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Treatment of Grand Mal Epilepsy as a Result of Abnormal Neuron Work in the Brain Using the Ketogenic Diet Method

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Abstract

Background: The nervous system is composed of a complex structure to support its highly organized work. Damage to the working mechanism of nervous systems can exert fatal impacts to the human body. One of the consequences of damage to the mechanism of action potentials is grand mal epilepsy. The purpose of this paper is to determine the structure, function, and mechanism of action of neurons, establish grand mal epilepsy as a result of damage to the working mechanism of neurons, and recognize the ketogenic diet as a non-pharmacological therapy for epilepsy patients. **Methods:** The research method used is descriptive qualitative research. **Results:** Nerve cells generally consist of dendrites for receiving stimuli, cell bodies for transmitting stimuli to the axon, and axons for transmitting stimuli to other nerve cells. Grand mal epilepsy is a nervous system disorder caused by the increased activity of sending electrical waves throughout the brain that can reach up to four times faster than normal. However, grand mal epilepsy patients suffer from an excessive number of seizures that may occur at any time. **Conclusions:** The ketogenic diet method is a high-fat and low-carbohydrate diet method that can reduce electrical activity in the brain. Ketone-containing fats have a stabilizing effect on the central nervous system, contributing to anticonvulsant and antiepileptic effects that may reduce the excessive number of seizures experienced by patients. The application of this diet should be balanced with the provision of additional intake of multivitamins, minerals, and fiber to balance the nutrients the body needs.

Keywords: brain; epilepsy; grand mal seizures; ketogenic diet; neuron

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Introduction

The nervous system is one of the most complex systems in the human body. This system is a coordination center for all the other systems within the human body. The nervous system works together with the hormone system to control every regulation and metabolism that occurs in the body (Murdock, 2016). The systematic and complex mechanism of the nervous system is a sign that the nervous system is designed to do complex work.

God has designed the nervous system to work in a specific and orderly manner. The regular work includes conveying information through sufficient stimuli for the brain to be able to determine the type and level of the response given to these stimuli. The transmission of this information generally occurs rapidly and corresponds to the basal excitability of neurons (the ability of neurons to respond to a minimum stimulus) in the brain. The transmission of information from one neuron to another occurs by sending substances called neurotransmitters that occur at the junction of one neuron to another (Michael-Titus, Revest & Shortland, 2007; Campbell et al., 2012).

In the nervous system, damage may occur in the form of excessive, sudden and repeated electrical discharges that cause the nerves to work abnormally, resulting in epilepsy. Epilepsy is a brain function disorder characterized by spontaneous and periodic seizures accompanied by loss of consciousness of the patient due to excessive and paroxysmal electrical discharge of brain neurons (Harsono, Kustiowati, & Gunadharma, 2015; Kristanto, 2017). Epilepsy occurs when the basal value of nervous system excitability exceeds the critical threshold value, causing patients to suffer (Guyton & Hall, 2016).

Epilepsy is classified as partial seizures or generalized seizures according to the location of the seizure. The occurrence of generalized seizures occupies a wider area of the brain, hence causing a more serious effect. One of the most common generalized seizures is grand mal epilepsy. The prevalence rate of patients with grand mal epilepsy ranges from 250,000 per year wherein infants and children it is quite high, in adults it is rare, and in the elderly it is quite high (Harsono, 2011).

The Indonesian Epilepsy Foundation stated that on a global scale, a significant number of people suffer from epilepsy. In 2016, the number of global citizens with epilepsy reached 60 million people, including 1.1-1.8 million Indonesians (Nurul, 2016). One of the most recent epilepsy cases was reported by Kristanto (2017), namely a case of grand mal (tonic-clonic) epilepsy that occurred in Denpasar, Bali. So far, there is no drug that can completely cure epilepsy. Currently available drugs are only capable of reducing the symptoms of epilepsy, such as muscle cramps and convulsions.

One of the non-pharmacological therapies that can be given to epilepsy patients is the ketogenic diet. The ketogenic diet is a special diet high in fat and low in carbohydrates that may help control seizures in several epilepsy patients (Wisnu, Berawi, & Wahyudo, 2017). If maintained, the ketogenic diet method can help normalize brain activity, including electrical activity in the brain. The advantages of this method include a decrease in the frequency of seizures as well as a reduction in the consumption of drugs and surgery (Raju, et al., 2011). People with epilepsy are highly recommended to consume more fat than carbohydrates because it can treat neurodegenerative disorders (Alharbi & Al-Sowayan, 2020).

