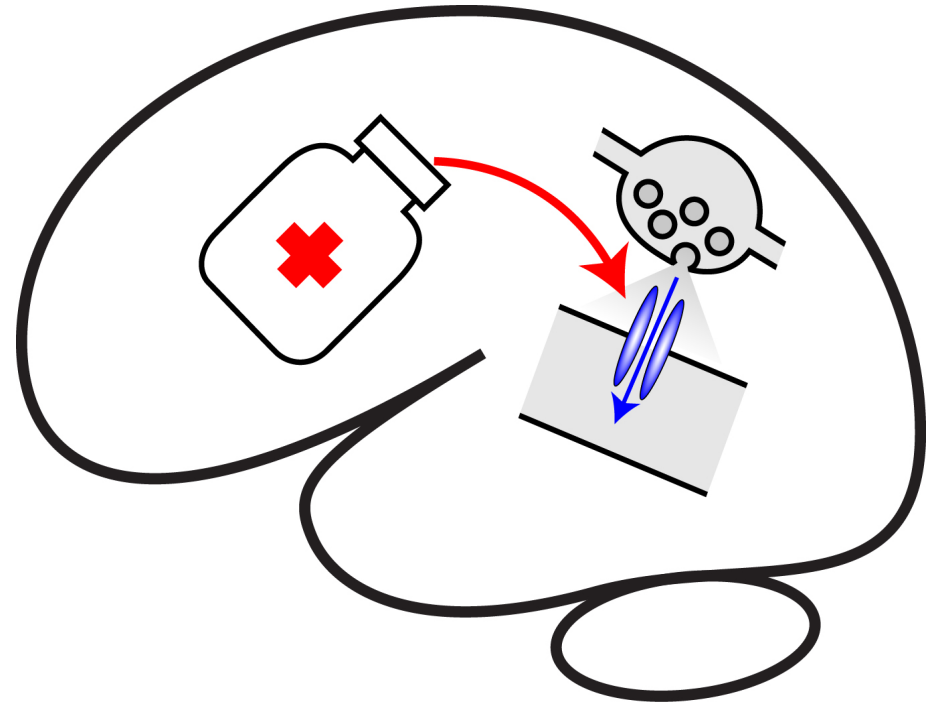


## 5.3 Benzodiazepines

### Cellular Mechanisms of Brain Function

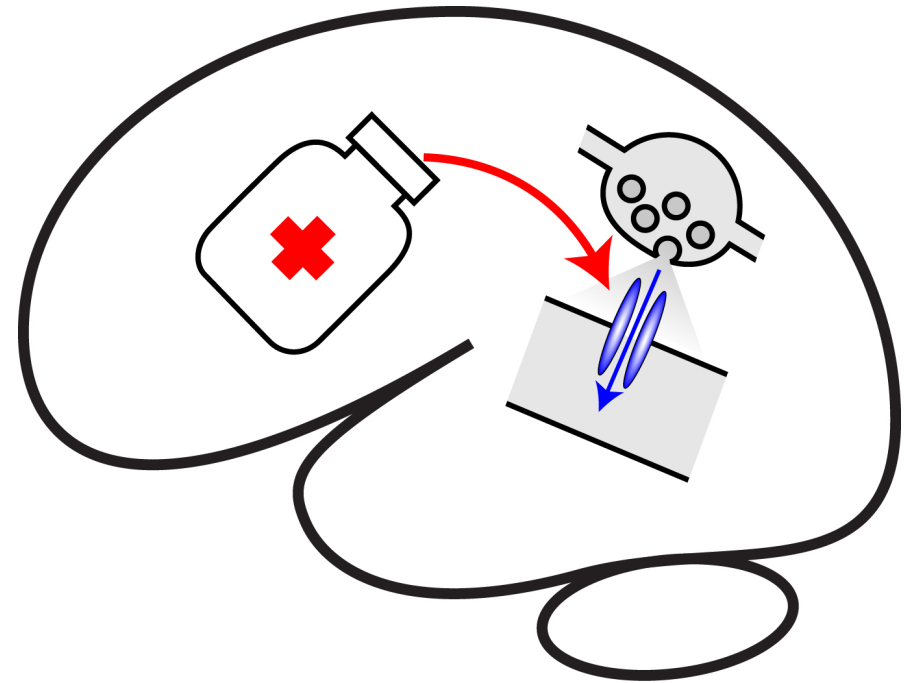
Prof. Carl Petersen



# Neuropharmacology

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# Benzodiazepines act upon GABA<sub>A</sub> receptors



