HIGH PRESSURE EFFECTS ON SPIKE GENERATION BY ISOLATED NMDA RECEPTOR SYNAPSE MAY ONLY PARTIALLY EXPLAIN CNS HYPEREXCITABILITY

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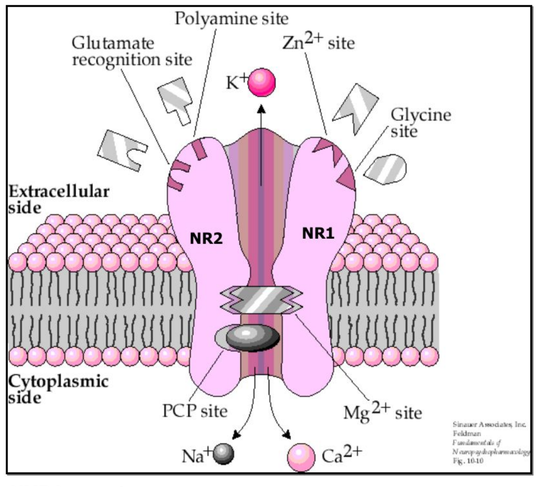
Introduction

Pressure above 1.1 MPa induces in mammals and humans the high pressure neurological syndrome (HPNS). HPNS is characterized by cognitive and motor decrements associated with sleep disorders, EEG changes, tremor, and convulsions.

Previous theories proposed that augmented response of the glutamatergic *N*-methyl-D-aspartate receptor (NMDAR) or reduced GABAergic inhibition may be involved.

Recently, we have reported that isolated NMDAR synaptic response was augmented at high pressure.

We now test whether this augmentation induces neuronal hyperexcitability. We studied high pressure effects on pharmacologically isolated NMDAR synaptic responses and on their efficacy in generating population spikes (PSs).



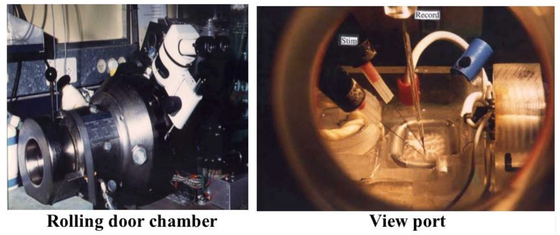
NMDA receptor

Schematic presentation of major NMDAR subunits and binding sites. All NMDARs appear to function as hetero-tetramer assemblies, composed of multiple NR1 subunits in combination with at least one type of NR2(A-D).

Materials & Methods

Preparation: conventional rat hippocampal coronal brain slices, constantly superfused with physiological solutions (30ºC, gas-saturated at normobaric pressure) introduced into the pressure chamber by means of high pressure pump. High pressure was attained by compressed helium.

Pressure chamber



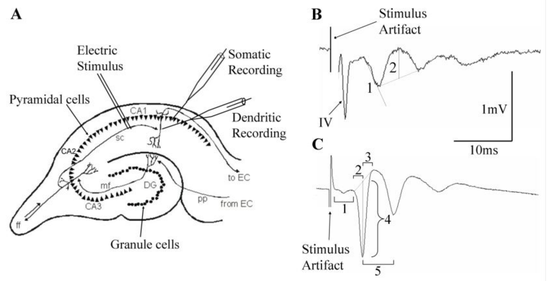


Fig. 1. Parameters of field potentials recorded at the hippocampal CA1 region.

A: a schematic diagram of the preparation. SC, Schaefer collaterals pathway.

B: apical dendrite layer recording: synaptic response slope (1) and population spike (PS) amplitude (2) measurements.

C: somatic recording, PS parameters for analysis are: delay (1), rise time (2), decay time (3) amplitude (4) of the first PS, and inter spike interval (ISI, 5).

IV, Input volley- indicating the extracellular recording of the presynaptic action potential of the Schaefer collaterals pathway.

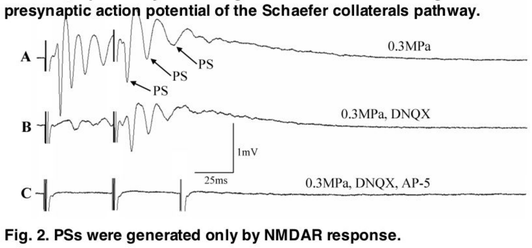


Fig. 2. PSs were generated only by NMDAR response.

The traces are shown chronologically. All electrophysiological recordings were under conditions of picrotoxin (50 μM), zero added Mg2+ and control pressure (0.3MPa).

A: Population spikes generated by intact early AMPAR and the late NMDAR components

B: Addition of DNQX (20 μM) blocked the AMPAR component leading to a significant depression of PS generation following the first stimulus.

C: AP-5 (25 μM) addition; the somatic synaptic response and PS generation were completely blocked. PS, Population spike.

Results

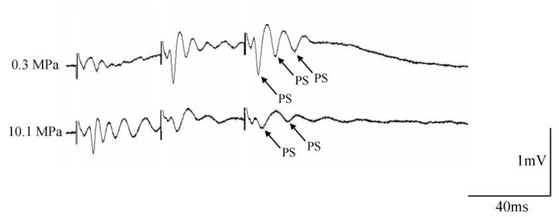


Fig. 3. High pressure favors earlier CA1 population spike (PS) generation.

Somatic recording of a train of three responses at 25 Hz under control (0.3 MPa) and high pressure (10.1 MPa) conditions. High pressure causes PS generation in response to an earlier stimulus in the train. At high pressure, first response is more excitable whereas second and third responses are depressed.

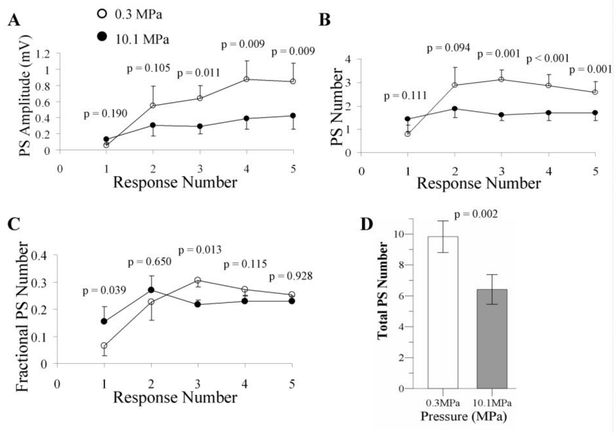


Fig. 4. High pressure reduces population spike (PS) amplitude and number following frequency stimulation.

A - C: frequency response at 25 Hz (means ± SEM, n = 6 - 11 for each point). p is shown for statistical difference between 'n' response's individual mean at 0.3 MPa vs. 10.1 MPa.

Third to fifth responses' PS amplitude (A) and number (B) are significantly decreased under hyperbaric conditions however, PSs appear earlier in the train (C).

D: The total PS number in a train is significantly reduced at high pressure (n = 9).

Conclusions

These results may partially explain the neuronal hyperexcitability observed at pressure.

It is postulated that significant hyperexcitability is attained at pressure only when the normal fast synaptic response (containing also AMPA receptor component) is intact.