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SEROTONIN

5-HT_2 receptors-mediated modulation of voltage-gated K^+ channels and neurophysiopathological correlates

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Abstract The activity of voltage-gated K^+ channels (Kv) can be dynamically modulated by several events, including neurotransmitter stimulated biochemical cascades mediated by G protein-coupled receptors such as 5-HT_2 receptors (5-HT_2Rs). Activation of 5-$HT_{2A/C}$R inhibits the *Shaker*-like K^+ channels Kv1.1 and Kv1.2, and this modulation involves the dual coordination of both RPTPα and distinct tyrosine kinases coupled to this receptor; 5-HT_2Rs–mediated modulation of Kv channels controls glutamate release onto prefrontal cortex neurons that might play critical roles in neurophysiological, neurological, and psychiatric conditions. Noticeably, hallucinogens modulate Kv channel activity, acting at 5-HT_2R. Hence, comprehensive knowledge of 5-HT_2R signaling through modulation of distinct K^+ channels is a pivotal step in the direction that will enable scientists to discover novel 5-HT functions and dysfunctions in the brain and to identify original therapeutic targets.

Keywords Serotonin receptor · 5-HT_{2A} · 5-HT_{2C} · Kv1.1 · Kv1.2 · Tyrosine phosphorylation · Kinase · Phosphatase · RPTPα · Cortical pyramidal neuron

Introduction

Voltage-gated potassium channels (Kv)

Voltage-gated potassium channels regulate numerous and heterogeneous cell functions. In particular, they shorten action potentials duration, modulate the release of neurotransmitters, and control the excitability, electrical properties and firing pattern of neurons in the brain (Hille 2001). The first Kv channel was cloned from the *Shaker* mutant of *Drosophila* in 1987 (Tempel et al. 1987). Several other genes encoding for Kv channels have been identified afterward from many different species. Based on sequence relatedness, Kv channels have been classified in subfamilies by using the abbreviation *Kvy.x* (Chandy and Gutman 1993).

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According to this standardized nomenclature, *Shaker*-related channels have been classified in the subfamily *Kv1.x* and each member numbered *Kv1.1* through *Kv1.8* (Fig. 1a). The same criteria have been used to classify channels related to the *Drosophila* subfamilies *Shab* (*Kv2.1* and *Kv2.2*), *Shaw* (*Kv3.1* to *3.4*), and *Shal* (*Kv4.1* to *Kv4.3*). The *Kv* α-subunits contain six transmembrane segments (S) with the N- and C-termini residing inside the cell (Fig. 1b). The S5, S6, and H5 loop linking them delimit the ion-conducting pore. The S4 segment of each subunit is composed of regularly spaced positively charged arginines and lysines and comprises the main voltage-sensor region that opens the channel by undergoing a conformational rearrangement upon membrane depolarization. A functional channel is composed of four homologous α-subunits. The first atomic structure description of a bacterial K^+ channel is regarded as a milestone in the history of ion channels (Doyle et al.1998). Subsequently, the entire crystal structure of mammalian Kv channels has been provided (Jiang et al. 2003a, b). The elucidation of the structures of the pore, voltage sensor, T1 domain, and β-subunit clarified many biophysical mechanisms controlling Kv channel *gating* (Fig. 2).

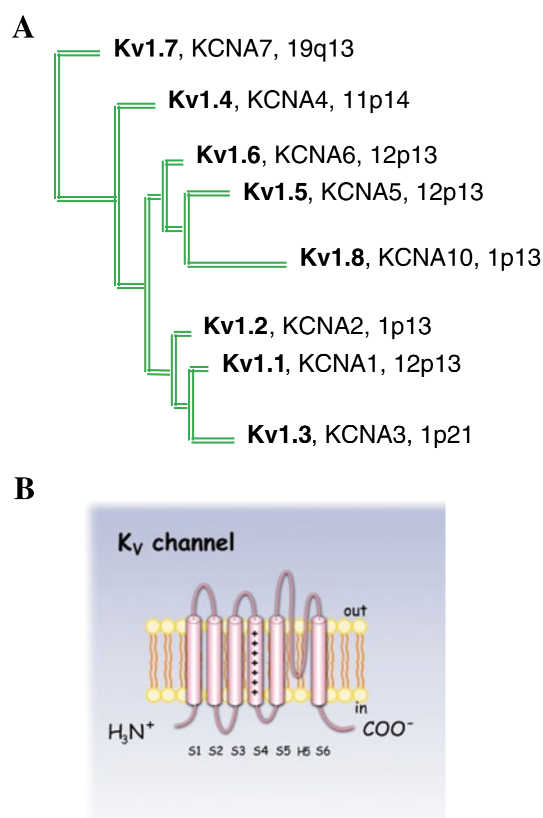

Fig. 1 **a** Phylogenetic tree for the Kv1 family. **b** Schematic diagram illustrating the predicted secondary structure of a K^+ channel α-subunit. A Kv subunit is composed of a voltage-sensing region (S1 through S4), a pore region (S5-H5-S6) with the N- and C-termini residing inside the cell. A functional channel is formed by the assembling of four α-subunits

