

Protein kinase CK2 and ion channels (Review)

MATHIAS MONTENARH and CLAUDIA GÖTZ

Medical Biochemistry and Molecular Biology, Saarland University, D-66424 Homburg, Saarland, Germany

Received May 26, 2020; Accepted July 28, 2020

DOI: 10.3892/br.2020.1362

Abstract. Protein kinase CK2 appears as a tetramer or higher molecular weight oligomer composed of catalytic CK2 α , CK2 α' subunits and non-catalytic regulatory CK2 β subunits or as individual subunits. It is implicated in a variety of different regulatory processes, such as Akt signalling, splicing and DNA repair within eukaryotic cells. The present review evaluates the influence of CK2 on ion channels in the plasma membrane. CK2 phosphorylates platform proteins such as calmodulin and ankyrin G, which bind to channel proteins for a physiological transport to and positioning into the membrane. In addition, CK2 directly phosphorylates a variety of channel proteins directly to regulate opening and closing of the channels. Thus, modulation of CK2 activities by specific inhibitors, by siRNA technology or by CRISPR/Cas technology has an influence on intracellular ion concentrations and thereby on cellular signalling. The physiological regulation of the intracellular ion concentration is important for cell survival and correct intracellular signalling. Disturbance of this regulation results in a variety of different diseases including epilepsy, heart failure, cystic fibrosis and diabetes. Therefore, these effects should be considered when using CK2 inhibition as a treatment option for cancer.

Contents

1. Introduction
2. CK2 and sodium channels
3. CK2 and potassium channels
4. CK2 and calcium channels
5. CK2 and anion channels
6. Conclusion

Correspondence to: Professor Mathias Montenarh, Medical Biochemistry and Molecular Biology, Saarland University, Building 44, D-66424 Homburg, Saarland, Germany
E-mail: m.montenarh@mx.uni-saarland.de

Key words: protein kinase CK2, ion channels, phosphorylation, review, protein-protein interaction

1. Introduction

Genes for 122 protein kinases have been identified in yeast cells, 540 in mice and 518 genes in the human genome (1). One of these protein kinases is protein kinase CK2, formerly known as casein kinase 2, which is a ubiquitously expressed, constitutively active serine/threonine and tyrosine kinase (2). In total, more than 500 protein substrates have been identified and CK2 is estimated to be responsible for up to 10% of the human phosphoproteome (3,4). CK2 is a soluble, readily extractable form in all eukaryotic cells. Moreover, Burnett and Kennedy (5) purified the soluble kinase activity from rat liver and named the enzyme according to 'casein', which was used as a substrate to analyse the kinase activity.

The CK2 holoenzyme is a tetramer, comprised of two catalytic α - or α' - and two non-catalytic β -subunits (6). The α -subunits are encoded by two distinct homologous genes, CSNK2A1 which encodes CK2 α (7) and CSNK2A2 which encodes CK2 α' (8). The β -subunit is encoded by CSNK2B (9). CK2 β is not a simple on-off regulator of the catalytic activity of CK2 α . It regulates thermostability, substrate specificity and the ability to attach and penetrate cell membranes (10-13). In addition to the tetramer, higher molecular weight forms of CK2 have been identified (14,15). Although the CK2 tetramer has a dissociation constant of around 4 nM (16,17) suggesting a permanent or a strong transient hetero complex, there is increasing evidence that the catalytic CK2 α subunits exist in the absence of CK2 β (18) and that CK2 β exists in the absence of CK2 α and CK2 α' (19,20).

CK2 α is known to have oncogenic potential (21). While no germline mutations in any of the CK2 genes have been described, patients with somatic mutations in the CSNK2A1 gene coding for CK2 α have been identified (22). These patients suffered from intellectual disability, hypotonia, speech problems, gastrointestinal problems and immune dysfunctions (23-25).

CK2 α and CK2 β are essential for embryonic development. For instance, mortality occurs in CK2 $\alpha^{-/-}$ embryos in mid-gestation, with defects in heart and neural tube (26). CK2 $\beta^{-/-}$ mice die shortly after implantation with no signs of apoptosis but reduced cell proliferation. Furthermore, CK2 $\beta^{-/-}$ blastocysts cannot develop an inner cell mass *in vitro* (27). It has also been revealed that CK2 α' knockout mice are viable but the male knockout mice exhibit globozoospermia (28). A recent review summarizes the knowledge about the role of CK2 in development and differentiation (29).

CK2 can use ATP as well as GTP as phosphate donor (30,31). Although CK2 is not responsible for the regulation of a single particular pathway, it can regulate various signalling pathways including NF κ B pathway, STAT3-, PTEN/PI3K/Akt- and the Wnt/ β -catenin pathway (32-37). In addition, CK2 may be involved in the regulation of stress- elicited pathways, such as proteotoxic stress, unfolded protein response and DNA damage pathways (38,39). It has previously been reported that the kinase activity of CK2 is elevated in rapidly proliferating cells and in particular in tumour cells (21). Multiple attempts have been conducted to develop inhibitors for the CK2 kinase activity (40-43) including the use of small organic compounds such as 5-3-chlorophenylamino)benzo[c][2,6]naphthyridine-8-carboxylic acid (CX-4945), 4,5,6,7-tetrabromo-1H-benzotriazole (TBB), 5,6-dichloro-1-beta-D-ribofuranosylbenz-imidazole (DRB), 2-dimethylamino-4,5,6,7-tetrabromo-1H-benzimidazole (DMAT), 5,6-dihydro-5-oxo-indolo-[1,2-a]-quinazoline-7-acetic acid (IQA), 1,3,8-trihydroxy-6-methylanthracene-9,10-dione (emodin) and a whole group of flavonoids, which can target the ATP binding site on the catalytic CK2 α or CK2 α' subunits (44-50). CX-4945 has been tested on more than 145 kinases and is demonstrated to be highly specific for CK2 and effective at micromolar concentrations (50). Recently, it was reported that CX-4945 also strongly inhibits cdc2 like kinases (51). Despite the large influence of CK2 on the human phosphoproteome, CX-4945 has been well tolerated in phase I clinical trials, (for example multiple myeloma clinical trial no. NT01199718), reviewed in (52).

CK2 is ubiquitously scattered within eukaryotic cells (53-56) and is present on the cell surface as an ecto-kinase (57). Moreover, CK2 is located in lipid rafts of brain synaptosomes and uterine cell membranes (58,59). In brain synaptosomes, inhibition of CK2 resulted in an enhanced neurotransmitter release (59). There is increasing evidence that CK2 phosphorylates numerous ion channels located within membranes. The present review evaluated ion channels in the plasma membrane as substrates or binding partners of CK2.

2. CK2 and sodium channels

There are two major classes of sodium channels in mammals known as the voltage gated sodium channels (VGSCs, Na $_v$) and the epithelial sodium channels (ENaCs) (60). A major physiological role for VGSCs is the generation of action potentials at the axonal initial segments (AIS) and in myelinated axons (61,62). The generation and propagation of action potentials requires the precise accumulation of the voltage-gated sodium channels, such as Na $_v$ 1.1, Na $_v$ 1.2 and Na $_v$ 1.6 at the AIS and in the nodes of Ranvier, which is achieved via ankyrin G scaffolding (Fig. 1A). It has been observed that the large intracellular domain of the VGSCs contains a highly conserved ankyrin G binding motif. However, the binding motif for the Na $_v$ s is also highly conserved on the polypeptide chain of ankyrin G (63,64). Brachet *et al* (62) reported that CK2 phosphorylates the ankyrin G binding motif on the polypeptide chain of Na $_v$ 1 (Fig. 1A). Moreover, mutation of the CK2 phosphorylation site on Na $_v$ 1 to a non-phosphorylatable alanine abrogated the Na $_v$ 1/ankyrin G interaction. This mutation, as well as the use of the CK2 kinase inhibitor DMAT, leads to

a decrease of Na $_v$ 1 at AIS (62). Thus, CK2 may be involved in the modulation of Na $_v$ 1 binding to ankyrin G as well as the accumulation of Na $_v$ 1 at AIS at least in young neurons. In agreement with these observations, CK2 is enriched in AIS and nodes of Ranvier (65).

