Editing of Neurotransmitter Receptor and Ion Channel RNAs in the Nervous System

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Abstract

The central dogma of molecular biology defines the major route for the transfer of genetic information from genomic DNA to messenger RNA to three-dimensional proteins that affect structure and function. Like alternative splicing, the post-transcriptional conversion of adenosine to inosine (A-to-I) by RNA editing can dramatically expand the diversity of the transcriptome to generate multiple, functionally distinct protein isoforms from a single genomic locus. While RNA editing has been identified in virtually all tissues, such post-transcriptional modifications have been best characterized in RNAs encoding both ligand- and voltage-gated ion channels and neurotransmitter receptors. These RNA processing events have been shown to play an important role in the function of the encoded protein products and, in several cases, have been shown to be critical for the normal development and function of the nervous system.

1 Introduction

The conversion of adenosine to inosine (A-to-I) by RNA editing is increasingly identified as a post-transcriptional modification in which genomically-encoded sequences are altered through the site-specific deamination of specific adenosine residue(s) in precursor and mature mRNAs, tRNAs and primary miRNA transcripts (Blow et al. 2006; Gerber et al. 1998; Gott and Emeson 2000). An inosine within the open reading frame (ORF) of an mRNA is read as guanosine during translation, which can lead to specific change(s) in the amino acid coding potential of the mRNA to alter the functional properties of the encoded protein product. Such alterations in the primary nucleotide sequence of mRNA transcripts can affect not only coding potential, but also can alter the structure, stability, translation efficiency and splicing patterns of the modified transcripts, thereby affecting numerous aspects of RNA function in the cell (Gott and Emeson 2000). For specific tRNAs, such editing events are often observed in the wobble position of the anticodon loop (position 34), playing a crucial role in protein synthesis by allowing alternative pairing with U, C, or A in the third position of codons (Crick 1966). Editing also has been shown to play an important role in miRNA expression and function, as A-to-I conversion can modulate the processing of miRNA precursors by Drosha and Dicer, alter the target selectivity of mature miRNAs and decrease miRNA stability (Kawahara et al. 2007; Yang et al. 2006).

2 Identification of A-to-I Editing Targets

A-to-I editing is generally identified as an adenosine to guanosine (A-to-G) discrepancy during comparisons of genomic and cDNA sequences that result from the base-pairing of cytosine to inosine (like guanosine) during reverse transcriptase-mediated first-strand cDNA synthesis. At least eight mRNA transcripts with A-to-I modifications in the ORF were initially noted in mammals, based upon the serendipitous identification of such A-to-G disparities (Table 1). Most notably, subunits of the α-amino-3-hydroxy-5-methyl-isoxazole-4-propionate (AMPA) subtype of ionotropic glutamate receptor (GluR-2, GluR-3 and GluR-4), subunits of the kainate subtype of glutamate-gated ion channel (GluR-5 and GluR-6) and transcripts encoding the 2C-subtype of serotonin receptor ($5HT_{2C}$) were shown to undergo A-to-I modifications that change the amino acid coding potential of the mature mRNAs, producing protein products with altered functional properties (Emeson and Singh 2001; Rueter and Emeson 1998). Recently, numerous laboratories have developed more directed approaches to identify mRNA targets of A-to-I editing, employing both biochemical and computer-based (*in silico*) strategies (Athanasiadis et al. 2004; Blow et al. 2004; Kikuno et al. 2002; Kim et al. 2004; Levanon et al. 2004; Ohlson et al. 2007). The earliest of these approaches took advantage of proposed sequence conservation surrounding editing sites in two evolutionarily distant species of fruit fly, *Drosophila melanogaster* and *Drosophila pseudoobscura* (Hoopengardner et al. 2003). By comparing sequences for 914 candidate genes that included ion channels, G-protein coupled receptors, proteins involved in fast synaptic neurotransmission and transcription factors, Hoopengardner and colleagues identified 41 genes containing regions within coding sequences that displayed unusually high sequence conservation compared with surrounding sequences. Further characterization of the mRNAs encoded by these genes allowed the identification of 16 additional edited RNA species in *Drosophila*, encoding primarily ligand- and voltage-gated ion channels and components of the synaptic release machinery (Hoopengardner et al. 2003). The identification of numerous editing targets in the *Drosophila* nervous system is consistent with the observation that the prominent phenotype observed in editing-deficient flies involves nervous system dysfunction and neurodegeneration (Hoopengardner et al. 2003; Palladino et al. 2000). Of the newly identified editing events in flies however, only transcripts from the *kcna1* gene, encoding a voltage-gated potassium channel ($K_v1.1$), have been validated as a target in the mammalian transcriptome (Bhalla et al. 2004; Hoopengardner et al. 2003).

More recently, additional *in silico* approaches have attempted to identify and validate A-to-G discrepancies between genomic and cDNA sequences on a genome/transcriptome-wide scale, predicting >12,000 editing sites in the human transcriptome of which >94% occur primarily in non-coding regions of RNA transcripts containing short interspersed elements (SINEs) of the Alu and L1 subclass (Athanasiadis et al. 2004; Blow et al. 2004; Kikuno et al. 2002; Kim et al. 2004; Levanon et al. 2004). Although the biological significance of editing in Alu sequences has not been fully examined, it has been proposed that the editing within this primate-specific class of SINE elements may modulate alternative splicing, chromatin structure and the retention of highly edited RNAs in the nucleus (Chen et al. 2008; Moller-Krull et al. 2008). Despite the success of *in silico* strategies in the

identification and validation of novel editing sites, few codon-altering (recoding) A-to-I modifications were identified in mRNAs. Among these additional editing targets are transcripts encoding filamin A (FLNA), bladder cancer associated protein (BLCAP), cytoplasmic FMR1 interacting protein 2 (CYFIP2) and insulin-like growth factor binding protein 7 (IGFBP7) (Table 1). Despite their expression in discrete regions of the brain, the role(s) for these proteins in central nervous system function or the consequences of editing have not been determined.

3 Mammalian ADAR enzymes

A-to-I editing of precursor and mature mRNAs and primary miRNA transcripts is mediated by a family of double-stranded RNA-specific adenosine deaminases (ADARs) that catalyze the hydrolytic deamination of the C-6 position within the purine ring (Polson et al. 1991) and have been the topic of numerous reviews (Bass 2002; Hogg et al. 2011; Nishikura 2010). In mammals, three ADAR proteins (ADAR1, ADAR2 and ADAR3) have been purified and their corresponding genes have been identified (Chen et al. 2000; Hough and Bass 1994; Kim et al. 1994; Liu et al. 1997; O'Connell et al. 1995). ADAR1 and ADAR2 have been shown to be expressed in almost all cell types examined (Melcher et al. 1996b; Wagner et al. 1990) and are able to convert A-to-I in extended regions of duplex RNA within pre-mRNAs, mRNAs, primary miRNA transcripts and viral RNAs (Berg et al. 2001; Luciano et al. 2004; Schaub and Keller 2002; Yang et al. 2006). The expression of *ADAR3* has been detected only in post-mitotic neurons in brain regions such as the amygdala and thalamus (Chen et al. 2000), yet ADAR3 has not demonstrated any catalytic activity using synthetic dsRNA or known ADAR substrates (Chen et al. 2000; Maas et al. 2003). ADAR1 and ADAR2 have overlapping yet distinct patterns of editing with some sites edited by only one enzyme and other sites edited equally well by both (Bass 2002; Hogg et al. 2011; Nishikura 2010).

