Neurosignals 2017;25:117-126
DOI: 10.1159/000485457
Published online: November 28
Accepted: October 26, 2017

Review

Neurons, Erythrocytes and Beyond –The Diverse Functions of Chorein

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Key Words
Chorea-acanthocytosis • Orai1 • Store operated Ca^{2+} entry • SGK1 • Lithium • Cytoskeleton • Exocytosis • Autophagy • Apoptosis

Abstract
Chorea-acanthocytosis (ChAc), a neurodegenerative disease, results from loss-of-function-mutations of the chorein-encoding gene VPS13A. Affected patients suffer from a progressive movement disorder including chorea, parkinsonism, dystonia, tongue protrusion, dysarthria, dysphagia, tongue and lip biting, gait impairment, progressive distal muscle wasting, weakness, epileptic seizures, cognitive impairment, and behavioral changes. Those pathologies may be paralleled by erythrocyte acanthocytosis. Chorein supports activation of phosphoinositide-3-kinase (PI3K)-p85-subunit with subsequent up-regulation of ras-related C3 botulinum toxin substrate 1 (Rac1) activity, p21 protein-activated kinase 1 (PAK1) phosphorylation, and activation of several tyrosine kinases. Chorein sensitive PI3K signaling further leads to stimulation of the serum and glucocorticoid inducible kinase SGK1, which in turn upregulates ORAI1, a Ca^{2+}-channel accomplishing store operated Ca^{2+}-entry (SOCE). The signaling participates in the regulation of cytoskeletal architecture on the one side and cell survival on the other. Compromised cytoskeletal architecture has been shown in chorein deficient erythrocytes, fibroblasts and endothelial cells. Impaired degranulation was observed in chorein deficient PC12 cells and in platelets from ChAc patients. Similarly, decreased ORAI1 expression and SOCE as well as compromised cell survival were seen in fibroblasts and neurons isolated from ChAc patients. ORAI1 expression, SOCE and cell survival can be restored by lithium treatment, an effect disrupted by pharmacological inhibition of SGK1 or ORAI1. Chorein, SGK1, ORAI1 and SOCE further confer survival of tumor cells. In conclusion, much has been learned about the function of chorein and the molecular pathophysiology of chorea-acanthocytosis. Most

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importantly, a treatment halting or delaying the clinical course of this devastating disease may become available. A controlled clinical study is warranted, in order to explore whether the *in vitro* observations indeed reflect the *in vivo* pathology of the disease.

Introduction

Lack of functional chorein, a protein encoded by VPS13A (vacuolar protein sorting-associated protein 13A) [1], is the molecular basis of chorea-acanthocytosis (ChAc) [2-8], a progressive autosomal recessive neurodegenerative disease causing a complex movements disorder and variable erythrocyte acanthocytosis [7, 9-11]. ChAc is a rare differential of Huntington's disease with a complex motor phenotype including generalized choreatic hyperkinesia, a peculiar feeding dystonia with tongue protrusion and tongue as well as lip biting, dysarthria, dysphagia, gait impairment with trunk instability due to sudden, violent spasms of the trunk, progressive distal muscle wasting and weakness, as well as increased plasma levels of creatine kinase [10-21]. The patients suffer in addition from epileptic seizures, cognitive impairment, and behavioral changes, such as obsessive-compulsive disorder [10, 12, 18, 22-25]. It has been speculated that chorein deficiency may foster the development of Alzheimer´s disease [26-28]. ChAc results in severe disability and early death of the affected patients [12]. Genetic knockout of chorein in mice leads to erythrocyte shape changes [24], neuronal apoptosis [29] and altered behavior [29]. In the striatum and hippocampus of those mice expression of the GABA(A) receptor-anchoring protein gephyrin and the GABA(A) receptor alpha1 (GABRA1) and gamma2 (GABRG2) subunits are increased [30].