Amiloride-sensitive epithelial sodium channels (ENaCs) mediate the transport of Na $^+$ ions across membranes of epithelial cells and are composed of α , β and γ subunits or δ , β and γ subunits (66). Alterations in the composition of the ENaCs are responsible for differences in conductance, open probability, sensitivity to amiloride, and sensitivity to extra-cellular protons (66). The activity of ENaC is regulated by various protein kinases such as protein kinase A (PKA), PKC, ERK1/2 and CK2 (67). CK2 phosphorylates the ENaC β subunit at serine 631 and the γ subunit at threonine 599 (68). Inhibition of the CK2 kinase activity as well as the use of ENaC subunits, in which both CK2 sites were mutated, demonstrates a reduced amiloride sensitive Na $^+$ transport (69). Furthermore, it was shown that CK2 directly binds to ENaC (68) and CK2 is transported to the cell membrane by wild-type ENaC, but not by ENaC, in which both CK2 phosphorylation sites are mutated (69). Regulation of ENaC by signalling molecules including hormones is critical for the regulation of electrolyte and water excretion and consequently for the regulation of blood pressure (70). Recently, the influence of CK2 on ENaC and sodium excretion was analysed in living organisms. For instance, Berman *et al* found that inhibition of CK2 kinase activity leads to a significant decrease in ENaC activity and natriuresis in mice. These results demonstrate that an appropriate regulation of ENaC by CK2 is necessary for fine regulation of the sodium concentration (71).

3. CK2 and potassium channels

The largest group of potassium channels are the voltage-gated channels known as K $_v$ channels (72). While ligand activated potassium channels also exist, their interaction with CK2 is yet to be elucidated. Similar to Na $_v$ s, K $_v$ s are located in different parts of the AIS and carry an ankyrin G binding site (73). Pharmacological inhibition of the CK2 kinase activity using TBB or tetrabromocinnamide acid (TBCA) prevents the distal redistribution of K $_v$ 7.3 channels along the AIS (74). Although not directly analysed by Lezmy *et al* (74), according to their results, it was suggested, that CK2 phosphorylates K $_v$ 7.2/3 to increase their affinity to ankyrin G (Fig. 1A). A possible explanation for these results is that inhibition of CK2 kinase activity may prevent the insertion of new K $_v$ 7.2/3 into the AIS. Alternatively, or in addition, CK2 may phosphorylate calmodulin, which increases its interaction with the K $_v$ 7.2 subunit, and is crucial for the aforementioned redistribution (Fig. 1B) (75).

The firing rate of neurons is generated by M-type K $^+$ current generated by channels that contain K $_v$ 7/KCNQ2-5 subunits (76). Physiological functioning of these channels is necessary to maintain physiological neuronal excitability, and dysfunction of these channels may result in neurological disorders such as epilepsy (77). The transport of the KCNQ2 channel from the endoplasmic reticulum to the plasma membrane is regulated by calmodulin. According to the aforementioned findings, CK2

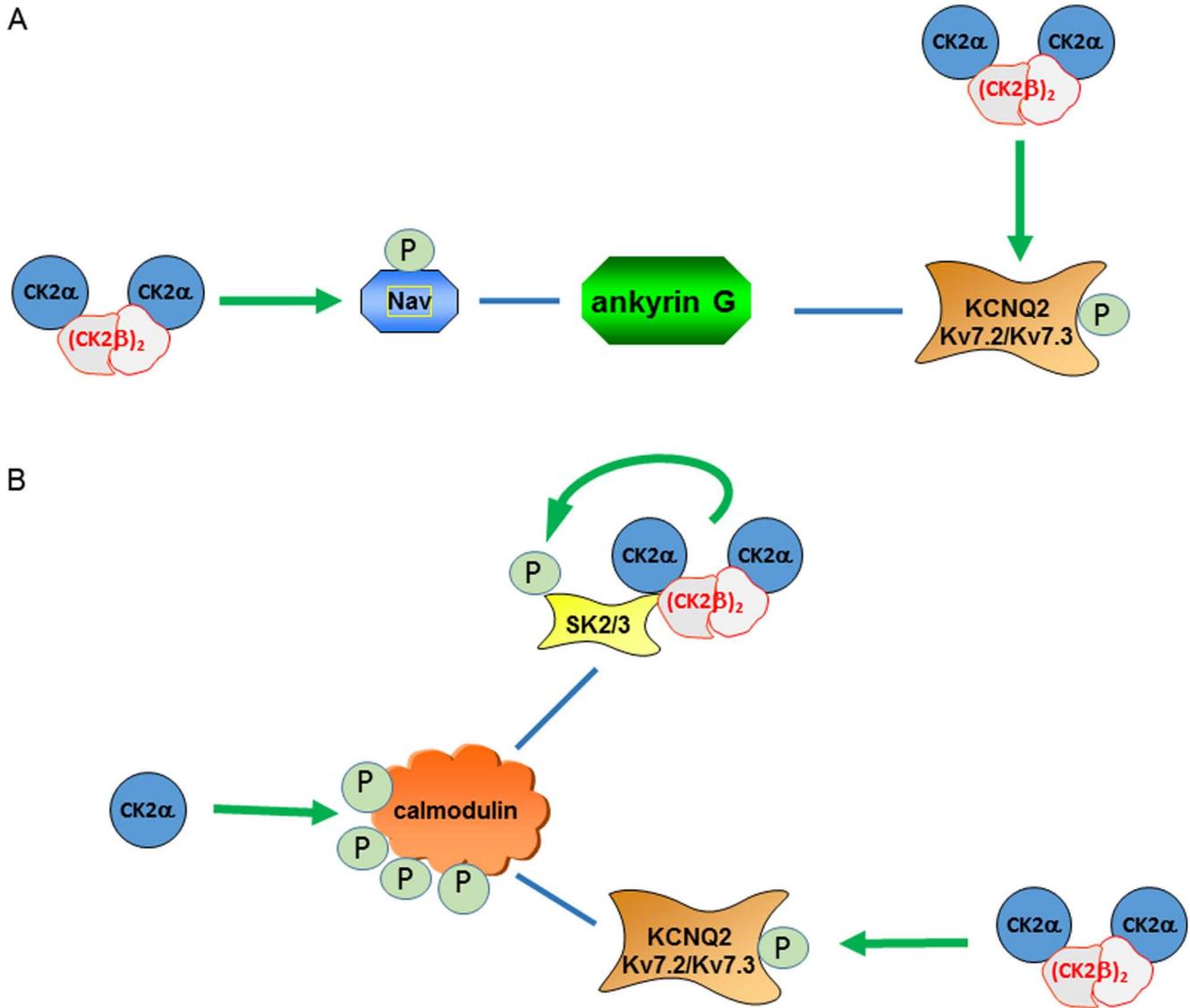


Figure 1. Influence of CK2 phosphorylation on binding of channel proteins to (A) ankyrin G or (B) calmodulin. Green arrows represent phosphorylation and interaction. Blue lines indicate an interaction. P, phosphate; CK2, casein kinase 2; SK, small conductance; KCNQ2, potassium voltage-gated channel subfamily Q member 2; Nav, sodium voltage-gated channels.

phosphorylation of KCNQ2 may be implicated in the transport of this channel to the plasma membrane. Moreover, the CK2 inhibitors TBB and TBCA have been used to study the interaction between ankyrin G and KCNQ2 and it was demonstrated that inhibition of CK2 kinase activity results in a reduced interaction of ankyrin G with KCNQ2 (Fig. 1A) (64,65,75). It has been observed that CK2, which accumulates at the AIS, phosphorylates calmodulin and thereby regulates the activity of KCNQ2. A previous study has also shown that ankyrin G binds stronger to Na_v1.2 than to KCNQ2 (64).

A second family of potassium channels comprises the Ca²⁺ activated transmembrane potassium channels, which are divided into big-conductance (BK), small conductance (SK) and intermediate conductance channels. SK channels are widely expressed in the central nervous system and the cardiovascular system, and are structurally similar K_vs. Gating of SK is achieved via the constitutive interaction between the pore-forming subunits and calmodulin. Binding and unbinding of Ca²⁺ ions to calmodulin are transduced

via conformational changes in channel opening and closure, respectively (78). SK channels couple the membrane potential to fluctuation in the intracellular Ca²⁺ concentration. Each of the four SK α-subunits harbours one bound calmodulin molecule (79). Moreover, calmodulin, which is phosphorylated by CK2 (80,81) inhibits SK channels (82-84). Calmodulin is phosphorylated by CK2α but not by the holoenzyme consisting of CK2α and CK2β. CK2 phosphorylation of calmodulin reduces the affinity of calmodulin for intracellular Ca²⁺ ions, which leads to a deactivation of the SK channel (82). Furthermore, this effect is reversed by protein phosphatase 2A (PP2A), which dephosphorylates calmodulin leading to a recovery of the Ca²⁺ binding affinity of calmodulin and thereby to a recovery of the channel activity (84).

