Bestrophin-1 (Best1) is a calcium-activated anion channel identified from retinal pigment epithelium where human mutations are associated with Best’s macular degeneration. Best1 is known to be expressed in a variety of tissues including the brain, and is thought to be involved in many physiological processes. This review focuses on the current state of knowledge on aspects of expression and function of Best1 in the brain. Best1 protein is observed in cortical and hippocampal astrocytes, in cerebellar Bergmann glia and lamellar astrocytes, in thalamic reticular neurons, in meninges and in the epithelial cells of the choroid plexus. The most prominent feature of Best1 is its significant permeability to glutamate and GABA in addition to chloride ions because glutamate and GABA are important transmitters in the brain. Under physiological conditions, both Best1-mediated glutamate release and tonic GABA release from astrocytes modulate neuronal excitability, synaptic transmission and synaptic plasticity. Under pathological conditions such as neuroinflammation and neurodegeneration, reactive astrocytes phenotypically switch from GABA-negative to GABA-producing and redistribute Best1 from the perisynaptic microdomains to the soma and processes to tonically release GABA via Best1. This implicates that tonic GABA release from reactive astrocyte via redistributed Best1 is a common phenomenon that occur in various pathological conditions with astrogliosis such as traumatic brain injury, neuroinflammation, neurodegeneration, and hypoxic and ischemic insults. These properties of Best1, including the permeation and release of glutamate and GABA and its redistribution in reactive astrocytes, promise us exciting discoveries of novel brain functions to be uncovered in the future.

Key words: Bestrophin-1, brain, glutamate, GABA, reactive astrocyte

Received May 30, 2017, Revised June 8, 2017, Accepted June 8, 2017
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In this review, we focus on the expression pattern and the function of Best1 in the brain. Although there are many remaining uncertainties, this review highlights the idea that Best1 is a multifunctional protein, functioning as an anion channel with unique properties as well as a key regulator of various important brain functions.

**MOLECULAR BIOLOGY AND STRUCTURE OF BEST1**

Best1 exhibits a significant level of phylogenetic conservation and have been unambiguously identified in every organism examined. The Best1 encoding gene VMD2 is located in a pericentric region on human chromosome 11q13. The human Best1 (hBest1) is approximately 68-kDa protein composed of 585 amino acids. Best1 has intracellular N-termini and 4 transmembrane domains which are highly conserved between species. A large cytosolic domain has approximately 280 amino acids including the C-terminus. In crystal structure analysis studies, Best1 forms homopentamers of five Best1 subunits comprising a continuous central pore in both prokaryotic Klebsiella [11] and eukaryotic chicken [12]. According to the secondary structure analysis of Best1, the Ca$^{2+}$-binding clasp consists of the acidic cluster (Glu300, Asp301, Asp302, Asp303 and Asp304) within the forth transmembrane domain and helix-turn-helix element within the first transmembrane domain of an adjacent subunit in chicken Best1 [12]. This Ca$^{2+}$ clasp serves as the binding pocket for Ca$^{2+}$ for the channel activation. Prokaryotic Best1 also has a loop structure in the fourth transmembrane domain that corresponds to a conserved carboxylate-rich segment (EDDDDFE) in eukaryotes [11]. These results implicate the structure-based conservation throughout the animal kingdom.

**BRAIN DISTRIBUTION OF BEST1**

From the early studies, Best1 has been known to be predominantly expressed in the retinal pigment epithelium (RPE) with the most of the available data coming from RT-PCR or Northern analysis or in situ hybridization (ISH) [9]. Until 2009, the expression profiles of the various Bestrophins in the brain had not been clearly established. Although mRNA of hBest1 was detected in various tissues, especially in the brain as described in Allen Brain Atlas with ISH and microarray (http://www.brain-map.org), the protein expression for hBest1 had been reported only in RPE. Even if the expression of hBest1 is highly restricted, the protein expression of mouse Best1 (mBest1), on the other hand, has been reported in other tissues such as the brain, colon, kidney, and trachea in addition to RPE. RNA transcript and protein of mBest1 also have been known to be expressed in the dorsal spinal cord and dorsal root ganglion (DRG) [13-15]. Notably, ISH data revealed that mBest1 mRNA was widely distributed in the brain, especially with higher levels in olfactory bulb, hippocampus, and cerebellum (Fig. 1) and prominent expression in both neurons and astrocytes [16]. mBest1 expression both in cortical neuron and astrocyte was also detected and confirmed by gene silencing for mBest1 with mBest1-shRNA using RT-PCR [16-18].