Chorein is expressed ubiquitously in the brain and in a wide variety of further tissues with particularly high expression in testis, kidney and spleen [31-33]. Chorein participates in the regulation of diverse functions [33, 34], including cytoskeletal architecture [33-35], exocytosis [12, 34, 36] and cell survival [12, 37].

Chorein is at least partially effective by binding to phosphatidylinositol lipids [38]. In yeast binding of Vps13 proteins to phosphatidylinositol lipids of the cell membrane provides membrane contact sites and contributes to the steering of vesicle trafficking. Along those lines, studies in Saccharomyces cerevisiae, Dictyostelium discoideum, Tetrahymena thermophila and Drosophila melanogaster point to the involvement of Vps13 proteins in cytoskeleton organization, vesicular trafficking, autophagy, phagocytosis, endocytosis, proteostasis, sporulation and mitochondrial function [38]. Chorein may support activation of phosphoinositide-3-kinase (PI3K)-p85-subunit [12, 39, 40] with subsequent increase of ras-related C3 botulinum toxin substrate 1 (Rac1) activity, and p21 protein-activated kinase 1 (PAK1) phosphorylation [39]. Phosphoproteomics of tyrosine phosphorylation in erythrocytes from ChAc patients pointed to altered function of the kinases FYN, ABL1, EGFR, FGFR1, IGF1R, TEC, TGFBR1 and BTK, as well as of the phosphatases PTPRC and ACP1 [41].

In differentiated PC12 cells, chorein is localized in the termini of extended neurites and partially co-localized with synaptotagmin I [42]. Chorein and synaptotagmin I are observed in dopamine containing dense-core vesicles (DCVs) [42].

The present brief review will address the role of chorein in cytoskeletal architecture and its impact on erythrocyte shape and endothelial cell stiffness, in exocytosis, platelet degranulation, and transmitter release as well as in neuronal and tumor cell survival.

Cytoskeletal architecture, erythrocyte shape and endothelial cell stiffness

Chorein interacts with the membrane cytoskeletal proteins β-adducin and β-actin and in erythrocytes from a ChAc patient markedly reduced β-adducin isoform 1 and β-actin protein levels have been observed [43]. As shown in chorein-overexpressing human embryonic

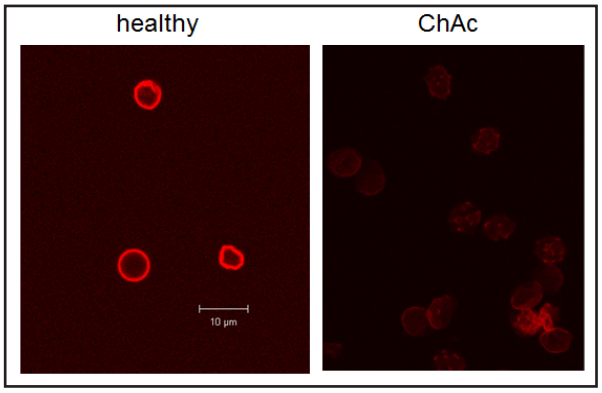

Fig. 1. Actin architecture (F-actin, phalloidin staining) in erythrocytes from healthy volunteers (left) and from patients with chorea-acanthocytosis (right) ChAc = chorea-acanthocytosis.

kidney 293 (HEK293) cells, chorein co-localizes and interacts with β-adducin (isoforms 1 and 2) and β-actin [43]. Gene-targeted ChAc-deficient mice express in the striatum only low levels of β-adducin isoform 1 [43]. Adducin and actin contribute to synaptic function and may thus participate in the pathophysiology of ChAc [43].

In both erythrocytes and fibroblasts isolated from chorea-acanthocytosis patients, actin microfilaments are depolymerized [34, 44] (Fig. 1). Moreover, the microtubular network as well as the intermediate filament networks of desmin and cytokeratins are deranged in fibroblasts from ChAc patients [34]. The disordered architecture is paralleled by decreased desmin and cytokeratin transcript levels. Thus, lack of functional chorein in ChAc fibroblasts leads to substantial structural disorganization of all cytoskeletal components [34].