SK2 channel phosphorylation by CK2 results in a deactivation of the channel, while dephosphorylation has the reverse effect (83). Allen *et al* (84) and Bildl *et al* (83) reported, that both CK2α and CK2β and PP2A bind to the cytoplasmic N- and

C-termini of SK channels to form a multiprotein complex at the plasma membrane of rat brains. Furthermore, PP2A binds to a region on the polypeptide chain of SK, which was previously identified as the PP2A binding site on the polypeptide chain of SV40 small T antigen and CK2 α (18,85). Positively charged compounds, such as spermine or poly-L-lysine, are known to stimulate the kinase activity of CK2 (79). The N-terminal domain of SK2 contains a cluster of positively charged residues close to the site of interaction with CK2 α and it was revealed that this region stimulated CK2 similar to poly-L-lysine (84). Within this complex, CK2 phosphorylates calmodulin, thereby reducing the Ca²⁺ sensitivity and accelerating channel deactivation (86).

Neurotransmitters, such as noradrenalin, inhibit SK2 channels independently of changes in the activity of the priming Ca²⁺ channels (82). In total, there are three homologous SK channels, namely SK1-3, expressed in the mammalian brain (87). Inhibition of CK2 by TBB or the use of a dominant-negative CK2 α K68M mutant strongly reduces the effect of noradrenalin on SK channels (82). However, the signalling pathway from the activated receptor to CK2 awaits further analysis.

The influence of CK2 and potassium channels in disease is yet to be fully elucidated. However, it has been shown that increased expression of CK2 in the infarct border is associated with reduced SK1/Kir2.1 protein levels (88). Furthermore, over-expression of CK2 suppressed the KCNJ2/Kir2.1 expression and inhibition of CK2 kinase activity enhanced KCNJ2/Kir2.1 expression (89). It has been shown that hypoxia leads to increased CK2 expression in the heart of male Wistar rats, and the CK2/Kir2.1 pathway may be a potential therapeutic target for ventricular arrhythmias (vAs) after myocardial infarction (89). CK2 phosphorylates the transcription factor SP1, which regulates the expression of the potassium inwardly rectifying channel subfamily J member 2 gene, encoding Kir2.1. The angiotensin 1 receptor antagonist valsartan reduces CK2 activation at the infarct border and increases Kir2.1 expression (89). These findings provide an insight into the pathophysiological molecular mechanisms which occur following myocardial infarction, and in particular, into the role of CK2 in this process.

The K_{Ca}2.2 channel represents the major isoform of voltage small conductance Ca²⁺ activated K⁺ channels in the hippocampus (90). The K_{Ca}2.2 channel is phosphorylated by CK2 (83,84) and gated by the intracellular assembly with calmodulin (91). CK2 phosphorylation leads to an impairment of the K_{Ca}2.2 channel activity. Previously, in a rat pilocarpine epilepsy model, it was reported that oral administration of the CK2 kinase inhibitor TBB enhances K⁺ currents and it blocks the occurrence of spontaneous epileptic activity (92). TBB also enhances the K_{Ca}2.2 protein level in the Cornu Ammonis (CA1) region from post status epilepticus (93). Moreover, there is a reduced expression of CK2 proteins in CA1 of epileptic animals (94). The mechanism for the reduced abundance of CK2 proteins remains to be elucidated.

4. CK2 and calcium channels

Ca²⁺ ions are essential for nearly all aspects of cell functions. Ca²⁺ channels in the plasma membrane play an important role in controlling intracellular calcium homeostasis (95). Recently, Afzal *et al* revealed that inhibition of CK2 with

high concentrations of TBB leads to a considerable loss of total cellular Ca²⁺ in prostate cancer cells. In addition, inhibition of CK2 results in a decrease of cytosolic Ca²⁺ levels, along with an increase in mitochondrial and endoplasmic levels of Ca²⁺ in these cells (96). Thus, these results indicate CK2 may be involved in the regulation of the intracellular Ca²⁺ homeostasis.

Ca²⁺ channels include voltage-gated (Ca_v) and ligand-gated channels. Voltage-gated channels (Ca_v) channels are sub-divided into L-type (Ca_v1.1- Ca_v1.4), P/Q-type (Ca_v2.1), N-type (Ca_v2.2), R-type (Ca_v2.3) and T-type (Ca_v3.1-Ca_v3.3) channels, while the ligand-gated channels include IP3-receptor type, ryanodine receptor type, store operated channels amongst others (97-100).

In response to membrane depolarization the conformation of Ca_v channels switches from a close to an open state, and Ca²⁺ influx via Ca_v channels serves as a second messenger to couple electric signalling to chemical signalling (99,100). The Ca²⁺ concentration controls a diverse range of intracellular events such as endocytosis, exocytosis, muscle contraction, synaptic transmission and metabolism (101) thus controlling proliferation, differentiation and development. Ca_v channels share a common subunit composition, where Ca_v α 1 subunits are pore forming, and Ca_v β and Ca_v δ as well as in some cases Ca_v γ , are ancillary subunits (99). The α_1 subunit is composed of four homologous transmembrane domains and cytoplasmic N- and C-termini. In addition to these subunits, calmodulin is also present in these complexes (102).

The L-type calcium current is critical for the development, function and regulation of many different cell types including physiologic functions of nerve and muscle cells (103). L-type calcium channels are implicated in the excitation-contraction coupling in cardiac, skeletal and smooth muscle, in the regulation of Ca²⁺ homeostasis and secretion, tissue development, neuron excitability, excitation-transcription coupling and in learning and memory in the brain, reviewed in (104). Furthermore, L-type Ca²⁺ channel activation results in uterine contraction of mice, the activation of which is suppressed by inhibition of CK2 (58). Ca_v1.1 is the L-type Ca²⁺ channel present in the skeletal muscle and Ca_v1.2 is the L-type channel present in the heart. Both of these channels are regulated via phosphorylation by a number of different protein kinases, such as PKA, Akt, PKC and CK2 (103). Multiple regulatory sites are located in the large C-terminal domain of Ca_v1.1 and Ca_v1.2 channels (105-107). For instance, the PKA phosphorylation site at serine 1700 was required for the stimulation of channel activity (108), while threonine 1704 phosphorylation by CK2 is necessary for the regulation of basal channel activity. Mice with mutations at these two phosphorylation sites have a significantly reduced basal L-type calcium current and a reduced response to β -adrenergic stimulation (109,110). In addition these mutant mice have an impaired contractile function, decreased exercise capacity and cardiac hypertrophy (109,110).

The L-type Ca²⁺ channel Ca_v1.2 regulates Ca²⁺ influx and initiates the human heartbeat (103,111). In immature but not mature, mouse cardiomyocytes, Kashihara *et al* (111) have shown that angiotensin II regulates Ca_v1.2 via the angiotensin type 1 receptor and induces a signalling cascade involving β -arrestin 2, which stimulates the tyrosine kinase src, thus

phosphorylating p27^{k_{ip}1}. This phosphorylation prevents p27^{k_{ip}1} from inhibiting the phosphorylation of a C-terminal fragment of Ca_v1.2 by CK2 (111). It has been reported that unphosphorylated p27^{k_{ip}1} is one of the very few proteins that specifically inhibits CK2 α' (112). Moreover, CK2 β binds to Ca_v1.2 and recruits p27^{k_{ip}1} and CK2 α' to the Ca_v1.2 complex (111). However, it remains unknown whether CK2 α' functions alone or as a holoenzyme consisting of CK2 α' and CK2 β .

A C-terminal fragment of Ca_v1.2 translocates to the nucleus and regulates transcription (113) of a variety of different genes, such as the gap junction protein Cx31.1, the axon guidance factor Netrin 4, the regulator of G-protein signalling RGS5 and the tight junction protein claudin19, which are implicated in neuronal signalling and excitability. This result suggested that Ca_v1.2 has a dual function as a channel and as a transcription factor. However, it is yet to be analysed whether the Ca_v1.2 C-terminus remains associated with CK2 α' /CK2 β after translocation to the nucleus. The mechanism that triggers the cleavage of the C-terminus is also not fully understood. It has been revealed that adenosine triphosphate regulates at least the activity of guinea pig Ca_v1.2 by direct binding to the channel in a dose dependent manner (114). In addition, as further studies have reported that calmodulin and Ca²⁺ regulate ATP binding activities, it was hypothesized that this channel-bound ATP is directly necessary as a phosphate donor for protein kinases, which phosphorylate Ca_v1.2.

