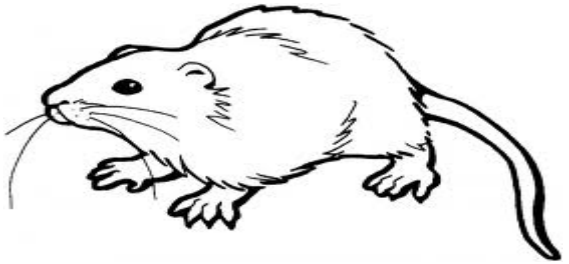
2. Maximal Electroshock (MES) in Mice

Procedure

before

Regimen

Standard Test



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Mice or rats

↓

Electrical shock

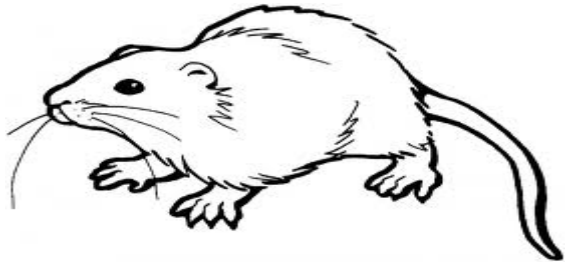
↓

2 min observation for the hind leg extensor tonic convulsion

A. Anticonvulsant Models

2. Maximal Electroshock (MES) in Mice

Evaluation



Response
(positive criterion)

↓

Disappearance of the hind leg extensor tonic convulsion

↓

Percent of inhibition of seizures relative to control (=model)

B. Antiepileptic Models

1. Genetic Epilepsy Animal Models

Principle

- Spontaneous epileptic animals are mutant and exhibit spontaneous recurrent seizures.

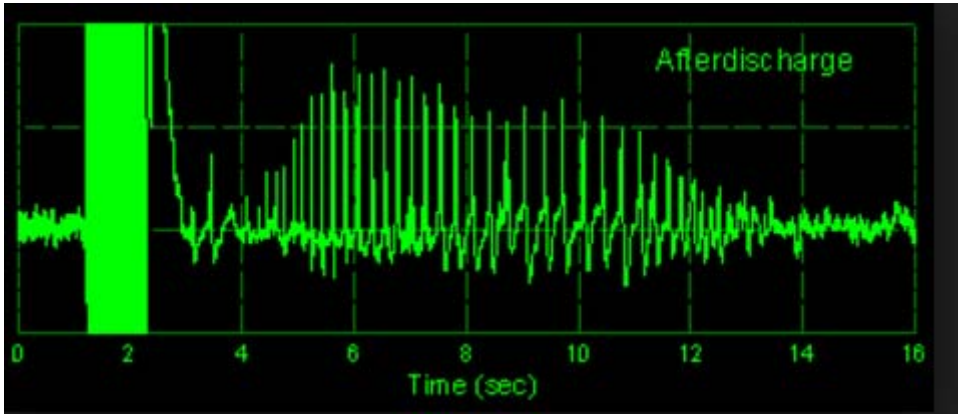
- These include several animal species such as dogs, rats, and mice.

B. Antiepileptic Models

2. Amygdala Kindling Model

What is **after-discharge???**

- A discharge of **neural impulses** (as by a ganglion cell) **after termination** of the **initiating stimulus**



B. Antiepileptic Models

2. Amygdala Kindling Model

What is kindling???

➔ It involves the delivery of

1. brief
2. initially subliminal (subthreshold)
3. electrical or chemical

} STIMULI to various areas of the brain.