The deranged regulation of actin polymerization presumably accounts for the shape change of acanthocytotic erythrocytes [39] and for a decrease of chlorpromazine-induced endovesiculation in acanthocytic erythrocytes from ChAc patients [35].

Expression of chorein is decreased in patients with Chronic Obstructive Pulmonary Disease [45]. To which extent the relative chorein deficiency of those erythrocytes affects the mechanical properties of those cells, remains to be shown.

Chorein is expressed in blood platelets [32]. The globular/filamentous actin ratio is higher in platelets from ChAc patients than in platelets from healthy volunteers [32]. Thus, similar to what was observed in erythrocytes [39] and fibroblasts [34], chorein deficiency of ChAc platelets results in actin depolymerization [32]. The cytoskeletal reorganization is paralleled again by altered phosphoinositide-3-kinase subunit p85 phosphorylation, and p21 protein-activated kinase (PAK1) phosphorylation [32].

Chorein is further expressed in endothelial cells [33]. Silencing of the VPS13A gene in those cells was followed by weakening of actin filaments, an increase of the soluble G-actin over filamentous F-actin ratio, cell softening and altered cell shape [33]. The observed effects were paralleled by and at least partially due to a decrease in FAK phosphorylation [33]. VPS13A silencing further up-regulated caspase 3 activity and triggered endothelial cell death [33]. Thus, chorein is a powerful regulator of cytoskeletal architecture, cell shape, mechanical stiffness and survival of vascular endothelial cells [33]. It is noteworthy that stiffness of endothelial cells impacts on release of NO and thus on peripheral vascular resistance and blood pressure [46, 47].

Exocytosis, transmitter release and platelet degranulation

In PC12 cells, chorein silencing compromises the expression of vesicle-associated membrane protein 8 (VAMP8) and reduces the number of vesicles [36]. As a result, chorein silencing blunts the stimulation of dopamine release following depolarization of the cell membrane by increase of extracellular K^+ [36, 42].

Blood platelets from ChAc patients similarly express less VAMP8 than platelets from healthy volunteers [32]. Along those lines, silencing of chorein decreases VAMP8 expression

in megakaryocytic (MEG-01) cells [32]. Degranulation of dense granules (ATP release) and of α granules (P-selectin exposure) following stimulation with collagen related peptide or TRAP is less pronounced in platelets from ChAc patients than in platelets from healthy volunteers [32]. Moreover, platelet aggregation following stimulation with different platelet agonists is reduced in platelets from ChAc patients as compared to platelets from healthy volunteers [32]. Thus, chorein deficiency decreases degranulation and aggregation of blood platelets [32].

Autophagy and cell survival

Chorein supports the survival of neurons and skeletal muscle cells [11]. Chorein overexpression confers survival of human embryonic kidney (HEK) cells during cell starvation, an effect attributed to interaction of chorein with α-tubulin and histone deacetylase 6, a known α-tubulin deacetylater and decisive component of basal autophagy [48]. Chorein deficient HEK cells accumulate autophagic markers and curtail autophagic flux [49]. Autophagy in turn strongly impacts on apoptosis [50-52]. In ChAc eythrocytes autophagy is decreased [53] and cytoplasmic levels of active Lyn and of autophagy-related proteins Ulk1 and Atg7 are enhanced [53]. In ChAc erythrocytes active Lyn forms with Heat-Shock-Protein HSP90&70 high-molecular-weight complexes which protect Lyn from proteasomal degradation [53]. The complexes bind to Ulk1 and Atg7 [53]. The association of chorein with Atg7 is compromised in ChAc erythrocytes. Impaired autophagy in ChAc erythrocytes leads to the cellular accumulation of multivesicular bodies and membrane remnants [53]. Moreover, the impaired autophagy in chorein deficient reticulocytes appears to delay the clearance of mitochondria and lysosomes [53]. According to observations in erythroid precursors from ChAc patients, chorein deficiency compromises erythropoiesis, increases active Lyn, leads to accumulation of the lysosmal membrane protein LAMP1 and of LAMP1-positive aggregates, and impairs the clearance of lysosomes and mitochondria [53]. Thus, chorein deficiency leads to accumulation of active Lyn, impairs autophagy, and thus compromises vesicle trafficking in erythroid maturation [53].

