ECRONICON OPEN ACCESS

EC NEUROLOGY
Short Communication

NMDA Receptors as Key Players for Decision-Making in Neuron

Susumu Ito[1,2]*, Osamu Yokoi[3] and Katsuhiko Hata[2,3]

[1]High-Tech Research Centre, Kokushikan University, Tokyo, Japan

[2]Department of Sports and Medical Science, Kokushikan University, Tokyo, Japan

[3]Department of Neuroscience, Research Centre for Mathematical Medicine, Tokyo, Japan

***Corresponding Author:** Susumu Ito, High-Tech Research Centre, Kokushikan University, Tokyo, Japan.

Received: August 04, 2021; **Published:** September 07, 2021

Keywords: *Long Term Potentiation; Long Term Depression; Critical Period; Tunnel Diode; Negative Resistance*

N-methyl D-aspartate (NMDA) receptors are an important topic that has been mentioned frequently in neurology in recent years, and a number of articles in this journal have dealt with this topic even in the last few years only [1-6].

NMDA receptors are a type of ionotropic glutamate receptors consisting with 4 subunits [7]. NMDA receptors have several properties not found in other glutamate receptors. They require small amounts of glycine or D-serine as coagonist and have attachment sites for modifying agents such as Zn^{2+}, phencyclidine (PCP) and polyamine, but the most distinctive and important feature is that they have low excitability due to channel blockade with Mg^{2+} at rest, whereas when activated they have considerable permeability to Ca^{2+}. These two properties make NMDA receptors a kind of yes/no decision maker for the neuron. The intracellular fluids of cells including neurons in the resting state are almost Ca^{2+}-free, and the influx of Ca^{2+} works as a signal for the initiation of cell-specific activities. Endocrine cells secrete endocrine, muscles contract and synaptic terminals of neurons secrete transmitters. NMDA receptors also work in the generation of neural oscillatory rhythms, such as swimming or walking [8].

When the membrane is hyperpolarised and NMDA receptor activated by glutamate (and glycine or D-serine), Mg^{2+} in the extracellular fluid tries to move into the neuron via the NMDA channel, but unlike Ca^{2+} it cannot pass the channel and blocks the passage of other cations. If the membrane potential is sufficiently depolarized, Mg^{2+} is removed and other cations including Ca^{2+} begin to pass the channel. So, the voltage current relationship of open NMDA receptor channel show negative inclination portion between about -80 mV and -30 mV of the membrane potential. . This apparent negative resistance makes the NMDA receptor an active element for the electrophysiological behaviour of the neuron, in the same way that magnetrons and tunnel diodes act as active elements with negative resistance in amplifiers, oscillators and memory elements in electronic circuits. (Fig. 1A, 1B).

When NMDA receptors are activated in the presence of glutamate and glycine or D-serine, positive feedback acts on the negative resistance area, causing the membrane potential to become unstable and to settle into two relatively stable states: a hyperpolarising region of around -70 mV and a depolarising region of around -40 mV. These two metastable states can be regarded as '0' or 'No' for hyperpolarisation and '1' or 'Yes' for depolarisation, and at the depolarisation side, switch becomes 'On' by the influx of Ca^{2+} through the NMDA channel to the events that follow. Fig. 1C and 1D shows schematically a response of a neurone to synaptic glutamate input with and without NMDA receptors and a typical pattern of NMDA receptor mediated bursting responses.

Some people emphasis the role of the NMDA receptor as a coincidence detector [9]. The coexistence of depolarisation and glutamatergic stimulation is a prerequisite for the activation of NMDA receptors, which then act as an AND circuit, which is important for the establishment of LTP and LDP. The timing of the input, called spike-timing-dependent plasticity (STDP), is thought to be important in determining whether LTP or LTD occurs, and various mechanisms have been proposed [10]. The model in which NMDA receptors alone can induce both LTP and LTD was proposed [10], and remains an interesting subject of research today [11].