The ADAR1 gene specifies two major protein isoforms, an interferon (IFN) inducible 150 kDa protein (p150) and a ubiquitous, constitutively expressed N-terminally truncated 110 kDa protein (p110), encoded by transcripts with alternative exon 1 structures that initiate from different promoters (George and Samuel 1999). The predicted protein sequence of ADAR1 indicates that it contains three copies of a dsRNA-binding motif (dsRBM), a motif shared among numerous dsRNA-binding proteins (Burd and Dreyfuss 1994; Fierro-Monti and Mathews 2000), a nuclear localization signal in the third dsRBM (Eckmann et al. 2001), and a region homologous to the catalytic domain of other known adenosine and cytidine deaminases. The amino-terminus of the p150 isoform also contains two Z-DNA binding domains, the first of which (Zα) overlaps with a leucine-rich nuclear export signal (Poulsen et al. 2001). The Z-DNA binding domains also have been proposed to tether ADAR1 to sites of transcription (Herbert and Rich 1996) or to mediate interactions between ADARs and other proteins (Poulsen et al. 2001). The locations of the nuclear localization and nuclear export sequences in ADAR1 are consistent with observations that the p150 isoform shuttles between the cytoplasm and the nucleus, whereas the p110 protein is localized predominantly to the nucleus (Eckmann et al. 2001; Fritz et al. 2009; Patterson and Samuel 1995; Strehblow et al. 2002). Alternative splicing within exon 7 of ADAR1 generates two distinct mRNA isoforms that differ by 26 amino acids that encode the linker region between the

third double-stranded RNA binding motif and the catalytic domain to affect site-selective editing efficiency (Liu et al. 1999; Liu et al. 1997). Total ablation of ADAR1 expression in mice results in embryonic lethality at day 11.5, manifested by liver disintegration (Hartner et al. 2004) and widespread apoptosis (Wang et al. 2004), suggesting that ADAR1 may promote survival of numerous tissues by editing dsRNAs required for protection against programmed cell death. Similar embryonic lethality also results from selective loss of the p150 isoform, indicating a critical role for this ADAR1 isoform in embryonic development (Ward et al. 2011). Humans that are heterozygous for an ADAR1 loss-of-function allele demonstrate dyschromatosis symmetrica hereditaria, a recessive genetic disorder characterized by pea-sized hyperpigmented and hypopigmented macules on the hands and feet (Gao et al. 2005; Miyamura et al. 2003; Suzuki et al. 2005), whereas no such phenotype is observed in mice that are heterozygous for an ADAR1-null allele (Hartner et al. 2004; Wang et al. 2004).

ADAR2 is an 80 kilodalton protein with structural features similar to those observed for ADAR1 (Melcher et al. 1996b). ADAR2 contains a nuclear localization signal and two dsRNA binding motifs, sharing approximately 25% amino acid sequence similarity with the dsRBMs of ADAR1. ADAR2 also contains an adenosine deaminase domain sharing 70% amino acid similarity with ADAR1, as well as three zinc-chelating residues conserved in the deaminase domain of both enzymes. As with ADAR1, multiple cDNA isoforms of ADAR2 have been identified in rats, mice and humans including alternative splicing events in mRNA regions encoding the deaminase domain and near the amino terminus (Gerber et al. 1997; Lai et al. 1997; Rueter et al. 1999). Of particular interest is an alternative splicing event that introduces an additional 47 nucleotides near the 5′-end of the ADAR2 coding region, resulting in a frameshift that is predicted to produce a 9 kD protein (82 aa) lacking the dsRBMs and catalytic deaminase domain required for protein function (Rueter et al. 1999). This alternative splicing event is dependent upon the ability of ADAR2 to edit its own pre-mRNA, converting an intronic adenosine-adenosine (AA) to an adenosine-inosine (AI) dinucleotide that effectively mimics the highly conserved AG sequence normally found at 3′-splice junctions. These observations indicate that RNA editing may serve as a novel mechanism for the regulation of alternative splicing and provides an autoregulatory strategy by which ADAR2 can modulate its own level of expression (Feng et al. 2006; Rueter et al. 1999). Ablation of ADAR2 expression in mutant mice results in death between postnatal day 0 (P0) and P20, as mutant animals become progressively seizure-prone after P12 (Higuchi et al. 2000).

4 ADAR Substrates in the Central Nervous System

4.1 Glutamate-gated ion channels

4.1.1 AMPA Receptors—Ionotropic glutamate receptors (iGluRs) are involved in fast synaptic neurotransmission and in the establishment and maintenance of synaptic plasticity critical to learning and memory. Three subtypes of iGluRs, named according to selective agonists for each receptor subtype, include N-methyl-D-aspartate (NMDA) receptors, α-amino-3-hydroxy-5-methyl-isoxazole-4-propionate (AMPA) receptors and kainate receptors (Ozawa et al. 1998). Ionotropic glutamate receptors are tetrameric and their subunits share a

similar core structure: three transmembrane segments (M1, M3 and M4), a pore loop (M2), a large extracellular N-terminal domain, and a highly-regulated, variably-sized C-terminal domain (Fig. 1). The N-terminus and a long hydrophilic region between the M3 and M4 transmembrane segments form a two-domain structure that is responsible for ligand-binding (Wollmuth and Sobolevsky 2004).

The first example of A-to-I editing in mammalian mRNAs was identified in transcripts encoding the GluR-2 subunit of the AMPA receptor in which a genomically-encoded glutamine codon (CAG) was altered to an arginine codon (CIG) (Melcher et al. 1995; Rueter et al. 1995; Sommer et al. 1991; Yang et al. 1995). The substitution of a positively-charged arginine residue for a neutrally-charged glutamine residue at the apex of the membrane reentrant pore loop (M2) changes the conductance properties of channels containing an edited GluR-2(R) subunit (Verdoorn et al. 1991). Heteromeric AMPA channels that contain the edited GluR-2(R) subunit are relatively impermeant to Ca^{2+} ions and show a linear current–voltage (I–V) relationship, whereas channels that lack or contain a non-edited GluR-2(Q) subunit show a double-rectifying I–V relationship and an increased Ca^{2+} conductance (Dingledine et al. 1992; Hollmann et al. 1991; Sommer et al. 1991; Verdoorn et al. 1991). Quantitative PCR analyses of adult rat, mouse and human brain RNA have demonstrated that virtually all GluR-2 transcripts encode this critical arginine residue within M2 while GluR-1, −3 and −4 transcripts encode only a glutamine at the analogous position (Higuchi et al. 2000; Sommer et al. 1991).