Cell death and cell survival are further dependent on alterations of cytosolic Ca^{2+} activity ($[Ca^{2+}]_i$) [54, 55]. $[Ca^{2+}]_i$ could be enhanced by Ca^{2+} release from intracellular stores with subsequent stimulation of the Ca^{2+} release activated Ca^{2+} channel subunits ORAI1, ORAI2 and/or ORAI3 [56] by the Ca^{2+} sensing proteins STIM1 and/or STIM2 [12, 57-59]. Upon stimulation with STIM1/2, the ORAI isoforms accomplish store-operated Ca^{2+} entry (SOCE). Regulators of ORAI1 and thus SOCE include the PI3K pathway [12, 60].

Stimulation of intracellular Ca^{2+} release and SOCE may trigger oscillations of cytosolic Ca^{2+} activity ($[Ca^{2+}]_i$) [61] due to intracellular Ca^{2+} release with transient activation of SOCE followed by subsequent Ca^{2+} extrusion [62]. The pulsating short-lived increases of $[Ca^{2+}]_i$ regulate several cellular functions such as Ca^{2+} dependent transcription factors and organization of the actin cytoskeleton without, unlike sustained increases of $[Ca^{2+}]_i$, compromising cell survival [63, 64]. The Ca^{2+} oscillations influence a variety of complex cellular functions [65, 66], such as entry into the S and the M phase of the cell cycle [67]. The $[Ca^{2+}]_i$ oscillations may further support cell survival [68, 69]. Accordingly, ORAI [56] and STIM [57] isoforms participate in the orchestration of survival, proliferation, and migration of tumor cells [70-73] and neural stem/progenitor cells [74]. In contrast to Ca^{2+} oscillations, sustained $[Ca^{2+}]_i$ increases trigger apoptosis [42-44].

Neurons generated from fibroblasts of patients with ChAc via induced pluripotent stem cells (iPSC) express less ORAI1 and STIM1 proteins than neurons generated from fibroblasts of healthy controls [12]. Accordingly, SOCE is smaller in ChAc neurons than in control neurons [12] (Fig. 2). The decreased SOCE of ChAc neurons is paralleled by an increased percentage of apoptotic cells [12] (Fig. 3). ORAI1 and STIM1 transcript levels and protein abundance, SOCE and cell survival are all increased by a 24 hours treatment with the antidepressant lithium [12, 37, 75], effects reversed by pharmacological inhibition of

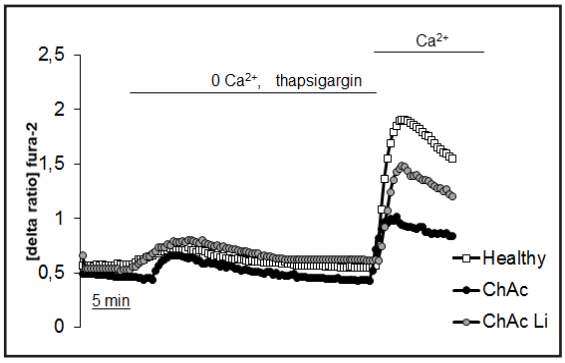

Fig. 2. Intracellular Ca^{2+} release and store-operated Ca^{2+} entry (SOCE) in neurons from healthy volunteers and from ChAc patients without or with lithium treatment. Fura-2 fluorescence-ratio in fluorescence spectrometry before and following extracellular Ca^{2+} removal, addition of thapsigargin (1 µM), and re-addition of extracellular Ca^{2+} in neurons generated from healthy volunteers (white squares) and from ChAc patients without (black circles) and with (grey circles) lithium (24 h, 2 mM) treatment.