Although the information about protein expression level of Best1 in the brain is very limited, it has been most thoroughly investigated in hippocampus and cerebellum in several studies by Western

![Fig. 1.](image) In situ hybridization analysis for detecting endogenous mBest1 transcript in whole-brain region. In situ hybridization results from coronal (top middle) and sagittal section (bottom left) using antisense probe for mBest1 mRNA. A higher-magnification view of boxed area (red box) in stratum radiatum in CA1 region of coronal section (right). In situ hybridization result using sense probe for mBest1 in coronal section (top left) was shown as a negative control.
Bestrophin-1 in the Brain

Western blot analysis showed that mBest1 is reliably expressed in cultured mouse cortical astrocyte [18] and in mouse hippocampal tissue [20]. In the brain tissue, mBest1 expression in astrocytes in both CA1 region [21, 22] and dentate gyrus (DG) [20] of hippocampus was detected by immunohistochemical analysis. Furthermore, the electron microscopic analysis with immunogold labeling revealed that astrocytic mBest1 in the molecular layer of DG and stratum radiatum of CA1 region of hippocampus was significantly localized at the microdomain (perisynaptic region) right at the synaptic junctions rather than at the soma or process [21, 22]. This unique and specific localization at the perisynaptic junction raises a possibility that Best1 can be a useful specific marker for an astrocytic perisynaptic junction (microdomain) in hippocampus.

Despite those unequivocal lines of evidence on protein and mRNA expression of mBest1 in the brain, many scientists have been led astray by the unexpected extremely low expression level of Best1 transcript in astrocytes and neurons in the popular transcriptome database available from the Brain RNA-Seq (http://web.stanford.edu/group/barres_lab/brain_rnaseq.html). Perhaps the inconsistency is came from the fact that astrocytes locally translate some of the gene transcripts such as Best1 mRNA preferentially in the distal processes and microdomains as recently described [23]. The locally transported mRNA in the distal processes and microdomains might have been diluted or lost during the harsh dissociation and cell-sorting procedures that are required for cell-type specific isolation and transcriptome analysis [24]. Future work is needed to test the possibility that mBest1 mRNA is transported to distal processes and microdomains to be locally translated.

mBest1 was also found beneath the basal membrane of the meninges and in the epithelial cells of the choroid plexus by immunohistochemical methods [25]. Recent reports confirmed that mBest1 is also expressed in almost all inhibitory neurons in thalamic reticular nucleus (TRN) by using TRN-neuron-specific gene-silencing of mBest1 by immunohistochemistry [26].

Meanwhile, in cerebellum, a significant expression of mBest1 was observed in Purkinje cells, Bergmann glia and lamellar astrocytes in the molecular layers, but not in granule cells [18]. The distribution of mBest1 within Bergmann glia in the cerebellum was distinguishable from hippocampal astrocytes because mBest1 was localized in the cell body as well as in the main processes of Bergmann glial cells [27]. The differential expression pattern of mBest1 in hippocampal astrocytes and Bergmann glia was functionally supported by the observation that the reversal potential of the mBest1-mediated whole cell current was shifted by about −40 mV from the predicted reversal potential (0 mV) due to the distal localization of mBest1 and incomplete space clamping, whereas the reversal potential was not shifted in Bergmann glial cells due to the nearby expression of mBest1 from the recording electrode [27].

