Protein kinase CK2 and ion channels (Review)

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Abstract. Protein kinase CK2 appears as a tetramer or higher molecular weight oligomer composed of catalytic CK2α, CK2α' subunits and non-catalytic regulatory CK2β 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

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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 CK2α (7) and CSNK2A2 which encodes CK2α' (8). The β-subunit is encoded by CSNK2B (9). CK2β is not a simple on-off regulator of the catalytic activity of CK2α. 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 CK2α subunits exist in the absence of CK2β (18) and that CK2β exists in the absence of CK2α and CK2α' (19,20).

CK2α 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 CK2α have been identified (22). These patients suffered from intellectual disability, hypotonia, speech problems, gastrointestinal problems and immune dysfunctions (23-25).

CK2α and CK2β 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 CK2α' 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 NFκB 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-caboxylic 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 CK2α or CK2α' 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 (ESCs) (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 $Na_v1.1$, $Na_v1.2$ and $Na_v1.6$ 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_vs 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_v1 (Fig. 1A). Moreover, mutation of the CK2 phosphorylation site on Na_v1 to a non-phosphorylatable alanine abrogated the Na_v1/ankyrin G interaction. This mutation, as well as the use of the CK2 kinase inhibitor DMAT, leads to a decrease of Na_v1 at AIS (62). Thus, CK2 may be involved in the modulation of Na_v1 binding to ankyrin G as well as the accumulation of Na_v1 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_vs, K_vs 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 $K_v7.3$ channels along the AIS (74). Although not directly analysed by Lezmy *et al* (74), according to their results, it was suggested, that CK2 phosphorylates $K_v7.2/3$ 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 $K_v7.2/3$ into the AIS. Alternatively, or in addition, CK2 may phosphorylate calmodulin, which increases its interaction with the $K_v7.2$ 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_v7/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