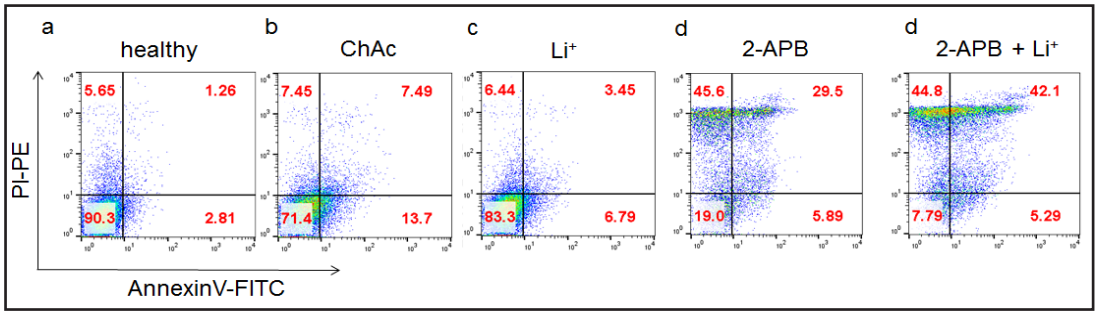

Fig. 3. Phosphatidylserine translocation and propidium iodide uptake in neurons from healthy volunteers and from ChAc patients without and with treatment with lithium or 2-APB. A-E. Representative dot blots of propidium iodide staining versus annexin-V-binding of neurons generated from healthy volunteers (A) and from ChAc patients (B-E) without treatment (B) and with lithium treatment (2 mM) alone (C), with 50 µM 2-APB (Ca^{2+} channel blocker) alone (D), and with both, lithium and 2-APB.

serum & glucocorticoid inducible kinase SGK1 or of ORAI1 [12]. Thus, chorein deficiency impairs the SGK1-dependent expression of ORAI1 and STIM1 thus leading to blunted SOCE and enhanced cell death, effects all reversed by lithium [12].

Similar observations were made in fibroblasts [37]. Fibroblasts of ChAc patients express less ORAI1 protein than fibroblasts of healthy controls [37]. Accordingly, SOCE is decreased and apoptosis enhanced in ChAc fibroblasts as compared to control fibroblasts [37]. Lithium again increases SOCE and pharmacological inhibition of ORAI1 decreases SOCE [37]. Lithium decreases suicidal death of ChAc fibroblasts, an effect abrogated by pharmacological ORAI1 inhibition [37].

The expression of ORAI1 is up-regulated by the PI3K-dependent [76] serum & glucocorticoid inducible kinase SGK1 [12, 77, 78]. The impaired activation of PI3K in chorein deficient cells [1-3] compromises activation of SGK1 and thus upregulation of ORAI1 [12]. PI3K signaling supports the survival of diverse cell types including cancer cells [48-51] and neurons [52-55].

Chorein does not only impact on neuronal, muscular cell and fibroblast survival, but may be similarly instrumental for the survival of tumor cells [60]. Chorein is expressed in various cancer cells [60]. Particularly strong chorein transcription was observed in drug resistant, poorly differentiated human ZF rhabdomyosarcoma cells [60]. In those cells chorein silencing downregulates phosphoinositide 3 kinase (PI-3K) [60], reduces ORAI1 expression and SOCE [60], decreases transcript levels and protein expression of anti-apoptotic BCL-2 and enhances the transcript levels of pro-apoptotic Bax [60]. Chorein silencing in rhabdomyosarcoma cells further leads to mitochondrial depolarization, caspase 3 activation and stimulation of early and late apoptosis [60]. Chorein silencing further decreases ORAI1 expression and SOCE [60]. Similar to chorein deficiency pharmacological inhibition of SGK1 decreases SOCE in rhabdomyosarcoma cells [60].