RNA editing is also responsible for an A-to-I modification in exon 13 of RNAs encoding the GluR-2, −3 and −4 AMPA receptor subunits to alter a genomically-encoded arginine (AGA) to a glycine (IGA) codon at position 764 (R/G site) to modulate the rate of recovery from receptor desensitization (Fig. 1). Because of faster recovery and a tendency for slower desensitization rates, heteromeric AMPA channels containing edited (glycine-containing) subunits show larger steady-state currents than the non-edited forms (Lomeli et al. 1994). Immediately following this edited codon, an alternative splicing event incorporates one of two mutually-exclusive exons referred to as 'flip' and 'flop' that encode a portion of the ligand-binding domain (Fig. 1) (Sommer et al. 1990). Combinations of editing and splicing generate a variety of channels with unique kinetic properties (Koike et al. 2000; Krampfl et al. 2002; Lomeli et al. 1994). Editing at the Q/R and R/G sites together, play a role in receptor trafficking, as editing of the Q/R site attenuates formation of GluR-2 homo-tetramers and leads to retention of the GluR-2(R) subunit in the endoplasmic reticulum (ER) (Greger et al. 2003; Greger et al. 2002; Greger et al. 2007). Indeed, non-edited GluR-2(Q) is released to form homomeric channels on the cell surface while edited subunits remain unassembled in the ER (Greger et al. 2003). Interestingly, several studies have shown that editing at the R/G site (Greger et al. 2006) and flip/flop alternative splicing (Coleman et al. 2006) also play roles in AMPA receptor trafficking.

To determine the biological significance of Q/R site editing, mutant mice were engineered to solely express the non-edited form of the GluR-2 transcript by Cre-mediated deletion of the editing complementary sequence (ECS), an intronic region required for formation of the RNA duplex that is essential for A-to-I conversion. A dominant-lethal phenotype was revealed as heterozygous mutant animals appeared healthy until postnatal day 14 (P14),

when they begin to develop seizures that lead to death by P20. This phenotype resulted from dramatically increased AMPA receptor permeability to Ca^{2+}, concomitant with neuronal degeneration (Brusa et al. 1995). In subsequent studies, mice homozygous for a null allele of ADAR2 were shown to die of seizures before P20, a phenotype nearly identical to that seen in mice deficient in GluR-2 editing (Q/R site). This early postnatal lethality was rescued by a targeted mutation in which the wild-type GluR-2 allele was modified to express transcripts with a genomically encoded arginine [GluR-2(R)], thereby circumventing the requirement for editing (Higuchi et al. 2000). Together, these studies highlight the physiological importance of GluR-2 editing (Q/R site) in normal brain function. However, it also should be noted that Ca^{2+}-permeable AMPA receptors have been identified following mechanical or ischemic brain injury (Rump et al. 1996; Spaethling et al. 2008) or in specific brain regions such as cerebellar Bergmann glia (Burnashev et al. 1992; Iino et al. 2001), yet this Ca^{2+} permeability is thought to result largely from an absence of GluR-2 subunit incorporation into functional AMPA channels rather than the absence of GluR-2 editing.

The editing of GluR-2 mRNA has been implicated recently in the etiology of sporadic amyotrophic lateral sclerosis (ALS), a progressive neurodegenerative disorder involving primarily motor neurons of the cerebral cortex, brain stem and spinal cord, eventually leading to death from respiratory failure (Naganska and Matyja 2011). The editing of GluR-2 transcripts (Q/R site) in spinal motor neurons of ALS patients appears to be inefficient compared to control patients or unaffected neurons (Hideyama et al. 2010), suggesting that the inclusion of the GluR-2(Q) subunit into heteromeric AMPA channels results in a Ca^{2+}-mediated excitotoxicity that contributes to cell death (Kawahara et al. 2004; Kawahara et al. 2003; Kawahara et al. 2006; Kwak and Kawahara 2005; Takuma et al. 1999). Support for this hypothesis was recently demonstrated in a mutant mouse line where ADAR2 expression was specifically ablated in ~50% of motor neurons using a conditional ADAR2-null allele in combination with *Cre* recombinase under the control of the vesicular acetylcholine transporter promoter. Motor neurons lacking ADAR2, expressing only non-edited GluR2(Q) subunits, were subject to a slow death, but could be rescued by expression of the Glur-2(R) allele (Hideyama et al. 2010), thus providing the first example of a human neurodegenerative disorder resulting from editing defects and further emphasizing the importance of GluR-2 editing in normal CNS function.

4.1.2 Kainate Receptors—Kainate (KA) receptors, like AMPA receptors, mediate fast excitatory neurotransmission and are widely expressed in a number of brain regions including the neocortex, the caudate/putamen, the CA3 region of the hippocampus, the reticular thalamus and the cerebellar granular layer (Seeburg 1993). There are five KA subunits encoded by distinct genes: GluR-5, GluR-6, GluR-7, KA-1 and KA-2. GluR-5 and GluR-6 form homomeric channels with a high affinity for kainate, but are not activated by AMPA (Bettler et al. 1990; Egebjerg et al. 1991). These two subunits are distinct from the other KA receptor subunits as their RNAs are modified by A-to-I editing (Sommer et al. 1991). Like GluR-2, RNAs for GluR-5 and GluR-6 have a Q/R editing site in a region encoding the hydrophobic pore domain (M2) which can alter the calcium permeability of heteromeric KA receptors containing a GluR-6 subunit (Egebjerg and Heinemann 1993). There are two additional editing sites in the M1 region of GluR-6 and editing leads to the

substitution of a valine (ITT) for a genomically-specified isoleucine (ATT) codon (I/V site) and the substitution of a cysteine (TIC) for a tyrosine (TAC) codon (Y/C site). These editing events provide the possibility of eight different edited variants of GluR-6 subunits, all of which are expressed to a varying extent in the CNS, although fully edited GluR-6 transcripts represent the most abundantly expressed isoform in the adult nervous system (Kohler et al. 1993; Ruano et al. 1995).