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Fig. 2. (a) Immunostaining of mBest1 in the molecular layer of DG (both sexes at 9 months of age; scale bar, 10 mm) from wild type and APP/PS1 Alzheimer’s disease model mouse. (b) Representative images of Best1 by immunogold electron microscopy labeling (black dots indicated by arrowheads) in DAB-stained astrocytes (outlined with dashed lines). Pre, presynaptic terminal; Post, postsynapse; scale bar, 300 nm. Bottom left, density of gold particles for Best1 in cell body, process and microdomain. *** p<0.001 (Student’s t-test). (c) Model diagram of memory impairment in Alzheimer’s disease.
Interestingly, the expression pattern of mBest1 in reactive astrocytes showed a markedly different pattern from normal astrocytes. In the brain of Alzheimer’s disease (AD) patient, astrocytes become reactive, particularly around amyloid plaques, as represented by a hypertrophy of the main processes and increased gial fibrillary acidic protein (GFAP) expression (Fig. 2a). In the brain of APP/PS1 mice which are widely-used transgenic mouse model for AD, a decreased intensity and fewer instances of punctate expression of mBest1 in astrocytic microdomains were observed by immunohistochemical analysis and The electron microscopic analysis with immunogold labeling (Fig. 2b) [20]. Reactive astrocytes are commonly observed not only in AD but also in other brain diseases, such as Parkinson’s disease, stroke, epilepsy and traumatic brain injury. Therefore mBest1 seems to be redistributed to the soma and processes of reactive astrocytes for possible function of astrocytes not only in the physiological condition but also in the pathological condition. The detailed information about the changes of mBest1 expression pattern in astrocyte might provide the clue for a general mechanism by reactive astrocytes in neurodegenerative diseases or brain injuries that accompany reactive astrocytes.

PHYSIOLOGICAL AND PATHOLOGICAL ROLES OF BEST1 IN THE BRAIN

A defining feature of Best1 has long been considered to be a chloride channel and a regulator of calcium channel participating in the function in normal fluid and ion transport in RPE cells. In demonstrating the role of Best1 in the brain, the most remarkable feature of Best1 is its permeability to large anions and osmolytes in addition to chloride ion. Several studies have demonstrated that Best1 conduct several monovalent anions including bromine (Br⁻), iodine (I⁻), thiocyanate (SCN⁻), bicarbonate (HCO₃⁻) and nitrate (NO₃⁻) [7, 28-30]. In cultured cortical astrocytes, Best1 was reported to encode functional calcium-activated anion channel which permeates large organic anions such as glutamate and isethionate [16]. Glutamate is well-known to be the major excitatory transmitter in the brain [31]. In hippocampal CA1 slice, astrocytes further exhibited permeability not only to glutamate but also to gluconate (Fig. 3a) [27]. The estimated permeability of glutamate relative to chloride (P glutamate/PCl) was around 0.67 for the heterologously expressed mBest1 [22], 0.47 for cultured cortical astrocytic mBest1 [16] and 0.53 for astrocytic mBest1 in hippocampal CA1 region (Fig. 3a) [27]. Considering the relative ionic size of glutamate compared to chloride, glutamate permeability of mBest1 should be regarded to be very high.

Another striking feature of Best1 is its permeability to γ-aminobutyric acid (GABA) (Fig. 3b) [18]. GABA is known as the major inhibitory transmitter in the brain. The permeability ratio of GABA relative to chloride (P GABA/PCl) was 0.27 for the heterologously expressed mBest1 and 0.19 for Bergmann glial mBest1 in cerebellum. Although the apparent GABA permeability seems to be relatively low compare to other anions, it should be noted that the permeating GABA is predominantly zwitterionic and only a small amount of GABA in anionic form is detected by voltage clamp recording system as a current. Therefore, the true permeability of GABA (including both zwitterionic and anionic forms) should be much higher than the apparent GABA permeability.

Contrary to those permeability ratio experiments, Long group reported that the chicken Best1 was not permeable to glutamate [12]. However, the method the authors used was a fluorescence-based flux assay which indirectly measured the ionic permeability by measuring the fluorescence change induced by an uptake of

Fig. 3. (a) Normalized voltage dependence of TFLLR-induced Best1 currents from astrocytes in hippocampal CA1 stratum radiatum region with various anions such as CsCl (n=6), Cs-glutamate (n=8), or gluconate (n=7) in pipette solution. (b) Normalized representative voltage dependence of Best1 current in HEK293T cells recorded with high Ca²⁺ pipette solution at the indicated intracellular GABA concentrations. In all cases, GABA was substituted for Cl⁻. (c) Anion permeability of chicken Best1 in liposome recorded by fluorescence-based flux assay.
protons (Fig. 3c). This method was an indirect measurement to record the pH change rather than a direct measurement of ionic current mediated by the flux of the ionic form of glutamate. Therefore, the results from the fluorescence-based flux assay as a method for measuring the glutamate permeability should be interpreted with caution. Future studies are needed to measure the precise permeability ratio of glutamate for the chicken Best1.

