EDORIUM Journals

Edorium J Cell Biol 2017;3:1–3.
www.edoriumjournalofcellbiology.com

EDITORIAL OPEN ACCESS

Protons: A neurotransmitter in the brain

Jianyang Du, Zubayer Hossain, Juthika Mandal

PROTONS ARE A POTENTIAL NEUROTRANSMITTER

A chemical may be classified as a neurotransmitter if it meets the following criteria [1]:

1. The chemical is present in the presynaptic cell.
2. Stimulation of the cell results in release of the chemical.
3. It is available in sufficient quantity in the presynaptic neuron to affect the postsynaptic neuron.
4. There are postsynaptic receptors and the chemical is able to bind to them.
5. A biochemical mechanism for inactivation is present.
6. Exogenous application of the chemical must mimic the endogenous response.
7. Blocking the receptor blocks the activity of neurotransmitter.

Studies raise the possibility that extracellular protons might act as a neurotransmitter. #1 is consistent with the presence of protons in presynaptic vesicles [2], although whether those protons reduce synaptic pH is uncertain. #2 and #3 have been tested recently [3]. #4 is consistent with the location of the proton receptor acid-sensing ion channel 1a (ASIC1a) in postsynaptic spines [4]. #5 is consistent with the finding that protons induce transient ASIC1a currents [3, 5]. #6 and #7 are supported by our previous data that extracellular application of protons induces long-term potentiation (LTP) in wild-type mice, and LTP is impaired in ASIC1a$^{-/-}$ mice [3]. However, other mechanisms might also alter synaptic pH, including neuron and glia metabolism, Na^+/H^+ exchanger activity, Cl^-/HCO_3^- exchanger activity, lactate production, etc. Thus, whether or not protons are a neurotransmitter, the data will provide important new insight into how alterations in pH control neural function.

Jianyang Du[1], Zubayer Hossain[1], Juthika Mandal[1]

Affiliations: [1]Department of Biological Sciences, The University of Toledo, Toledo, Ohio, USA.

Corresponding Author: Jianyang Du, Department of Biological Sciences, The University of Toledo, 2801 W Bancroft St Toledo, Ohio, USA, 43606; Email: Jianyang.du@utoledo.edu

Received: 12 May 2017
Published: 24 May 2017

SYNAPTIC CLEFT pH SHIFT DURING SYNAPTIC TRANSMISSION

Although overall changes in extracellular pH in the brain are tightly balanced by homeostatic mechanisms, pH fluctuations in specific micro-regions, such as the synaptic cleft, may be dramatic [2]. Changes in interstitial pH have been shown in a variety of preparations. The Chesler lab detected pH increases in CA1 hippocampal slices during the antidromic stimulation of CA1 neuronal population using a concentric pH microelectrode and showed that local alkaline transients lasted for seconds [6]. However, other experimental paradigms revealed that synchronous activation of nerve cells induces a rapid acidification that can precede or preclude early alkaline transients [7]. In these experiments, it was suggested that the acidified synaptic vesicles (pH 5.67) transiently influence local extracellular pH upon vesicle release [2]. Consistent with this, a rapid, apparent acid transient was recorded with the synaptic transmission in hippocampal slices following the stimulation of Schaffer collaterals, although a later study using a fluorescein-dextran probe to measure pH was only able to detect an alkaline shift within the same time frame [8]. In strong support of a model where an acid transient occurs in the synaptic cleft due to the release of protons from synaptic vesicles, a patch clamp study showed that vesicular protons feedback to block nearby presynaptic pH-sensitive Ca^{2+} channels [9]. The differing observations in these previous studies of how pH changes with synaptic transmission are due in part to the limitations of previous techniques for measuring pH changes that occur in a micro-region and on a rapid time

scale. Thus, studies that incorporate new techniques to measure local extracellular pH changes during synaptic transmission are necessary to address this question.

BRAIN pH FLUCTUATION AND ITS POTENTIAL ROLE IN SYNAPTIC TRANSMISSION AND LONG-TERM POTENTIATION

There are two major counteracting processes that control pH in the brain. Briefly, the aerobic and anaerobic utilization of glucose in neuron and glia metabolism generates CO_2, and/or lactic acid, which results in an acidic pH shift. In response to these changes in metabolism, an enhancement of neural activity causes an increase in local blood flow that facilitates the clearance of CO_2, which is expired through the respiratory system, leading to local alkaline pH shifts. The rapid dynamics of metabolism and CO_2 clearance suggest that physiological changes in brain pH may have significant consequences for behavior, learning, and memory [6]. An intriguing idea that has emerged from studies of pH-dependent alteration in excitability is that highly localized pH transients might play a signaling role in neuronal communication. It is quite possible that changes in neuronal excitability and synaptic plasticity, hitherto solely attributed to intracellular Ca^{2+} transients, may include a significant component mediated by pH shift [10], and that protons may function as a neurotransmitter to effect these changes.