Electrophysiological studies have revealed that channels with editing events in the M1 region of GluR-6 exhibit increased calcium permeability when the M2 pore encodes an arginine at the Q/R site, in direct contrast to the decreased calcium permeability shown for R-containing GluR-2 channels (Kohler et al. 1993). When the M1 region of GluR-6 is not edited, encoding an isoleucine and tyrosine at the I/V and Y/C sites, respectively, the presence of an arginine in M2 does little to alter calcium permeability (Kohler et al. 1993). Recombinant homomeric receptors composed of unedited kainate receptor subunits [GluR-5(Q) and GluR-6(Q)] demonstrate additional functional differences from those containing edited receptor isoforms [GluR-5(R) and GluR-6(R)], including a linear I–V relationship rather than double-rectifying properties, a single low conductance state rather than multiple conductance states and a highly significant increase in the permeability of Cl⁻ ions (Chittajallu et al. 1999). The physiological relevance of these functional alterations has yet to be identified however, as studies of mutant mice capable of expressing only the edited GluR-5(R) isoform had no obvious developmental abnormalities or deficits in a number of behavioral paradigms (Sailer et al. 1999). While mutant mice solely expressing the non-edited GluR-6(Q) subunit appeared normal, they exhibited increased NMDA receptor-independent long-term potentiation in hippocampal slices and increased susceptibility to kainate-induced seizures, suggesting a role for GluR-6 (Q/R site) editing the modulation of synaptic plasticity and seizure vulnerability (Vissel et al. 2001).

4.2 The serotonin 2C receptor (5HT$_{2C}$)

Serotonin (5-hydroxytryptamine; 5HT) is a monoaminergic neurotransmitter that modulates numerous sensory and motor processes as well as a wide variety of behaviors including sleep, appetite, pain perception, locomotion, thermoregulation, hallucinations, and sexual behavior (Werry et al. 2008). The multiple actions of 5HT are mediated by specific interaction with multiple receptor subtypes. Pharmacological, physiologic and molecular cloning studies have provided evidence for fifteen distinct 5HT receptor subtypes which have been subdivided into seven families (5HT$_1$–5HT$_7$) based on relative ligand binding affinities, genomic structure, amino acid sequence similarities and coupling to specific signal transduction pathways (Barnes and Sharp 1999; Bockaert et al. 2006; Hoyer et al. 1994; Hoyer et al. 2002). The 5HT$_2$ family of receptors includes three receptor subtypes: 5HT$_{2A}$, 5HT$_{2B}$ and 5HT$_{2C}$, which belong to the G-protein-coupled receptor (GPCR) superfamily. The G-protein:5HT$_{2C}$ receptor interactions occur in highly conserved regions of the second and third intracellular loops to potentiate subsequent signal transduction pathways via G$\alpha_{q/11}$, G$\alpha_{12/13}$ and Gα_i to modulate effector molecules such as phospholipases C, D and A$_2$, as well as the extracellular signal-regulated kinases 1 and 2 (Berg et al. 1994; Berg et al. 1998; Werry et al. 2005; Werry et al. 2008). 5HT$_{2C}$ mRNA expression has been shown to be widely distributed in neocortical areas, hippocampus,

nucleus accumbens, amygdala, choroid plexus, dorsal striatum and substantia nigra (Pasqualetti et al. 1999; Pompeiano et al. 1994), suggestive of physiologic roles in reward behavior, locomotion, energy balance, and also when dysregulated, in the development of certain disease states such as obesity, epilepsy, anxiety, sleep disorders and motor dysfunction (Giorgetti and Tecott 2004). Many of these anatomical predictions for $5HT_{2C}$ function have been supported by analyses of $5HT_{2C}$-null mice that exhibit adult-onset obesity, seizures and decreased cocaine-mediated locomotor activity and reward behavior (Abdallah et al. 2009; Brennan et al. 1997; Giorgetti and Tecott 2004; Rocha et al. 2002; Tecott et al. 1995).

RNA transcripts encoding the $5HT_{2C}$ receptor undergo up to five A-to-I editing events that predict alterations in the identity of three amino acids within the second intracellular loop of the receptor to generate as many as 24 receptor isoforms from 32 edited mRNA species (Fig. 2) (Burns et al. 1997; Wang et al. 2000). Sequence analysis of cDNAs isolated from dissected rat, mouse and human brains predicted the region-specific expression of 7 major $5HT_{2C}$ isoforms encoded by eleven distinct mRNA (Abbas et al. 2010; Burns et al. 1997; Morabito et al. 2010; Niswender et al. 1999), suggesting that differentially edited $5HT_{2C}$ receptors may serve distinct biological functions in those regions in which they are expressed. Sequencing studies have further revealed that edited mRNAs encoding isoforms with valine, serine and valine (VSV) or valine, asparagine and valine (VNV) at amino acids 157, 159 and 161 are the most highly expressed in a majority of dissected brain regions isolated from human and rat/mouse brains, respectively (Burns et al. 1997; Fitzgerald et al. 1999), whereas the major $5HT_{2C}$ transcripts in the choroid plexus encode the less edited (INV) and non-edited (INI) receptor isoforms (Burns et al. 1997; Morabito et al. 2010). Functional comparisons in heterologous expression systems, between the non-edited (INI) and the fully-edited (VGV) $5HT_{2C}$ isoforms revealed a 40-fold decrease in serotonergic potency to stimulate phosphoinositide hydrolysis for the VGV isoform due to reduced $G_{q/11}$-protein coupling efficiency and decreased coupling to other signaling pathways (Burns et al. 1997; Niswender et al. 1999; Price et al. 2001). In addition, cells expressing more highly edited $5HT_{2C}$ receptors (e.g. VSV and VGV) demonstrate considerably reduced (or absent) constitutive activation in the absence of ligand compared to cells expressing the non-edited isoform (Niswender et al. 1999). This reduction in coupling efficiency and constitutive activity derives from a difference in the ability of edited $5HT_{2C}$ isoforms to spontaneously isomerize to the active R* conformation, a form of the receptor that interacts efficiently with G-proteins in the absence of agonist (Burns et al. 1997; Niswender et al. 1999). As a consequence, the observed potency of agonists with increased affinity for the R* state is disproportionately reduced (Werry et al. 2008) and the 'functional selectivity' of receptor stimulus may be lost (Berg et al. 2001). More recent studies have indicated that alterations in $5HT_{2C}$ editing are observed in suicide victims with a history of major depression (Berg et al. 2001; Gurevich et al. 2002b; Iwamoto and Kato 2003), and in response to antidepressant and antipsychotic treatment (Englander et al. 2005; Gurevich et al. 2002b), suggesting that editing of $5HT_{2C}$ transcripts may be involved in psychiatric disorders and also may represent a homeostatic mechanism whereby $5HT_{2C}$ receptor signaling is stabilized in the face of changing synaptic serotonergic input (Englander et al. 2005; Gurevich et al. 2002a).

Chronic administration of IFN-α for the treatment of hepatitis C, hairy cell leukemia, AIDS-related Kaposi's sarcoma, chronic myelogenous leukemia, and melanoma have been shown to produce depressive symptoms that adversely affect disease outcome because of their negative impact on a patient's quality of life, their interference with treatment adherence, and the development of serious complications, including suicide (Ademmer et al. 2001; Valentine et al. 1998; Zdilar et al. 2000). The mechanism by which chronic IFN-α treatment induces depression has yet to be established, although serotonin-mediated effects have been implicated (Cai et al. 2005; Lotrich et al. 2009; Menkes and MacDonald 2000). *In vitro* studies have demonstrated that IFN-α treatment of glioblastoma cell lines can alter the editing pattern for $5HT_{2C}$ transcripts by increasing the expression of the IFN-inducible isoform of ADAR1 (p150) (Yang et al. 2004), providing a mechanism by which cytokines could induce depression by affecting the editing of numerous ADAR targets in the nervous system to alter subsequent neurotransmitter receptor function.

