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The sour side of vitamin C might mediate neuroprotective, anticonvulsive and antidepressant-like effects

Udo Bonnet[a,b,*]

[a] Department of Psychiatry, Psychotherapy, and Psychosomatic Medicine, Evangelisches Krankenhaus Castrop-Rauxel, Academic Teaching Hospital of the University Duisburg-Essen, Castrop-Rauxel, Germany

[b] Department of Psychiatry and Psychotherapy, Faculty of Medicine, LVR-Hospital Essen, University of Duisburg-Essen, Essen, Germany

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ABSTRACT

In animal experiments, neuroprotective, anticonvulsive and antidepressant-like properties have been increasingly attributed to administrations of ascorbic acid (AA, vitamin C) in at least medium (low millimolar) doses, which however await validation in well controlled clinical studies. In mammalian cortical and subcortical neurons, small to modest acidification (< 0.4–0.5 pH-units) is belonging to the key strategies for controlling local excitability and is associated with neuroprotection, e.g. by limiting excitotoxicity. Such acidifications are furthermore involved in the mechanisms of some anticonvulsants and antidepressants. As AA-transport and regulation of intracellular pH (pHi) are closely interwoven on the level of special transmembrane solute carriers, I suppose that the aforementioned beneficial AA-effects might be based upon a discrete "hormetic" acidification of cortical and or subcortical neurons via an AA-mediated weakening of their pHi-regulation. This assumption is supported by findings in non-neuronal cells suggesting both, intracellular acidification and inhibition of a core-element of the pHi-regulation apparatus by millimolar AA. In mammalian subcortical neurons, there is already first evidence of a modest acidification after adding low millimolar AA.

Introduction

Most mammals produce ascorbic acid (AA, vitamin C) from glucose in the liver. But humans, guinea pigs and some bats cannot synthesize AA and are dependent on dietary sources of this water-soluble vitamin [1,2]. After oral intake of AA, fasting plasma concentrations are tightly controlled at < 100 μM in humans [3]. As single oral doses exceed 200 mg, intestinal absorption decreases, urine excretion increases and ascorbate bioavailability is reduced [3]. AA is essential for repair of every tissue in the body and is belonging to the physiologic key antioxidants to cope with reactive species (e.g. free radicals) originating from natural aerobic, xenobiotic or pathological metabolism, i.e. involving mitochondrial and non-mitochondrial sources, such as activation of monoamine oxidase, xanthine oxidase, nitric oxide synthase, cyclooxygenase, lipoxygenase, cytochrome p450 and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [4,5]. Reactive species are suggested to induce tissue damage and microvascular dysfunction but can also result from tissue damage and inflammation [4,5]. Determining the cause-effect relationship between reactive species and tissue damage is rather complex if taken into account that reactive species must not be necessarily detrimental and are required to maintain normal cell functioning – e.g. cell signaling and apoptosis require special redox reactions [4,5]. A balanced relationship between antioxidants such as AA and reactive species is assumed to obtain appropriate cell functioning [4,5]. In case of preponderance of reactive species, oxidative stress should occur which has been brought into connection with aging and a multitude of chronic, often slowly progressing diseases including neurodegeneration, epileptic and affective disorders [6,7]. However, this "oxidative stress theory of diseases" has not been proven as so far any antioxidant has met the criteria of efficacy for drug approval [8].

The brain is particularly vulnerable to oxidative damage owning to its high oxygen demand and wealth of mitochondria as well as its poor repair capacity [7]. Especially hippocampus and neocortex neurons are known to accumulate AA in low mM-ranges even under restricted dietary conditions, which is largely driven by the sodium- and energy dependent transmembrane vitamin C-transporter (SVCT2, Fig. 1) [1]. Some, but not all studies found evidence for an ascorbate-deficiency in neuropsychiatric disorders and there are still controversial results of clinical studies about the efficacy of adjunctive ascorbate with the best

* Address: Department of Psychiatry, Psychotherapy, and Psychosomatic Medicine, Evangelisches Krankenhaus Castrop-Rauxel, Academic Teaching Hospital of the University Duisburg-Essen, Castrop-Rauxel, Germany.
E-mail address: udo.bonnet@uni-due.de.