Modulation of Ca_v2.1 channel activity serves a key role in inter-neuronal communication and synaptic plasticity as well as in the regulation of exocytosis of insulin from storage granules of the human pancreas especially at low glucose concentrations (115). Ca²⁺ influx via Ca_v2.1 promotes channel inactivation (116). In a recent study we identified Ca_v2.1 as a substrate and as a binding partner for CK2 (117). Inhibition of CK2 by CX-4945 enhances the intracellular Ca²⁺ level, which corresponds with an increase in insulin secretion from pancreatic β -cells (117). Moreover, quercetin is a potent inhibitor of CK2 at IC₅₀ values <1 μ M (118), which induces insulin secretion by direct activation of L-type calcium channels in pancreatic β -cells.

A transient Ca²⁺ micro-domain is essential for synaptic exocytosis leading to the fast release of neurotransmitters (119). Ca_v2.1 is regulated by interaction with its β -subunit, by SNARE proteins binding to Ca_v2.1, and by Ca²⁺-calmodulin attached to the C-terminal tail of the Ca_v2.1 α 1A subunit (120). As aforementioned, CK2 phosphorylates calmodulin (80,81), but it has to be elucidated whether CK2 phosphorylation affects the calmodulin/Ca_v2.1 interaction.

In total, at least two other proteins, including syntaxin-1 and synaptotagmin-1, specifically interact with Ca_v2.1 channels by binding to a synaptic protein interaction site within an intracellular loop of the channel (121,122). CK2 is present in the membrane micro-domains from rat brain nerve endings and it phosphorylates syntaxin-1 at serine 14 as assessed using phospho-specific antibodies (59). This N-terminal segment of syntaxin-1 including the CK2 phosphorylation site is involved in direct protein-protein interactions and leads to alterations in the neurotransmitter release (59). Furthermore, it has been demonstrated that the CK2 phosphorylation of syntaxin-1

may play a role in the pathophysiology of schizophrenia (123). Therefore, these data might suggest a differential regulation of Ca_v2.1 by CK2, where syntaxin-1 and synaptotagmin-1 are phosphorylated by the CK2 holoenzyme while calmodulin is phosphorylated by CK2 α alone.

5. CK2 and anion channels

Chloride or bicarbonate are transported across membranes by complex membrane proteins called anion channels. The transport of chloride and bicarbonate ions results in alterations of the pH within cells and also in alterations in the transport of water (124). A reduction in chloride and bicarbonate concentrations leads to a disease called cystic fibrosis. The cystic fibrosis transmembrane conductance regulator (CFTR) is an example of an anion channel present in epithelial cells and is a member of the family of ATP binding cassette (ABC) proteins (125,126). The activity of CFTR is, in part regulated by the cAMP-dependent protein kinase PKA (126). In addition, CK2 is implicated in the regulation of CFTR (127-133). It has been reported that TBB treatment of Calu-3 cells resulted in a significant inhibition of the basolateral Cl⁻/HCO₃⁻ exchanger. Treatment with the more efficient and specific inhibitor CX-4945 completely abolishes Cl⁻/HCO₃⁻ exchanger activity.

Recently, it has been revealed that CK2 is required for the physiological expression of the Ca²⁺ activated Cl⁻ channel anoctamin 1 (ANO1), previously known as TMEM16A, in the plasma membrane. ANO1 is stimulated via G-protein coupled receptors (134). Small interfering RNA knockdown of CK2 α' or inhibition of the kinase activity by TBB or CX-4945 leads to a reduced expression in the plasma membrane and an inhibition of the whole cell current in airways epithelial cells (134). Furthermore, these treatments result in an inhibition of cell proliferation. However, it remains to be analysed whether CK2 α' directly phosphorylates ANO1 alone or as a CK α' /CK2 β holoenzyme and whether CK2 α might have the same effect.

CK2 is not only stimulatory for the functions of channels. It inhibits the lipid flippase ABCA1, which is a CFTR related protein (135). A total of three residues, threonine 1,242, threonine 1,243 and serine 1,255 in the cytoplasmic part of ABCA1 have been identified as CK2 phosphorylation sites (135). Moreover, mutation analysis and the use of CK2 specific inhibitors has revealed that CK2 phosphorylation affects flippase activity, apolipoprotein AI and AII binding and phospholipid and cholesterol efflux (80,135).

The cellular uptake of a wide range of endogenous and exogenous molecules including many clinically used drugs is mediated by solute carrier transporters (SLC), which are transmembrane proteins (136). SLC4A2 is another member of the Cl⁻/HCO₃⁻ exchanger in human airway epithelia cells, which is phosphorylated by CK2 and whose activity is reduced by inhibition of CK2 by TBB or CX-4945 or by knockdown experiments, suggesting that CK2 may be a key regulator of trans-epithelial transport in human airways (137). However, it remains unknown whether CK2 regulates SLC4A2 directly or indirectly by regulating calmodulin. CK2 has also been shown to influence the activity of the nucleoside transporters SLC29A1 and SLC29A2, previously known as ENT1 and ENT2, respectively (138).

Table I. CK2 phosphorylation of channel proteins.

First author, year	Substrates of CK2	Function	(Refs.)
Brachet <i>et al.</i> , 2010	Na _v 1	Interaction with ankyrin G	(62)
Shi <i>et al.</i> , 2002	ENaC β-subunit and γ-subunit	Amiloride sensitive Na ⁺ transport	(68)
Xu and Cooper, 2015; Brechet <i>et al.</i> , 2008	K _v 7.2/3	Distribution of K _v 7.2/3 along AIS	(64,65)
Zhang <i>et al.</i> , 2014	Calmodulin/SK	Regulation of SK channel activity	(86)
Xu <i>et al.</i> , 2020; Fuller <i>et al.</i> , 2010; Scheuer <i>et al.</i> , 2020	Ca _v 1.2, Ca _v 1.1, Ca _v 2.1	Ca ²⁺ transport	(103,108,117)
Cesaro <i>et al.</i> , 2013; Luz <i>et al.</i> , 2011	CFTR	Chloride/bicarbonate transport	(127,128)
Roosbeek <i>et al.</i> , 2004	ABCA1	Regulation of flippase activity	(135)
Ibrahim <i>et al.</i> , 2017	SLC4A2	Chloride/bicarbonate transport	(137)
Stolk <i>et al.</i> , 2005	SLC29A1, SLC29A2	Nucleoside transport	(138)

CK2, protein kinase CK2; SK, small conductance; ENaC, Amiloride-sensitive epithelial sodium channels; Ca_v, Ca²⁺ voltage-gated channels; SLC4A2, solute carrier family 4 member 2; K_v, potassium voltage-gated channels; CFTR, cystic fibrosis transmembrane conductance regulator; ABCA1, ATP binding cassette subfamily A member 1; AIS, axonal initial segments; Na_v, sodium voltage-gated channels.

Table II. Binding of CK2 to channel proteins.

First author, year	CK2 binding partner	Function	(Refs.)
Shi <i>et al.</i> , 2002	ENaC	Transport to the plasma membrane	(68)
Bildl <i>et al.</i> , 2004; Allen <i>et al.</i> , 2007	SK channels	Formation of multi-protein complex at the plasma membrane of rat brain increase of CK2 kinase activity	(83,84)
Kashihara <i>et al.</i> , 2017	Ca _v 1.2	Recruitment of p27 ^{kip1} and CK2α' to the membrane	(111)
Scheuer <i>et al.</i> , 2020	Ca _v 2.1	Ca ²⁺ transport	(117)

CK2, protein kinase CK2; SK, small conductance; ENaC, Amiloride-sensitive epithelial sodium channels; Ca_v, Ca²⁺ voltage-gated channels.

6. Conclusion

In conclusion, protein kinase CK2 is implicated in central cellular processes, such as regulation of cell proliferation, differentiation, RNA splicing, DNA repair and angiogenesis. The present review has summarized the knowledge regarding the regulation of cation and anion channels. This regulation is achieved either by direct phosphorylation of proteins building the channels (Table I) or via phosphorylation of platform proteins such as calmodulin and ankyrin G (Fig. 1), which are responsible for binding, transport and physiological orientation of channel proteins into the plasma membrane. In addition, CK2 subunits bind to certain proteins which compose the channels (Table II), which might reflect an enzyme /substrate interaction or a currently unknown function. Regulation of the intracellular ion concentration contributes to an altered membrane potential, which influences cellular excitability of a variety of different cell systems including neuronal and muscle cells. Moreover, the intracellular ion concentrations plays an important role in a variety of different conditions such as heart failure, epilepsy, cystic fibrosis and diabetes. These effects have been considered when CK2 inhibitors are used for the treatment

of cancer. Furthermore, the knowledge of the role of CK2 in the regulation of ion channels in the plasma membrane may facilitate the targeting CK2 for the regulation of intracellular ion concentrations and ultimately cellular signalling.

