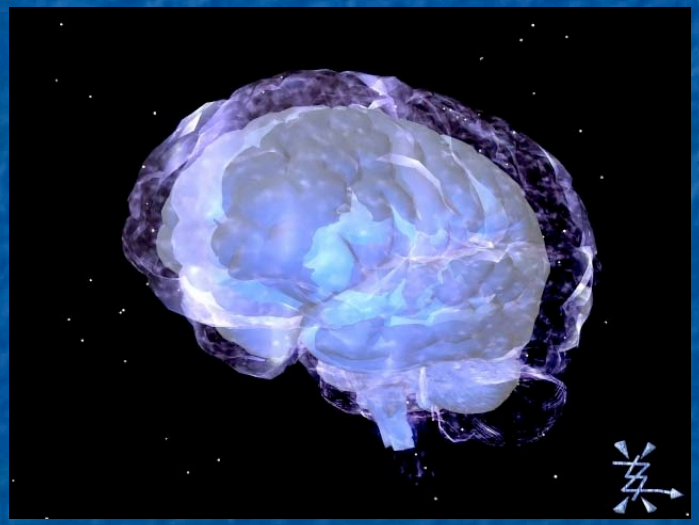
INVOLVEMENT OF GABAERGIC NEUROTRANSMISSION

IN NEUROCHEMICAL DISTURBANCES

UNDER A SINGLE OR REPETITIVE NITROGEN NARCOSIS



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Nitrogen Narcosis

A neurological syndrome composed by motor and cognitive disturbances related to the increased partial pressure of nitrogen …

- Neurochemical studies (in the central nervous system)
  - Decreased activity of the nigro-striatal dopaminergic pathway

Other gases	CHARACTERISTICS	PRESSURE	DA LEVEL
NITROGEN	Anesthetic under pressure	(3MPa)	↘ (-20%)
Nitrous Oxide	Anesthetic Gas	(0.1 MPa)	↘ (-20%)
Argon	Anesthetic under pressure	(2MPa)	↘ (-20%)
Helium	Non Anesthetic	(3MPa)	↗ (+20%)

