Electrophysiology of Benign Familial Neonatal Seizures and the Current Therapeutic Approach

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Abstract Every year, 5 million people worldwide are identified for having epilepsies, with neonatal seizures accounting for approximately 2 per 1000 cases of term infants (Epilepsy, n.d.; Krawiec & Muzio, 2023). Specifically, some patients with a history of benign familial neonatal seizures were found to be more likely to get epilepsies in their later life. However, due to the high ethical standards being imposed on research involving neonatal populations, neonatal seizures and their anti-convulsant treatments are not as well-understood as other seizures. This is problematic, as the neonatal seizures should not be treated based on adjusting doses of conventional anticonvulsants for adults. This approach is not favorable as neonates have distinctive physiological characteristics that can be different from adults. Thus, simply adjusting the dose of the drugs may have sub- or supra-therapeutic effects, or even lead to lethal effects on the neonatal patients. The focus of this paper is to explain the electrophysiological cause of benign familial neonatal seizures and the therapeutical attempts that had been done to treat the syndrome.

INTRODUCTION

Benign familial neonatal seizure (BFNS) is a rare epilepsy syndrome. This disease typically occurs the first few days from birth, yet the patients generally do not display irregular electrical activities on development, cognition, and interictal electroencephalogram (EEG) records (Bayat et al., 2021). However, in some cases, focal or multi-focal readings were noticed on interictal EEG, as BFNS induces clonic seizures (Singh & Raj, 2008). Singh & Raj (2) also noted that ictal EEG can initially present short periods of electrical activity cessation just before the emergence of abnormal spikes and wave readings. These abnormal readings usually last for a few minutes (Singh & Raj, 2008).

BFNS is an inheritable disease. It is passed down to family members in an autosomal dominant trend with about 85% penetrance (Maljevic & Lerche, 2014; Plouin & Kaminska, 2013). The term "benign" in BFNS was given to its name, due to good clinical outcomes generally witnessed in these patients (Plouin & Kaminska, 2013). In many cases, the disease was found to be reversible; the patients could naturally remit to retain normal cognitive functions without the need for any pharmacological interventions (Maljevic & Lerche, 2014). For instance, in one family study including 69 BFNS patients, 68% of them remitted epileptic episodes within 6 weeks from birth (Tharp, 2002).

The rarity of this disease could partially be associated with this benign aspect of the disease. Singh & Raj (2008) pointed out that the family members of BFNS patients may expect spontaneous remission of the disease in their neonatal patients, based on their family history of BFNS. The family members may be less likely to request medical support for their neonatal patients. Or, often the episodes of seizures in the disease itself may be deemed as supernatural events in low- and middle-income countries (Singh & Raj, 2008). By treating BFNS as a minor disease or supernatural event, there could have been fewer reports of the incidences.

There is a need to scientifically investigate BFNS, as 15% of the recovered patients develop later episodes of epilepsy after remission (Panayiotopoulos, 2005). For instance, there is a limited understanding of the genetic or environmental causes of BFNS (Maljevic & Lerche, 2014). Also, in the same family study with the 69 patients, described above (Tharp, 2002), 16% of the BFNS patients had another onset of seizures around the age of 8 years. Additionally, out

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of these patients, 50% kept having more seizures in older age. Another study also found that 40% of its 10 BFNS families with private mutations on potassium ion channel receptors had slower psychomotor and cognitive maturity than other families without private mutations (Steinlein et al., 2007).

Currently, there is not much understanding on the BFNS and its treatment. For the scope of this paper, the ion channel defects related to the cause of BFNS and current pharmacological approach to the disease will be discussed.

DISCUSSION

Defective ion channels in BFNS

Human brain activities rely on ion channel functions, as it functions based on the electrical activities in its regions. Each type of channel establishes membrane potential and thereby determines the electrical activity. Hence, changes in the ion channels of brains can disrupt normal electrical activity, causing nearby neurons to simultaneously change their activities which can lead to epilepsies (Anwar et al., 2020).