➔ After 10 to 15 days of stimulation, the after-discharges reach a

1. stable
2. maximum
3. characteristic

} SEIZURE

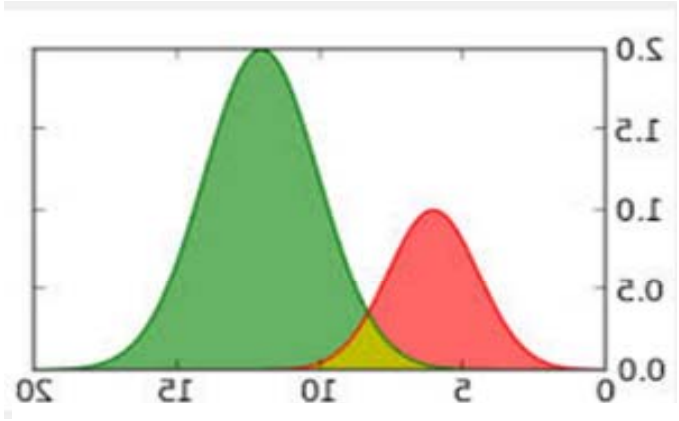
➔ Subsequent stimulation then REGULARLY elicits seizures.

B. Antiepileptic Models

2. Amygdala Kindling Model

N.B.:

- Amygdala electrical stimulation lowers the after-discharge threshold



B. Antiepileptic Models

2. Amygdala Kindling Model

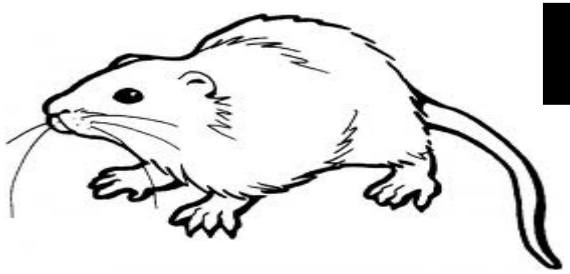
Principle

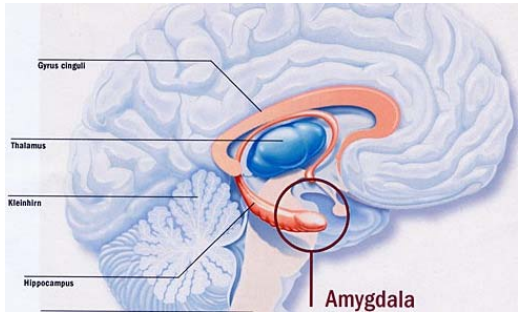
Kindling inducer — **Electrical stimulation**