Potassium channels are the most diverse class of ion channels. A major reason for this large diversity is that besides forming homomeric complexes with identical α-subunits, they may assemble as heteromeric channels (i.e., different types of α-subunits may heteropolymerize) which display properties often markedly different from the parental homomeric channels (Ruppersberg et al. 1990; Isacoff et al. 1990). Notable examples are the heteromeric Kv1.1/Kv1.2 or Kv1.1/Kv1.4 channels (Wang et al. 1993, 1994; Sheng et al. 1994). The need for such a large number of K^+ channels that dampen neuronal excitability remains unclear. Kv family members exhibit diverse expression patterns in central e peripheral nervous systems and are found tightly clustered within distinct neuronal compartments (Trimmer and Rhodes 2004). The excitability of these neurons can be controlled by both the intrinsic activity of Kv channels and the receptors-mediated modulation of these channel types. Knowledge of the precise targeting of Kv channels and their modulation by 5-HT_2 receptors (5-HTRs) has important implications for defining the roles played by distinct Kv channels and 5-HT_2Rs in neuronal function and dysfunction.

5-HT_2 receptors

The 5-HT_2Rs family comprises three main types of receptors, namely 5-HT_{2A}, $5\text{-HT}_{2B,}$ and 5-HT_{2C}, which share high structural and functional homology (Di Giovanni et al. 2006). The overall effects of unselective 5-HT_2Rs agonists in rodents range from increased motor activity, hyperthermia, head twitches (mice), wet dog shakes (rats), increased secretion of cortisol, ACTH, renin, and prolactin. In humans, these agonists cause hallucinations (Di Giovanni et al. 2011). A description of the transduction signaling promoted by 5-HT_2Rs has been recently recapitulated (see Millan et al 2008). Here, we reviewed the previously unexamined findings concerning the distinct receptor subtypes that clearly use Kv channels as effectors, such as 5-HT_{2A}Rs and 5-HT_{2C}Rs.

5-HT_{2A}Rs

These receptors are highly expressed in forebrain regions such as cortical areas (pre-frontal cortex, entorhinal and pyriform cortex, claustrum), caudate nucleus, nucleus accumbens, olfactory tubercle, and hippocampus. At the cellular level, 5-HT_{2A}Rs have been localized in cortical pyramidal (projection) neurons, local interneurons (GABA*ergic*), cultured astrocytes, and glioma cells (Deecher et al. 1993; Meller et al. 2002). In the

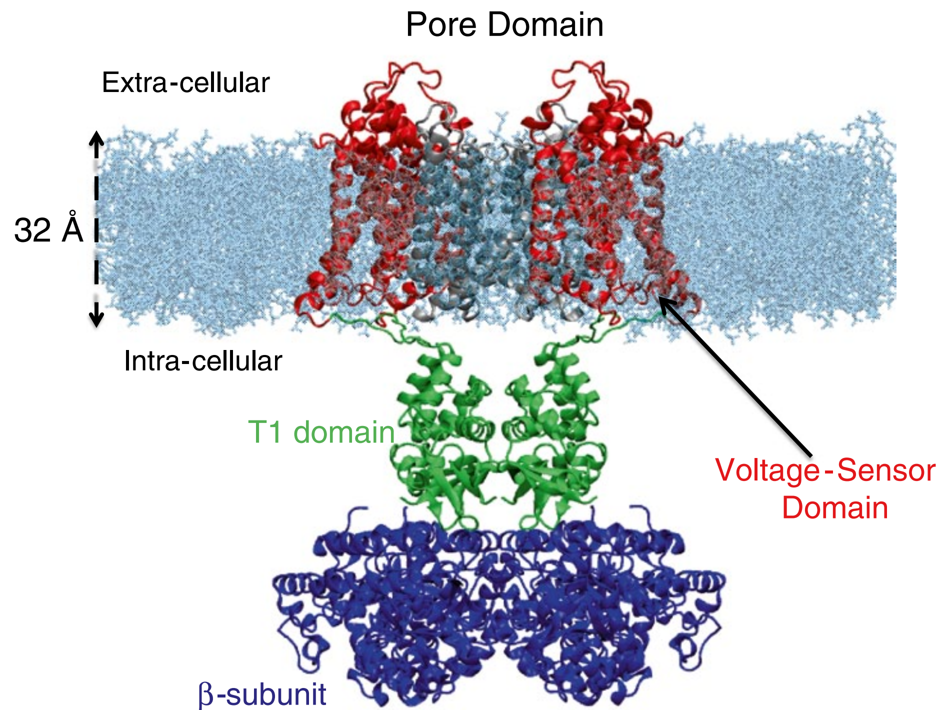

Fig. 2 Architecture of a voltage-gated K^+ channel. Three-dimensional image illustrating the structure of the Kv1.2/2.1 chimera. The secondary structure elements are shown as ribbons and are colored *red* (voltage-sensing domains), *gray* (ion-conducting pore), *green* (T1 domain), and *blue* (accessory β-subunits). Only two monomers (facing each other) of the tetramer have been depicted for clarity. The lipids of the membrane bilayer are shown as *light blue* colored sticks (*Courtesy of Dr. Alessandro Grottesi*) (color figure online)