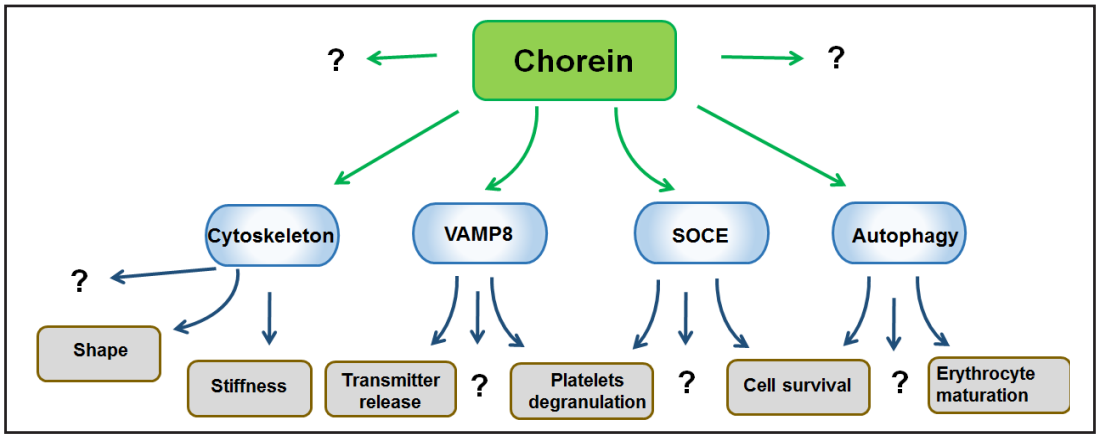

Fig. 4. Chorein sensitive functions in human cells. The question marks point to the many further putative chorein sensitive functions.

It is tempting to speculate that decreased ORAI1 and SOCE could contribute to neuronal death in other neurodegenerative diseases. Lithium has been shown to favorably influence the clinical course of several neurodegenerative diseases [79-81], such as Huntington´s chorea, Alzheimer´s disease, Parkinson´s disease, amyotrophic lateral sclerosis as well as spinocerebellar ataxias type 1 and type 3 [12, 79-83]. Mechanisms involved in the neuroprotective effect of lithium include direct or Akt-mediated inhibition of glycogen synthase kinase GSK-3β, Akt-mediated inhibition of the proapoptotic forkhead box class O transcription factor Foxo3a and murine double minute (MDM), induction of autophagy by inhibition of inositol monophosphatase, stimulation of production and activity of neuroprotective brain derived neurotrophic factor BDNF, up-regulation of anti-apoptotic protein Bcl-2, as well as down-regulation of pro-apoptotic transcription factor p53, of the pro-apoptotic proteins Bad and Bax, of glutamate excitotoxicity, of calpain and of oxidative stress [12, 81, 84]. By inhibiting glycogen synthase kinase GSK3β,lithium may modify the activity of carriers [85, 86] and channels [86]. Moreover, lithium may inhibit toll-like receptor TLR4 expression in astrocytes and thus counteract inflammation [87]. In neuronal cultures generated from ChAc patients, the anti-apoptotic effect is disrupted by pharmacological inhibition of ORAI1, an observation suggesting but not proving that the in vitro effect of lithium is due to up-regulation of the Ca^{2+} channel [12].

Conclusions

Within the past few years tremendous progress has been made in deciphering multiple functions of the clinically highly relevant protein chorein (Fig. 4). Most importantly, therapeutic opportunities have been identified. Additional effort is, however, required to fully understand the diverse ramifications of chorein dependent functions. Most importantly, treatments shown to be effective *in vitro* need to be tested in clinical trials on patients suffering from chorea-acanthocytosis. It is hoped that we are close to the ultimate goal of chorein related research, i.e. the development of a treatment halting or at least slowing the clinical course of this devastating genetic disorder.

Acknowledgements

The authors acknowledge the meticulous preparation of the manuscript by Lejla Subasic.

Disclosure Statement

The authors have nothing to disclose.

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