Acknowledgements

Not applicable.

Funding

This work was supported by the Rolf M. Schwiete Stiftung, Mannheim, Germany (grant nos. 06/2015 and 2020-006).

Availability of data and materials

Not applicable.

Authors' contributions

MM and CG performed literature research, wrote the paper, and read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

- Manning G: Genomic overview of protein kinases. *WormBook* 1-19, 2005.
- Litchfield DW: Protein kinase CK2: Structure, regulation and role in cellular decisions of life and death. *Biochem J* 369: 1-15, 2003.
- Salvi M, Sarno S, Cesaro L, Nakamura H and Pinna LA: Extraordinary pleiotropy of protein kinase CK2 revealed by weblogo phosphoproteome analysis. *Biochim Biophys Acta* 1793: 847-859, 2009.
- de Villavicencio-Diaz T, Rabalski AJ and Litchfield DW: Protein kinase CK2: Intricate relationships within regulatory cellular networks. *Pharmaceuticals (Basel)* 10: 27, 2017.
- Burnett G and Kennedy EP: The enzymatic phosphorylation of proteins. *J Biol Chem* 211: 969-980, 1954.
- Boldyreff B, Meggio F, Pinna LA and Issinger OG: Protein kinase CK2 structure-function relationship: Effects of the β subunit on reconstitution and activity. *Cell Mol Biol Res* 40: 391-399, 1994.
- Wirkner U, Voss H, Lichter P, Ansorge W and Pyerin W: The human gene (CSNK2A1) coding for the casein kinase II subunit alpha is located on chromosome 20 and contains tandemly arranged Alu repeats. *Genomics* 19: 257-265, 1994.
- Ackermann K, Neidhart T, Gerber J, Waxmann A and Pyerin W: The catalytic subunit alpha' gene of human protein kinase CK2 (CSNK2A2): Genomic organization, promoter identification and determination of Ets1 as a key regulator. *Mol Cell Biochem* 274: 91-101, 2005.
- Albertella MR, Jones H, Thomson W, Olavesen MG and Campbell RD: Localization of eight additional genes in the human major histocompatibility complex, including the gene encoding the casein kinase II beta subunit (CSNK2B). *Genomics* 36: 240-251, 1996.
- Raaf J, Brunstein E, Issinger OG and Niefind K: The interaction of CK2alpha and CK2beta, the subunits of protein kinase CK2, requires CK2beta in a preformed conformation and is enthalpically driven. *Protein Sci* 17: 2180-2186, 2008.
- Meggio F, Boldyreff BS, Marin O, Pinna LA and Issinger OG: CK2: Role of the beta-subunit on the stability and specificity of the recombinant reconstituted holoenzyme. *Eur J Biochem* 204: 293-297, 1992.
- Boldyreff BS, Meggio F, Pinna LA and Issinger O-G: Casein kinase-2 structure-function relationship: Creation of a set of mutants of the β subunit that variably surrogate the wildtype β subunit function. *Biochem Biophys Res Commun* 188: 228-234, 1992.
- Rodriguez FA, Contreras C, Bolanos-Garcia V and Allende JE: Protein kinase CK2 as an ectokinase: The role of the regulatory CK2beta subunit. *Proc Natl Acad Sci USA* 105: 5693-5698, 2008.
- Lolli G, Pinna LA and Battistutta R: Structural determinants of protein kinase CK2 regulation by autoinhibitory polymerization. *ACS Chem Biol* 7: 1158-1163, 2012.
- Lolli G, Naressi D, Sarno S and Battistutta R: Characterization of the oligomeric states of the CK2 alpha2beta2 holoenzyme in solution. *Biochem J* 474: 2405-2416, 2017.
- Raaf J, Guerra B, Neundorf I, Bopp B, Issinger OG, Jose J, Pietsch M and Niefind K: First structure of protein kinase CK2 catalytic subunit with an effective CK2 β -competitive ligand. *ACS Chem Biol* 8: 901-907, 2013.
- Raaf J, Bischoff N, Klopffleisch K, Brunstein E, Olsen BB, Vilk G, Litchfield DW, Issinger OG and Niefind K: Interaction between CK2 α and CK2 β , the subunits of protein kinase CK2: Thermodynamic contributions of key residues on the CK2 α surface. *Biochemistry* 50: 512-522, 2011.
- Heriche JK, Lebrin F, Rabilloud T, LeRoy D, Chambaz EM and Goldberg Y: Regulation of protein phosphatase 2A by direct interaction with casein kinase 2alpha. *Science* 276: 952-955, 1997.
- Lüscher B and Litchfield DW: Biosynthesis of casein kinase II in lymphoid cell lines. *Eur J Biochem* 220: 521-526, 1994.
- Guerra B, Siemer S, Boldyreff B and Issinger OG: Protein kinase CK2: Evidence for a protein kinase CK2 β subunit fraction, devoid of the catalytic CK2 α subunit, in mouse brain and testicles. *FEBS Lett* 462: 353-357, 1999.
- Trembley JH, Wang G, Unger G, Slaton J and Ahmed K: CK2: A key player in cancer biology. *Cell Mol Life Sci* 66: 1858-1867, 2009.
- Benveniste EN, Gray GK and McFarland BC: Protein kinase CK2 and dysregulated oncogenic inflammatory signaling pathways Protein kinase CK2 cellular function in normal and disease states Springer e-book, 2015
- Okur V, Cho MT, Henderson L, Retterer K, Schneider M, Sattler S, Niyazov D, Azage M, Smith S, Picker J, *et al*: De novo mutations in CSNK2A1 are associated with neurodevelopmental abnormalities and dysmorphic features. *Hum Genet* 135: 699-705, 2016.
- Owen CI, Bowden R, Parker MJ, Patterson J, Patterson J, Price S, Sarkar A, Castle B, Deshpande C, Splitt M, *et al*: Extending the phenotype associated with the CSNK2A1-related Okur-Chung syndrome-A clinical study of 11 individuals. *Am J Med Genet A* 176: 1108-1114, 2018.
- Trinh J, Huning I, Budler N, Hingst V, Lohmann K and Gillessen-Kaesbach G: A novel de novo mutation in CSNK2A1: Reinforcing the link to neurodevelopmental abnormalities and dysmorphic features. *J Hum Genet* 62: 1005-1006, 2017.
- Lou DY, Dominguez I, Toselli P, Landesman-Bollag E, O'Brien C and Seldin DC: The alpha catalytic subunit of protein kinase CK2 is required for mouse embryonic development. *Mol Cell Biol* 28: 131-139, 2008.
- Buchou T, Vernet M, Blond O, Jensen HH, Pointu H, Olsen BB, Cochet C, Issinger OG and Boldyreff B: Disruption of the regulatory b subunit of protein kinase CK2 in mice leads to a cell-autonomous defect and early embryonic lethality. *Mol Cell Biol* 23: 908-915, 2003.
- Xu X, Toselli PA, Russell LD and Seldin DC: Globozoospermia in mice lacking the casein kinase II a' catalytic subunit. *Nat Genet* 23: 118-121, 1999.
- Götz C and Montenarh M: Protein kinase CK2 in development and differentiation. *Biomed Rep* 6: 127-133, 2016.
- Niefind K, Pütter M, Guerra B, Issinger OG and Schomburg D: CTP plus water mimic ATP in the active site of protein kinase CK2. *Nat Struct Biol* 6: 1100-1103, 1999.
- Lin WJ, Tuazon PT and Traugh JA: Characterization of the catalytic subunit of casein kinase II expressed in *Escherichia coli* and regulation of activity. *J Biol Chem* 266: 5664-5669, 1991.
- Guerra B: Protein kinase CK2 subunits are positive regulators of AKT kinase. *Int J Oncol* 28: 685-693, 2006.
- Shehata M, Schnabl S, Demirtas D, Hilgarth M, Hubmann R, Ponath E, Badryna S, Lehner C, Hoelbl A, Duechler M, *et al*: Reconstitution of PTEN activity by CK2 inhibitors and interference with the PI3-K/Akt cascade counteract the antiapoptotic effect of human stromal cells in chronic lymphocytic leukemia. *Blood* 116: 2513-2521, 2010.
- Wang S and Jones KA: CK2 controls the recruitment of Wnt regulators to target genes in vivo. *Curr Biol* 16: 2239-2244, 2006.
- Gao Y and Wang HY: Casein kinase 2 Is activated and essential for Wnt/beta-catenin signaling. *J Biol Chem* 281: 18394-18400, 2006.
- Ponce DP, Yefi R, Cabello P, Maturana JL, Niechi I, Silva E, Galindo M, Antonelli M, Marcelain K, Armisen R and Tapia JC: CK2 functionally interacts with AKT/PKB to promote the β -catenin-dependent expression of survivin and enhance cell survival. *Mol Cell Biochem* 356: 127-132, 2011.
- Ponce DP, Maturana JL, Cabello P, Yefi R, Niechi I, Silva E, Armisen R, Galindo M, Antonelli M and Tapia JC: Phosphorylation of AKT/PKB by CK2 is necessary for the AKT-dependent up-regulation of β -catenin transcriptional activity. *J Cell Physiol* 226: 1953-1959, 2011.
- Götz C and Montenarh M: Protein kinase CK2 in the ER stress response. *Ad Biological Chemistry* 3A: 1-5, 2013.
- Montenarh M: Protein kinase CK2 in DNA damage and repair. *Transl Cancer Res* 5: 49-63, 2016.
- Cozza G, Pinna LA and Moro S: Protein kinase CK2 inhibitors: A patent review. *Expert Opin Ther Pat* 22: 1081-1097, 2012.