BFNS is caused by a single gene mutation on the KCNQ2 gene in chromosome 20q13.3 or the KCNQ3 gene in chromosome 8q24 (Fister et al., 2013). The mutation can express defective potassium channels that lead to the disease (Fister et al., 2013). The KCNQ2 and KCNQ3 genes encode for the tetrameric voltage-gated potassium channels, Kv7.2 and Kv7.3 channels, respectively (Maljevic & Lerche, 2014; Tharp, 2002). The Kv7.2 and Kv7.3 channels are located in central nervous system, specifically in axon initial segments (part of axon for stimulating action potentials) and at nodes of Ranvier (part of axon transmitting action potentials) (Maljevic & Lerche, 2014; Wulff et al., 2009). Expression of either genes can translate into homomeric receptors, while the co-expression can result in heteromeric receptors (N. A. Singh et al., 2003). The heteromeric receptors can exhibit different potency from homomeric receptors to different anticonvulsant drugs (Maljevic & Lerche, 2014).

In the receptors, each tetrameric subunit is composed of six transmembrane proteins, and both amino and carboxyl terminus (C-terminus) are located intracellularly (Figure 1). The C-terminus of each subunit consists of regions to bind regulatory proteins and are involved in attaching to other subunits (Maljevic & Lerche, 2014). The fourth segment of each subunit (S4) has positively charged arginine residues, and it serves to detect voltages (Maljevic & Lerche, 2014). The sequence between the fifth and sixth segments (S5-S6) changes the shape upon the identified voltage difference on S4 (Maljevic & Lerche, 2014). This conformation change in S5-S6 can alter the pore formation intracellularly (Maljevic & Lerche, 2014).

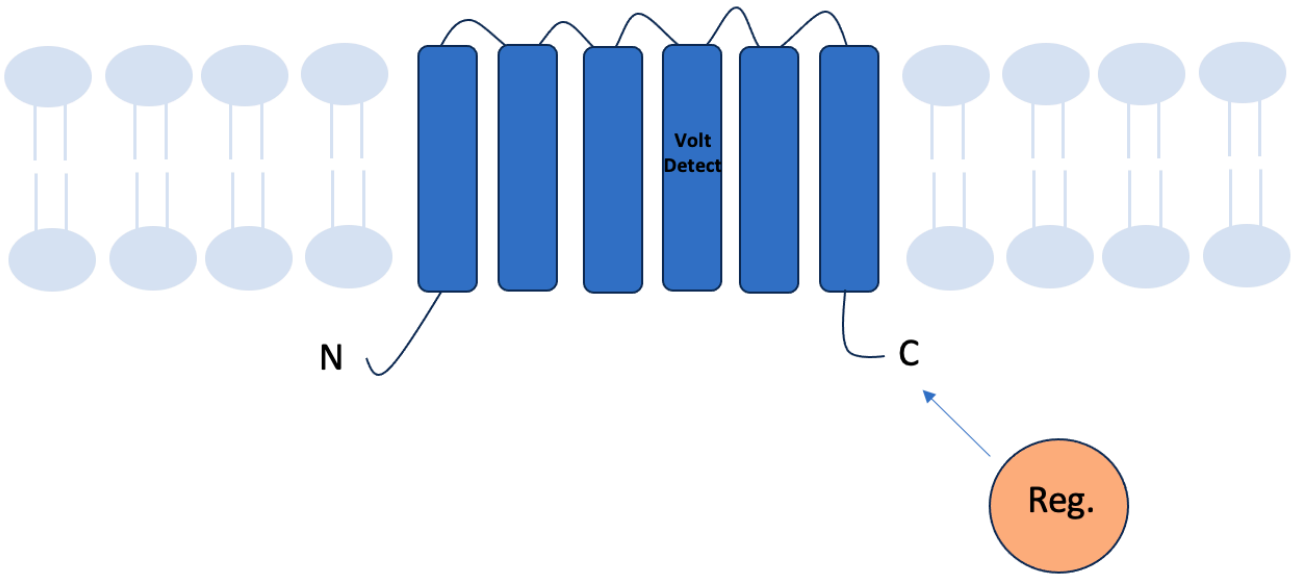

Figure 1: Voltage-gated potassium channel subunit. Regulatory protein (annotated as "Reg.") binds to C-terminus of each subunit, and fourth segment of the transmembranes (annotated as "voltage detect") has a positively-charged arginine residue for its function as a voltage detector.