The high permeability to glutamate and GABA renders a distinctive function to Best1 in the brain because glutamate and GABA are important excitatory and inhibitory transmitters, respectively. Best1 was observed to mediate calcium-dependent glutamate and GABA release from astrocytes upon activation of G protein-coupled receptor (GPCR) or any other stimulation that causes intracellular calcium increase by using the sniffer-patch clamp recording [18, 20, 22]. Best1 shows substantial activation even at resting levels of intracellular calcium which results in constitutive release of GABA at such intracellular calcium levels. This is due to its median effective concentration (EC50) for Ca2+ of 150 nM, which is near the resting calcium concentration [18]. To investigate the function of GABA-permeable glial Best1 in the cerebellum, knockdown of Best1 by cell-type specific gene silencing of Best1 using lentivirus carrying Best1-shRNA was performed [18, 32]. As a result, it was revealed that glial Best1 was responsible for the tonic release of GABA that leads to modulation of granule cell excitability via tonic inhibition in cerebellum.

Contrary to these previous findings, Diaz et al., reported that Best1 channel does not mediate tonic GABAergic current in cerebellar granule cells [33]. Unfortunately, the authors’ claim was based only on pharmacological evidence using NPPB (5-nitro-2-(3-phenylpropylamino)benzoic acid) as a specific Best1 channel blocker. However, NPPB which they used in their experiments cannot serve as a specific blocker to Best1 channel because it blocks almost all of chloride and anion channels [33], and is notorious for having many side effects such as blocking some potassium channels and calcium channels [34]. In particular, the authors claimed that NPPB enhanced, instead of blocked, tonic GABA current within 4 to 5 minutes. As a matter of fact, the initial enhancement of tonic GABA current was also observed in the original report by Lee et al., 2010. However, the initial enhancement by NPPB was eventually decreased and longer application of NPPB blocked the tonic GABA current by 10 min of NPPB application [18]. Fortunately, Lee et al., 2010 went to the trouble of developing and utilizing cell-type specific gene-silencing method by lentiviral shRNA [18] which is far more specific to Best1 than NPPB. Therefore, the NPPB-based results reported by Diaz, et al., 2011 cannot be qualified to support their claim that Best1 does not mediate tonic GABAergic currents.

Meanwhile, hippocampal astrocytes do not release GABA under normal condition due to the absence of GABA. This is because Best1-mediated tonic GABA release depends on the presence of GABA in astrocyte [20, 32]. Hippocampal astrocytes release glutamate upon GPCR (G protein-coupled receptor) activation at the microdomains adjacent to glutamatergic synapses where mBest1 is preferentially expressed [22]. Activation of astrocyte specific Gq protein-coupled receptor (GqPCR), PAR1 (protease-activated receptor-1), by its specific peptide agonist TFLLR causes an IP3R (inositol 1,4,5-trisphosphate receptor) mediated Ca2+ increase, which further activates the opening of Best1 channel to release glutamate at the microdomains [35]. The released glutamate through Best1 resulted in activation of GluN2A-containing N-methyl-D-aspartate receptor (NMDAR) and NMDAR-dependent potentiation of synaptic responses [21]. Furthermore, the threshold for inducing NMDAR-dependent long-term potentiation (LTP) was lowered when astrocytic Best1-mediated glutamate release accompanied LTP induction [21], indicating that astrocytic glutamate is significant in modulating synaptic plasticity.

A few studies demonstrated the functions of Bestrophin in dorsal root ganglia (DRG) and spinal cord. Best1 expression was upregulated and Best1-mediated calcium-activated chloride current was enhanced in DRG neurons after peripheral nerve axotomy [36] or spinal nerve ligation [15]. These results have suggested the function of Best1 in nociceptive processing. Another following study reported that the genetic ablation of Best1 using both knockout mice and RNA interference strategies induced a decrease in neurite outgrowth velocity in cultured injured sensory neurons [37]. Therefore, Best1 can be a positive player in the regenerative process of the mechanosensitive afferent fibers after peripheral nerve injury. Best1 is suggested to have a function in the regeneration of injured sensory neurons as well as the maintenance of neuropathic pain. These studies raise the possibility for Best1 as clinically useful target for treating neuropathic pain and nerve injury.