While the editing of $5HT_{2C}$ transcripts has been shown to modulate multiple aspects of $5HT_{2C}$ receptor signaling and expression in heterologous systems (Berg et al. 2001; Burns et al. 1997; Fitzgerald et al. 1999; Flomen et al. 2004; Marion et al. 2004; Niswender et al. 1999; Price et al. 2001; Wang et al. 2000), until recently, the physiologic importance for the existence of multiple $5HT_{2C}$ isoforms had not been fully explored. Mutant mice solely expressing the fully-edited isoform of the $5HT_{2C}$ receptor display several phenotypic characteristics of Prader-Willi Syndrome (PWS), a maternally-imprinted human disorder resulting from a loss of paternal gene expression on chromosome 15q11–13 (Goldstone 2004; Nicholls and Knepper 2001). Mutant mice display a failure to thrive, decreased somatic growth and neonatal muscular hypotonia, followed by post-weaning hyperphagia, in addition to a strain-specific neonatal lethality that is shared with other mouse models of PWS (Chamberlain et al. 2004). These observations are consistent with recent analyses indicating that $5HT_{2C}$ RNA editing is increased in autopsy samples from PWS patients (Kishore and Stamm 2006) and a mouse model (PWS-IC^{del}) that also demonstrates alterations in $5HT_{2C}$-related behaviors (Doe et al. 2009). Previous studies have shown that a maternally imprinted small nucleolar RNA within the Prader-Willi critical region (*snord115*) can alter both the splicing and editing of $5HT_{2C}$ transcripts (Kishore and Stamm 2006), providing a provoking and straightforward mechanism by which $5HT_{2C}$ RNA processing patterns may be linked with the 15q11–13 locus.

4.3 The α3 subunit of the GABA$_A$ receptor (Gabra3)

γ-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the vertebrate central nervous system. The GABA$_A$ subtype of GABA receptor is a ligand-gated chloride channel composed of an assembly of five individual subunits, of which there are nineteen classes (α1–6, β1–3, γ1–3, δ, ε, ρ1–3, θ, and π) (Olsen and Sieghart 2008, 2009). Different combinations of these subunits generate pharmacologically and functionally distinct isoforms of the GABA$_A$ receptor, which typically contain two α subunits (D'Hulst et al. 2009). The GABA$_A$ receptor is a target for many classes of drugs including barbiturates, benzodiazepenes, ethanol, anti-convulsants and anesthetics (D'Hulst et al. 2009; Fisher 2009; Henschel et al. 2008; Jenkins et al. 2001; Korpi et al. 2007; Low et al. 2000;

MacDonald et al. 1989; Meera et al. 2010; Mehta and Ticku 1999; Mohler and Okada 1977; Rudolph et al. 1999; Speth et al. 1980).

The α3 subunit of GABA$_A$ chloride channels is encoded by the *Gabra3* gene, which is located on the X chromosome in both humans and mice (Bell et al. 1989; Derry and Barnard 1991). The mouse Gabra3 transcript was first identified as a potential substrate of A-to-I editing using microarray analyses of whole mouse brain RNA that co-immunoprecipitated with ADAR2. This enriched RNA population was further analyzed using a bioinformatics paradigm designed to identify extended regions of dsRNA (e.g. stem-loop structures) within the enriched transcripts (Ohlson et al. 2005; Ohlson et al. 2007). Using this method, an RNA editing event was found in a region encoding sequences immediately adjacent to the extracellular transmembrane 2/3 linker of the α3 subunit (Fig. 3), a region known to be important for channel gating (Ernst et al. 2005). Subsequent sequence analyses verified the presence of an editing site which causes the recoding of a genomically-encoded isoleucine (ATA) to methionine (ATI) codon in cDNA clones isolated from adult mouse brain (Enstero et al. 2010; Rula et al. 2008; Wahlstedt et al. 2009).

To examine functional changes caused by editing, two groups have utilized heterologous expression systems, in which an edited (M) or a non-edited (I) version of the α3 subunit [α3(I) or α3(M)] was expressed along with two additional GABA$_A$ subunits to form a functional GABA$_A$ channel for electrophysiological analyses in human embryonic kidney (HEK) cells. These experiments revealed that GABA$_A$ heteromers containing a non-edited α3(I) subunit have faster activation and deactivation kinetics and slower desensitization than those containing the edited α3(M) isoform. In addition, channels with α3(I) subunits are more outwardly rectifying, assisting in the inhibition of action potentials (Nimmich et al. 2009; Rula et al. 2008). The EC$_{50}$ of GABA for the non-edited is approximately 50% of that observed for channels containing the edited α3 subunit, although the effect of various allosteric modulators is not altered (Nimmich et al. 2009). While all six GABA$_A$ α subunits contain a homologous, conserved isoleucine in their third transmembrane domain, only the α3 subunit is edited (Nimmich et al. 2009; Rula et al. 2008). However, mutational analysis revealed that substitution of a methionine for an isoleucine in the analogous position in the α1 subunit resulted in similar functional alterations (Nimmich et al. 2009). In addition to the electrophysiological changes resulting from the editing of the Gabra3 RNA, more recent studies have revealed that GABA$_A$ receptor trafficking and localization are also affected by A-to-I conversion at the I/M site (Daniel et al. 2011). GABA$_A$ receptors with an α3(M) subunit were expressed to a lesser extent on the cell surface than heteromeric channels containing a non-edited α3(I) isoform, and α3(M) protein levels were significantly decreased. The substitution of a methionine for an isoleucine in the analogous position of the α1 subunit also modulated receptor cell-surface expression, indicating the importance of this amino acid residue for receptor trafficking (Daniel et al. 2011).