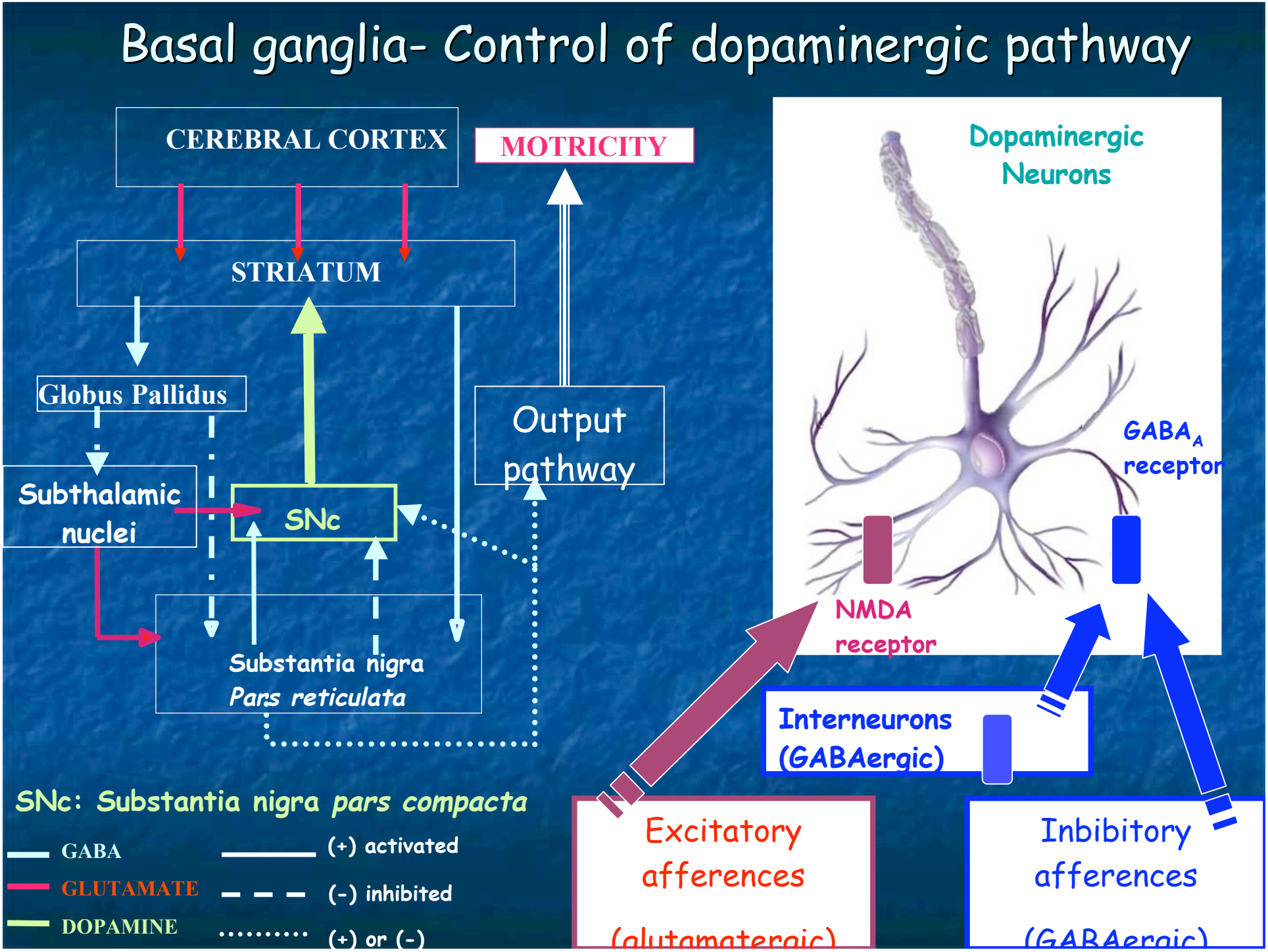
REPETITIVE EXPOSURES

Reversal effect:
(Lavoute et al, 2005)

√ DA 10%

¬ Striatal Dopamine (DA) :
anesthetic effect rather than pressure *per se* effect

Basal ganglia- Control of dopaminergic pathway



Action mechanism of nitrogen narcosis

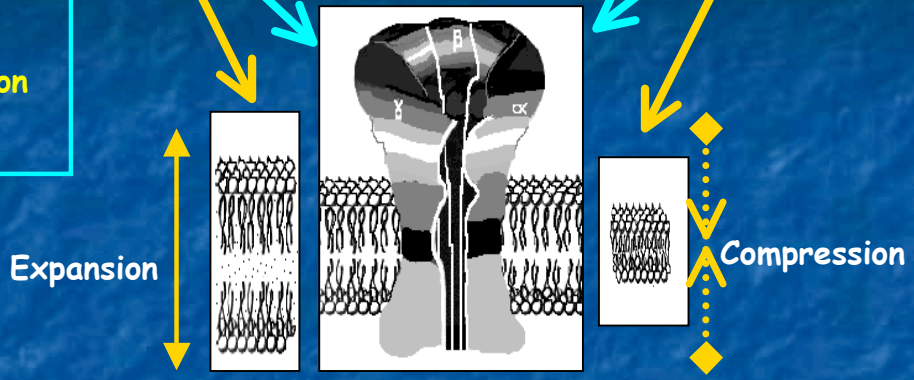
Proteic theory:

binding/interaction with ion channels associated with ~~receptors~~

(Franks and Lieb, 1994)

NITROGEN

PRESSURE



Lipidic theory:

Molecules of gas disolved in bi-lipidic layers of ~~membrane cells~~

(Miller *et al.* 1973)

Ionotropic receptors are the main target of volatile anesthetics

Nitrous oxide

(Jevtovic-todorovic et al, 1998)