# Structure of GABA<sub>A</sub> receptors

GABA<sub>A</sub> receptor genes

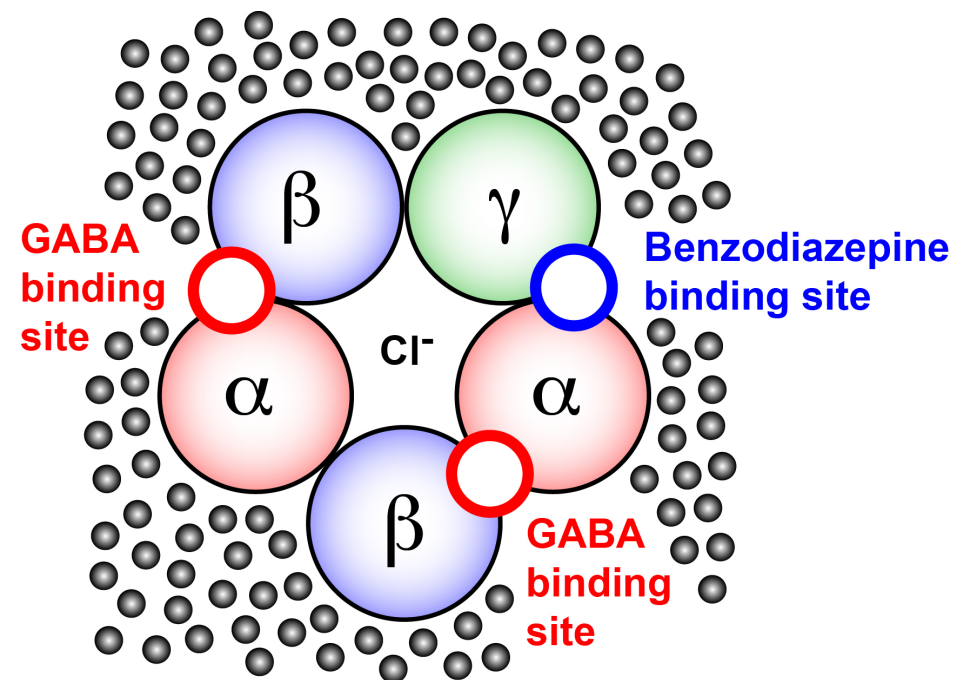
$\alpha 1, \alpha 2, \dots, \alpha 6$

$\beta 1, \beta 2, \beta 3, \beta 4$

$\gamma 1, \gamma 2, \gamma 3$

$\rho 1, \rho 2, \rho 3, \delta, \pi, \varepsilon, \theta$

GABA<sub>A</sub> receptor

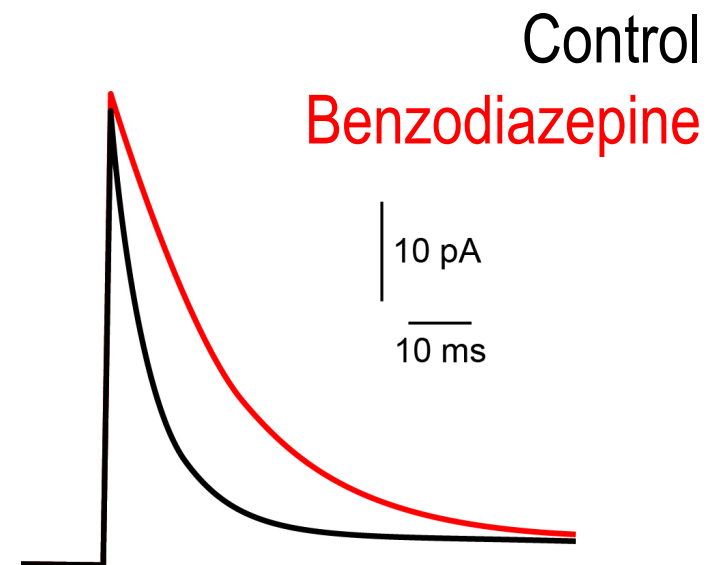


# Benzodiazepines potentiate GABA<sub>A</sub> currents

Benzodiazepines do not activate GABA<sub>A</sub> receptors on their own, but only potentiate GABA-evoked currents.