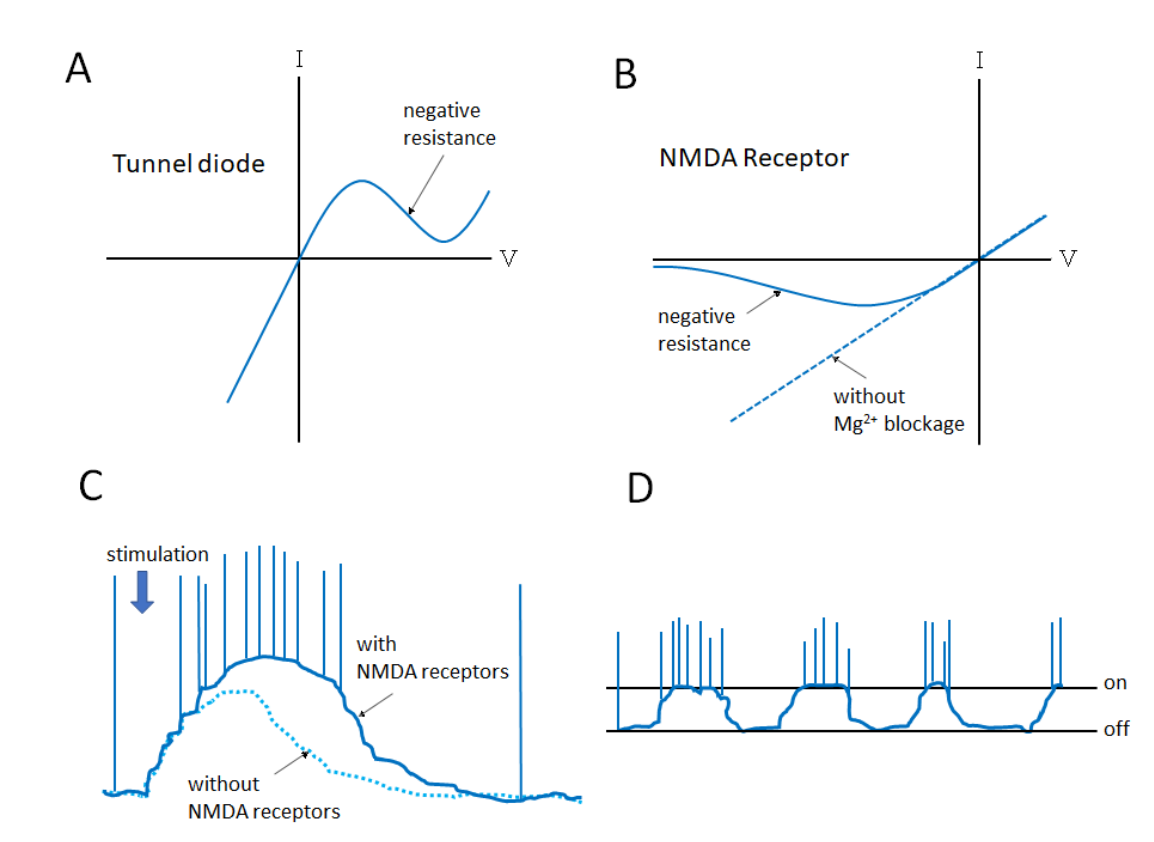

Figure 1: *NMDA receptors as active circuit element having negative resistance property. Negative resistance refers to the negative slope of the VI curve in certain active devices, most famously in tunnel diodes (A). The negative resistance of NMDA receptors is achieved by Mg2+ blockage on the hyperpolarised side (B). This negative resistance boosts the stimulated depolarisation response in the presence of NMDA receptors, leading to an increase in the response, especially in its duration (C). Sustained burst responses in vivo and in vitro also involve NMDA receptors, which exhibit a bistable state, switching on and off across the negative resistance zone (D).*

NMDA receptors play an important role in determining the fate of neurons and functional changes in the brain. During neonatal brain development, NMDA receptors are known to be strongly involved in spontaneous neural network activities called giant depolarization potentials (GDPs) in vitro or sharp waves (SPWs) in vivo, together with paradoxically excitatory GABA receptors, which play an important role in the establishment of neural networks [12]. NMDA receptors have also been shown to contribute strongly in the critical period of ocular dominance [13]. It is also known that NMDA receptors is involved in the induction or prevention of neuronal apoptosis depending on the site of NMDA receptors [14].