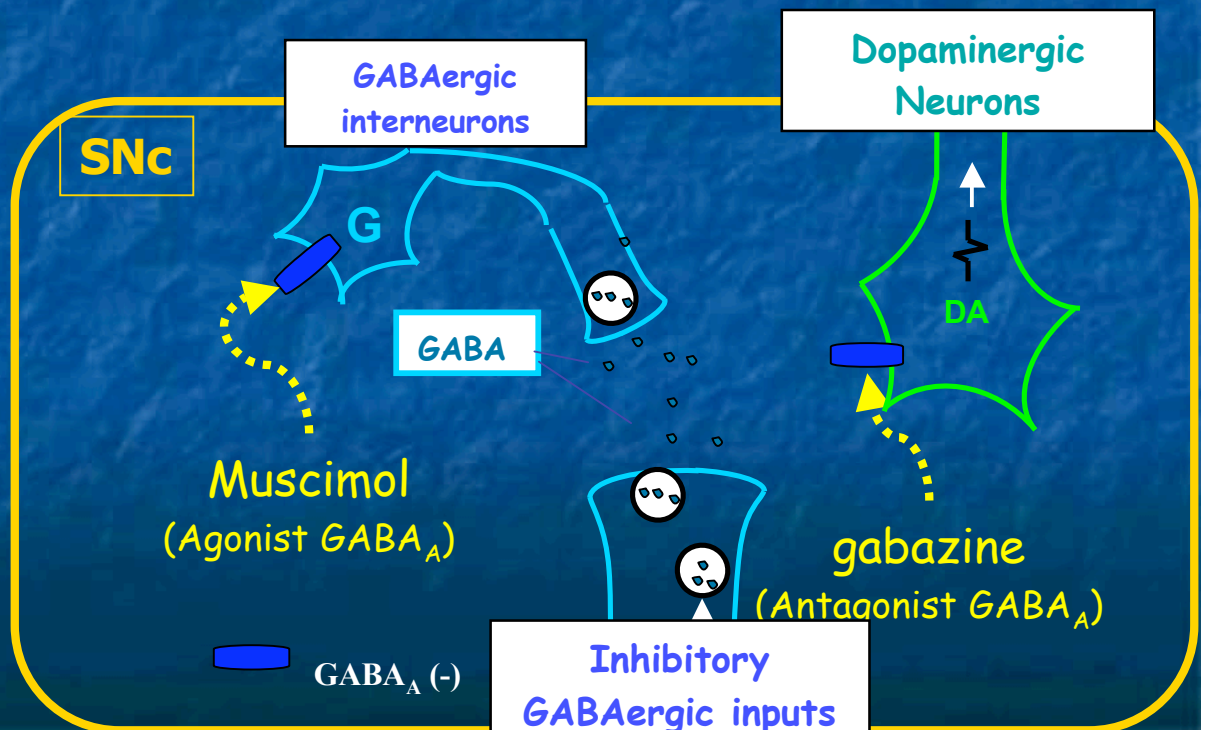
Antagonist of NMDA

(Lavoute et al, 2006)

Nitrogen

What about

$GABA_A$ receptor ?