Normally, the Kv7.2 and Kv7.3 receptors open at voltages below the action potential threshold and are responsible for establishing muscarinic current (M-current), a "noninactivating slow [potassium] current" (Maljevic & Lerche, 2014). This M-current is important in preventing rapid firing of action potentials, and many pharmaceutical industries tried to discover muscarinic agonists to modulate the current and ultimately the synaptic plasticity (Maljevic & Lerche, 2014; Tharp, 2002; Wulff et al., 2009). Both homomeric and heteromeric receptors can generate M-current, but it was found that the M-current produced by the heteromeric receptors was at 10 times the magnitude than by the equally co-expressed homomeric receptors in an in vitro model (Maljevic & Lerche, 2014).

Over 60 mutations in the KCNQ2 gene and 6 mutations in the KCNQ3 gene were identified in families with BFNS to cause the disease (Heron et al., 2007; Maljevic & Lerche, 2014). In one study, Heron et al (10) discovered that 44% of the participants from their 9 family cases had deletions or duplications in the KCNQ2 gene. Moreover, roughly 50% of the mutations in the KCNQ2 gene lead to a loss of a large number of the last amino acids in the sequence, generating shorter subunits for the potassium receptors (Heron et al., 2007; Tharp, 2002).

The single gene mutations in the KCNQ2 and KCNQ3 genes lead to a loss of functions in both the homomeric and heteromeric channels (Kv7.2/Kv7.3) (Maljevic & Lerche, 2014; N. A. Singh et al., 2003). The mutations can elicit the loss of functions involving various mechanisms. For instance, a single gene mutation in the genes can lead to changes in gating functions, lower receptor expression, or generation of mutant proteins altering the normal receptor functions (Maljevic et al., 2008). The severity of the loss of functions may differ, as the effects can be complete or partial (Heron et al., 2007). Generally, the complete loss of function leads to the production of drastically smaller M-current, while the partial loss of function leads 20-25% decrease (Maljevic et al., 2008). Yet, this 20-25% reduction is a change in magnitude in the M-current great enough to trigger epilepsies (Maljevic et al., 2008).

In BFNS, the mutations could be found in Kv7.2 receptors at the C-terminus, S5-S6 sequence, S4 voltage-sensing segment, and S1-S2 region (Figure 2a). On the other hand, the mutations were in Kv7.3 receptors at the S5-S6 sequence (Figure 2b) (Maljevic & Lerche, 2014). The mutations in the C-terminus can disrupt the assembly of the subunits to form the channel (Maljevic & Lerche, 2014). Also, the mutation at the C-terminus can impede the transportation of the receptors to the brain membrane (Maljevic & Lerche, 2014). In the S4 segment, the mutations in the positively charged arginine residues lower the likelihood of detecting the change in voltage (Maljevic & Lerche, 2014). However, the mutations in other residues of the S4 segment alter the gating and thus conductance of potassium ions (Maljevic & Lerche, 2014). Congruently, the mutation (E119G) in the S1 to S2 region can increase the chances of action potential firings, most likely due to its close ionic interaction with S4 arginine residue (Maljevic et al., 2008; Wuttke et al., 2008). The mutations in S5-S6 segments, the domain essential to create an opening for potassium ion conductance, were found to be more prone to cause patients resulting with harmful clinical phenotypes, such as intellectual disability (Steinlein et al., 2007).

Although other ion channels (e.g. voltage-gated sodium or calcium channels) are known to be located near potassium channels, it is only the mutations in the voltage-gated potassium channel genes known to be directly associated with the cause of BFNS so far (Berkovic et al., 2004; Kannan et al., 2023). However, interestingly, the voltage-gated sodium channel gene SCN2A mutation on chromosome 2q24 was found to be associated with benign familial neonatal-and-infantile seizures, which typically occur later in infants around 11 weeks of age (Berkovic et al., 2004; Striano et al., 2006).