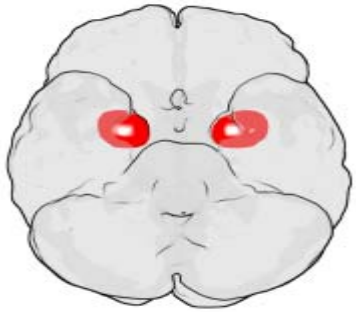
- repetitive
- subconvulsive

↓

to one amygdala





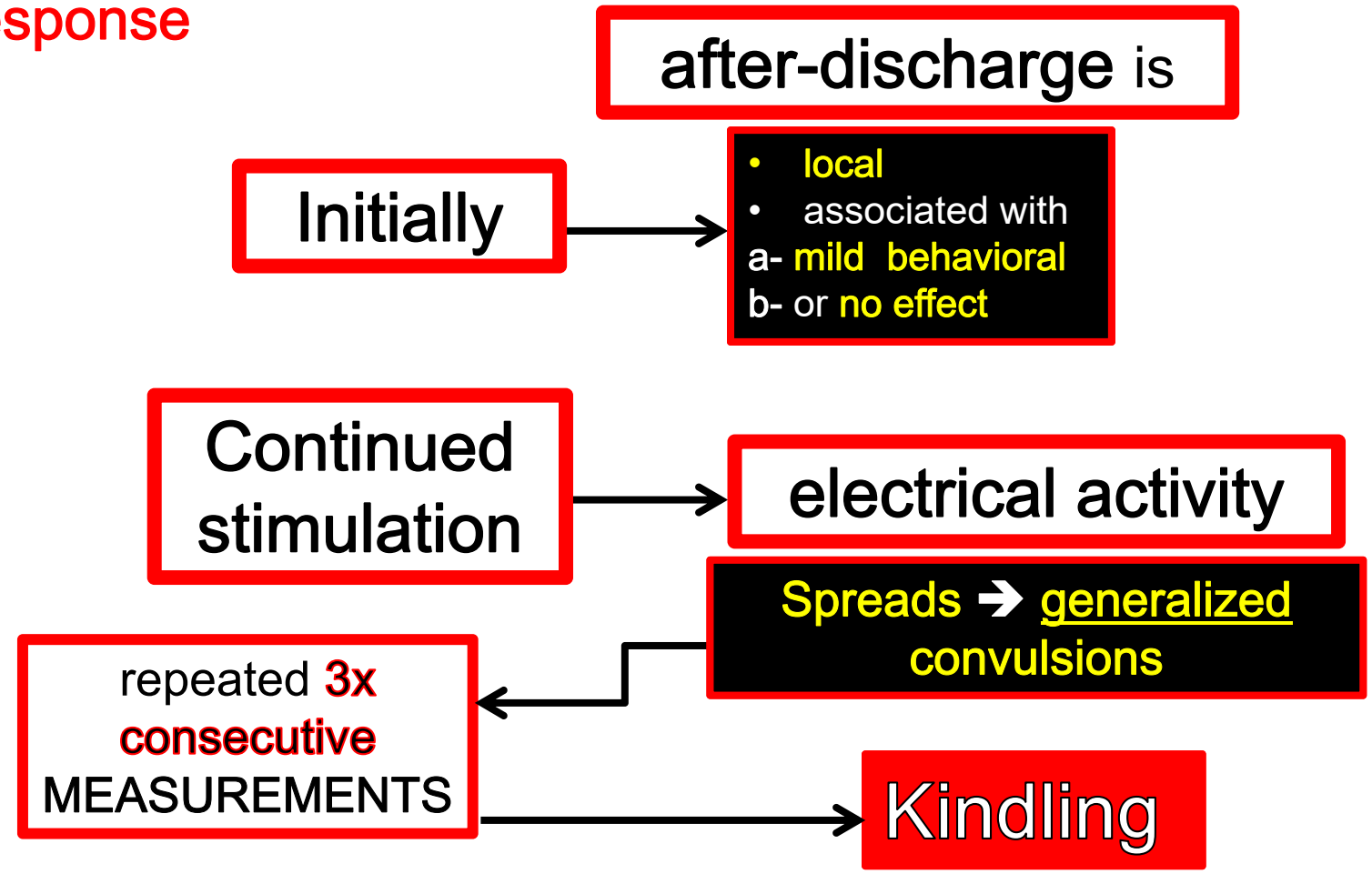


Amygdala area in the rat brain

B. Antiepileptic Models

2. Amygdala Kindling Model

Response



B. Antiepileptic Models

2. Amygdala Kindling Model

Procedure

before each electrical stimulation

Regimen

Standard Test

↓

Adult male rats

↓

implanted with an electrode in the right amygdala

↓

For 10-15 days daily subthreshold electrical stimulation

←

Kindling

B. Antiepileptic Models

2. Amygdala Kindling Model

Evaluation

Repetitive subconvulsive amygdala stimulation

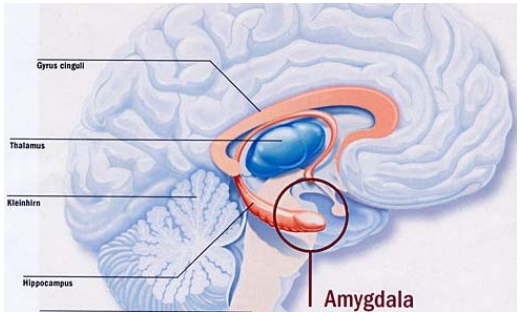
↓

↓after-discharge threshold

Response

↓

seizure



Brain areas in rat

B. Antiepileptic Models

2. Amygdala Kindling Model

Seizure severity is classified into stages

tonic-clonic convulsion (stage 5)

Kindling is defined when

at least 3 consecutive stage 5 seizures (tonic-clonic convulsion)