Materials and methods

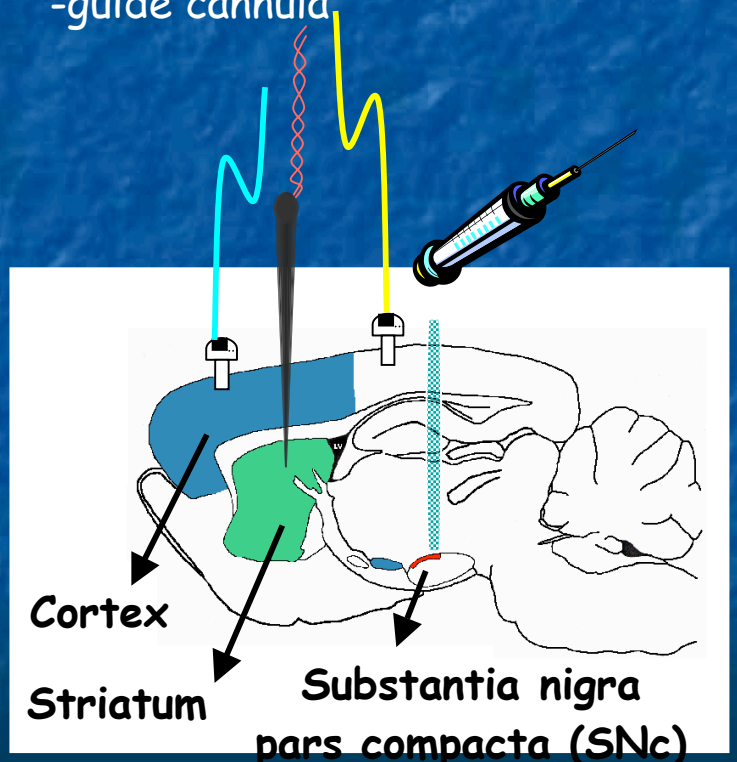
Animal preparation and Surgery

Under general anesthesia,

- **working electrode**

-**Reference** and **auxiliary** electrodes

-guide cannula



Measurements of dopamine level

✓Every 3 minutes

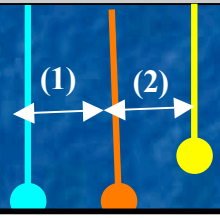
✓In freely-moving rats

✓In normobaric / hyperbaric conditions

➢ **Differential pulse voltammetry (DPV) :**

(1) $U_{REF} - U_{work}$ = applied tension

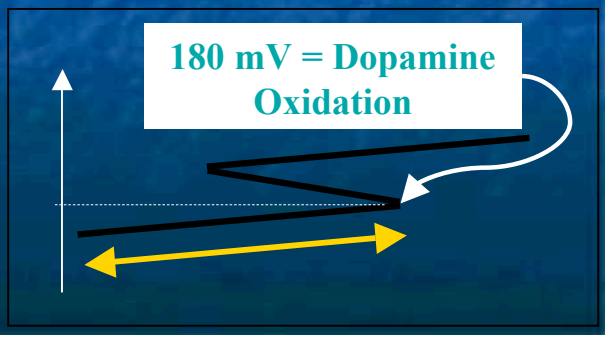
(2) $U_{AUX} - U_{work}$ = measured tension



κ e^- = κ of Tension

Dopamine γ Dioxyquinone + $2H^+$ + $2e^-$
(OXIDATION)

Amplitude of Peak = Dopamine concentration

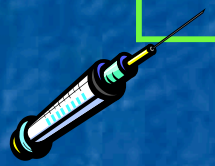


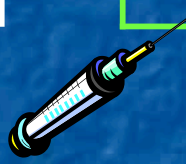
Experimental Protocol

FIRST EXPOSURE
Nitrogen (3 MPa)

5 DAILY EXPOSURES TO NITROGEN				
1MPa	1MPa	1MPa	1MPa	1MPa

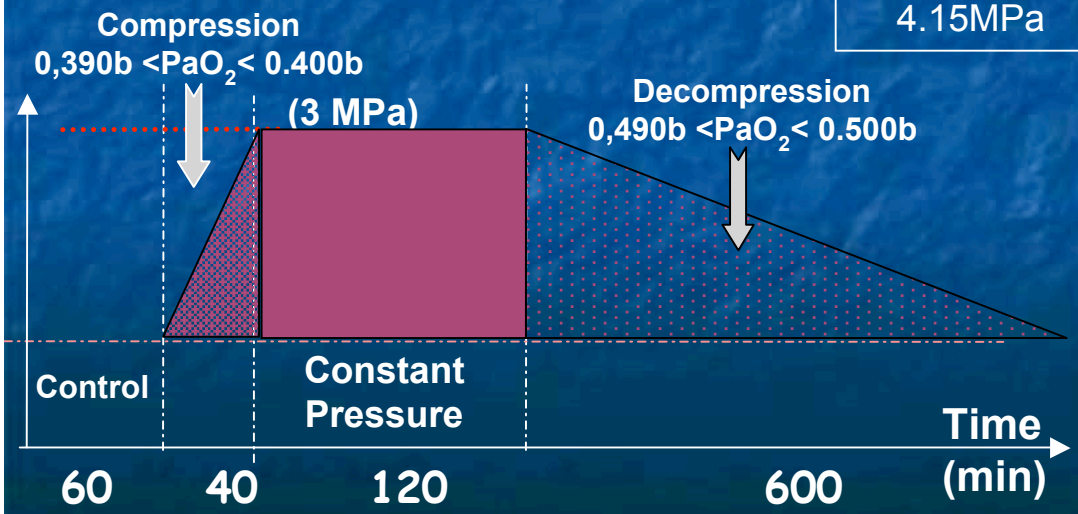
SECOND EXPOSURE
Nitrogen (3 MPa)





- Muscimol ($GABA_A$ interneurons)
- Gabazine ($GABA_A$ dopaminergic neurons)