Pharmacological treatment for BFNS

Despite the self-limiting nature of the disease, neonatal seizures are important to be diagnosed and treated, as they may end up with unfavorable health outcomes (Spoto et al., 2021). The most effective antiepileptic drugs to treat neonatal seizures including BFNS are not well understood. Although neonatal seizure happens to approximately 3 out of every 1000 newborns (Panayiotopoulos, 2005), there are not many drugs approved to conduct the necessary clinical research on neonates (Spoto et al., 2021). This is most likely due to ethical and safety concerns in performing scientific research on newborns. Therefore, not much information on the complications and efficacies of neonatal antiepileptic drugs is available for clinicians to practice.

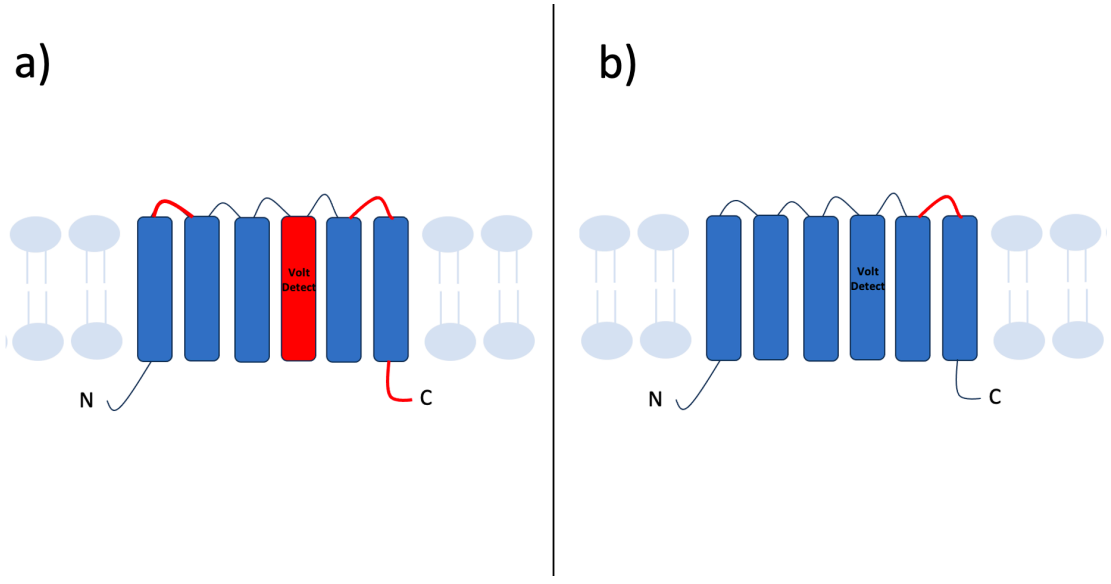

Figure 2: Sites for mutations on the voltage-gated potassium channel subunit that can lead to benign familial neonatal seizures (a) for 7.2 receptors. (b) for 7.3 receptors.

Once, the pharmacological interventions that can directly target the functions of Kv7 channels were viewed as a promising candidate to effectively treat the patients. As an adjunctive treatment, retigabine was often used for BFNS (Spoto et al., 2021). Its mechanism of action directly interacts with voltage-gated Kv7 channels (Maljevic & Lerche, 2014). Specifically, retigabine opens Kv7.2 and Kv7.3 channels and facilitates the establishment of M-current (Maljevic & Lerche, 2014). It accomplishes this through the interaction at the S5 and S6 segments of the channels, allowing them to be kept at their open states (Maljevic & Lerche, 2014). This drug thus prevents seizures by eliciting M-currents to trigger the hyper-polarizations (Maljevic & Lerche, 2014). Despite being the unique "Kv7 channel opener" (Maljevic & Lerche, 2014), the drug was unfortunately withdrawn from production in 2016 and clinical implementation in 2017 by its manufacturer company, GlaxoSmithKline (Brickel et al., 2020). This decision was made by the company since the drug was not clinically utilized very often (Brickel et al., 2020). The complications involving skin discoloration and optical pigmentation contributed to limiting the clinical use of retigabine (Brickel et al., 2020).