hypothalamus, 5-HT_{2A}R mRNA is more abundantly localized to paraventricular nucleus neurons that release CRH (Gundlah et al. 1999); 5-HT_{2A}Rs have been implicated in schizophrenia, depression, and psychotomimetic effects of hallucinogens, such as LSD. The mescaline analog DOI, which stimulates 5-HT_2R, enhances glutamate release onto layer V pyramidal neurons (Aghajanian and Marek 1997); 5-HT_{2A}Rs stimulation by 5-HT has also been implicated in hyperexcitation of frontal cortex, sensory perturbations, sleep difficulties, and psychosis (Vollenweider et al. 1997; Hermle et al. 1998; Oberndorfer et al. 2000).

5-HT_{2C}Rs

The highest concentration of this receptor is observed in the choroid plexus. However, they are widely distributed in several areas of the cortex (olfactory nucleus, pyriform, cingulate, and retrosplenial), limbic system (nucleus accumbens, hippocampus, amygdala), basal ganglia (caudate nucleus, substantia nigra), and hypothalamus (arcuate region) (Di Giovanni et al. 2006, 2011; Gundlah et al. 1999). In the external globus pallidus, 5-HT_{2C}Rs are likely located presynaptically, on the axon terminals of afferent neurons. Relatively high expression levels of 5-HT_{2C}Rs are in CA1, CA2, and CA3 hippocampal pyramidal neurons (Molineaux et al. 1989) which are densely innervated by serotonergic terminals from the raphe nucleus. An overlapping expression pattern of Kv1.1 and Kv1.2 channels and 5-HT_{2C} receptors has been observed in several brain areas including the vestibular nuclei, the dentate gyrus, CA3, and dopamine (DA) neurons (Veh et al. 1995; Wang et al. 1994; Molineaux et al. 1989). Indeed, 5-HT_{2C}Rs immunoreactivity has been shown in tyrosine hydroxylase (TH)–positive neurons, validating the localization of 5-HT_{2C}R in ventral tegmental area (VTA) dopaminergic neurons. The 5-HT_{2C}R protein was also found to be co-localized with the GABA synthetic enzyme glutamic acid decarboxylase (GAD), confirming the presence of the 5-HT_{2C}R also in GABA*ergic* neurons within the VTA (Bubar and Cunningham 2007). However, 5-HT_{2C}Rs are found in other CNS regions, including the paraventricular nucleus of the hypothalamus and the ventromedial hypothalamic nucleus (Di Giovanni et al. 2006; Hoffman and Mezey 1989); 5-HT_{2C}R intracellular signalling relates to a coupling with the $G_{q/11}$-protein (Saltzman et al. 1991). This receptor stimulates phospholipase C generating diacylglycerol and inositol 1,4,5-trisphosphate (IP3) which elicits the release of Ca^{2+} ions from intracellular stores. This receptor may also couple to phospholipase A2 (PLA2) or a Gαi protein, in heterologous expression systems and to phospholipase D via Gα13 or to proteins containing a PDZ domain. Cultured cortical neurons express 5-HT_{2C}Rs with constitutive activity (Chanrion et al. 2008) that is also displayed toward PLC. A receptor–agonist-independent association of 5-HT_{2C}Rs with β-arrestins has been described. This interplay leads to constitutive internalization that is prevented by inverse agonists (Marion et al. 2004; Chanrion et al. 2008). The central 5-HT_{2C}R activation affects the behavior of rodents

and humans inducing hypo-locomotion, hypo-phagia, anxiety, and hyperthermia. The function of 5-HT_{2C}Rs appears up-regulated in neuropsychiatric disorders in which DA neurotransmission is altered, chronically (i.e., Parkinson's disease, tardive dyskinesia, addiction). Concerning addiction to drugs of abuse, it has been shown that 5-HT_{2C}R agonists reduce self-administration cocaine. However, cannabinoids rewarding effects mediated by activation of the mesolimbic dopaminergic system, are prevented by SB242084 a selective 5-HT_{2C}R antagonist (Di Matteo et al. 2000), and by blocking the interactions between 5-HT_{2C}R and the phosphatase PTEN (*phosphatase with tensin homology*) (Ji et al. 2006; Di Giovanni et al. 2011).

5-HT_{2A}R modulation of Kv channels

Blockade of Kv1.1-, Kv1.2-, and Kv1.6-containing channels by α-dendrotoxin (DTX) results in spontaneous depolarization and spiking in cortical synaptosomes (Tibbs et al. 1989, 1996). In slices of rat prefrontal cortex, focal stimulation of 5-HT_{2A}Rs with 5-HT (20 μM) dramatically increases glutamate release onto layer V pyramidal neurons, as inferred by increased spontaneous EPSCs (Fig. 3) (Lambe et al. 2000; Lambe and Aghajanian 2001); 5-HT and 4-AP, a Kv1 channel blocker, preferentially induce EPSC in layer V neurons compared with levels induced in neurons in layers II/III or VI (Lambe et al. 2000; Lambe and Aghajanian 2001).