B. Antiepileptic Models

2. Amygdala Kindling Model

Antiepileptic activity

↓

↓ Seizure severity stages

↓

↓ Number of seized animals

B. Antiepileptic Models

3. Chemical-induced Kindling Model (Pentylenetertazole (PTZ)-induced Kindling)

Principle

Kindling inducer

Dose of PTZ

- repetitive
- subconvulsive

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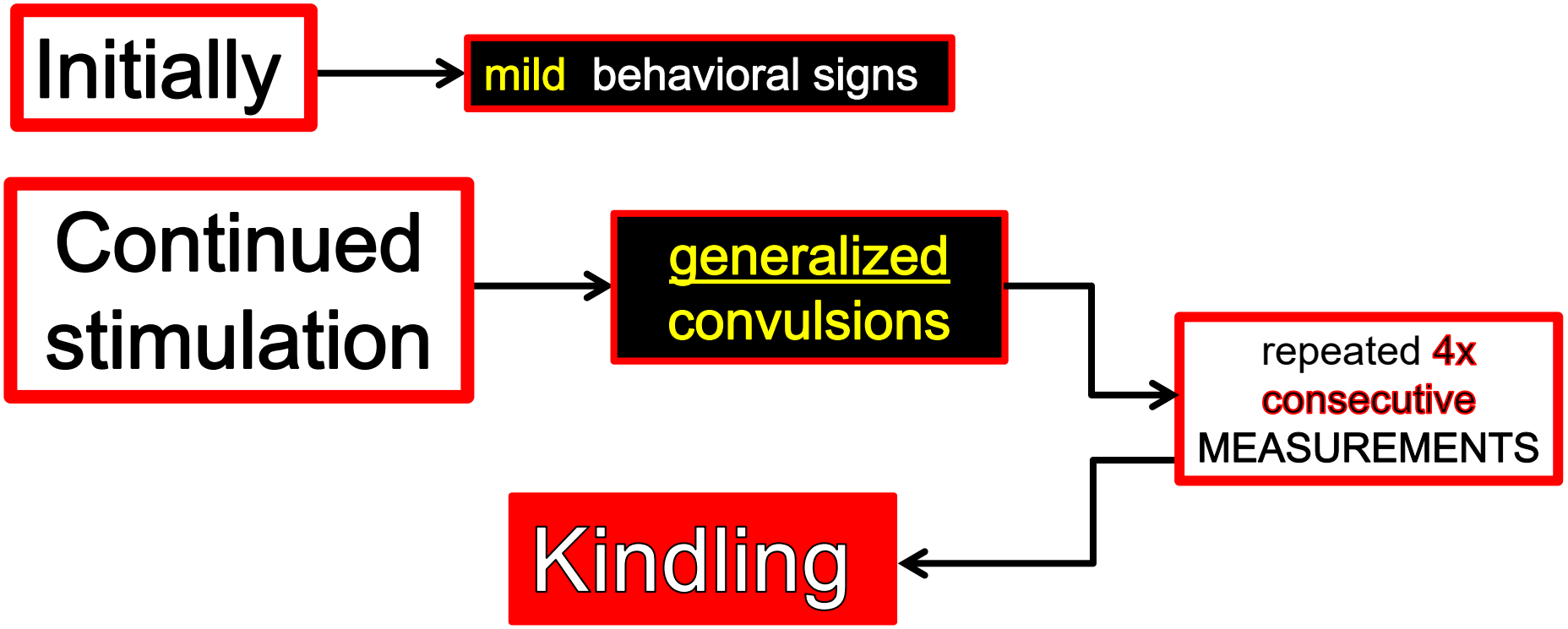
SC or IP route of administration

B. Antiepileptic Models

3. Chemical-induced Kindling Model (Pentylenetertazole (PTZ)-induced Kindling)

Response



B. Antiepileptic Models

3. Chemical-induced Kindling Model (Pentylenetertazole (PTZ)-induced Kindling)

Procedure

Every day
(during AND before each PTZ administration)