Methods

The research method used is descriptive qualitative research based on a literature review. This research method was chosen to gain insight and achieve a better understanding of a health-related phenomenon (Kim, Sefcik & Bradway, 2017). The purpose of this literature review is to: 1) determine the structure, function, and mechanism of action of human neurons, 2) disturbances in the working mechanism of neurons that cause grand mal epilepsy, and 3) find out how to treat grand mal epilepsy using the ketogenic diet method.

Result

Structure, Function, and Mechanism of Action of Neurons

Neurons, also called nerve cells, are the most basic part of the nervous system that function as signal transmitters by utilizing electrical charges across the plasma membrane (Reece, Urry, Cain, Wasserman, Minorsky, Jackson, 2014). There are three types of neurons that have different shapes and functions. These neurons include: 1) sensory neurons, 2) motor neurons, and 3) interneurons (Figure 1).

Sensory neurons or afferent neurons are neuron cells that carry stimuli from the organ receiving stimuli to the central nervous system (CNS) that consists of the brain and spinal cord. Motor neurons or efferent neurons are neuron cells that carry stimuli from the CNS to effectors such as muscles and glands. Interneurons or association neurons are a type of cell in the CNS that create local connections and connect sensory nerve cells and motor nerve cells (Raven et al., 2011).

Each nerve cell has at least 3 important parts, namely: 1) dendrites, 2) the cell body, and 3) the axon (Figure 2). Dendrites are the recipients of information from other nerve cells and are in charge of delivering signals to the cell body. The cell body is where most of the nerve cell organelles are located, and are hence responsible for transmitting signals to the axon. Another function of the cell body is to produce neurotransmitters, chemicals that are stored in secretory vesicles at the end of the axon (Kiernan & Rajakumar, 2014). Axons function to transmit signals out of the cell body to other nerve cells and transmit responses to receptors (Reece et al, 2014).

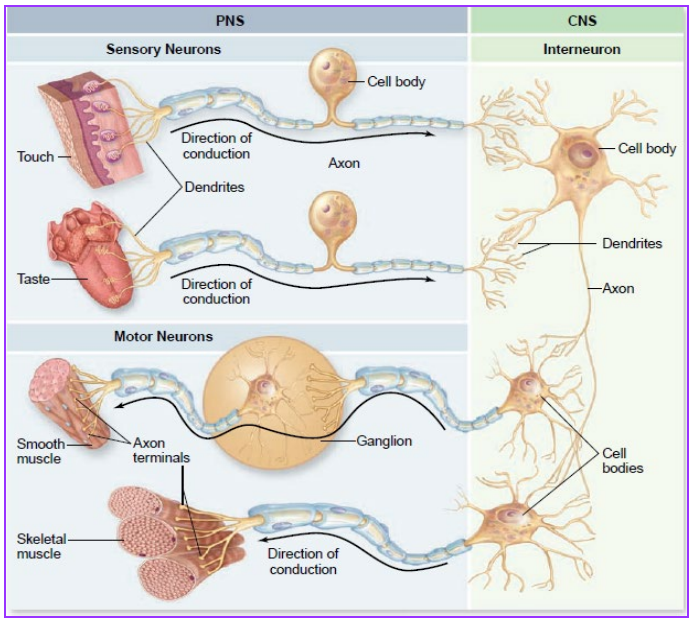

Figure 1. Types of neurons (Raven et al, 2011 p. 888)