41. Cozza G: The development of CK2 inhibitors: From traditional pharmacology to in silico rational drug design. *Pharmaceuticals (Basel)* 10: 26, 2017.
42. Prudent R and Cochet C: New protein kinase CK2 inhibitors: Jumping out of the catalytic box. *Chem Biol* 16: 112-120, 2009.
43. Bollacke A, Nienberg C, Borgne ML and Jose J: Toward selective CK2 α and CK2 α' inhibitors: Development of a novel whole-cell kinase assay by Autodisplay of catalytic CK2 α' . *J Pharm Biomed Anal* 121: 253-260, 2016.
44. Battistutta R, Sarno S, De Moliner E, Papinutto E, Zanotti G and Pinna LA: The replacement of ATP by the competitive inhibitor emodin induces conformational modifications in the catalytic site of protein kinase CK2. *J Biol Chem* 275: 29618-29622, 2000.
45. Battistutta R, De Moliner E, Sarno S, Zanotti G and Pinna LA: Structural features underlying selective inhibition of protein kinase CK2 by ATP site-directed tetrabromo-2-benzotriazole. *Protein Sci* 10: 2200-2206, 2001.
46. Pagano MA, Bain J, Kazimierzczuk Z, Sarno S, Ruzzene M, Di Maira G, Elliott M, Orzeszko A, Cozza G, Meggio F and Pinna LA: The selectivity of inhibitors of protein kinase CK2. An update. *Biochem J* 415: 353-365, 2008.
47. Sarno S, De Moliner E, Ruzzene M, Pagano MA, Battistutta R, Bain J, Fabbro D, Schoepfer J, Elliott M, Furet P, *et al*: Biochemical and three-dimensional-structural study of the specific inhibition of protein kinase CK2 by [5-oxo-5,6-dihydro-indolo-(1,2-a)quinazolin-7-yl]acetic acid (IQA). *Biochem J* 374: 639-646, 2003.
48. Sarno S, Reddy H, Meggio F, Ruzzene M, Davies SP, Donella-Deana A, Shugar D and Pinna LA: Selectivity of 4,5,6,7-tetrabromobenzotriazole, an ATP site-directed inhibitor of protein kinase CK2 ('casein kinase-2'). *FEBS Lett* 496: 44-48, 2001.
49. Pierre F, Chua PC, O'Brien SE, Siddiqui-Jain A, Bourbon P, Haddach M, Michaux J, Nagasawa J, Schwaebe MK, Stefan E, *et al*: Discovery and SAR of 5-(3-chlorophenylamino) benzo[c][2,6]naphthyridine-8-carboxylic acid (CX-4945), the first clinical stage inhibitor of protein kinase CK2 for the treatment of cancer. *J Med Chem* 54: 635-654, 2011.
50. Siddiqui-Jain A, Drygin D, Streiner N, Chua P, Pierre F, O'Brien SE, Bliesath J, Omori M, Huser N, Ho C, *et al*: CX-4945, an orally bioavailable selective inhibitor of protein kinase CK2, inhibits prosurvival and angiogenic signaling and exhibits anti-tumor efficacy. *Cancer Res* 70: 10288-10298, 2010.
51. Lee JY, Yun JS, Kim WK, Chun HS, Jin H, Cho S and Chang JH: Structural basis for the selective inhibition of Cdc2-like kinases by CX-4945. *Biomed Res Int* 2019: 6125068, 2019.
52. Chua MM, Ortega CE, Sheikh A, Lee M, Abdul-Rassoul H, Hartshorn KL and Dominguez I: CK2 in cancer: Cellular and biochemical mechanisms and potential therapeutic target. *Pharmaceuticals (Basel)* 10: 18, 2017.
53. Faust M, Jung M, Günther J, Zimmermann R and Montenarh M: Localization of individual subunits of protein kinase CK2 to the endoplasmic reticulum and to the Golgi apparatus. *Mol Cell Biochem* 227: 73-80, 2001.
54. Faust M, Schuster N and Montenarh M: Specific binding of protein kinase CK2 catalytic subunits to tubulin. *FEBS Letters* 462: 51-56, 1999.
55. Faust M, Günther J, Morgenstern E, Montenarh M and Götz C: Specific localization of the catalytic subunits of protein kinase CK2 at the centrosomes. *Cell Mol Life Sci* 59: 2155-2164, 2002.
56. Faust M and Montenarh M: Subcellular localization of protein kinase CK2: A key to its function? *Cell Tissue Res* 301: 329-340, 2000.
57. Montenarh M and Götz C: Ecto-protein kinase CK2, the neglected form of CK2 (review). *Biomed Rep* 8: 307-313, 2018.
58. Suhas KS, Parida S, Gokul C, Srivastava V, Prakash E, Chauhan S, Singh TU, Panigrahi M, Telang AG and Mishra SK: Casein kinase 2 inhibition impairs spontaneous and oxytocin-induced contractions in late pregnant mouse uterus. *Exp Physiol* 103: 621-628, 2018.
59. Gil C, Falques A, Sarro E, Cubi R, Blasi J, Aguilera J and Itarte E: Protein kinase CK2 associates to lipid rafts and its pharmacological inhibition enhances neurotransmitter release. *FEBS Lett* 585: 414-420, 2010.
60. Hernandez CM and Richards JR: Physiology, sodium channels. StatPearls Publishing 2020.
61. Savio-Galimberti E, Gollub MH and Darbar D: Voltage-gated sodium channels: Biophysics, pharmacology, and related channelopathies. *Front Pharmacol* 3: 124, 2012.
62. Brachet A, Leterrier C, Irondelle M, Fache MP, Racine V, Sibarita JB, Choquet D and Dargent B: Ankyrin G restricts ion channel diffusion at the axonal initial segment before the establishment of the diffusion barrier. *J Cell Biol* 191: 383-395, 2010.
63. Grubb MS and Burrone J: Building and maintaining the axon initial segment. *Curr Opin Neurobiol* 20: 481-488, 2010.
64. Xu M and Cooper EC: An Ankyrin-G N-terminal gate and protein kinase CK2 dually regulate binding of voltage-gated sodium and KCNQ2/3 potassium channels. *J Biol Chem* 290: 16619-16632, 2015.
65. Bréchet A, Fache MP, Brachet A, Ferracci G, Baude A, Irondelle M, Pereira S, Leterrier C and Dargent B: Protein kinase CK2 contributes to the organization of sodium channels in axonal membranes by regulating their interactions with ankyrin G. *J Cell Biol* 183: 1101-1114, 2008.
66. Giraldez T, Rojas P, Jou J, Flores C and Alvarez de la Rosa D: The epithelial sodium channel delta-subunit: New notes for an old song. *Am J Physiol Renal Physiol* 303: F328-F338, 2012.
67. Baines D: Kinases as targets for ENaC regulation. *Curr Mol Pharmacol* 6: 50-64, 2013.
68. Shi HK, Asher C, Yung YV, Kligman L, Reuveny E, Seger R and Garty H: Casein kinase 2 specifically binds to and phosphorylates the carboxy termini of ENaC subunits. *Eur J Biochem* 269: 4551-4558, 2002.
69. Bachhuber T, Almaca J, Aldehni F, Mehta A, Amaral MD, Schreiber R and Kunzelmann K: Regulation of the epithelial Na⁺ channel by protein kinase CK2. *J Biol Chem* 283: 13225-13232, 2008.
70. Hanukoglu I and Hanukoglu A: Epithelial sodium channel (ENaC) family: Phylogeny, structure-function, tissue distribution, and associated inherited diseases. *Gene* 579: 95-132, 2016.
71. Berman JM, Mironova E and Stockand JD: Physiological regulation of the epithelial Na⁺ channel by casein kinase II. *Am J Physiol Renal Physiol* 314: F367-F372, 2017.
72. Wulff H, Castle NA and Pardo LA: Voltage-gated potassium channels as therapeutic targets. *Nat Rev Drug Discov* 8: 982-1001, 2009.
73. Misonou H: Precise localizations of voltage-gated sodium and potassium channels in neurons. *Dev Neurobiol* 78: 271-282, 2018.
74. Lezmy J, Lipinsky M, Khrapunsky Y, Patrich E, Shalom L, Peretz A, Fleidervish IA and Attali B: M-current inhibition rapidly induces a unique CK2-dependent plasticity of the axon initial segment. *Proc Natl Acad Sci USA* 114: E10234-E10243, 2017.
75. Kang S, Xu M, Cooper EC and Hoshi N: Channel anchored protein kinase CK2 and protein phosphatase 1 reciprocally regulate KCNQ2-containing M-channels via phosphorylation of calmodulin. *J Biol Chem* 289: 11536-11544, 2014.
76. Jentsch TJ: Neuronal KCNQ potassium channels: Physiology and role in disease. *Nat Rev Neurosci* 1: 21-30, 2000.
77. Greene DL and Hoshi N: Modulation of Kv7 channels and excitability in the brain. *Cell Mol Life Sci* 74: 495-508, 2017.
78. Kshatri AS, Gonzalez-Hernandez A and Giraldez T: Physiological roles and therapeutic potential of Ca²⁺ activated potassium channels in the nervous system. *Front Mol Neurosci* 11: 258, 2018.
79. Meggio F, Boldyreff BS, Marin O, Marchiori F, Perich JW, Issinger OG and Pinna LA: The effect of polylysine on CK-2 activity is influenced by both the structure of the protein/peptide substrates and subunit composition of the enzyme. *Eur J Biochem* 205: 939-945, 1992.
80. Meggio F, Brunati AM and Pinna LA: Polycation-dependent, Ca²⁺-antagonized phosphorylation of calmodulin by casein kinase-2 and a spleen tyrosine protein kinase. *FEBS Lett* 215: 241-246, 1987.
81. Sacks DB, Davis HW, Crimmins DL and McDonald JM: Insulin-stimulated phosphorylation of calmodulin. *Biochem J* 286: 211-216, 1992.
82. Maingret F, Coste B, Hao J, Giamarchi A, Allen D, Crest M, Litchfield DW, Adelman JP and Delmas P: Neurotransmitter modulation of small-conductance Ca²⁺-activated K⁺ channels by regulation of Ca²⁺ gating. *Neuron* 59: 439-449, 2008.
83. Bildl W, Strassmaier T, Thurm H, Andersen J, Eble S, Oliver D, Knipper M, Mann M, Schulte U, Adelman JP and Fakler B: Protein kinase CK2 is coassembled with small conductance Ca²⁺-activated K⁺ channels and regulates channel gating. *Neuron* 43: 847-858, 2004.
84. Allen D, Fakler B, Maylie J and Adelman JP: Organization and regulation of small conductance Ca²⁺-activated K⁺ channel multiprotein complexes. *J Neurosci* 27: 2369-2376, 2007.