Regimen

Standard Test

Adult male rats or mice

↓

are administered a
subconvulsive dose of **PTZ**
on every other day

↓

Animals are observed for
30 min in Plexicages

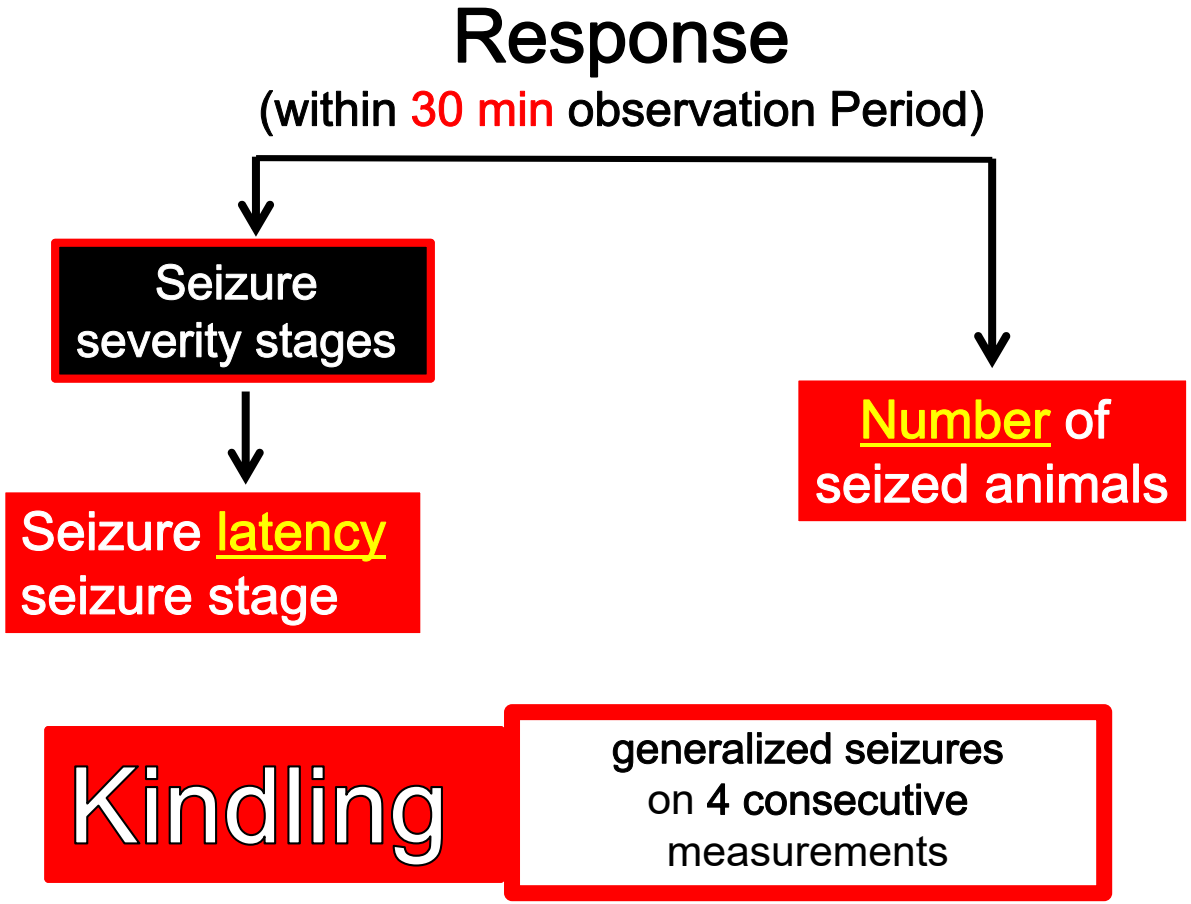
↓

Seizure severity stages

B. Antiepileptic Models

3. Chemical-induced Kindling Model (Pentylenetertazole (PTZ)-induced Kindling)

Evaluation



B. Antiepileptic Models

3. Chemical-induced Kindling Model (Pentylenetertazole (PTZ)-induced Kindling)

Evaluation