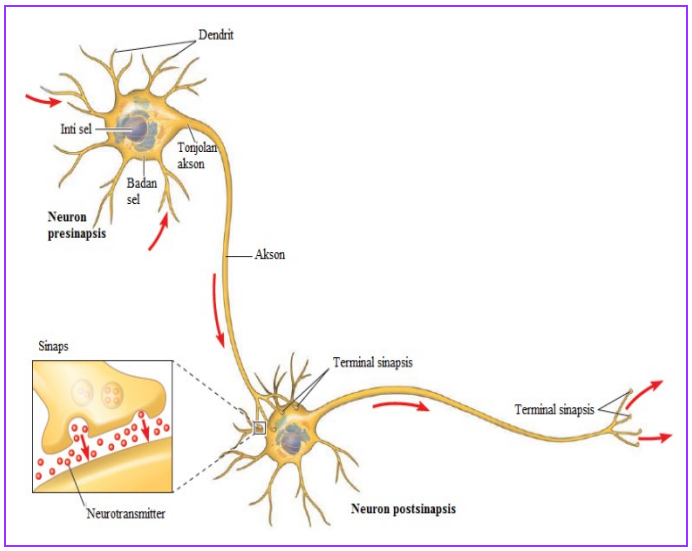

Figure 2. Structure of neurons (Reece et al, 2014 p. 1062)

The mechanism for conducting electrical impulses that occur in the brain is as follows (Reece, 2014): 1) dendrites receive stimuli from previous nerve cell receptors so that there is a potential change in the nerve cell membrane, 2) the stimulus is transmitted to the cell body, 3) action potentials are generated at the axon ridges and transmitted along the axons, 4) impulses are transmitted to other nerve cells via synapses (Figure 2).

The activity of conducting impulses in the form of electricity occurs continuously in the human brain. If the activity of the neurons in the brain is disturbed, the body's coordination will also be disrupted (Fransiscan Health, 2018a). One of the neurological disorders that

can occur in the human body is epilepsy. Epilepsy is a disorder characterized by chronic, recurrent, and paroxysmal changes in neurological function due to abnormalities in the electrical activity of the brain (Noradina, 2016).

Structure, Function, and Mechanism of Neuron Action in Grand Mal Epilepsy Patients

In general, there is no difference between the structure and function of neurons in normal people and patients with grand mal epilepsy. The difference between the two lies in the working mechanism of the brain in generating and transmitting electrical stimuli. Neurons in the brains of people who do not suffer from grand mal epilepsy must work according to the body's needs in order to respond to stimuli.

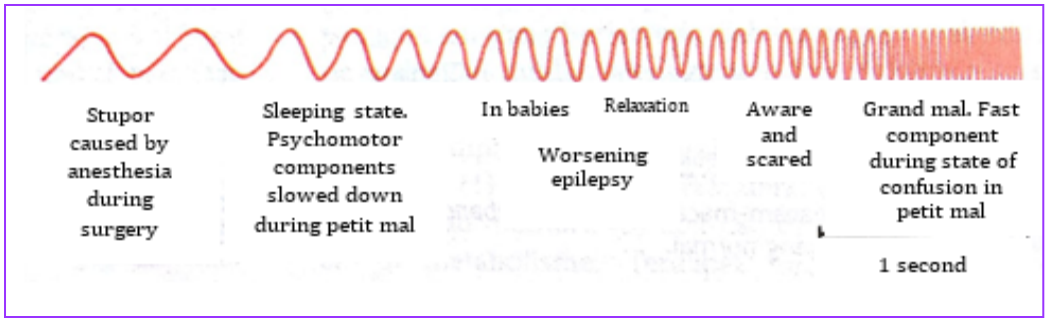

Figure 3. EEG results of human brain waves under various conditions (Guyton & Hall, 2016 p. 721)

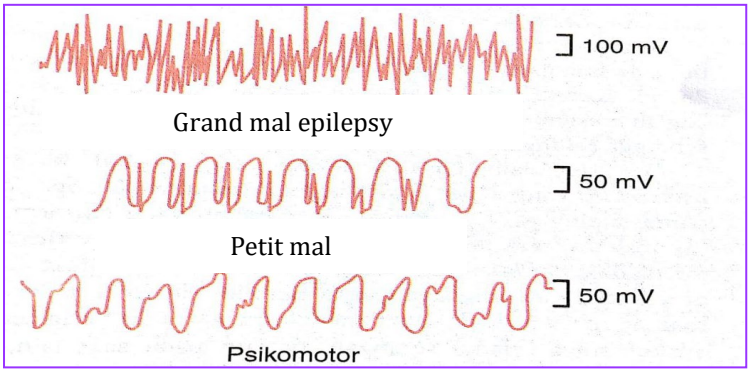

Figure 4. EEG results of human brain waves with epilepsy (Guyton & Hall, 2016 p. 721)