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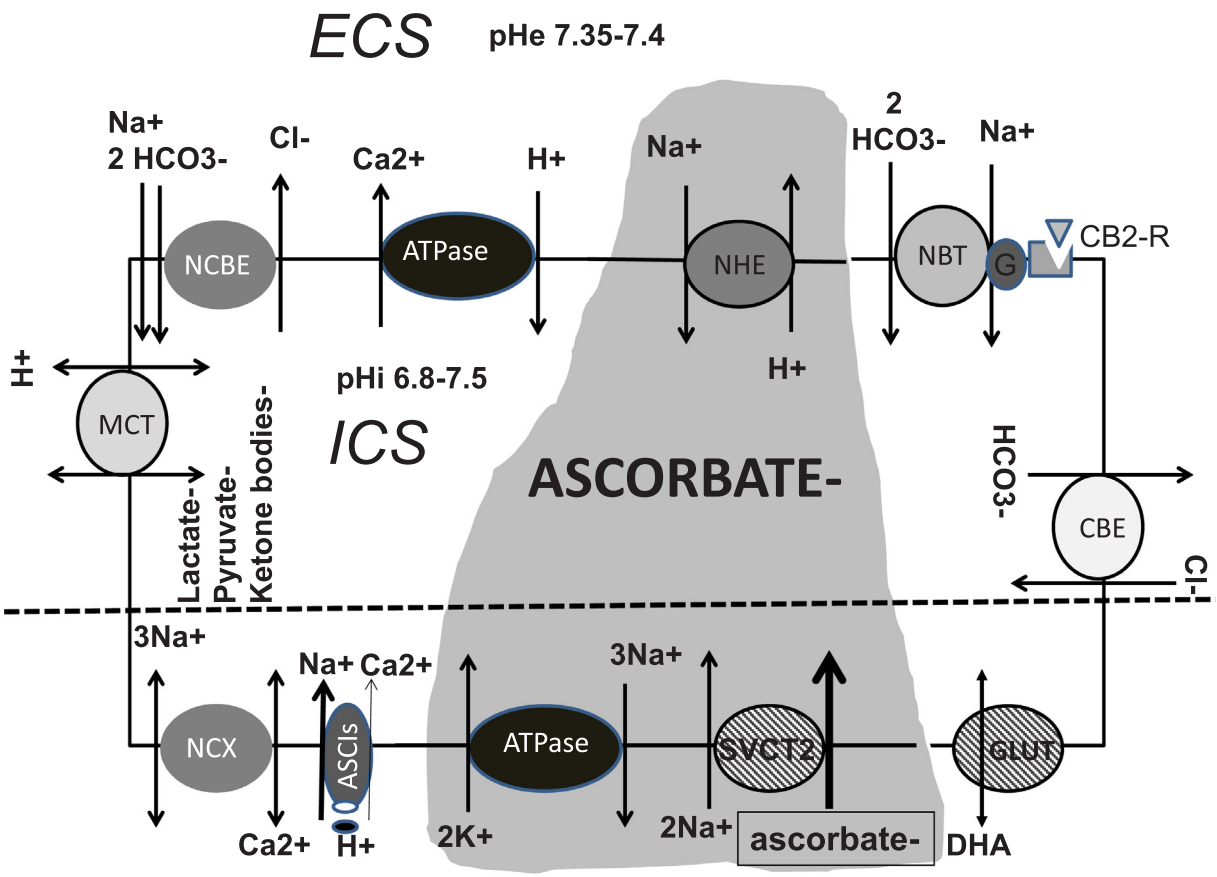

Fig. 1. Hypothetical scheme of the interrelationship between AA and neuronal pHi-regulation whose main transmembrane transport elements (acid exchangers and acid loaders [33–37] are shown above the dashed line. A tight pHi-regulation is essential for nearly every cell function because extra H^+-binding to proteins will make their native net valences becoming more cationic or less anionic, thereby influencing their shape and possibly their characteristic functions. pHi-microdomains close to the neuronal cell membrane might be formed by different local mixes (and activation) of acid exchangers and acid loaders and, of course, would have the potential to fine-tuning the local neuronal activity and plasticity [34,38]. An interaction of ascorbate and NHE1 (sodium-hydrogen exchange subtype 1) was already found in non-neuronal cells [39,40], hand-drawn figure. ECS (extracellular space), ICS (intracellular space), Dehydroascorbic acid (DHA), GLUT (sodium-independent glucose-transporter), SVCT2 (sodium-dependent vitamin C transporter 2, (Na(+)/HCO_3(−)-cotransporters (NBCs) such as the electroneutral NBCE (Na(+)-dependent Cl(−)/HCO3(−)-exchanger or the electrogenic NBT (Na(+)-dependent HCO_3(−)-transporter); CBE (Na(+)-independent Cl(−)/HCO_3(−)-exchangers), MCT2 (monocarboxylate-transporter, type 2), ASIC (acid-sensing ion channels), NCX (Na(+)/Ca(2+)-exchanger). Recently, evidence was found of a NBT-activation by stimulation of postsynaptic cannabinoid-2-receptors (CB2-R) in rodent hippocampal pyramidal cells [41]. A detailed differentiation of NBCs including further cloned subtypes as well as the whole NHE-family is presented elsewhere (e.g. [36,37].