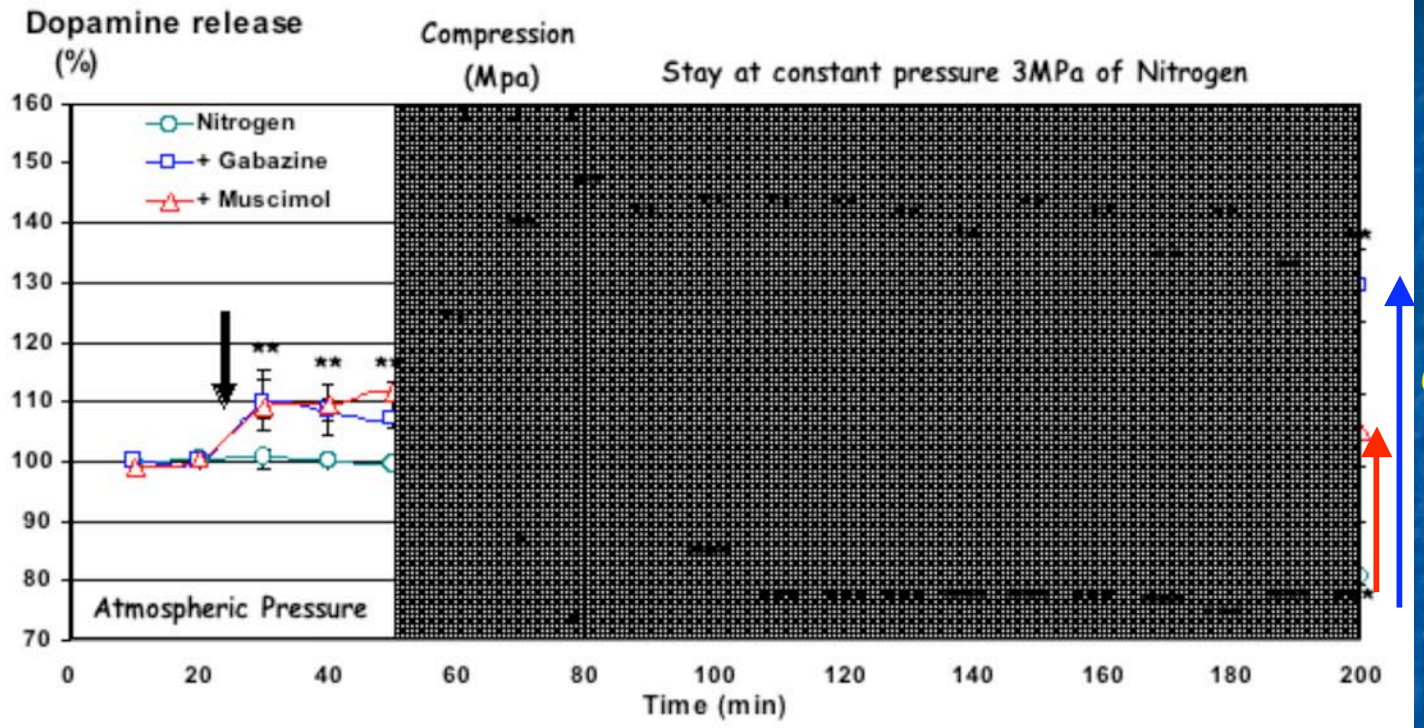
Pressure exposure



ANESTHETIC THRESHOLD OF NITROGEN

RATS		MEN	SYMPTOMS
1MPa	25%	0.3MPa	Appearance threshold
3MPa	75%	0.8MPa	Well established
4.15MPa	100%	1.2MPa	-Loss of consciousness -Loss of righting reflex

First exposure to nitrogen narcosis (3 MPa)



$GABA_A$ DA cells (sensitization)

+50%

$GABA_A$ on interneurons (unchanged)