Neurons in the brains of people with grand mal epilepsy release excessive electrical charges from neurons in all areas of the brain in the cerebral cortex, in the interior of the cerebrum, and even in the brainstem. Increased electrical discharge activity in people with epilepsy can reach four times more than normal. The difference in electrical activity of the brain can be measured to detect abnormalities in the brain using an electroencephalogram (EEG). (Figure 3 & Figure 4)

The mechanism of action of neurons in patients with grand mal epilepsy is caused by an imbalance between excitation and inhibition, resulting in hyperexcitability that causes seizures. Internally, there is a mutation or abnormality in the electrolyte channels of neuron cells. Some known mutations are Na+, Ca2+, and K+ channel mutations. This mutation causes the continuous entry of Na+ and Ca2+ into cells, resulting in a paroxysmal depolarization shift (PDS) (Anindhita, 2017).

The hyperexcitability of one neuron cell will affect the surrounding neuron cells. A group of neurons that trigger abnormal activity simultaneously is known as hypersynchrony. When one neuron is activated, the surrounding neuron cells will also be activated. If the surrounding neuron cells are activated at the same time, a large excitation potential will be formed and cause clinical symptoms. The spread of hypersynchronous

PDS throughout the ictal and interictal hemispheres depends on the activity of interneurons in the thalamus, which are mostly inhibitory (Kristanto, 2017).

Discussion

Causes and Types of Epilepsy

Epilepsy, also called seizure, is a nerve disorder that causes patients to experience repeated seizures at any time (Tigerholm, 2012). Epilepsy is characterized by uncontrolled excessive activity of part of or all of the central nervous system (Guyton & Hall, 2016). Epilepsy occurs when overactive nerve cells send out strong and fast electrical charges that interfere with normal brain function. During a seizure, brain cells can fire up to four times their normal level of electricity and affect how a person behaves, moves, thinks, or feels (Camfield & Fisher, 2008). Based on the explanation above, epilepsy is a disorder of the brain that causes seizures due to excessive activity of sending electrical waves in the brain that can occur at any time.

According to Engel, Birbeck, Diop, Jain, & Palmini (2005), there are three factors that can cause a person to suffer from epilepsy, namely (1) individual brain susceptibility to produce seizures in response to epileptogenic disorders, (2) specific epileptogenic disorders, which could be an acquired brain injury or genetic disorder, (3) the precipitating event that causes a seizure occurs at a specific point in time. These factors are predisposing factors (biological, psychological and social cultural factors). People who have predisposing factors for epilepsy will have an attack if the basal value of nervous system excitability exceeds the critical threshold value. As long as the excitability level is kept below the threshold value, epileptic seizures will not occur (Guyton & Hall, 2016). In addition, there are several other factors that cause this epilepsy, including abnormal brain development, brain injury due to loss of consciousness, infection of the brain, high fever in children under 5 years old, heredity (genetic), loss of oxygen to the brain, stroke, brain lesions or tumors, toxic materials, and other unknown causes (Camfield & Fisher, 2008).

There are 3 stages of symptoms that arise in epilepsy patients, namely (1) pre-ictal, otherwise known as the period of time before the seizure, (2) ictal, which is the when the seizure activity actually occurs, and, (3) post-ictal, which is the period of time after the seizure. During ictal, patients may behave or act differently. Patients may be confused, do not know their names or where they are and may need time to rest and sleep. Additionally, symptoms that appear in the post-ictal stage are headache, numbness or tingling in certain body parts, confusion, muscle aches, unusual sensations (tastes, smells, etc.), extreme tiredness, bowel control (stools) or a weakened bladder (urine) (Schachter, 2006).

Epilepsy can be divided into three main groups: 1) grand mal epilepsy, 2) petit mal epilepsy, and 3) focal epilepsy. This literature review paper will focus on discussing grand mal epilepsy as it is the most serious type of epileptic seizure (Fransiscan Health, 2018b).

Grand Mal Epilepsy Causes and Symptoms

The cause of the onset of overactivity in neurons during a grand mal attack is due to the massive and simultaneous activation of a large number of intertwined neurons throughout the brain. The main factor thought to stop attacks after a few minutes is neuronal exhaustion. The second factor is active inhibition by inhibitory neurons that are activated by previous attacks (Guyton & Hall, 2016).