evidence for a putative beneficial effect in treatment of major depression so far [9]. Well controlled studies with patients of Alzheimer's or Parkinson's disease or epileptic disorders are still missing [9,10]. Nevertheless, mounting results of animal experiments are quite promising [9–11] as shown below in detail.

AA and neuroprotection effect

Most likely, SVCT2 serves as a key compound of a powerful intracellular (and via a special transplasma membrane electron transport system also extracellular) defense system against oxidative stress [1,2]. In support, AA was shown to represent the major low molecular weight cytosolic reducing agent in neuron-rich brain areas such as hipppocampus and neocortex (ascorbate/glutathione ratio is 4; in glia-rich areas, this ratio is found to be 0.24) suggesting a key strategic task in neuroprotection [12]. In this context, administration of AA reduced the formation of protein-aggregates involved in the pathogenesis of various neurodegenerative diseases and was demonstrated to protect neuroblastoma cells from β-amyloid apoptosis [13–16]. Parenteral AA decreased infarct sizes in both, primate and rodent models [14–16]. Also, this vitamin protected adult rat brain against pentylenetetrazol-induced apoptotic neurodegeneration [17] and reduced damage in the hippocampus during seizures [10,18]. AA-mediated neuroprotection deemed to overlap with neuromodulatory features, e.g. stimulation of catecholamine synthesis, dopamine D1- and D2 receptor-antagonism, inhibition of acetylcholinesterase and strengthening the resilience of neurons against glutamate-excitotoxicity [1,16].

AA and anticonvulsant effect

Low brain AA-levels promoted seizures in mouse models of decreased brain AA-transport and Alzheimer's disease [11]. Of note, AA suppressed epileptiform activity in various experimental epilepsy models and may prevent seizure activity [19,20]. Most recently, a case-control study found significantly lower AA-levels in the blood of 40 generalized epileptic adult patients [21]. Therefore, AA is currently discussed as an auxiliary treatment of epilepsy [10] and clinical trials of AA as add-on anticonvulsive therapy are underway [22]. However, the mechanisms of the neuroprotective and anticonvulsive ascorbate effects are still obscure and primarily attributed to a consolidation of cell membranes by scavenging reactive species-activity that originates e.g. from lipid peroxidation or increased energy metabolism during pronounced seizure activity [10,21].

AA and antidepressant effect

The biological core hypothesis of depression disorder based upon monoamine deficiency in the central and most likely autonomous nervous system [23]. All approved antidepressants can stimulate intracellular pathways following postsynaptic activation of serotonin and catecholamine receptors to different extents through different mechanisms, the vast majority by slowing the cellular degeneration of monoamines [23]. Current research is underway to analyze the role of extra- and postsynaptic co-activation of glutamate non-NMDA-receptors and the consecutive stimulation of cellular mTORC1-pathway being supposed to mediate more rapid clinical antidepressant response and adaptive resilience via more rapid generation of neurotrophins – needed for synaptic plasticity and hippocampal neurogenesis (neurotrophin hypothesis) [24–26]. At this point, it is interesting that AA-mediated neuroprotection deemed to overlap with neuromodulatory features, e.g. stimulation of catecholamine synthesis [1,16]. To precise, AA was found to strongly enhance neuronal synthesis of norepinephrine from dopamine [27]. Indeed, there is first evidence of an antidepressant-like effect of AA in animal experiments [28,29]. Intriguingly, this effect appeared to include increased mTORC1 signaling, which was shared with ketamine [28,29], a drug being at this juncture extensively under study due to its unique rapid antidepressant response in human treatment-resistant depression [26]. First small but well controlled proof-of-concept studies found a beneficial effect of medium-dosed AA (1000 mg/day) adjunctive to fluoxetine (10–20 mg/day) in pediatric major depression [30] and a lack of antidepressant efficacy in adult MDD when AA was used as an adjunct to up to 60 mg/day citalopram [31]. A previous open label study found fluoxetine and citalopram able to reverse markers of oxidative stress including decreased plasma AA-levels in MDD-patients [32].