Spontaneous EPSCs were also enhanced by DTX (200 nM), suggesting that this toxin mimics the effects of 5-HT. A comparison of the effects of DTX and other potassium channel blockers revealed selectivity of EPSC induction by blockers with affinity for Kv1.2 subunits (Lambe and Aghajanian 2001). Indeed, compounds able to block Kv1.2 (i.e., 4-AP and DTX) induce EPSCs similar to those induced by 5-HT. Whereas, *rAgitoxin2* (Kv1.1, Kv1.3, and Kv1.6 blocker), *Toxin K* (Kv1.1 blocker), *rMargatoxin* (Kv1.3 blocker), and *TEA* (unspecific blocker of Kv and other K^+ channels that has no effect on Kv1.2) were ineffective. The ability of μ-opioids and thalamic lesions to substantially reduce DTX-induced EPSCs and the selective occlusion of 5-HT-induced EPSCs by DTX suggest that blockade of Kv1.2-containing potassium channels is part of the mechanism underlying 5-HT-induced glutamate release from thalamo-cortical terminals. A model explaining the possible mechanisms for 5-HT_{2A}R-mediated inhibition of Kv1.2-containing potassium channels, which lead to TTX-sensitive glutamate release from thalamo-cortical terminals, has been proposed (Fig. 4) (Lambe and Aghajanian 2001). Assuming the presynaptical localization of 5-HT_{2A}Rs, it has been proposed that these Gq-coupled receptors activate an intracellular pathway capable of inhibiting both the Kv1.2-containing channels and the calcium-activated potassium channels (Fig. 4a) (Lambe and Aghajanian, 2001). This model is consistent with previously reported inhibition of Kv1.2 channels by 5-HT_{2C}Rs activation (see below Imbrici et al. 2000). Alternatively, a postsynaptic model suggests the ability of the Gq-coupled 5-HT_{2A}R to release a retrograde messenger capable of bringing about blockade or inhibition of the aforementioned potassium channels (Fig. 4b). This evidence suggests that 5-HT_{2A}Rs agonists enhance cortical arousal and result in subepileptic states by inhibiting Kv1 channels. Indeed, 4-AP has been shown to accelerate waking after anesthesia in humans (Sia et al. 1982); DTX administration to mice causes hypersensitivity and hyperreactivity to sound and touch (Harvey and Karlsson 1980; Silveira et al. 1988); administration of low doses of 4-AP to horses results in excitation and exaggerated responses to external stimuli (Klein and Hopkins 1981). Noteworthy, *loss of function* mutations in *Kv1.1* channels causes *episodic ataxia type 1* (EA1), an autosomal dominant neurological disorder characterized by myokymia, epilepsy, and attacks of ataxic gait

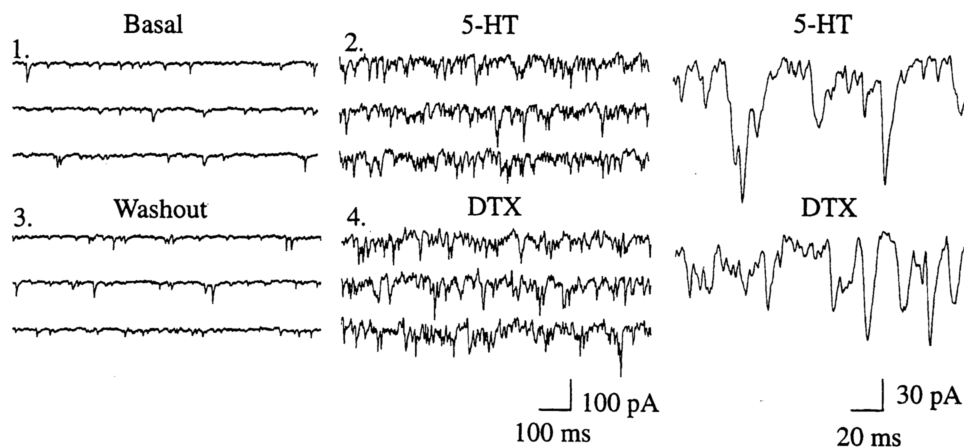

Fig. 3 5-HT and DTX increase the frequency and amplitude of $EPSC_S$ in layer V of neocortical pyramidal neurons. Whole-cell recordings from one cell during baseline (*1*), 5-HT (*2*) (20 μM, 40 s), 5-min washout (*3*), and DTX (*4*) (200 nM, 10 min). In the *right column*, a portion of the sweep from the adjacent column (i.e., 5-HT and DTX) has been enlarged. From Lambe and Aghajanian 2001 with permission of the Society for Neuroscience