In the mature brain, activation of GABA$_A$ receptors produces a hyperpolarizing influx of chloride ions. While the α1 subunit is the predominant α subtype in the adult brain, the α2, α3 and α5 subtypes are much more highly expressed in the developing CNS (Laurie et al. 1992). In the developing nervous system however, the chloride gradient in cells is reversed from that of mature neurons, causing chloride ions to flow out from GABA$_A$ channels in

response to GABA stimulation. This chloride efflux creates an excitatory response to GABA that can stimulate action potentials as well as relieve the voltage-dependent block of NMDA receptors (Leinekugel et al. 1999). These depolarizing currents occur during a period of robust synaptic development and are crucial for a number of developmental processes including proliferation and synaptogenesis (Ben-Ari 2007; Cancedda et al. 2007; Ge et al. 2006). Concomitant with the age-dependent switch from excitation to inhibition for heteromeric $GABA_A$ receptors is the changing expression of α3 subunit which begins to decline at P7 from the elevated levels observed during embryogenesis (Bosman et al. 2002; Daniel et al. 2011; Hutcheon et al. 2004; Laurie et al. 1992; Rula et al. 2008; Wahlstedt et al. 2009). The editing of Gabra3 transcripts has a reversed developmental pattern however, as editing is low during embryonic development and increases dramatically into adulthood (Ohlson et al. 2007; Rula et al. 2008; Wahlstedt et al. 2009). This developmental pattern of α3 subunit expression provides for the generation of high levels of embryonic $GABA_A$ receptors containing the non-edited a3(I) subunit that are ideally suited to respond to prolonged elevations of GABA, thereby producing robust, long-lived depolarization that may trigger the production of sodium and calcium-mediated action potentials (Rula et al. 2008). Editing of Gabra3 transcripts remains nearly constant after birth in humans (Nicholas et al. 2010), suggesting that the most important role for the non-edited α3(I) isoform is played out during embryogenesis and early development, while the α3(M) subunit, encoded by edited Gabra3 transcripts, is essential throughout the remainder of life for normal inhibitory function.

4.4 Voltage-gated potassium channel (Kv1.1)

Voltage-gated K^+ (Kv) channels are key regulators of neuronal membrane excitability, functioning to control resting membrane potentials (Pongs 1999), spontaneous firing rates (Enyedi and Czirjak 2010), the back propagation of action potentials into dendrites (Hoffman et al. 1997) and neurotransmitter release (Ishikawa et al. 2003). Kv channel protein subunits are encoded by at least 40 different genes in humans, and are grouped into twelve subfamilies (Gutman et al. 2005; Jan and Jan 1997). Neurons typically express multiple types of Kv channels with distinct time- and voltage-dependent properties and subcellular distributions that differentially contribute to the regulation of firing properties and signal integration. Kv channels are formed by the tetrameric assembly of integral membrane protein subunits (MacKinnon 1991) that each contain six transmembrane segments (S1–6) and intracellular amino- and carboxyl-termini (Fig. 4) (Baldwin et al. 1992; Gutman et al. 2005; MacKinnon 1991). Each functional channel consists of four α-subunits arranged around a central axis that generate an ion conduction pathway formed by the S6 segments, a K^+ ion selectivity filter formed by the connecting loops between the S5 and S6 segments and a transmembrane voltage sensor (S4 segment) sensor responsible for voltage-dependent gating which contains basic amino acid residues at every third position (Doyle et al. 1998; Long et al. 2005).

The first cloned potassium channel gene was encoded by the *Shaker* locus in *Drosophila* (Kamb et al. 1987; Papazian et al. 1987; Tempel et al. 1987). Subsequently, a Kv channel gene (*Kcna1*) exhibiting amino acid sequence similarity to *Shaker* was cloned in mice and humans (Curran et al. 1992; Tempel et al. 1988) and shown to encode the Kv1.1 α-subunit,

a member of the Kv1 subfamily of voltage-gated potassium channels (Curran et al. 1992; Klocke et al. 1993). The Kv1 subfamily, also known as the *Shaker*-related family, consists of eight different genes (Kv1.1–1.8) (Gutman et al. 2005). Kv1.1 channels are delayed rectifiers that open upon cell depolarization and mediate an outward potassium current, thereby repolarizing the cell and attenuating the action potential (Baranauskas 2007). The Kv1.1-subtype of Kv1 channels is expressed in brain, skeletal muscle, heart, retina and pancreatic islets (Gutman et al. 2005). The Kv1.1 subunit forms both homomeric and heteromeric channels with other members of the Kv1 family, generating extensive functional diversity, as subunit composition greatly affects the kinetic and pharmacological properties (Al-Sabi et al. 2010; Coleman et al. 1999; Deal et al. 1994; Rasband et al. 2001; Schmidt et al. 1999; Shamotienko et al. 1997; Sokolov et al. 2007). In mammals, the tetramer of α-subunits is joined by four associated β-subunits, giving a 4α-4β stoichiometry (Parcej et al. 1992; Rhodes et al. 1997). An inactivating particle belonging to the β-subunits binds to the inner vestibule of the channel pore region shortly after channel activation to block current flow (Fig. 4), a process known as fast inactivation (Rettig et al. 1994).

In addition to forming a variety of channels types with other Kv1.x subunits, transcripts encoding the Kv1.1 subunit are diversified further by RNA editing. An isoleucine (ATT) to valine (ITT) codon change occurs as the result of an A-to-I editing event to recode a conserved isoleucine (Ile^{400}) within the Kv family of voltage-gated potassium channels in a region encoding the sixth transmembrane domain (S6), which lines the inner vestibule of the ion-conducting pore (Fig. 4) (Bhalla et al. 2004; Hoopengardner et al. 2003). The extent of editing varies within different regions of the brain, with highest levels in medulla, spinal cord and thalamus (Hoopengardner et al. 2003). Kv1.1 channels containing edited Kv1.1(V) subunits display a 20-fold decrease in the inactivation rate at negative membrane potentials that may result from a reduced affinity for the binding of the inactivating particle of the β-subunits (Bhalla et al. 2004). In addition to reduced inactivation by the gating particle, editing of Kv1.1 RNAs also reduced the blockage of Kv1.1 channels by endogenous, highly unsaturated signaling lipids such as arachidonic acid, docosahexaenoic acid and anandamide by reducing the affinity of the pore residues for these blocking agents (Decher et al. 2010). Highly unsaturated fatty acids have been shown previously to convert non-inactivating Kv channels to rapidly inactivating channels (Honore et al. 1994; Oliver et al. 2004) through occlusion of the permeation pathway, similar to drugs that produce 'open-channel block'. Open-channel block by drugs and lipids was strongly reduced in Kv1.1 channels whose amino acid sequence was altered by RNA editing in the pore cavity and in Kv1.x heteromeric channels containing edited Kv1.1 subunits (Decher et al. 2010). In the *Drosophila* Shaker (Kv1), Shab (Kv2) and squid sqKv2 channels, the position analogous to I^{400} in Kv1.1, is also edited to produce an isoleucine-to-valine substitution that reduces the sensitivity of these channels to highly unsaturated fatty acids (Bhalla et al. 2004; Decher et al. 2010; Patton et al. 1997; Ryan et al. 2008).

Previous studies have indicated that mutant animals with alterations in the fast inactivation rate of $K_v1.1$ have been shown to have behavioral and neurologic deficits associated hippocampal learning deficits (Giese et al. 1998) and episodic ataxia type-1 (Herson et al. 2003). In a rat model of chronic epilepsy, a 4-fold increase in Kv1.1 editing levels was

observed in the entorhinal cortex of chronic epileptic animals and a reduced potency for the seizure-inducing Kv open channel blocker, 4-aminopyridine (4-AP), suggesting that increased editing of Kv1.1 transcripts contributes to the reduced ictogenic potential of 4-AP (Streit et al. 2011). These observations indicate that the combined effects of open-channel block of Kv1 channels by highly unsaturated lipids together with differential RNA editing can alter the pharmacology of Kv1.x channels and may contribute to the fine-tuning of neuronal signaling in different brain regions.