Development of the hypothesis

All these beneficial-properties assigned to AA (the neuroprotective, the anticonvulsive and the antidepressant features) can be explained by mild to modest drops (< 0.04–0.5 pH-units) of the intracellular pH (pHi) of central neurons, too [34,35,42–44] as shown below in further detail. This is especially interesting, because AA serves as an enzyme-cofactor in numerous metabolic reactions and this cofactor activity is based upon its ability to undergo redox reactions [5]. Technically, the redox potential of vitamin C directly depends on the pH ("redox buffer"; ascorbic acid ↔ ascorbyl free radical + e− ↔ dehydroascorbic acid + 2H+ + 2e−) and at physiological pH, 99.95% of vitamin C will be present as a mono-anion (ascorbate−, pKa1: 4.2) serving the cells as an excellent hydrogen donor antioxidant (2 ascorbate free radical° − + H+ ↔ ascorbate− + dehydroascorbic acid) [1,2]. In fact, results of recent and previous experiments in non-neuronal tissues (human erythroleukaemia cells, rodent primary astrocyte cultures and rat colonic crypt cells) indicated a modest AA-related acidification [39,40]. There is indirect evidence that this acidification is mediated by specific biological mechanisms, e.g. inhibiting transmembrane pHi-regulators (i.e. subtype 1 of the sodium-proton exchanger-family (NHE) (Fig. 1)) by AA [39,40]. This is particularly interesting if looking at the physiological level, where transmembrane AA-transporters are closely related to bicarbonate and proton exchangers, the latter all elements of the cellular pH-regulation system [36,45]. In mammalian subcortical neurons, there is first evidence of an acidifying effect of low millimolar AA when administered to rodent hippocampal neurons (Fig. 2). Therefore, I assume that a mild cytoplasmatic acidification of cortical and subcortical neurons resulting from at least medium doses of dietary AA contributes to its neuroprotective, anticonvulsive and antidepressant-like properties. In the following, some key results linking small to modest acidifications of cortical and subcortical neurons with beneficial effects are presented.

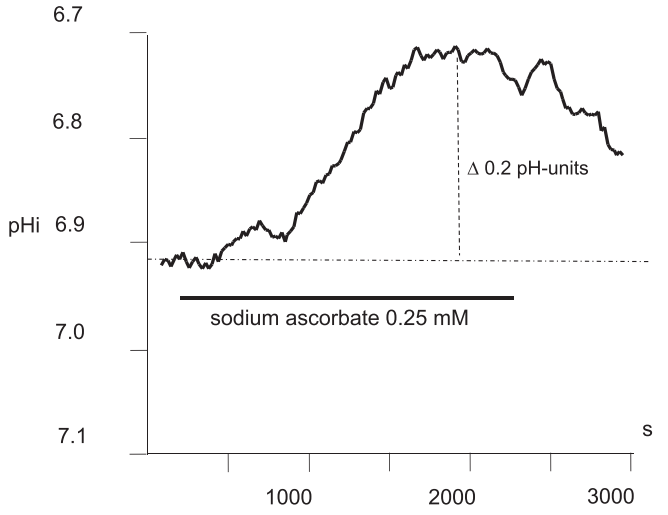

Fig. 2. AA-related acidification (0.2 pH-units) of a superficial BCECF-loaded CA3-pyramidal cell in a guinea pig hippocampal slice preparation (for detailed methods c.f. [33,34]). The trend to return to baseline pHi in the presence of AA after reaching the steady-state pHi (vertical dotted line) points to a stimulation of the neuronal pH-regulation. The resting pHi prior to AA-administration was 6.92 (horizontal dotted line). AA = ascorbic acid.

Intracellular acidification and neuroprotection effect

NMDA-induced superoxide production and neuronal death were prevented by intracellular acidification by as little as 0.2 pH units [46]. The generation of amyloid precursor protein could be reduced by intracellular acidification [47]. Additionally, a protective role of lactate had been related to modest intracellular acidification [38] which could to limit excitotoxicity [34,48].