PROTON RECEPTORS: ACID-SENSING ION CHANNELS

Acid-sensing ion channels (ASICs) are members of the degenerin/epithelial Na^+ channel (DEG/ENaC) family. To date, six proteins of the ASIC family have been identified (ASIC1a, ASIC1b, ASIC2a, ASIC2b, ASIC3 and ASIC4). ASICs assemble as homo- or hetero-trimers to form proton-gated, voltage-insensitive, Na^+ and Ca^{2+} permeable channels that are activated by extracellular protons [11]. ASIC1a is expressed in many areas in the brain, and previous studies in mice showed that it contributes to many brain functions and disorders; these include hippocampal learning and memory, anxiety, depression, stroke, neurodegeneration, seizures, Inflammation, and nerve injury [12]. Recent studies indicated that ASIC1a is particularly abundant in the amygdala and other fear circuit structures and is required for normal responses in tests of both conditioned and unconditioned fear behavior [13]. Also, some studies showed that ASIC1a is located postsynaptically and is required for synaptic plasticity [3].

Keywords: Acid-sensing ion channels, Neurotransmitter, Protons, Synaptic transmission

How to cite this article

Du J, Hossain Z, Mandal J. Protons: A neurotransmitter in the brain. Edorium J Cell Biol 2017;3:1–3.

Article ID: 100005C06JD2017

****

doi:10.5348/C06-2017-5-ED-1

****

Acknowledgements
J.D. is supported by the American Heart Association Scientist Development Grant (15SDG25700054) and The University of Toledo start-up fund.

Author Contributions
Jianyang Du – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Zubayer Hossain – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Juthika Mandal – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

Copyright

REFERENCES

1. Cowan WM, Südhof TC, Stevens CF. Synapses. 1ed. Baltimore: Johns Hopkins University Press; 2001.
2. Miesenböck G, De Angelis DA, Rothman JE. Visualizing secretion and synaptic transmission with pH-sensitive green fluorescent proteins. Nature 1998 Jul 9;394(6689):192–5.
3. Du J, Reznikov LR, Price MP, et al. Protons are a neurotransmitter that regulates synaptic plasticity in the lateral amygdala. Proc Natl Acad Sci U S A 2014 Jun 17;111(24):8961–6.
4. Zha XM, Wemmie JA, Green SH, Welsh MJ. Acid-sensing ion channel 1a is a postsynaptic proton receptor that affects the density of dendritic spines. Proc Natl Acad Sci U S A 2006 Oct 31;103(44):16556–61.
5. Kreple CJ, Lu Y, Taugher RJ, et al. Acid-sensing ion channels contribute to synaptic transmission and inhibit cocaine-evoked plasticity. Nat Neurosci 2014 Aug;17(8):1083–91.
6. Chesler M. Regulation and modulation of pH in the brain. Physiol Rev 2003 Oct;83(4):1183–221.
7. Syková E, Svoboda J. Extracellular alkaline-acid-alkaline transients in the rat spinal cord evoked by peripheral stimulation. Brain Res 1990 Apr 2;512(2):181–9.
8. Gottfried JA, Chesler M. Temporal resolution of activity-dependent pH shifts in rat hippocampal slices. J Neurophysiol 1996 Oct;76(4):2804–7.
9. DeVries SH. Exocytosed protons feedback to suppress the Ca^{2+} current in mammalian cone photoreceptors. Neuron 2001 Dec 20;32(6):1107–17.
10. Kaila K, Ransom RB. pH and Brain Function. 1ed. New York: Wiley-Liss; 1998.
11. Waldmann R, Lazdunski M. H(+)-gated cation channels: Neuronal acid sensors in the NaC/DEG family of ion channels. Curr Opin Neurobiol 1998 Jun;8(3):418–24.
12. Chu XP, Xiong ZG. Physiological and pathological functions of acid-sensing ion channels in the central nervous system. Curr Drug Targets 2012 Feb;13(2):263–71.
13. Ziemann AE, Allen JE, Dahdaleh NS, et al. The amygdala is a chemosensor that detects carbon dioxide and acidosis to elicit fear behavior. Cell 2009 Nov 25;139(5):1012–21.