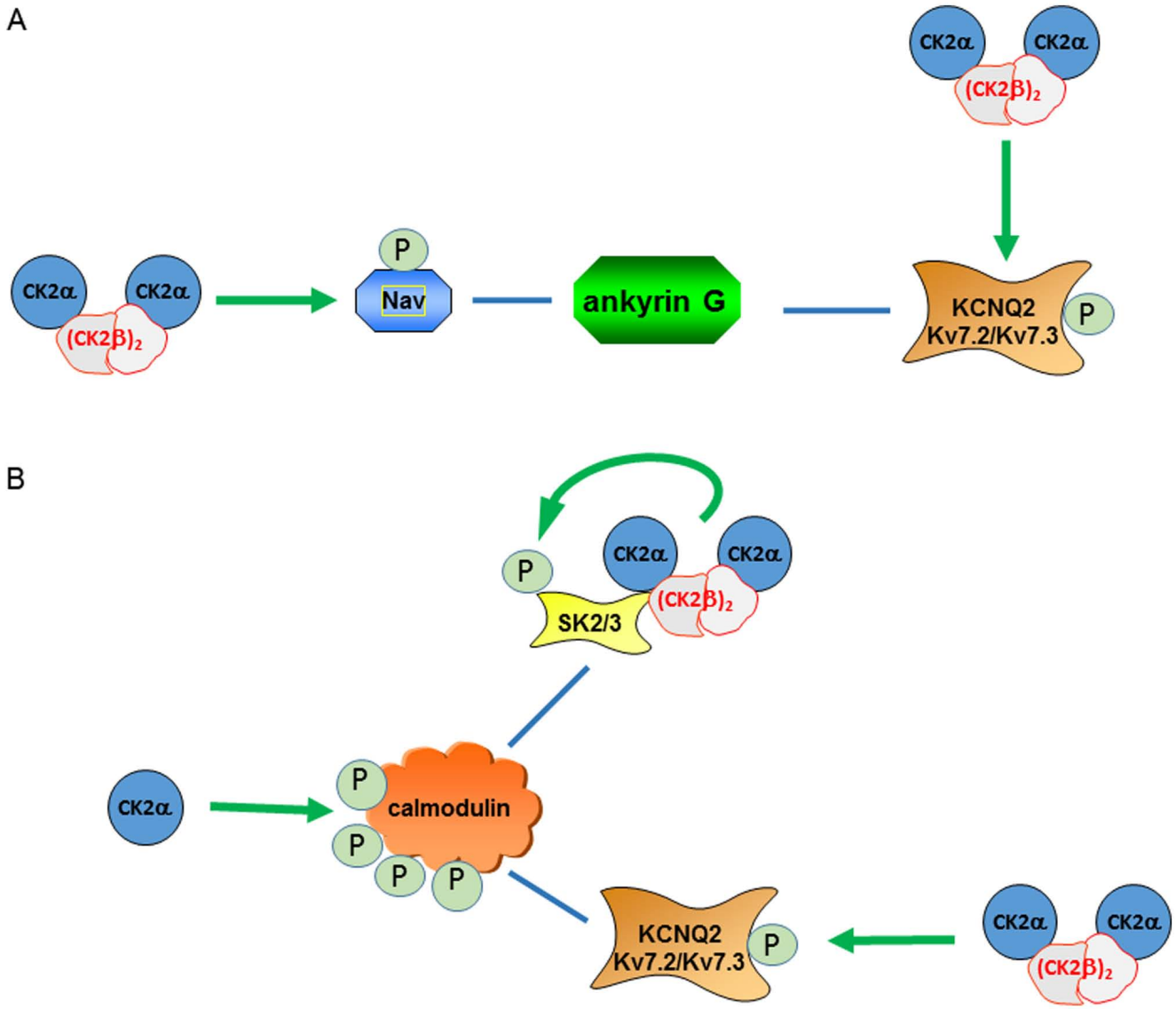

Figure 1. Influence of CK2 phosphorylation on binding of channel proteins to (A) ankyrin G or (B) calmodulin. Green arrows represent phosphorylation and interaction. Blue lines indicate an interaction. P, phosphate; CK2, casein kinase 2; SK, small conductance; KCNQ2, potassium voltage-gated channel subfamily 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 Ca^{2+} 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 Ca^{2+} 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 Ca^{2+} 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 Ca^{2+} 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 Ca^{2+} 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 CK2α (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 CK2α and it was revealed that this region stimulated CK2 similar to poly-L-lysine (84). Within this complex, CK2 phosphorylates calmodulin, thereby reducing the Ca^{2+} sensitivity and accelerating channel deactivation (86).

Neurotransmitters, such as noradrenalin, inhibit SK2 channels independently of changes in the activity of the priming Ca^{2+} 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 CK2α 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, overexpression 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 Ca^{2+} 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 Cornus 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

Ca^{2+} ions are essential for nearly all aspects of cell functions. Ca^{2+} 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 Ca^{2+} levels, along with an increase in mitochondrial and endoplasmic levels of Ca^{2+} in these cells (96). Thus, these results indicate CK2 may be involved in the regulation of the intracellular Ca^{2+} homeostasis.

Ca^{2+} 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 Ca^{2+} influx via Ca_v channels serves as a second messenger to couple electric signalling to chemical signalling (99,100). The Ca^{2+} 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 $Ca_v\alpha1$ subunits are pore forming, and $Ca_v\beta$ and $Ca_v\delta$ as well as in some cases $Ca_v\gamma$, 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 Ca^{2+} homeostasis and secretion, tissue development, neuron excitability, excitation-transcription coupling and in learning and memory in the brain, reviewed in (104). Furthermore, L-type Ca^{2+} 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 Ca^{2+} 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 Ca^{2+} channel $Ca_v1.2$ regulates Ca^{2+} 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 $p27^{kip1}$. This phosphorylation prevents $p27^{kip1}$ from inhibiting the phosphorylation of a C-terminal fragment of $Ca_v1.2$ by CK2 (111). It has been reported that unphosphorylated $p27^{kip1}$ is one of the very few proteins that specifically inhibits CK2α' (112). Moreover, CK2β binds to $Ca_v1.2$ and recruits $p27^{kip1}$ and CK2α' to the $Ca_v1.2$ complex (111). However, it remains unknown whether CK2α' functions alone or as a holoenzyme consisting of CK2α' and CK2β.

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 CK2α'/CK2β 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 Ca^{2+} 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). Ca^{2+} 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 Ca^{2+} level, which corresponds with an increase in insulin secretion from pancreatic β-cells (117). Moreover, quercetin is a potent inhibitor of CK2 at IC_{50} values <1 μM (118), which induces insulin secretion by direct activation of L-type calcium channels in pancreatic β-cells.

A transient Ca^{2+} 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 Ca^{2+}- calmodulin attached to the C-terminal tail of the $Ca_v2.1\alpha1A$ 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 CK2α 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^-/HCO_3^- exchanger. Treatment with the more efficient and specific inhibitor CX-4945 completely abolishes Cl^-/HCO_3^- exchanger activity.

Recently, it has been revealed that CK2 is required for the physiological expression of the Ca^{2+} 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 CK2α' 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 CK2α' directly phosphorylates ANO1 alone or as a CKα'/CK2β holoenzyme and whether CK2α 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^-/HCO_3^- 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 *et al*, 2010	Na_v1	Interaction with ankyrin G	(62)
Shi *et al*, 2002	ENaC β-subunit and γ-subunit	Amiloride sensitive Na^+ transport	(68)
Xu and Cooper, 2015; Brechet *et al*, 2008	$K_v7.2/3$	Distribution of $K_v7.2/3$ along AIS	(64,65)
Zhang *et al*, 2014	Calmodulin/SK	Regulation of SK channel activity	(86)
Xu *et al*, 2020; Fuller *et al*, 2010; Scheuer *et al*, 2020	$Ca_v1.2$, $Ca_v1.1$, $Ca_v2.1$	Ca^{2+} transport	(103,108,117)
Cesaro *et al*, 2013; Luz *et al*, 2011	CFTR	Chloride/bicarbonate transport	(127,128)
Roosbeek *et al*, 2004	ABCA1	Regulation of flippase activity	(135)
Ibrahim *et al*, 2017	SLC4A2	Chloride/bicarbonate transport	(137)
Stolk *et al*, 2005	SLC29A1, SLC29A2	Nucleoside transport	(138)

CK2, protein kinase CK2; SK, small conductance; ENaC, Amiloride-sensitive epithelial sodium channels; Ca_v, Ca^{2+} 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 *et al*, 2002	ENaC	Transport to the plasma membrane	(68)
Bildl *et al*, 2004; Allen *et al,* 2007	SK channels	Formation of multi-protein complex at the plasma membrane of rat brain increase of CK2 kinase activity	(83,84)
Kashihara *et al*, 2017	$Ca_v1.2$	Recruitment of $p27^{kip1}$ and CK2α' to the membrane	(111)
Scheuer *et al*, 2020	$Ca_v2.1$	Ca^{2+} transport	(117)

CK2, protein kinase CK22; SK, small conductance; ENaC, Amiloride-sensitive epithelial sodium channels; Ca_v, Ca^{2+} 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.

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

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Competing interests

The authors declare that they have no competing interests.

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