Intracellular acidification and anticonvulsant effect

A mild lactate-mediated pHi-drop in human neocortical pyramidal cells was found to reduce the epileptiform activity of these cells [38]. This corresponds with mild acidifications being found in rodent hippocampal neurons during the administration of some clinical and experimental anticonvulsants [34,44,49]. Furthermore, ketogenic acidification is associated with anticonvulsive activity [38].

Intracellular acidification and antidepressant effect

A couple of antidepressants have been shown to be associated with a mild acidification in cortical and subcortical neurons [34]. Furthermore, electroconvulsive therapy most likely acidifies regional neurons of interest transiently [38] and acute sleep deprivation – belonging also to the biological therapies for the treatment of depression [50] – is associated with further increases of brain lactate [51] which itself has the potency to acidify cortical and subcortical neurons mildly [38].

Evaluation of the hypothesis

In animal studies; AA and ketamine [26,52] should be compared with respect to their effects on neuronal pHi and pHi-regulation in neuron-rich areas, e.g. hippocampal pyramidal neurons. Moreover, activation of mTORC1 is worth to be studied on possible effects on neuronal pH because this pathway is assumed to be important for synaptic plasticity modulation in various neuropsychiatric disorders including mood disorders, epilepsy and neurodegeneration [53]. Conversely, intracellular acidification has been already found to reduce mTORC1-activity [54,55] what makes the cytoplasmic pH valuable to play the role of a negative feedback modulator of the mTORC1-activity.

In vitro ammonium prepulse technique [35] would be helpful to study the effect of AA and ketamine on pHi-regulation. If pHi-regulation is delayed by AA after an ammonium pulse, the rotatory removal of sodium, bicarbonate or chloride from the bath medium can contribute to identify the affected elements of the pHi-regulation system [36,38].

On the clinical level, the efficacy of at least medium dosed AA (250–500 mg q.i.d given per os) should be studied in double-blind placebo-controlled studies in cohorts with patients suffering from major depression, probable Alzheimer's dementia or certain epileptic disorders. In the first step, AA should be studied adjunctive to treatment-as-usual in these disorders over 12 weeks. If this is beneficial, then in a second step, medium to high-dosed AA-monotherapy is recommended to be tested in these disorders, again under well placebo-controlled conditions – however, now using additional biomarkers, e.g. measurement of the parenchymal pH by special magnetic resonance imaging techniques [56,57] in neuron-rich vs. glia-rich brain regions of interest.

Discussion

Regarding intracellular acidifications, the "beneficial" hormesis zone [35,58] is assumed to be below 0.4–0.5 pH-units [35,59]. I suppose that AA-mediated pHi-drops not exceeding this zone are advantageous to control increased excitability, aberrant synaptic plasticity and neuronal viability. Acidifications as well as alkaline shifts above 0.5 pH-units were associated with predominantly harmful effects on cell functioning and survival [33,38,60]. Typically, a weakening of the neuronal pH-regulation by different means was followed with acidifications within this "hormetic zone" [35,61]. Especially, an inhibition of the sodium proton subtype 1-transporter (NHE1) – a core element of pHi-regulation – was demonstrated to possess powerful anticonvulsive, neuro- and cardio-protection effects in vitro and in vivo [43,44,49,62]. Furthermore, in the forced swimming test and spontaneous alternation behavior test mouse-models, NHE1-attenuation via amiloride was observed to reduce behavioral depression and to improve memory [43]. There is first, though indirect evidence in experiments of non-neuronal cells that AA might be affect this NHE-driven pH-regulation [39,40] which is recommended here to be verified in studies on mammalian cortical and subcortical neurons. When found in its di-anionic form (pKa2 11.8) AA exerts even pro-oxidant effects, especially in the presence of catalytic metal ions [2]. The concentration of di-anionic ascorbate is known to increase by a factor 10 for every pH-unit increase [2], providing further evidence for a cytoprotective potential of a neuronal pHi-drop, e.g. by AA itself.

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Declaration of Competing Interest

The author contributed to a patent hold by Marion Roussel, Germany: "Use of an inhibitor of the Na^+/H^+ exchanger for the production of a medicament for the treatment or prophylaxis of disturbances of the central nervous system". Publication Date: April 28, 2003. Application Number: 10424107, http://patents.justia.com/patent/20040097544 (assessed at 01/08/2019).