On the other hand, phenobarbital is administered for neonatal seizures, including BFNS (Spoto et al., 2021), as a traditional first-line treatment even though it has about 50% efficacy (Slaughter et al., 2013). Phenobarbital, as a barbiturate, facilitates the transport of chloride ions across the membrane via GABAA receptors, causing hyper-polarizations to suppress electrical excitability in the brain (Nobay & Acquisto, 2023). However, a study ironically discovered that phenobarbital may worsen the occurrence of seizures (Maeda et al., 2014). Maeda et al (18) explained that as there is a small number of potassium-chloride cotransporters present in neonatal brains, there is usually a natural build-up of intracellular chloride ions. Because barbiturates allow the extracellular flow of these chloride ions, they can produce depolarization (Maeda et al., 2014). In other words, this drug can amplify the firing of action potentials, which cause seizures.

Over the last 10 years, levetiracetam has become more commonly utilized as a first-line treatment to intervene in neonatal seizures (Spoto et al., 2021). The increase in clinical use is due to the better pharmacokinetics relative to other drugs (e.g. bioavailability over 95% and faster onset of peak concentrations) (Mruk et al., 2015). Moreover, the drug is useful in that mitigates the release of excitatory neurotransmitters from presynaptic vesicles; its mechanism of action does not involve the change of chloride ion gradient in neurons (Mruk et al., 2015). Thus, unlike phenobarbital, the generation of paradoxical depolarization is not expected in the use of levetiracetam.

Outside of the pharmacological interventions, Maljevic & Lerche (2014) suggested that the advancement of gene therapy could be beneficial as the potential treatment for BFNS. For example, Maljevic & Lerche (2014) described that previous in vivo studies noted the suppression of electrical excitability, after the viral insertion of the light-activated opsin proteins to the animal models. They explained that the stimulated halorhodopsins decreased the level of repetitive action potentials via the increased conductance of chlorine ions (Maljevic & Lerche, 2014). Maljevic & Lerche (2014) also suggested that the Kv7 receptors could be a great target for future studies on the viral interventions for BFNS.

CONCLUSIONS

The autosomal dominant mutations in KCNQ2A and KCNQ3A genes can cause defects in various segments of Kv7.2 and Kv7.3 channels. These mutant channels in the brain membrane lead to BFNS by generating smaller conductance of potassium ions, thereby making the brain membrane more prone to action potential firing. These mutations in Kv channels are known to be the only channels associated with BFNS, yet this could be due to the rare incidence reports that limits the understanding of BFNS. The mutation in the SCN2A gene is associated with the familial neonatal-infantile seizures, which happen in later onset than BFNS. Future research on other types of ion channels or environmental sources may further the knowledge of BFNS to find more optimal therapeutic interventions.

Generally, many drugs that are used for neonatal seizures are found to not be efficacious, due to the paucity of clinical drug research conducted on newborn subjects. Although retigabine was the only drug that directly opened the closed states of Kv7.2 and Kv7.3 receptors for BFNS, it is now discontinued from the market due to its harmful side effects and scarcity in clinical use (Brickel et al., 2020). Nowadays, the first-line therapeutics for BFNS include phenobarbital and levetiracetam. The former drug generates an influx of chloride ions via activation of GABAA receptors, causing hyperpolarization to slow down the repetitive firings. However, as the receptor expressions in neonatal brains are different from those of adult brains, phenobarbital can exacerbate seizures by causing an efflux of chloride ions and hence depolarization. On the other hand, levetiracetam has increasingly been used clinically, as it can prevent seizures by decreasing the discharge of excitatory neurotransmitters into the synaptic cleft. This mechanism of action by levetiracetam is favorable, as it does not involve changing the flow of the chloride ions that may trigger depolarizations, as found in the use of phenobarbital. Interestingly, a study on gene therapy was also recommended by scientists (Maljevic & Lerche, 2014) to discover a novel treatment for BFNS patients. Therefore, further research on both the pathology of BFNS and more effective pharmacological treatments is suggested.

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CONFLICT OF INTERESTS

The author declares no conflict of interest.

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