Patients who experience grand mal attacks generally have a hereditary predisposing factor for epilepsy which exists in every 1 in 50 to 100 patients. In such patients, factors that can increase the excitability of the abnormal "epileptogenic" circuit sufficient to induce an attack include (Guyton & Hall, 2016): 1) intense emotional arousal, 2) alkalosis due to excessive breathing, 3) medication medication, 4) fever, 5) noise or blinding light.

A grand mal seizure usually lasts one to four minutes, starting with stiffness of the limbs, followed by jerking of the face and limbs. Wetting or soiling of clothing can also occur as a result of the seizure (Schachter, 2006). In addition, the symptoms that appear include seizures characterized by a state of post-seizure depression throughout the nerves.

Patients remain in a stuporous state (deep asleep, but there is a response to pain) for one to several minutes after the seizure ends and then often remain tired and sleep for hours afterward (Guyton & Hall, 2016). It is possible that these grand mal attacks are not only caused by abnormal activation of the thalamus and cerebral cortex but also by abnormal activation of the brain's own activation system located below the thalamus.

Prior to the attack, the patient usually feels symptoms of dizziness or irritation. The seizure begins with an epileptic cry. The patient then loses consciousness and falls. In the initial phase, namely the tonic phase, generalized muscle spasm occurs and lasts a few seconds. During the next phase, the clonic phase, there are repeated sharp muscle jerks such as tongue bites, salivation and urinary incontinence. When the muscle twitching stops, the patient remains unconscious for about 30 minutes and then feels confused and drowsy for several hours. Towards the end of the attack, alternating tonic and spasmodic muscle contractions (muscle cramps) referred to as tonic-clonic spasms occur. Often, the patients bite their tongue and may experience difficulty in breathing, which sometimes causes cyanosis (lack of oxygen in the blood). Moreover, signals that are transmitted from the brain to the viscera (organs in the chest and abdominal cavities) often lead to the process of micturition (spontaneous expulsion of urine) and defecation (excretion of food waste in the form of feces) (Guyton & Hall, 2016). While recovering electrical waves in the brain, patients usually suffer from headaches and stiffness or injury from a fall. Frequent complaints of back pain and muscle spasms so hard that they cause vertebral fractures have also been noted. This type of epilepsy can usually be controlled with a single drug (Ginsberg, 2008).

The Ketogenic Diet Method

The term ketogenic diet or ketogenic diet therapy (KDT) refers to dietary therapy with a food composition that produces a ketogenic state of human metabolism (Roehl & Sewak, 2017). The classic ketogenic diet is high in fat (90% of total calories), low in carbohydrates (2-4% of total calories), and moderate in protein. As a result, the production of ketones in the body is expected to increase through fat metabolism with the aim of mimicking a fasting state in body tissues to shift the main source of calories from carbohydrates to fat (Williams & Cervenka, 2017; Cervenka & Kossoff, 2013; McNally & Hartman, 2012).

According to Elger & Schmidt (2008), the ketogenic diet is a non-pharmacological therapy to control the excessive number of seizures. This diet will cause a state of ketosis as it produces ketones which function to reduce the frequency of epileptic seizures. Low levels of carbohydrates cause the body to use fat as the main energy source. As a result of reducing carbohydrate consumption, the central nervous system is forced to find alternative energy sources that are obtained from the overproduction of acetyl coenzyme A (CoA). This condition causes the production of ketone bodies by the liver to be above the standard (Wishnu, Berawi, & Wahyudo, 2017).

Ketogenesis or production of ketone bodies (KB) occurs in the liver, where fatty acid-derived-acetyl-CoA is transported to extrahepatic tissues for terminal oxidation. These KBs are involved in various important metabolic pathways such as acid oxidation (FAO), gluconeogenesis, tricarboxylic acid (TCA) cycle, de novo lipogenesis, and sterol biosynthesis. This metabolic mechanism provides an alternative energy source, especially under a fasting state, where the availability of carbohydrates is limited while the availability of fatty acids is increased, therefore serving as the main energy source. The ketone body-hydroxybutyrate (BHB) in particular, has traditionally been considered an alternative source of energy supply and metabolism in humans by providing a significant fuel source for the brain in a carbohydrate-restricted state. Brain cells are capable of producing energy from glucose and ketones and are therefore considered metabolically flexible. During periods of very low carbohydrate intake, BHB is a major source of energy for neurons (Wells, Swaminathan, Paseka, & Hanson, 2020).