References

[1] Harrison FE, May JM. Vitamin C function in the brain: vital role of the ascorbate transporter SVCT2. Free Radic Biol Med 2009;46(6):719–30.
[2] Du J, Cullen JJ, Buettner GR. Ascorbic acid: chemistry, biology and the treatment of cancer. Biochim Biophys Acta 2012;1826(2):443–57.
[3] Ohno S, Ohno Y, Suzuki N, Soma G, Inoue M. High-dose vitamin C (ascorbic acid) therapy in the treatment of patients with advanced cancer. Anticancer Res 2009;29(3):809–15.
[4] Alkadi H. A review on free radicals and antioxidants. Infect Disord Drug Targets 2018. [Epub ahead of print].
[5] Kehrer JP, Klotz LO. Free radicals and related reactive species as mediators of tissue injury and disease: implications for Health. Crit Rev Toxicol 2015;45(9):765–98.
[6] Black CN, Bot M, Scheffer PG, Cuijpers P, Penninx BW. Is depression associated with increased oxidative stress? A systematic review and meta-analysis. Psychoneuroendocrinology 2015;51:164–75.
[7] Pearson-Smith JN, Patel M. Metabolic dysfunction and oxidative stress in epilepsy. Int J Mol Sci 2017;18(11).
[8] Ghezzi P, Jaquet V, Marcucci F, Schmidt HHHW. The oxidative stress theory of disease: levels of evidence and epistemological aspects. Br J Pharmacol 2017;174(12):1784–96.
[9] Kocot J, Luchowska-Kocot D, Kiełczykowska M, Musik I, Kurzepa J. Does vitamin C influence neurodegenerative diseases and psychiatric disorders? Nutrients 2017;9(7).
[10] Sawicka-Glazer E, Czuczwar SJ. Vitamin C: a new auxiliary treatment of epilepsy? Pharmacol Rep 2014;66(4):529–33.
[11] Warner TA, Kang JQ, Kennard JA, Harrison FE. Low brain ascorbic acid increases susceptibility to seizures in mouse models of decreased brain ascorbic acid transport and Alzheimer's disease. Epilepsy Res 2015;110:20–5.
[12] Rice ME, Russo-Menna I. Differential compartmentalization of brain ascorbate and glutathione between neurons and glia. Neuroscience 1998;82(4):1213–23.
[13] Domitrović R. Vitamin C in disease prevention and therapy. Review. Vitamin C in disease prevention and therapy. Biochem Med 2006;16(2):107–25.
[14] Covarrubias-Pinto A, Acuña AI, Beltrán FA, Torres-Díaz L, Castro MA. Old things new view: ascorbic acid protects the brain in neurodegenerative disorders. Int J Mol Sci 2015;16(12):28194–217.
[15] Hassan W, Noreen H, Castro-Gomes V, Mohammadzai I, da Rocha JB, Landeira-Fernandez J. Association of oxidative stress with psychiatric disorders. Curr Pharm Des 2016;22(20):2960–74.
[16] Moretti M, Fraga DB, Rodrigues ALS. Preventive and therapeutic potential of ascorbic acid in neurodegenerative diseases. CNS Neurosci Ther 2017;23(12):921–9.
[17] Naseer MI, Ullah I, Ullah N, Lee HY, Cheon EW, Chung J, et al. Neuroprotective effect of vitamin C against PTZ induced apoptotic neurodegeneration in adult rat brain. Pak J Pharm Sci 2011;24(3):263–8.
[18] Dong Y, Wang S, Zhang T, Zhao X, Liu X, Cao L, et al. Ascorbic acid ameliorates seizures and brain damage in rats through inhibiting autophagy. Brain Res 2013;1535:115–23.
[19] Ayyildiz M, Coskun S, Yildirim M, Agar E. The effects of ascorbic acid on penicillin-induced epileptiform activity in rats. Epilepsia 2007;48(7):1388–95.