5 Conclusions

Initially identified as an RNA modification in the anticodon loop of tRNAs from animal, plant and eubacterial origin (Bjork 1995), the deamination of adenosine-to-inosine has become increasingly recognized as a critical RNA processing event to generate diversity in both the transcriptome and proteome (Blow et al. 2006; Gerber et al. 1998; Gott and Emeson 2000). Early studies found mRNA targets of editing based upon the chance identification of adenosine to guanosine (A-to-G) discrepancies between genomic and cDNA sequences that result from the similar base-pairing properties of inosine and guanosine during cDNA synthesis. These mRNA recoding events involved transcripts encoding proteins important for synaptic signaling including ionotropic glutamate receptor subunits (GluR-2, −3, −4, −5 and −6; Fig. 1) and the 2C-subtype of serotonin receptor (Fig. 2). This bias for editing events in the nervous system was thought to reflect either a complexity of neuronal function that requires extensive proteome diversity or simply the small number of neuroscience-focused laboratories that initially were examining this novel RNA processing event. Using primarily transcripts encoding the GluR-2 subunit of the AMPA receptor or synthetic duplex RNAs, numerous groups made significant early advances concerning the molecular mechanisms underlying A-to-I conversion including both the *cis*-active regulatory sequences/structures and the enzymes (ADARs) responsible for editing using heterologous expression and *in vitro* editing systems (Higuchi et al. 1993; Kim and Nishikura 1993; Lomeli et al. 1994; Maas et al. 1996; Melcher et al. 1996b; Melcher et al. 1995; O'Connell et al. 1995; Polson and Bass 1994; Rueter et al. 1995; Yang et al. 1995). While the identification of this limited repertoire of substrates proved to be invaluable, the serendipitous nature of such substrate identification raised numerous questions regarding the number of RNAs modified by A-to-I conversion and those tissues in which they were expressed.

While ADAR1 and ADAR2 have been shown to be expressed in almost all cell types examined (Melcher et al. 1996b; Wagner et al. 1990), the observation that ADAR expression levels are greatest in the brain (Melcher et al. 1996a; Melcher et al. 1996b), accompanied by the development of a candidate-based approach to identify mRNA targets of A-to-I editing in *Drosophila* (Hoopengardner et al. 2003), further supported the idea that editing was enriched in the nervous system. The majority of ADAR targets identified using this strategy were voltage- or ligand-gated ion channels or components of the synaptic vesicular release machinery and independently identified substrates for editing in *Drosophila* also encoded nervous system signaling components including the paralysis (*para*) voltage-gated Na⁺ channel (Hanrahan et al. 2000), the cacophony (*cac*) voltage-gated Ca²⁺ channel (Peixoto et al. 1997; Smith et al. 1998) and the glutamate-gated Cl⁻ channel (*DrosGluCl-a*) (Semenov and Pak 1999). In addition, flies lacking *Drosophila* ADAR

(dADAR) expression exhibited extreme behavioral deficits including temperature-sensitive paralysis, locomotor uncoordination, tremors which increased in severity with age and neurodegeneration (Palladino et al. 2000). Despite this apparent preponderance of editing events in the nervous system, few studies have focused upon editing in peripheral tissues. More recent studies using a transcriptome-wide analysis of neuronal and non-neuronal tissues (cerebellum, frontal lobe, corpus callosum, diencephalon, small intestine, kidney and adrenal gland) identified and validate numerous, novel editing events in multiple transcripts, yet the extent of editing for these RNAs was generally less for tissues outside the central nervous system (Li et al. 2009). The recent development of massively parallel, high-throughput sequencing strategies (Bentley et al. 2008; Mortazavi et al. 2008) should provide an effective strategy for the identification of A-to-G discrepancies between genomic and cDNA sequences from multiple tissues in a single organism. This experimental paradigm not only provides for a quantitative analysis of novel editing sites, but also reduces the possibility that any observed A-to-G disparity results from a single nucleotide polymorphism.

From alterations in coding potential to changes in structure, stability, translation efficiency and splicing, RNA editing can affect almost all aspects of cellular RNA function. In most cases, RNA editing of protein-coding genes has been shown to generate multiple protein isoforms and to diversify protein function. While the first ten years of inquiry into the mechanisms of A-to-I conversion provided dramatic advances in our understanding of the enzymatic activities and biochemical mechanisms underlying this RNA processing event, the second decade of study has largely focused upon further identification of ADAR substrates and a determination of how such editing-mediated changes in coding potential can affect protein function. The ultimate biological relevance of RNA editing resides with the specific substrates that are modified by this process. As we enter a third decade of investigation, many investigators will strive to further identify RNA targets of A-to-I conversion using state-of-the art sequencing technologies. Other laboratories will examine the functional consequences of identified recoding sites in novel ADAR targets and determine whether dysregulation of editing for specific transcripts is associated with an alteration in phenotype or associations with human disorders.

Acknowledgments

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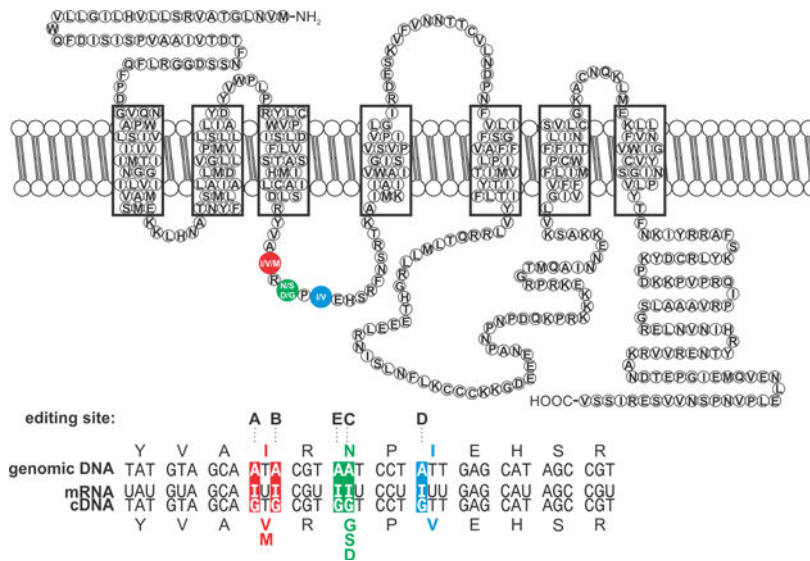
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Figure 1. Summary of the RNA editing events in mouse transcripts encoding ionotropic glutamate receptor subunits

A schematic representation of the proposed topology for GluR subunits is presented, based upon the topology determined for GluR-1 (Hollman, 1994), indicating the relative positions of editing sites. The genomic, mRNA and amino acid sequences surrounding the edited regions are shown and modified nucleosides are presented in inverse lettering.