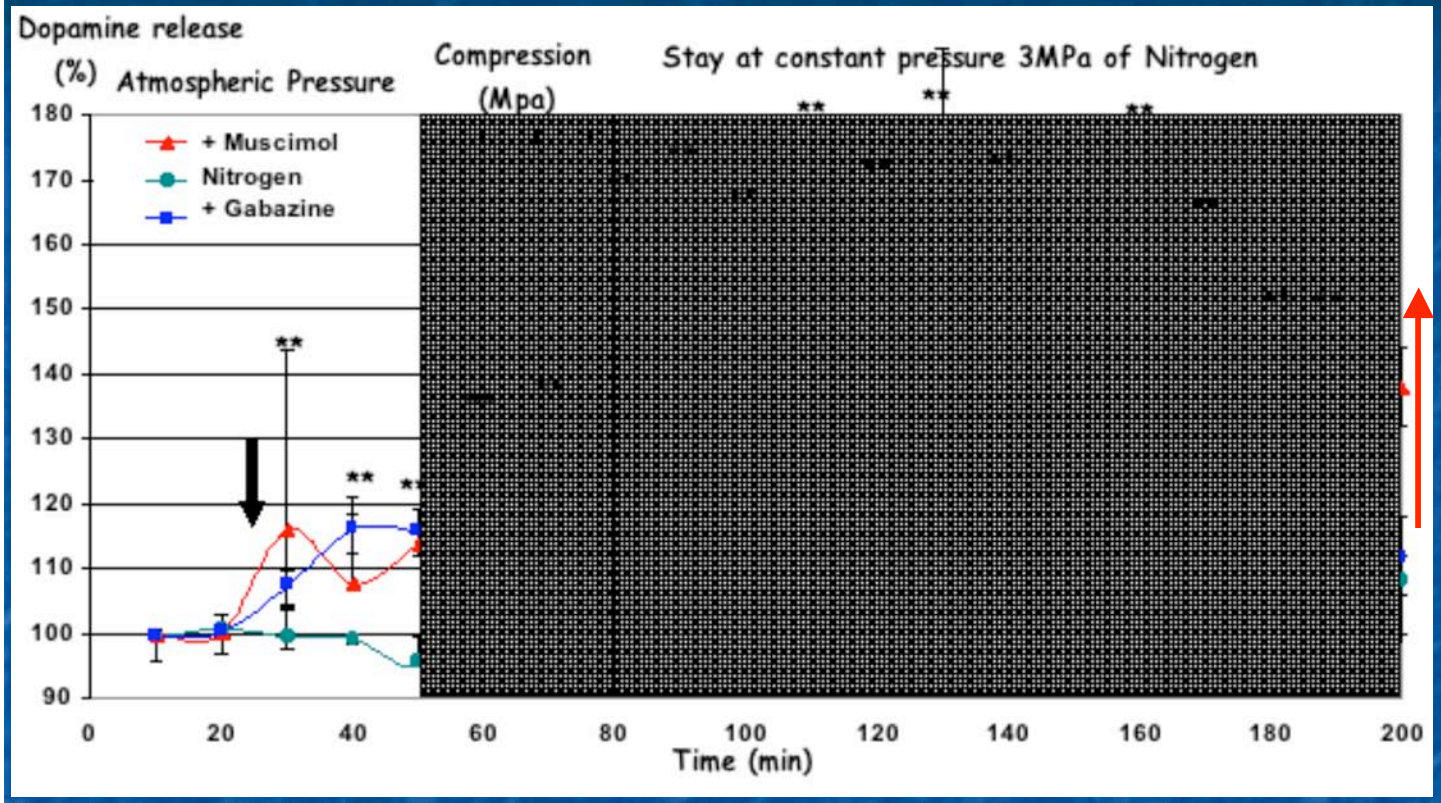
+20%

-20%

- Nitrogen-induced decrease of dopamine (-20%)
  - is due to a facilitation GABAergic input to dopaminergic pathway
  - Sensitization of $GABA_A$ receptors

Second exposure to 3MPa nitrogen, After repetitive exposures

Results (2)



$GABA_A$ on interneurons (sensitization)