[20] Tutkun E, Arslan G, Soslu R, Ayyildiz M, Agar E. Long-term ascorbic acid administration causes anticonvulsant activity during moderate and long-duration swimming exercise in experimental epilepsy. Acta Neurobiol Exp (Wars) 2015;75(2):192–9.
[21] Das A, Sarwar MS, Hossain, Karmakar P, Islam MS, Hussain, et al. Elevated serum lipid peroxidation and reduced vitamin C and trace element concentrations are correlated with epilepsy. Clin EEG Neurosci 2018. [Epub ahead of print].
[22] Deifalla SM. Trial of vitamin C as add on therapy for children with idiopathic epilepsy. ClinicalTrials.gov.2015. 2015 [accessed at 01/08/2019]9. https://clinicaltrials.gov/ct2/show/NCT02369822.
[23] Hirschfeld RM. History and evolution of the monoamine hypothesis of depression. J Clin Psychiatry 2000;61(Suppl. 6):4–6.
[24] Liu B, Liu J, Wang M, Zhang Y, Li L. From serotonin to neuroplasticity: evolvement of theories for major depressive disorder. Front Cell Neurosci 2017;11:305.
[25] Boku S, Nakagawa S, Toda H, Hishimoto A. Neural basis of major depressive disorder: beyond monoamine hypothesis. Psychiatry Clin Neurosci 2018;72(1):3–12.
[26] Gould TD, Zarate Jr. CA, Thompson SM. Molecular pharmacology and neurobiology of rapid-acting antidepressants. Annu Rev Pharmacol Toxicol 2018. [Epub ahead of print].
[27] May JM, Qu ZC, Nazarewicz R, Dikalov S. Ascorbic acid efficiently enhances neuronal synthesis of norepinephrine from dopamine. Brain Res Bull 2013;90:35–42.
[28] Rosa PB, Neis VB, Ribeiro CM, Moretti M, Rodrigues AL. Antidepressant-like effects of ascorbic acid and ketamine involve modulation of GABAA and GABAB receptors. Pharmacol Rep 2016;68(5):996–1001.
[29] Moretti M, Budni J, Freitas AE, Rosa PB, Rodrigues AL. Antidepressant-like effect of ascorbic acid is associated with the modulation of mammalian target of rapamycin pathway. J Psychiatr Res 2014;48(1):16–24.
[30] Amr M, El-Mogy A, Shams T, Vieira K, Lakhan SE. Efficacy of vitamin C as an adjunct to fluoxetine therapy in pediatric major depressive disorder: a randomized, double-blind, placebo-controlled pilot study. Nutr J 2013;12:31.
[31] Sahraian A, Ghanizadeh A, Kazemeini F. Vitamin C as an adjuvant for treating major depressive disorder and suicidal behavior, a randomized placebo-controlled clinical trial. Trials 2015;16:94.
[32] Khanzode SD, Dakhale GN, Khanzode SS, Saoji A, Palasodkar R. Oxidative damage and major depression: the potential antioxidant action of selective serotonin re-uptake inhibitors. Redox Rep 2003;8(6):365–70.
[33] Chesler M. Regulation and modulation of pH in the brain. Physiol Rev 2003;83(4):1183–221.
[34] Bonnet U, Bingmann D, Wiltfang J, Scherbaum N, Wiemann M. Modulatory effects of neuropsychopharmaca on intracellular pH of hippocampal neurones in vitro. Br J Pharmacol 2010;159(2):474–83.
[35] Bonnet U, Bingmann D, Speckmann EJ, Wiemann M. Levetiracetam mediates subtle pH-shifts in adult human neocortical pyramidal cells via an inhibition of the bicarbonate-driven neuronal pH-regulation – implications for excitability and plasticity modulation. Brain Res 2018. [Epub ahead of print].
[36] Ruffin VA, Salameh AI, Boron WF, Parker MD. Intracellular pH regulation by acid-base transporters in mammalian neurons. Front Physiol 2014;5:43.