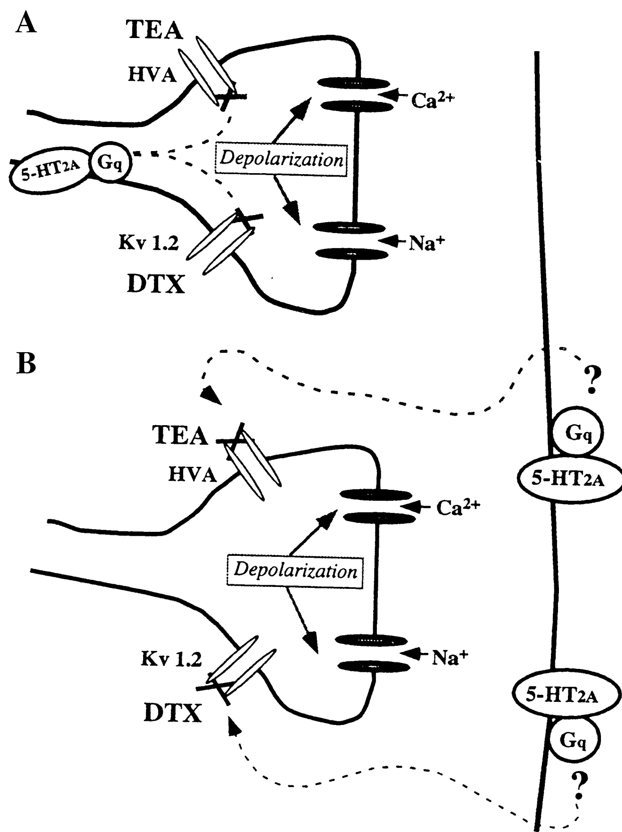

Fig. 4 Models depicting two possible mechanisms for 5-HT_{2A}R-mediated inhibition of Kv1.2-containing channels, leading to glutamate release from thalamocortical terminals. The 5-HT_{2A}R responsible for inducing EPSCs could be located presynaptically or postsynaptically. **a** A presynaptic model suggests that the Gq-coupled receptor activates an intracellular pathway capable of inhibiting both the Kv1.2-containing channels and the high-voltage or calcium-activated K^{+} channels. This model could be either direct or indirect through an intervening excitatory interneuron. **b** A postsynaptic model suggests the ability of the Gq-coupled 5-HT_{2A}R to release a retrograde messenger capable of bringing about blockade or inhibition of the aforementioned K^{+} channels. From Lambe and Aghajanian 2001 with permission of the Society for Neuroscience

precipitated by external stimuli such as unexpected loud noise, abrupt movements, and emotional stress (D'Adamo et al. 1998, 1999, 2012). Some patients report depression as an additional symptom. In rodents, similar mutations in *Kv1.1* channels cause ataxia, seizures and exaggerated responses to stress or sudden acoustic stimuli (D'Adamo et al. 2013).

5-HT_{2C}R modulation of Kv channels

The overall functional properties of 5-HT_{2C}Rs are retained in heterologous expression systems. Indeed, upon 5-HT_{2C}Rs expression in *Xenopus laevis* oocytes, an endogenous Ca^{2+}-dependent chloride current is activated by 5HT application; 5-HT exposure of oocytes, expressing 5-HT_{2C}Rs and either Kv1.1 or Kv1.2 channels, inhibited both K^{+} currents in a dose-dependent manner (Fig. 5) (Imbrici et al. 2000). Activation of 5-HT_{2C}Rs also suppresses *RBK1* channel activity, a rat brain K^{+} channel homolog to Kv1.1 (Hoger et al. 1991; Kavanaugh et al. 1991). Intracellular injection of inositol triphosphate or Ca^{2+} mimicked the 5-HT inhibitory actions on Kv1 channels (Guillemare et al. 1992; Attali et al. 1992). Imbrici et al. (2000) also investigated the transduction and molecular mechanisms underlying the 5-HT_{2C}R-mediated inhibition of the Kv1.1 and Kv1.2 channel activity. The tyrosine phosphatase inhibitor, orthovanadate, inhibited both Kv1.1 and Kv1.2 currents. Consistently, the cytoplasmic microinjection of genistein, a tyrosine kinase inhibitor, dose-dependently slowed the time course of current inhibition mediated by the 5-HT_{2C}R. These results demonstrated the involvement of tyrosine phosphorylation/dephosphorylation mechanisms in this process. The target residues for these kinases were identified by sequential site-directed mutagenesis of all the intracellular tyrosine residues in Kv1.1 and by co-expressing these mutants with the 5-HT_{2C} receptor in oocytes. In summary, it was found that distinct tyrosine residues residing in the N-terminal domain of the channels were involved in current inhibition caused by 5-HT. Nevertheless, neither of the two residues identified completely abolished the effects mediated by the 5-HT_{2C}R activation. A possible explanation for this is that either phosphorylation of additional tyrosine residues is required for complete current suppression or that other pathways, not necessarily involving tyrosine phosphorylation, may be simultaneously activated by 5-HT_{2C}R. Indeed, it has been shown that downstream effectors, such as protein kinase C (PKC), the GTP-binding protein RhoA, the protein tyrosine kinases PYK2 and Src, play an important role in suppressing Kv1.x currents (Peretz et al. 1996; Boland and Jackson 1999; Moran et al. 1991; Canchero et al. 1998; Lev et al. 1995; Holmes et al. 1996). In contrast, RPTPα, a receptor protein tyrosine phosphatase highly expressed in the central nervous system, stimulates the activity of Kv1.2 channels. RPTPα physically associates with the intracellular domains of Kv1.2, reducing the tyrosine phosphorylation of the channel (Sap et al. 1990; Tsai et al. 1999). Based on this evidence, it was investigated whether RPTPα may play a role in the 5-HT_{2C} receptor-mediated inhibition of Kv1.1 and Kv1.2 channel activity. Indeed, co-expression of RPTPα markedly slowed the time course of Kv1.1 and Kv1.2 current inhibition by 5-HT_{2C}R activation. By contrast, co-expression of the tyrosine phosphatase SHP2 had no effect on channel activity. In conclusion, these investigations showed that 5-HT_{2C}R activation suppresses Kv1.1 and Kv1.2 currents by phosphorylating