85. Pallas DC, Shahrik LK, Martin BL, Jaspers S, Miller TB, Brautigam DL and Roberts TM: Polyoma small and middle T antigens and SV40 small t antigen form stable complexes with protein phosphatase 2A. *Cell* 60: 167-176, 1990.
86. Zhang M, Meng XY, Cui M, Pascal JM, Logothetis DE and Zhang JF: Selective phosphorylation modulates the PIP2 sensitivity of the CaM-SK channel complex. *Nat Chem Biol* 10: 753-759, 2014.
87. Stocker M, Krause M and Pedarzani P: An apamin-sensitive Ca²⁺-activated K⁺ current in hippocampal pyramidal neurons. *Proc Natl Acad Sci USA* 96: 4662-4667, 1999.
88. Jiang ZS, Srisakuldee w, Soulet F, Bouche G and Kardami E: Non-angiogenic FGF-2 protects the ischemic heart from injury, in the presence or absence of reperfusion. *Cardiovasc Res* 62: 154-166, 2004.
89. Li X, Hu H, Wang Y, Xue M, Li X, Cheng W, Xuan Y, Yin J, Yang N and Yan S: Valsartan upregulates Kir2.1 in Rats Suffering from Myocardial Infarction via Casein Kinase 2. *Cardiovasc Drugs Ther* 29: 209-218, 2015.
90. Stocker M and Pedarzani P: Differential distribution of three Ca(2+)-activated K(+) channel subunits, SK1, SK2, and SK3, in the adult rat central nervous system. *Mol Cell Neurosci* 15: 476-493, 2000.
91. Xia XM, Fakler B, Rivard A, Wayman G, Johnson-Pais T, Keen JE, Ishii T, Hirschberg B, Bond CT, Lutsenko S, *et al*: Mechanism of calcium gating in small-conductance calcium-activated potassium channels. *Nature* 395: 503-507, 1998.
92. Brehme H, Kirschstein T, Schulz R and Kohling R: In vivo treatment with the casein kinase 2 inhibitor 4,5,6,7-tetrabromotriazole augments the slow afterhyperpolarizing potential and prevents acute epileptiform activity. *Epilepsia* 55: 175-183, 2013.
93. Bajorat R, Porath K, Kuhn J, Gossia E, Goerss D, Sellmann T, Köhling R and Kirschstein T: Oral administration of the casein kinase 2 inhibitor TBB leads to persistent KCa2.2 channel up-regulation in the epileptic CA1 area and cortex, but lacks anti-seizure efficacy in the pilocarpine epilepsy model. *Epilepsy Res* 147: 42-50, 2018.
94. Schulze F, Muller S, Guli X, Schumann L, Brehme H, Riffert T, Rohde M, Goerss D, Rackow S, Einsle A, Kirschstein T and Kohling R: CK2 inhibition prior to status epilepticus persistently enhances K_{Ca}2 function in CA1 which slows down disease progression. *Front Cell Neurosci* 14: 33, 2020.
95. Clapham DE: Calcium signaling. *Cell* 131: 1047-1058, 2007.
96. Afzal M, Kren BT, Naveed AK, Trembley JH and Ahmed K: Protein kinase CK2 impact on intracellular calcium homeostasis in prostate cancer. *Mol Cell Biochem* 470: 131-143, 2020.
97. Pankratov Y and Lalo U: Calcium permeability of ligand-gated Ca²⁺ channels. *Eur J Pharmacol* 739: 60-73, 2014.
98. Prakriya M and Lewis RS: Store-operated calcium channels. *Physiol Rev* 95: 1383-1436, 2015.
99. Zamponi GW, Striessnig J, Koschak A and Dolphin AC: The physiology, pathology, and pharmacology of voltage-gated calcium channels and their future therapeutic potential. *Pharmacol Rev* 67: 821-870, 2015.
100. Zamponi GW: A crash course in calcium channels. *ACS Chem Neurosci* 8: 2583-2585, 2017.
101. Catterall WA: Structure and regulation of voltage-gated Ca²⁺ channels. *Annu Rev Cell Dev Biol* 16: 521-555, 2000.
102. Christel C and Lee A: Ca²⁺-dependent modulation of voltage-gated Ca²⁺ channels. *Biochim Biophys Acta* 1820: 1243-1252, 2012.
103. Xu L, Sun L, Xie L, Mou S, Zhang D, Zhu J and Xu P: Advance in L-type calcium channel structures, functions and molecular modeling. *Curr Med Chem*: Jul 14, 2020, Doi: 10.2174/0929867327666200714154059 Online ahead of print.
104. Weiss S, Oz S, Benmocha A and Dascal N: Regulation of cardiac L-type Ca²⁺ channel CaV1.2 via the β-adrenergic-cAMP-protein kinase A pathway: Old dogmas, advances, and new uncertainties. *Circ Res* 113: 617-631, 2013.
105. Hulme JT, Lin TW, Westenbroek RE, Scheuer T and Catterall WA: Beta-adrenergic regulation requires direct anchoring of PKA to cardiac CaV1.2 channels via a leucine zipper interaction with A kinase-anchoring protein 15. *Proc Natl Acad Sci USA* 100: 13093-13098, 2003.
106. De Jongh KS, Murphy BJ, Colvin AA, Hell JW, Takahashi M and Catterall WA: Specific phosphorylation of a site in the full-length form of the alpha 1 subunit of the cardiac L-type calcium channel by adenosine 3',5'-cyclic monophosphate-dependent protein kinase. *Biochemistry* 35: 10392-10402, 1996.
107. Peterson BZ, DeMaria CD, Adelman JP and Yue DT: Calmodulin is the Ca²⁺ sensor for Ca²⁺-dependent inactivation of L-type calcium channels. *Neuron* 22: 549-558, 1999.
108. Fuller MD, Emrick MA, Sadilek M, Scheuer T and Catterall WA: Molecular mechanism of calcium channel regulation in the fight-or-flight response. *Sci Signal* 3: ra70, 2010.
109. Fu Y, Westenbroek RE, Scheuer T and Catterall WA: Basal and β-adrenergic regulation of the cardiac calcium channel CaV1.2 requires phosphorylation of serine 1700. *Proc Natl Acad Sci USA* 111: 16598-16603, 2014.
110. Fu Y, Westenbroek RE, Scheuer T and Catterall WA: Phosphorylation sites required for regulation of cardiac calcium channels in the fight-or-flight response. *Proc Natl Acad Sci USA* 110: 19621-19626, 2013.
111. Kashihara T, Nakada T, Kojima K, Takeshita T and Yamada M: Angiotensin II activates CaV 1.2 Ca²⁺ channels through β-arrestin2 and casein kinase 2 in mouse immature cardiomyocytes. *J Physiol* 595: 4207-4225, 2017.
112. Hauck L, Harms C, Rohne J, Gertz K, Dietz R, Endres M and von HR: Protein kinase CK2 links extracellular growth factor signaling with the control of p27(Kip1) stability in the heart. *Nat Med* 14: 315-324, 2008.
113. Gomez-Ospina N, Tsuruta F, Barreto-Chang O, Hu L and Dolmetsch R: The C terminus of the L-type voltage-gated calcium channel Ca(V)1.2 encodes a transcription factor. *Cell* 127: 591-606, 2006.
114. Feng R, Xu J, Minobe E, Kameyama A, Yang L, Yu L, Hao L and Kameyama M: Adenosine triphosphate regulates the activity of guinea pig Cav1.2 channel by direct binding to the channel in a dose-dependent manner. *Am J Physiol Cell Physiol* 306: C856-C863, 2014.
115. Braun M, Ramracheya R, Bengtsson M, Zhang Q, Karanauskaite J, Partridge C, Johnson PR and Rorsman P: Voltage-gated ion channels in human pancreatic beta-cells: Electrophysiological characterization and role in insulin secretion. *Diabetes* 57: 1618-1628, 2008.
116. Yang SN and Berggren PO: The role of voltage-gated calcium channels in pancreatic beta-cell physiology and pathophysiology. *Endocr Rev* 27: 621-676, 2006.
117. Scheuer R, Philipp SE, Becker A, Nalbach L, Ampofo E, Montemarh M and Götz C: Protein kinase CK2 controls CaV2.1-dependent calcium currents and insulin release in pancreatic β-cells. *Int J Mol Sci* 21: 4668, 2020.
118. Lolli G, Cozza G, Mazzorana M, Tibaldi E, Cesaro L, Donella-Deana A, Meggio F, Venerando A, Franchin C, Sarno S, *et al*: Inhibition of protein kinase CK2 by flavonoids and tyrphostins. A structural insight. *Biochemistry* 51: 6097-6107, 2012.
119. Catterall WA: Voltage-gated calcium channels. *Cold Spring Harb Perspect Biol* 3: a003947, 2011.
120. Kahle JJ, Gulbahce N, Shaw CA, Lim J, Hill DE, Barabási AL and Zoghbi HY: Comparison of an expanded ataxia interactome with patient medical records reveals a relationship between macular degeneration and ataxia. *Hum Mol Genet* 20: 510-527, 2011.
121. Rettig J, Sheng ZH, Kim DK, Hodson CD, Snutch TP and Catterall WA: Isoform-specific interaction of the alpha1A subunits of brain Ca²⁺ channels with the presynaptic proteins syntaxin and SNAP-25. *Proc Natl Acad Sci USA* 93: 7363-7368, 1996.
122. Hilfiker S, Pieribone VA, Nordstedt C, Greengard P and Czernik AJ: Regulation of synaptotagmin I phosphorylation by multiple protein kinases. *J Neurochem* 73: 921-932, 1999.
123. Castillo MA, Ghose S, Tamminga CA and Ulery-Reynolds PG: Deficits in syntaxin 1 phosphorylation in schizophrenia prefrontal cortex. *Biol Psychiatry* 67: 208-216, 2010.
124. Hwang TC, Yeh JT, Zhang J, Yu YC, Yeh HI and Destefano S: Structural mechanisms of CFTR function and dysfunction. *J Gen Physiol* 150: 539-570, 2018.
125. Fajac I and De BK: New horizons for cystic fibrosis treatment. *Pharmacol Ther* 170: 205-211, 2017.
126. Csanady L, Vergani P and Gadsby DC: Structure, gating, and regulation of the CFTR anion channel. *Physiol Rev* 99: 707-738, 2019.
127. Cesaro L, Marin O, Venerando A, Donella-Deana A and Pinna LA: Phosphorylation of cystic fibrosis transmembrane conductance regulator (CFTR) serine-511 by the combined action of tyrosine kinases and CK2: The implication of tyrosine-512 and phenylalanine-508. *Amino Acids* 45: 1423-1429, 2013.