[37] Orlowski J, Grinstein S. Na+/H+ exchangers. Compr Physiol 2011;1(4):2083–100.
[38] Bonnet U, Bingmann D, Speckmann EJ, Wiemann M. Small intraneuronal acidification via short-chain monocarboxylates: first evidence of an inhibitory action on over-excited human neocortical neurons. Life Sci 2018;204:65–70.
[39] Lane DJ, Robinson SR, Czerwinska H, Lawen A. A role for Na+/H+ exchangers and intracellular pH in regulating vitamin C-driven electron transport across the plasma membrane. Biochem J 2010;428(2):191–200.
[40] Aldajani MM, Vanicek CN, Alhazzaa N, Lysyy T, Agarwal R, Geibel JP. Acute effects of vitamin C exposure on colonic crypts: direct modulation of pH regulation. Cell Physiol Biochem 2017;44(1):377–87.
[41] Stempel AV, Stumpf A, Zhang HY, Özdoğan T, Pannasch U, Theis AK, et al. Cannabinoid type 2 receptors mediate a cell type-specific plasticity in the hippocampus. Neuron 2016;90(4):795–809.
[42] Xiong ZQ, Saggau P, Stringer JL. Activity-dependent intracellular acidification correlates with the duration of seizure activity. J Neurosci 2000;20(4):1290–6.
[43] Ali A, Ahmad FJ, Pillai KK, Vohora D. Evidence of the antiepileptic potential of amiloride with neuropharmacological benefits in rodent models of epilepsy and behavior. Epilepsy Behav 2004;5(3):322–8.
[44] Ali A, Ahmad FJ, Dua Y, Pillai KK, Vohora D. Seizures and sodium hydrogen exchangers: potential of sodium hydrogen exchanger inhibitors as novel anticonvulsants. CNS Neurol Disord Drug Targets 2008;7(4):343–7.
[45] Chang YN, Geertsma ER. The novel class of seven transmembrane segment inverted repeat carriers. Biol Chem 2017;398(2):165–74.
[46] Lam TI, Brennan-Minnella AM, Won SJ, Shen Y, Hefner C, Shi Y, et al. Intracellular pH reduction prevents excitotoxic and ischemic neuronal death by inhibiting NADPH oxidase. Proc Natl Acad Sci USA 2013;110:E4362–8.
[47] Vingtdeux V, Hamdane M, Bégard S, Loyens A, Delacourte A, Beauvillain JC, et al. Intracellular pH regulates amyloid precursor protein intracellular domain accumulation. Neurobiol Dis 2007;25(3):686–96.
[48] Tombaugh GC. Mild acidosis delays hypoxic spreading depression and improves neuronal recovery in hippocampal slices. J Neurosci 1994;14(9):5635–43.
[49] Zhao H, Carney KE, Falgoust L, Pan JW, Sun D, Zhang Z. Emerging roles of Na^+/H^+ exchangers in epilepsy and developmental brain disorders. Prog Neurobiol 2016;138–140:19–35.
[50] Dallaspezia S, Benedetti F. Sleep deprivation therapy for depression. Curr Top Behav Neurosci 2015;25:483–502.
[51] Lundgaard I, Lu ML, Yang E, Peng W, Mestre H, Hitomi E, et al. Glymphatic clearance controls state-dependent changes in brain lactate concentration. J Cereb Blood Flow Metab 2017;37(6):2112–24.
[52] Bonnet U. How much alcohol is in ketamine's antidepressant action? Life Sci 2017;168:54–7.
[53] Ryskalin L, Limanaqi F, Frati A, Busceti CL, Fornai F. mTOR-related brain dysfunctions in neuropsychiatric disorders. Int J Mol Sci 2018;3019(8).
[54] Fonseca BD, Diering GH, Bidinosti MA, Dalal K, Alain T, Balgi AD, et al. Structure-activity analysis of niclosamide reveals potential role for cytoplasmic pH in control of mammalian target of rapamycin complex 1 (mTORC1) signaling. J Biol Chem 2012;287(21):17530–45.
[55] Balgi AD, Diering GH, Donohue E, Lam KK, Fonseca BD, Zimmerman C, et al. Regulation of mTORC1 signaling by pH. PLoS One 2011;6(6):e21549.
[56] Riehemann S, Hübner G, Smesny S, Volz HP, Sauer H. Do neuroleptics alter the cerebral intracellular pH value in schizophrenics? – a (31)P-MRS study on three different patient groups. Psychiatry Res 2002;114(2):113–7.
[57] Magnotta VA, Heo HY, Dlouhy BJ, Dahdaleh NS, Follmer RL, Thedens DR, et al. Detecting activity-evoked pH changes in human brain. Proc Natl Acad Sci USA 2012;109(21):8270–3.
[58] Rattan IS. Hormesis in aging. Aging Res Rev 2008;7:63–78.
[59] Xiang Z, Bergold PJ. Synaptic depression and neuronal loss in transiently acidic hippocampal slice cultures. Brain Res 2000;881(1):77–87.
[60] Siesjo BK, Bendek G, Koide T, Westerberg E, Wieloch T. Influence of acidosis on lipid peroxidation in brain tissues in vitro. J Cereb Blood Flow Metab 1985;5:253–8.
[61] Bonnet U, Leniger T, Wiemann M. Alteration of intracellular pH and activity of CA3-pyramidal cells in guinea pig hippocampal slices by inhibition of transmembrane acid extrusion. Brain Res 2000;872(1–2):116–24.