Benzodiazepines increase the affinity of GABA for binding to the GABA<sub>A</sub> receptor.

Benzodiazepines prolong the duration of IPSCs.



# Amino acid sequences of GABA<sub>A</sub> receptors

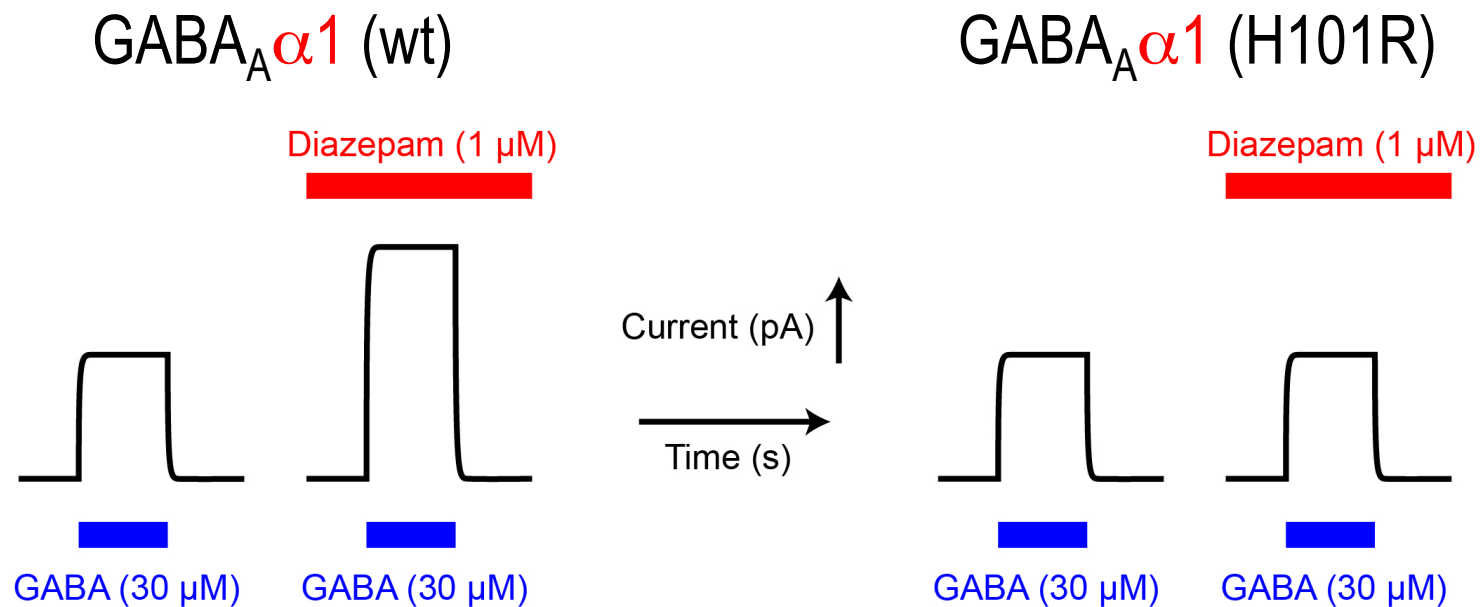
Not all GABA<sub>A</sub>- $\alpha$  subunits are sensitive to benzodiazepines. Benzodiazepines potentiate GABA<sub>A</sub> receptors containing the  $\alpha 1$ ,  $\alpha 2$ ,  $\alpha 3$  or  $\alpha 5$  subunits, but it has no effect upon  $\alpha 4$  /  $\alpha 6$ .