+50%

ineffective

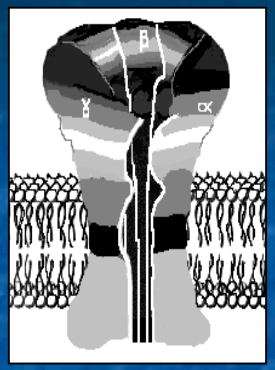
+10%

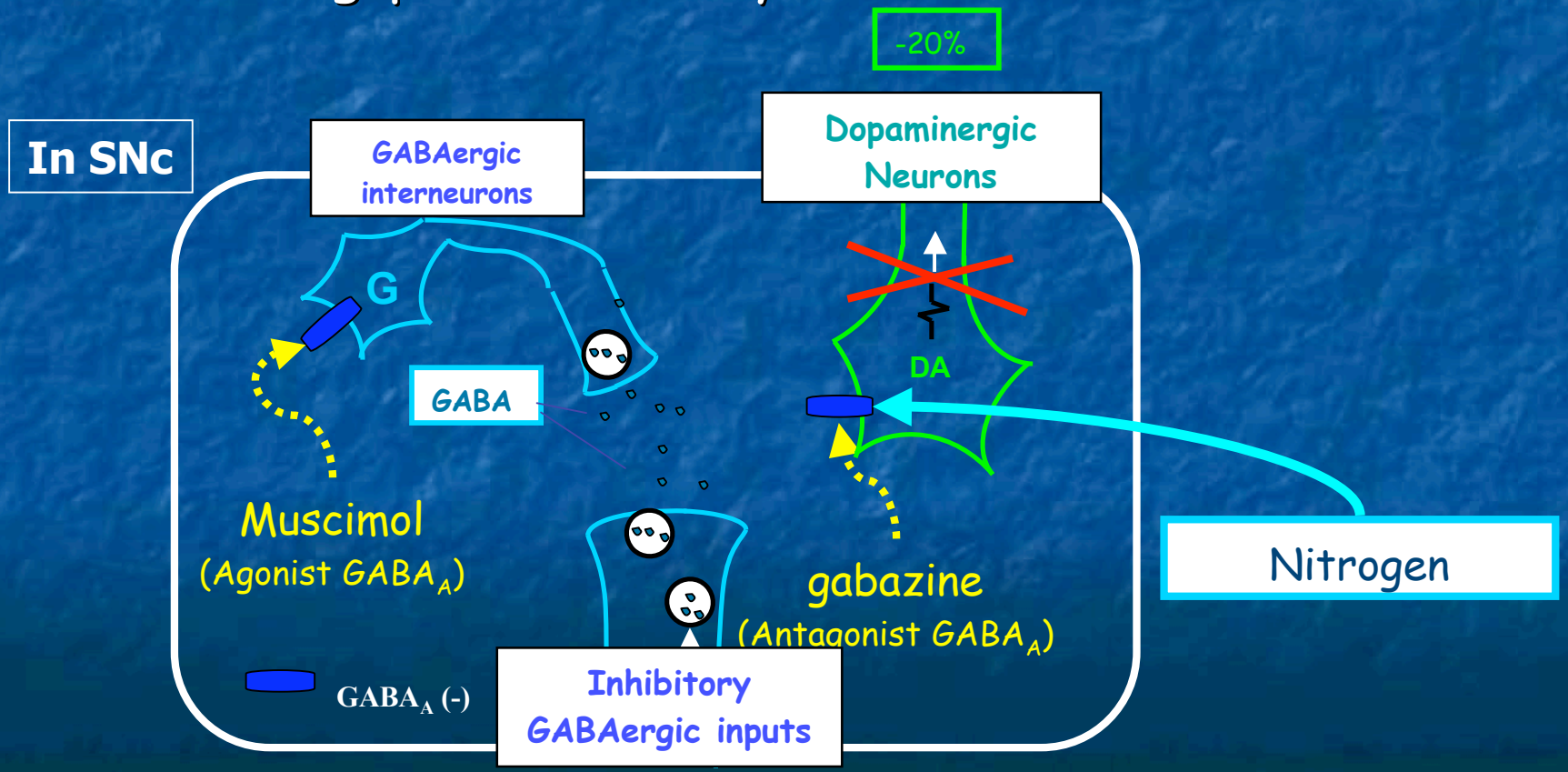
$GABA_A$ on DA cells (desensitization)

- Reversal effect of repetitive nitrogen exposure (+10% DA)
  - ¬ GABAergic input (desinhibition) on DA cells
  - Desensitization of $GABA_A$ receptors located on DA cells

Conclusion (1)

- Action mechanism of nitrogen:
  - Co-agonist of $GABA_A$ receptors on DA cells
  - Binding-protein theory





Conclusion (2)

- Repetitive exposures to nitrogen:
- Desensitization of $GABA_A$ receptors on DA cells
- Nitrogen addiction
- Such as alcohols, solvents …