Since NMDA receptors play a crucial role in brain function, their malfunction can cause many types of neurological disorders including Alzheimer's disease, Huntington's disease, Parkinson's disease [15,16], Schizophrenia [17] and notably Anti-NMDA receptor encephalitis [2,3,6].

Acknowledgements

We are grateful to Ms Keiko Narazaki for her help in preparing the figure.

Bibliography

1. Monu Yadav., *et al*. "Developing New Antipsychotic Agents: The Need to Understand Potential Targets". *EC Neurology* 12.8 (2020): 23-25.

2. Cruz Daniel., et al. "Hypersexuality and Acute Psychosis in a Male Teenager with Anti N-Methyl-D-Aspartate Receptor Encephalitis". EC Neurology 11.8 (2019): 663-666.

3. Smit Shah., *et al*. "Anti N-Methyl D-Aspartate Receptor Encephalitis: Case Report and Literature Review". *EC Neurology* 10.3 (2018): 157-162.

4. Susumu Ito and Katsuhiko Hata. "A Brief View of the Central Nervous System with a Focus on Synaptic and Extrasynaptic Transmission". *EC Neurology* 12.5 (2020): 54-60.

5. N Ya Gridina., *et al*. "Some Aspects of the Systemic Mechanism of Brain Malignant Gliomas Progression and Methodological Approaches to its Correction". *EC Neurology* 12.4 (2020): 80-90.

6. Anikó Papp., *et al*. "N-Methyl-D-Aspartate Receptor Encephalitis Masking Creutzfeldt-Jakob Disease". *EC Neurology* 10.8 (2018): 653-657.

7. SPH Alexander., *et al*. "The Concise Guide to PHARMACOLOGY 2019/20: Ion channels". *British Journal of Pharmacology* 176 (2019) S142-S228.

8. Wen-Chang Li., *et al*. "Specific Brainstem Neurons Switch Each Other into Pacemaker Mode to Drive Movement by Activating NMDA Receptors". *Journal of Neuroscience* 30.49 (2010): 16609 –16620

9. Henry R Bourne and Roger Nicoll. "Molecular machines integrate coincident synaptic signals". *Cell* 72 (1993) 65–75.

10. Natalia Caporale and Yang Dan. "Spike Timing–Dependent Plasticity: A Hebbian Learning Rule". *Annual Review of Neuroscience* 31.1 (2008): 25-46.

11. Elie L Bienenstock., *et al*. "Theory for the development of neuron selectivity: orientation specificity and binocular interaction in visual cortex". *Journal of Neuroscience* 2.1 (1982): 32–48.

12. Katsuhiko Hata., *et al*. "Multicoding in neural information transfer suggested by mathematical analysis of the frequency-dependent synaptic plasticity in vivo". *Scientific Reports* 10.13974 (2020).

13. Xavier Leinekugel., *et al*. "Ca^{2+} Oscillations Mediated by the Synergistic Excitatory Actions of GABAA and NMDA Receptors in the Neonatal Hippocampus". *Neuron* 18.2 (1997): 243-255.

14. N B Sawtell., *et al*. "NMDA receptor-dependent ocular dominance plasticity in adult visual cortex". Neuron 38 (2003) 977–98. *Erratum Neuron* 39 (2003): 727.

15. Giles E Hardingham., *et al*. "Extrasynaptic NMDARs oppose synaptic NMDARs by triggering CREB shut-off and cell death pathways". *Nature Neuroscience* 5.5 (2002): 405-414.

16. Matthew P Parsons and Lynn A Raymond. "Extrasynaptic NMDA receptor involvement in central nervous system disorders". *Neuron* 82 (2014): 279-293.

17. David Olivares., *et al*. "N-methyl D-aspartate (NMDA) receptor antagonists and memantine treatment for Alzheimer's disease, vascular dementia and Parkinson's disease". *Current Alzheimer Research* 9.6 (2012): 746-758.

18. Joseph T Coyle. "NMDA Receptor and Schizophrenia: A Brief History". *Schizophrenia Bulletin* 38.5 (2012): 920–926.

Volume 13 Issue 10 October 2021