Amino acid sequences:

|            |     |                        |     |
|------------|-----|------------------------|-----|
| $\alpha 1$ | 94  | WTPDTFF <b>H</b> NGKKS | 106 |
| $\alpha 2$ | 94  | WTPDTFF <b>H</b> NGKKS | 106 |
| $\alpha 3$ | 119 | WTPDTFF <b>H</b> NGKKS | 131 |
| $\alpha 4$ | 92  | WTPDTFF <b>R</b> NGKKS | 104 |
| $\alpha 5$ | 98  | WTPDTFF <b>H</b> NGKKS | 110 |
| $\alpha 6$ | 93  | WTPDTFF <b>R</b> NGKKS | 105 |

# Point mutations in GABA<sub>A</sub> receptors

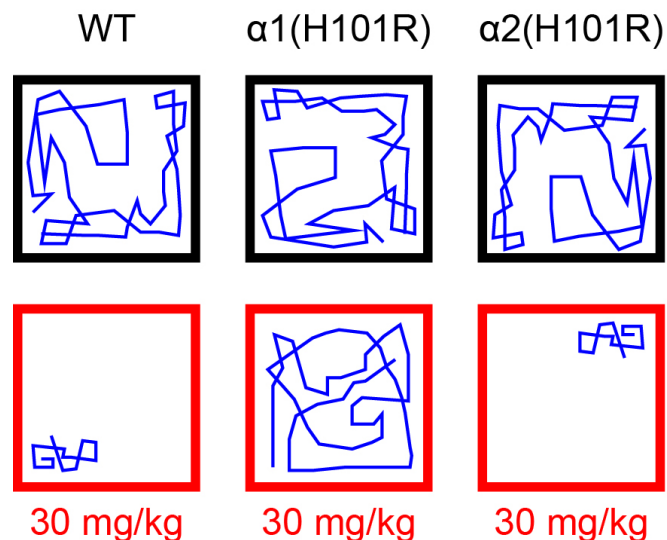
Molecular biologists have discovered how to make genetic mutations. In the laboratory, we can therefore change **H** (histidine) to **R** (arginine).



# Mutating GABA<sub>A</sub> receptors in the mouse genome

Through genome editing, we can change **H** (histidine) to **R** (arginine) in specific subunits of GABA<sub>A</sub> receptors in living mice.

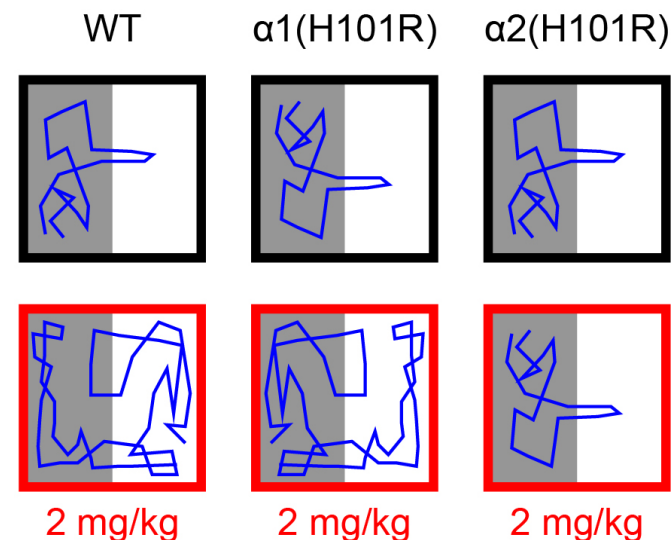
## Sedation via GABA<sub>A</sub>- $\alpha$ 1



Control

Diazepam

## Anxiolysis via GABA<sub>A</sub>- $\alpha$ 2





# Benzodiazepines

- Benzodiazepines act upon specific subtypes of GABA<sub>A</sub> receptors.
- Benzodiazepines acting upon GABA<sub>A</sub>- $\alpha$ 1 receptors mediate a sedative effect in mice (sleep).
- Benzodiazepines acting upon GABA<sub>A</sub>- $\alpha$ 2 receptors mediate an anxiolytic effect (anti-anxiety).