128. Luz S, Kongsuphol P, Mendes AI, Romeiras F, Sousa M, Schreiber R, Matos P, Jordan P, Mehta A, Amaral MD, *et al*: Contribution of casein kinase 2 and spleen tyrosine kinase to CFTR trafficking and protein kinase A-induced activity. *Mol Cell Biol* 31: 4392-4404, 2011.
129. Mehta A: Cystic fibrosis as a bowel cancer syndrome and the potential role of CK2. *Mol Cell Biochem* 316: 169-175, 2008.
130. Pagano MA, Arrigoni G, Marin O, Sarno S, Meggio F, Treharne KJ, Mehta A and Pinna LA: Modulation of protein kinase CK2 activity by fragments of CFTR encompassing F508 may reflect functional links with cystic fibrosis pathogenesis. *Biochemistry* 47: 7925-7936, 2008.
131. Treharne KJ, Xu Z, Chen JH, Best OG, Cassidy DM, Gruenert DC, Hegyi P, Gray MA, Sheppard DN, Kunzelmann K and Mehta A: Inhibition of protein kinase CK2 closes the CFTR Cl channel, but has no effect on the cystic fibrosis mutant deltaF508-CFTR. *Cell Physiol Biochem* 24: 347-360, 2009.
132. Venerando A, Pagano MA, Tosoni K, Meggio F, Cassidy D, Stobbart M, Pinna LA and Mehta A: Understanding protein kinase CK2 mis-regulation upon F508del CFTR expression. *Naunyn Schmiedebergs Arch Pharmacol* 384: 473-488, 2011.
133. Pagano MA, Marin O, Cozza G, Sarno S, Meggio F, Treharne KJ, Mehta A and Pinna LA: Cystic fibrosis transmembrane regulator fragments with the Phe508 deletion exert a dual allosteric control over the master kinase CK2. *Biochem J* 426: 19-29, 2010.
134. Pinto MC, Schreiber R, Lérias J, Ousingsawat J, Duarte A, Amaral M and Kunzelmann K: Regulation of TMEM16A by CK2 and its role in cellular proliferation. *Cells* 9: 1138, 2020.
135. Roosbeek S, Peelman F, Verhee A, Labeur C, Caster H, Lensink MF, Cirulli C, Grooten J, Cochet C, Vandekerckhove JL, *et al*: Phosphorylation by protein kinase CK2 modulates the activity of the ATP binding cassette A1 transporter. *J Biol Chem* 279: 37779-37788, 2004.
136. Bai X, Moraes TF and Reithmeier RAF: Structural biology of solute carrier (SLC) membrane transport proteins. *Mol Membr Biol* 34: 1-32, 2017.
137. Ibrahim SH, Turner MJ, Saint-Criq V, Garnett J, Haq IJ, Brodlić M, Ward C, Borgo C, Salvi M, Venerando A and Gray MA: CK2 is a key regulator of SLC4A2-mediated Cl-/HCO₃⁻ exchange in human airway epithelia. *Pflugers Arch* 469: 1073-1091, 2017.
138. Stolk M, Cooper E, Vilks G, Litchfield DW and Hammond JR: Subtype-specific regulation of equilibrative nucleoside transporters by protein kinase CK2. *Biochem J* 386: 281-289, 2005.



This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.