The Ketogenic Diet Method in Treating Grand Mal Epilepsy

Treatment of seizures with diet therapy was carried out in the days of Hippocrates who stated that it was necessary to return the body to its original state by fasting (Cervenka & Kossoff, 2013). The state of the body that is fasting can be imitated by applying the ketogenic diet method. The ketogenic diet is a high-fat, low-carbohydrate diet. In this diet method, fat acts as the main energy source. In principle, fat contains ketones which have a stabilizing effect on the central nervous system (CNS) (Neal, Chaffe, Schwartz, Lawson, Edwards, Fitzsimmons, Cross, 2008).

Previous studies reported that the exact mechanism of the ketogenic diet is unknown, but ketone bodies have been hypothesized to contribute to its anticonvulsant and antiepileptic effects (McDaniel, Rensing, Thio, Yamada, & Wong, 2011; McNally & Hartman, 2012; Zengin et al., 2015). The results of recent studies have proven the previous hypothesis correct, for this diet will create a state of ketosis that can reduce the frequency of epileptic seizures in several ways, namely: (1) anticonvulsive effects of ketone bodies, (2) decreased excitability of neurons by ketone bodies, and (3) effects on the mammalian target of rapamycin (mTOR) pathway (Wisnu, Berawi, & Wahyudo, 2017).

The effectiveness of the ketogenic diet in treating grand mal epilepsy has been tested. Raju, et al., (2011) stated that 26% of epileptic patients who had been on the ketogenic diet did not experience seizures while 58% of patients experienced a decrease in the frequency of seizures by more than 50% after undergoing the 4:1 ketogenic diet for 3 months. On the other hand, Seo (2007) stated that 55% of patients were seizure-free while 85% of patients experienced a decrease in seizures exceeding 50% after maintaining a ketogenic diet for 3 months as well (Seo, Lee, Lee, Kang, & Kim, et al. 2007). Liu, et al., (2018) also reported that the outcomes of the ketogenic diet were seizure freedom, seizure reduction by 50% or more, and seizure reduction <50%.

Unfortunately, the ketogenic diet followed by patients with grand mal epilepsy also has weaknesses in its implementation. The main drawback of the ketogenic diet is the emergence of various gastrointestinal side effects and the difficulty of consuming the diet due to the unappetizing taste. The most common gastrointestinal side effects are nausea, vomiting, constipation, and diarrhea (Raju et al., 2011). The application of the ketogenic diet method must be balanced with the consumption of multivitamins, minerals, and fiber so that the body's micronutrient needs are still met. If this dietary method is applied while ignoring the fulfillment of other nutrients, then patients will experience negative impacts on the body such as gastrointestinal problems in the form of nausea, vomiting, constipation, and diarrhea (Wisnu, Berawi, & Wahyudo, 2017).

Conclusions

The general structure of a neuron is the dendrites, cell body, and axon. The mechanism of action potentials is that the dendrites receive stimulation from the receptor then the receptor is forwarded to the cell body so that the action potential is generated by the axon ridge/hill, then the stimulus is transmitted along the axon to be passed on to other nerve cells. Disorders of the mechanism of action potentials that occur in the brain can cause grand mal epilepsy. Neurons in the brains of people with grand mal epilepsy release excessive electrical charges from neurons in all areas of the brain in the cerebral cortex, in the interior of the cerebrum, and even in the brainstem. Increased electrical discharge activity in people with epilepsy can reach four times than normal. Grand mal seizures typically last four minutes and cause symptoms such as loss of consciousness and muscle spasms or cramps. The ketogenic diet method can be used as non-pharmacological therapy for grand mal epilepsy patients. The ketogenic diet method which is high in fats but low in carbohydrates have a stabilizing effect on the central nervous system and is known to exert anticonvulsant and antiepileptic effects. However, patients must ensure that their diet is balanced with enough multivitamins, minerals, and fiber to meet the body's micronutrient needs and avoid negative gastrointestinal effects.

Declaration Statement

The authors reported no potential conflict of interest.

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