In addition to mediating anion transport, Best1 has also been shown to regulate intracellular calcium signaling in human RPE by affecting the kinetics of L-type voltage-dependent calcium channels or regulating the release of calcium stores in response to ATP [38–40]. However, there is no report about the role of Best1 in the brain related to regulatory function in calcium homeostasis. Future study is needed to test this possibility in the brain.

The distribution pattern of Best1 was shown to dynamically change within cellular compartments from the distal microdomain near synaptic junction to the soma and processes of reactive astrocytes in hippocampus of the brain under pathological conditions such as AD model mice (Fig. 2b) [20]. Reactive astrocytes undergo dramatic morphological changes and various alterations...
in gene expression have been observed. The most noticeable change in reactive astrocytes was the phenotypical switch from GABA-lacking to GABA-containing reactive astrocytes in DG of hippocampus under the pathological condition including AD [20, 41]. Reactive astrocytes which have GABA showed redistribution of Best1 to soma and processes and could release GABA tonically via Best1. Tonomically released GABA from reactive astrocytes impairs synaptic transmission, synaptic plasticity and spatial memory by inhibiting dentate granule cell excitability (Fig. 2c) [20]. Reactive astrocytes are generally observed in the brain with injuries, psychiatric disorders and diseases as diverse as trauma, infection, neurodegeneration, and ischemia. Therefore, it is possible that tonic GABA release from reactive astrocyte via redistributed Best1 is a general mechanism (Fig. 4) that occur in various diseases. Future work is needed to explore these exciting possibilities.

Since the first Best1 knockout mouse was generated [39], a second knockout mouse was independently produced recently [42]. And many studies utilizing these knockout mice followed. However, there seems to be no sign of behavioral defects in these Best1 knockout mice. Surprisingly, Best1 knockout does not exhibit a phenotype reminiscent of a bestrophinopathy [39, 42]. In terms of the brain function, the lack of a predominant phenotype is probably because of the fact that the role of Best in the aberrant tonic GABA release could be observed only in pathological conditions. From this point of view, people with eye disease-causing mutations can be expected to have a symptom of resistance to both tonic GABA inhibition and memory impairment. In contrast, the physiological role of Best1 in tonic GABA release in cerebellum is expected to negatively control the voluntary movement coordination, muscular activity balance and motor learning behavior. Therefore, there is an interesting possibility that people carrying mutations in Best1 would show improved motor coordination and motor learning.

Best1 expression in the meninges and the choroid plexus suggests a function of Best1 for regulatory machinery for ambient GABA levels during neocortical development [25]. Best1 can work as non-neuronal sources for ambient GABA which can modulate the properties of neural progenitors in the developing brain. Although neuronal Best1 function was not investigated, the fact that Best1 was found to be exclusively expressed in neuron of TRN raise the potential roles of Best1 in neurons. Neuronal Best1 in TRN is suggested to have function in tonic GABA release and electrogentic role to control neuronal excitability, action potential shape and time course, and rhythmic burst discharges of TRN neurons. Future studies are needed to test these exciting possibilities.

Taken together, Best1 serves multiple functions in the brain,
which originate from the channel’s unique ability to permeate important transmitters such as glutamate and GABA (Fig. 4). The novel role of reactive astrocytes is attributed to Best1’s unique property of redistribution from the microdomains to soma and processes, in combination with turning on of GABA production in reactive astrocytes (Fig. 4, right). These results in a fascinating phenotypic switch from the glutamate-releasing normal astrocyte to the GABA-releasing reactive astrocytes. Understanding the expression pattern and functions of Best1 in the brain would provide a wider understanding of the mechanisms of various brain diseases as well as the retinal homeostasis, from which Best1 was originally identified.

ACKNOWLEDGEMENTS

This work was supported by Creative Research Initiative Program, Korean National Research Foundation (2015R1A3A2066619) and the National Research Council of Science & Technology (NST) grant by the Korea government (MSIP) (No. CRC-15-04-KIST).

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