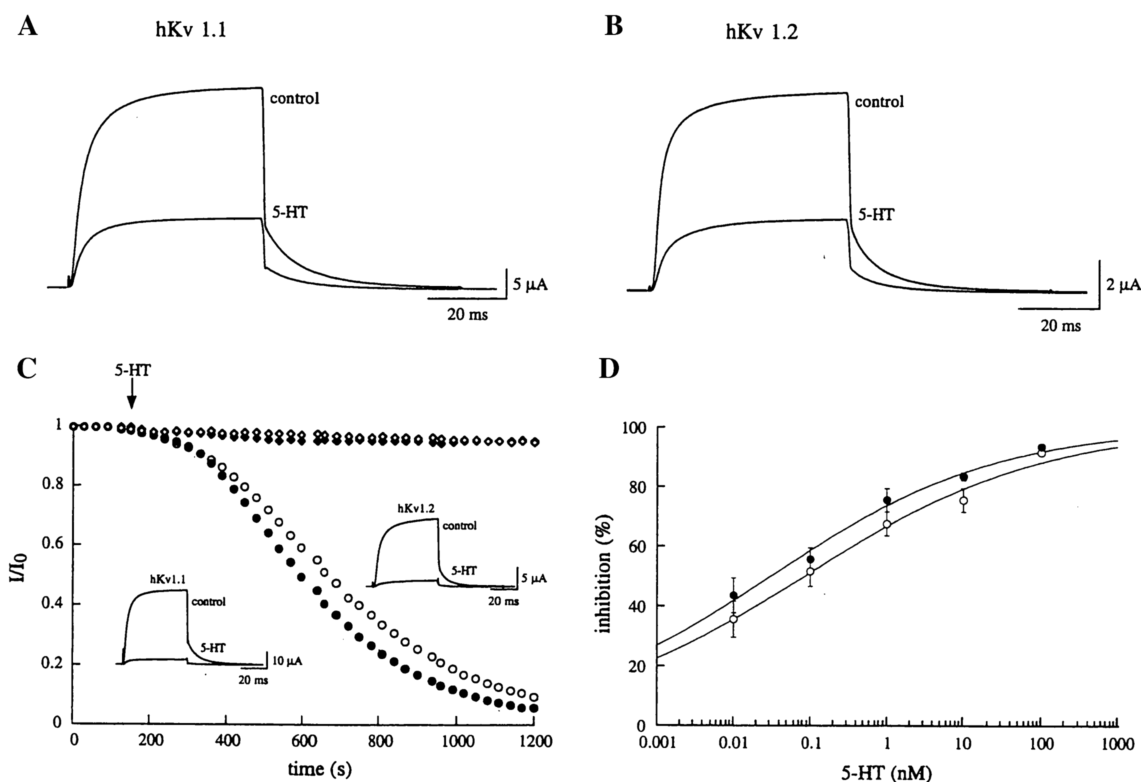

Fig. 5 5-HT_{2C} receptor activation inhibits hKv1.1 and hKv1.2 currents. Current traces recorded from *Xenopus* oocytes expressing the human 5-HT_{2C} receptor and either Kv1.1 (**a**) or Kv1.2 (**b**) channels. Currents were evoked by depolarizations to +20 mV from the holding potential of −80 mV, before (control) and 20 min after the superfusion of 5-HT (1 nM). Tail currents were recorded at −50 mV. **c** Time course of hKv1.1 (*closed symbols*) and hKv1.2 (*open symbols*) current inhibition caused by the activation of 5-HT_{2C} receptor. Current amplitudes were evoked every 30 s by depolarizing pulses to +20 mV and normalized to the control current (I_0). The *arrow* indicates the time of 5-HT (100 nM) application. The effect of the application of 5-HT (100 nM) on oocytes expressing hKv1.1 (*closed diamonds*) and hKv1.2 (*open diamonds*) channels, in the absence of 5-HT_{2C} receptor, is also depicted. The *insets* show two additional recordings illustrating the inhibitory effect of 5-HT (100 nM). **d** Concentration–response relationships for 5-HT inhibition of hKv1.1 (*closed symbols*) and hKv1.2 (*open symbols*) currents. The data points represent the % of current inhibition, recorded at +20 mV, and plotted as a function of 5-HT concentration (mean ± SEM, $n = 6$). Lines represent the fit with the equation: $I = 100\,[5\text{-HT}]^n/([5\text{-HT}]^n + K_D^n)$ from which the K_D values were calculated. From Imbrici et al. (2000) with permission of Pflügers Archiv-European Journal of Physiology