Figure 2. Summary of RNA recoding events in serotonin 2C receptor RNA and protein isoforms
Schematic representation of the predicted topology and primary amino acid sequence for the mouse 5HT$_{2C}$ receptor is presented along with the positions of amino acid alterations within the second intracellular loop resulting from RNA editing events (*colored circles*). Nucleotide and predicted amino acid sequence alignments between 5HT$_{2C}$ genomic, mRNA and cDNA sequences are shown; the positions of the five editing sites (A–E) are indicated and nucleotide discrepancies and predicted alterations in amino acid sequence are shown with colors corresponding to each codon in which they reside.
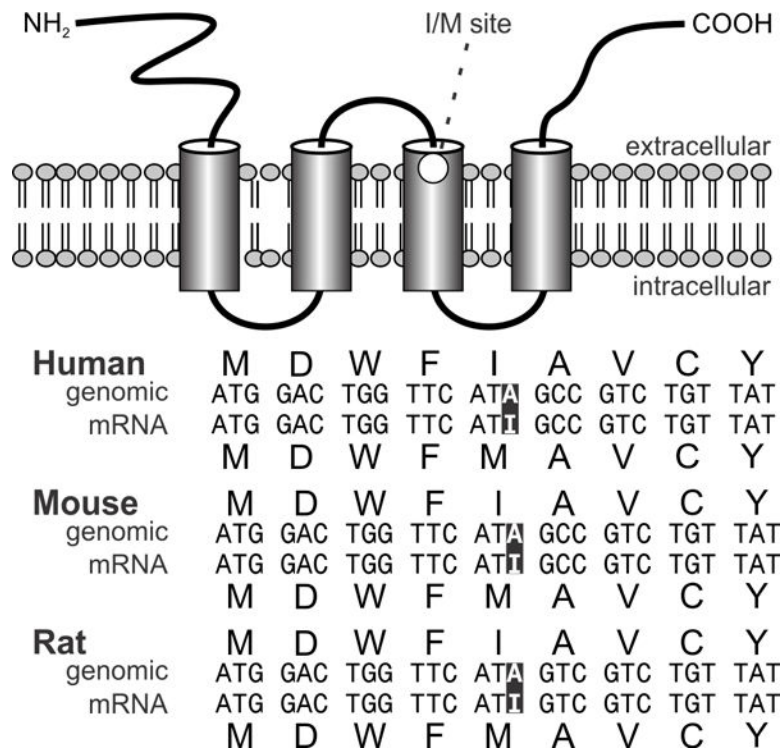
Figure 3. Conservation of RNA editing in mammalian Gabra3 transcripts
The predicted topology for the α3-subunit of the GABA$_A$ receptor is shown with the position of the editing-dependent amino acid alteration (I/M site) immediately adjacent to the extracellular transmembrane 2/3 linker. Nucleotide and predicted amino acid sequence alignments between Gabra3 genomic and mRNA from several mammalian species are shown with the positions of the I/M editing site presented with inverse lettering.
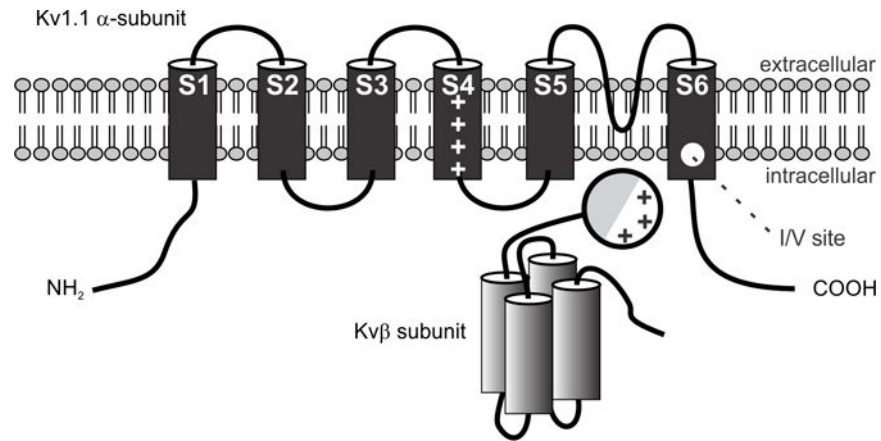
Figure 4. Schematic diagram of the structures of mammalian Kv α- and β-subunits comprising voltage-gated K⁺ channels of the Shaker-related subfamily

Shown is the proposed topology for α-subunits expressing non-inactivating K-channels and a possible topology for Kvβ1 which contains four α-helices and an amino terminal inactivating ball domain with lipophilic (shaded) and charged regions. This domain swings upon depolarization into the pore and causes rapid inactivation of the channel. The position of the transmembrane voltage sensor (S4), the K⁺ ion selectivity filter (S5–S6 linker) and the I/V editing site in the α-subunit are indicated (Adapted from Heinemann, 1994).

Table 1

Functional consequence of A-to-I editing

Gene	Protein	AA change(s)	Function	References
Gria2	GluR-2 subunit of AMPA subtype of ionotropic glutamate receptor	Q>R R>G	Modulation of Ca^{2+} permeability Modulation of receptor desensitization	Sommer, 1991 Lomeli, 1994
Gria3	GluR-3 subunit of AMPA subtype of ionotropic glutamate receptor	R>G	Modulation of receptor desensitization	Lomeli, 1994
Gria4	GluR-4 subunit of AMPA subtype of ionotropic glutamate receptor	R>G	Modulation of receptor desensitization	Lomeli, 1994
Grik1	GluR-5 subunit of kainate subtype of ionotropic glutamate receptor	Q>R	Modulation of Ca^{2+} permeability	Sailer, 1999
Grik2	GluR-6 subunit of kainate subtype of ionotropic glutamate receptor	Q>R I>V Y>C	Modulation of Ca^{2+} permeability	Heinemann, 1993 Kohler, 1993
Htr2c	5-hydroxytryptamine (serotonin) receptor 2C	I>V, M N>S, G, D I>V	Modulation of constitutive activity and G-protein coupling efficacy	Burns, 1997 Wang, 2000
Kcna1	Voltage-gated K+ channel, shaker-related subfamily (Kv1.1)	I>M	Modulation of channel inactivation	Bhalla, 2004
Gabra3	γ-aminobutyric acid (GABA) A receptor, subunit α3	I>M	Activation/inactivation kinetics Receptor trafficking	Rula, 2008 Daniel, 2011
Blcap	bladder cancer associated protein homolog	Q>R Y>C	Not determined	Levanon, 2005
Flna	filamin, alpha	Q>R	Not determined	Levanon, 2005
Igfbp7	insulin-like growth factor binding protein 7	K>R R>G	Not determined	Levanon, 2005
Cyfip2	cytoplasmic FMR1 interacting protein 2	K>E	Not determined	Levanon, 2005