specific tyrosine residues of the channel, and this process is coordinated by RPTPα and not by tyrosine phosphatase SHP2 (Imbrici et al. 2000). This evidence also demonstrated that Kv1 channels probably exist in a phosphorylated/dephosphorylated equilibrium that is coordinated by the action of tyrosine kinases and phosphatases. However, the distinct tyrosine kinases coupled to 5-HT_{2C}R await molecular identification. Kv channel inhibition mediated via 5-HT_{2C}R activation is almost irreversible. The rate of protein phosphorylation/dephosphorylation, specific proteolysis, or channel internalization phenomena may play a role. In oocytes co-expressing the mouse 5-HT_{1C}R (termed 5-HT_{2C}R after 1994) and mouse Kv1.3 channel, addition of 100 nM 5-HT causes a complete and sustained suppression of Kv1.3 currents. In contrast, 5-HT has no effect on mouse Kv3.1 currents when co-expressed with this receptor. Protein kinase C did not play a role in this transduction pathway. Moreover, the first 146 amino acids from the N-terminal, containing putative tyrosine kinase and PKA phosphorylation sites, were dispensable for 5-HT-mediated suppression of Kv1.3 currents. This study showed that the mouse Kv1.3 channel is capable of being modulated by 5-HT via 5-HT_{2C}R in a G protein and Ca^{2+}-dependent manner (Aiyar et al. 1993) but with substantial differences compared with the Kv1.1 and Kv1.2. These observations indicate that a specific functional coupling between Kv channels and 5-HT_{2C} receptor may occur in vivo, whereby Kv channels play key roles in controlling neuronal excitability. Neurophysiologically, 5-HT_{2C}Rs modulation of Kv channels through tyrosine-dependent-pathways is expected to increase neuronal excitability, discharge frequency, and the release of neurotransmitters (Fig. 6). Therefore, 5-HT modulation of this class of channels would affect the transmission of inputs between specific neurons. This view is

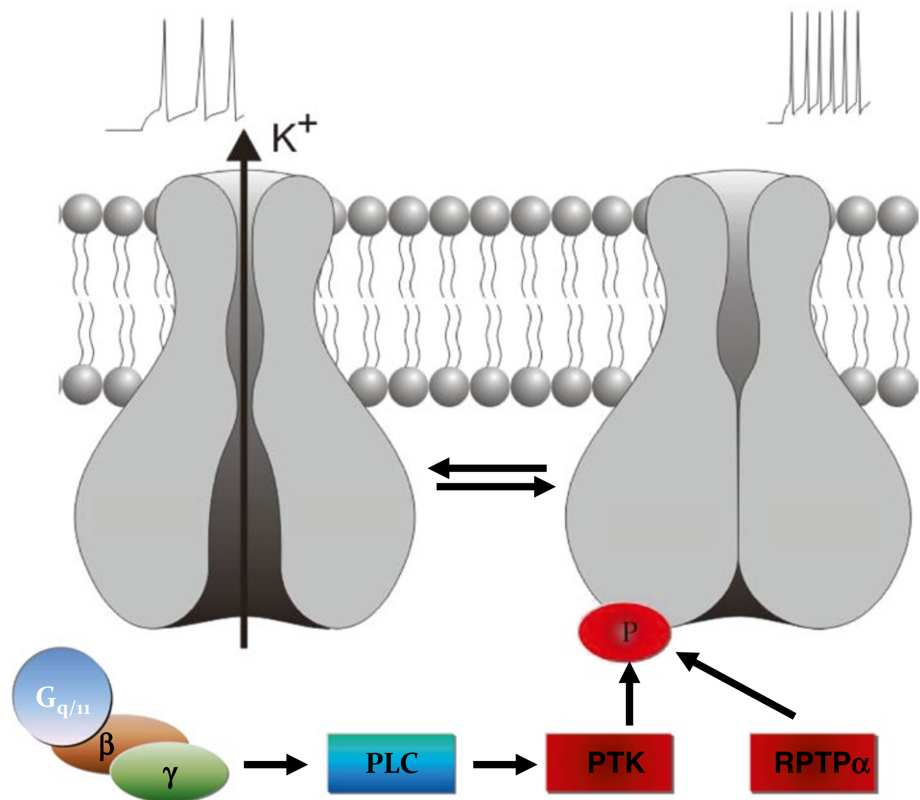

Fig. 6 Model for the role of Kv1 in neuronal excitability and modulation by 5-HT_2R; 5-$HT_{2C}R$ is coupled to the $G\alpha q_{/11}$-protein. This receptor stimulates phospholipase C, generating diacylglycerol and inositol 1,4,5-trisphosphate (IP3) which elicits the release of Ca^{2+} ions form intracellular stores. The dual coordination of both RPTPα and specific tyrosine kinases coupled to this receptor controls the phosphorylated/dephosphorylated state of Kv1 channels and neuronal excitability in opposite ways. Typically, tyrosine phosphorylation results in Kv1 channels' closure, membrane depolarization, neuronal hyper-excitability, and increased firing rate

consistent with evidence showing that the firing rate of some substantia nigra interneurons is accelerated upon 5-HT_2R activation (Pessia et al. 1994). Consequently, an increased frequency of $GABA_A$ receptor-mediated spontaneous IPSCs could be recorded from DA cells in this area (Pessia et al. 1994); 5-HT also regulates the firing pattern of CA1 neurons by modulating several K^+ conductance (Colino and Halliwell 1987). Regrettably, neither of these studies demonstrated the molecular identity of the K^+ channels involved in the 5-HT-mediated effects making any neurophysiological correlate highly speculative.

Kv currents can be modulated by a number of other receptors, including the M1 muscarinic acetylcholine receptor, the epidermal growth factor receptor (EGF), or insulin treatment (Lev et al. 1995; Holmes et al. 1996; Bowlby et al. 1997; Fadool et al 1997; Felsch et al. 1998; Canchero et al 1998). The phosphorylation of multiple tyrosine residues of the Kv subunit has been involved in these processes (Lev et al. 1995; Holmes et al. 1996; Bowlby et al. 1997; Fadool et al 1997). Moreover, downstream effectors, such as protein kinase C (PKC), the GTP-binding protein RhoA, the protein tyrosine kinases PYK2 and Src, play an important role in suppressing Kv1.x currents (Peretz et al. 1996; Boland and Jackson 1999; Canchero et al 1998; Moran et al. 1991; Lev et al. 1995; Holmes et al. 1996). Besides controlling the activity of Kv1.2 channels, RPTPα has also been proposed as a key mediator of neuronal migration and synaptic plasticity from the Schaffer collateral pathway to CA1 pyramidal neurons involving glial function (Petrone et al. 2003). Recently, it has been shown that non-receptor tyrosine phosphatase PTPϵ plays a role in fine-tuning cortical neuron excitability through its multifaceted modulation of K^+ channels that likely include Kv1.1 and Kv1.2 (Ebner-Bennatan et al. 2012). Hence, as future directions, it would be very informative to investigate whether 5-HT exerts its actions in the brain by modulating the activity of K^+ channels through these downstream effectors.

5-HT_2R modulation of Kv channels in smooth muscle and epithelial cells

5-$HT_{2A}R$ activation inhibits Kv1.5 and native Kv currents in pulmonary artery smooth muscle cells via phospholipase C, protein kinase C, tyrosine kinase, and a caveolae pathway. Moreover, Kv1.5 channels were internalized when cells were stimulated with 5-HT, and this was prevented by concanavalin A, an inhibitor of endocytotic processes (Cogolludo et al. 2006).

5-HT acting at 5-$HT_{2C}Rs$ reduces the rate of CSF secretion. Kv1.1 and Kv1.3 channels are expressed in the choroid plexus epithelium and make a significant contribution to the whole-cell K^+ conductance (Speake et al. 2004). Single-channel recordings have shown that the open

probability of K^+ channels in the apical membranes of mouse choroid plexus epithelial cells is reduced by 5-HT (Hung et al. 1993). Furthermore, this Kv conductance is inhibited by 5-HT_{2C}R activation through the actions of PKC (Speake et al. 2004).

Concluding remarks

5-HT_2Rs have been implicated in numerous physiological, neurological, and psychiatric disorders including, food intake, hyperthermia, frontal cortex hyperexcitation, sensory perturbations, sleep difficulties, psychosis, anxiety, schizophrenia, depression, Parkinson's disease, tardive dyskinesia, psychotomimetic effects of hallucinogens, and drug addiction. The studies reviewed here demonstrated that distinct actions of 5-HT, through 5-HT_2Rs, are mediated by Kv channels. Although the core features of transduction via 5-HT_2R are well established, much still remains to be learned in particular with regard to 5-HT_2R-K^+ channels coupling in neuronal and non-neuronal cells in physiological and pathological conditions. Certainly, 5-$HT_{2A/C}$R–Kv1.2 channels coupling controls cortical excitability and the actions of hallucinogens. However, it would be very intriguing to investigate whether disruption of such coupling plays a role in the above-mentioned disorders. Noteworthy, distinct antidepressants act preferentially via K^+ channels. Thus, from a clinical and pharmacological perspective, K^+ channels or the second messenger system involved in the 5-HT_2R-K^+ channels coupling should be further considered as targets for specific therapeutic interventions.

In conclusion, understanding the specific actions of 5-HT_2R on distinct K^+ channel types is a pivotal step in the direction that will enable researchers to discover novel 5-HT functions and dysfunctions in the brain and to identify original therapeutic targets.

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