Influence Blocking by Gadolinium in Calcium Diffusion on Synapse Model: A Monte Carlo Simulation Study

Sutresno A.[1]*, Haryanto F.[1], Viridi S.[1], Arif I.[1]

[1]PhD, Nuclear Physics and Biophysics Research Division, Faculty of Mathematics and Natural Sciences, Institute Teknologi Bandung Jl. Ganesha 10 Bandung 40132, Indonesia

ABSTRACT

Background: Gadolinium (Gd^{3+}) is a chemical element belonging to the lanthanide group and commonly used in magnetic resonance imaging (MRI) as a contrast agent. However, recently, gadolinium has been reported deposition in the body after a patient receives multiple injections. Gadolinium is a potent block and competes with calcium diffusion into the presynaptic. There has not been a precise mechanism of gadolinium blocking calcium channel as a channel of calcium diffusion to presynaptic until now.

Objective: This study aims to investigate the mechanism of calcium influx model and the effect of neurotransmitter release to the synaptic cleft influenced by the presence of Gd^{3+}.

Material and Methods: Monte Carlo Cell simulation was used to analyze simulation and also Blender was used to create and visualize the model for synapse. The synapse modeled by a form resembling the actual synapse base on a spherical shape.

Results: The presence of gadolinium around the presynaptic has been disturbing diffusion of calcium influx presynaptic. The result shows that the presence of gadolinium around the presynaptic has caused a decrease in the amount of calcium influx presynaptic. These factors contribute to reducing the establishment of the active membrane, then the amount of synaptic vesicle docking and finally the amount of released neurotransmitter.

Conclusion: Gadolinium and calcium compete with each other across of calcium channel. The presence of gadolinium has caused a chain effect for signal transmission at the chemical synapse, reducing the amount of active membrane, synaptic vesicle docking, and releasing neurotransmitter.

Citation: Sutresno A, Haryanto F, Viridi S, Arif I. Influence Blocking by Gadolinium in Calcium Diffusion on Synapse Model: A Monte Carlo Simulation Study. *J Biomed Phys Eng*. 2020;10(3):251-260. doi: 10.31661/jbpe.v0i0.1155.

Keywords

Monte Carlo Cell; Synapses; Diffusion; Contrast Agents; Gadolinium Blocking; Gadolinium

Introduction

Gadolinium (Gd^{3+}) is a chemical substance belonging to the lanthanide group used in magnetic resonance imaging (MRI) as a contrast agent. The first gadolinium approved as contrast agent appeared in 1988 [1,2]. The reason for using gadolinium as a contrast agent is the quality enhancement of an image of MRI. It typically makes diseased tissue appear brighter than the surrounding tissue. The characteristic of free gadolinium is extremely toxic and can cause central lobular necrosis of the liver, enzyme inhibition, a variety of hematologi-

*Corresponding author:
A. Sutresno
Department of Physics, Faculty of Mathematics and Natural Sciences, Institut Teknologi Bandung, Jalan Ganesa 10, Bandung, West Java, 40132, Indonesia
E-mail: adita1204@gmail.com

Received: 8 April 2019
Accepted: 25 April 2019

cal abnormalities [3], nephrogenic systemic fibrosis (NSF) [4,5] and many of the voltage calcium channel blocking [3,6,7]. Recently, Kanda, T. et al. and Barbieri, S. et al. found that gadolinium accumulates in the brain especially in dentate nuclei and globus pallidus and makes high signal intensity have an effect on unenhanced T1-weighted MR images after multiple injections of gadolinium [8-10].

The presence of gadolinium in the body needs to be alerted because it is a foreign material inserted into the body. Gadolinium has potent to block and competes with Calcium (Ca^{2+}) in the body, especially influx to calcium channel [6,11]. Disturbance of the Calcium diffusion can affect the release of neurotransmitters from presynaptic to postsynaptic through the synaptic cleft. Physically, Gadolinium has a similar crystallographic radius as Calcium to be exactly radius Gd^{3+} (0.94 Å) and radius of Ca^{2+} (0.99 Å) [11].

The mechanism of Ca^{2+} diffusion influx to the presynaptic as the signal transmission at chemical synapses initiated when a potential action invades into presynaptic. The action potential causes the opening of voltage-gated calcium channels in the presynaptic membrane. The opening of these channels causes a rapid influx of Ca^{2+} into the presynaptic terminal because the concentration of Ca^{2+} inside the presynaptic is lower than outside the presynaptic. The existence of Ca^{2+} triggers synaptic vesicle exocytosis, thereby releasing the neurotransmitters contained in the vesicles and initiating synaptic transmission to the synaptic cleft and postsynaptic [12,13].

The magnitude of the potential action at the presynaptic affects the average number of open calcium channels that proportionally affect the amount of Ca^{2+} influx to the presynaptic. With the reduced presynaptic Ca^{2+} influx, the probability of synaptic vesicle fusion also reduced that it results in less neurotransmitter release each presynaptic action potential [14]. The reduction of neurotransmitters means disruption of chemical transmission from one neuron to the next neuron. One of the causes of the reduced number of Ca^{2+} influx into presynaptic is the presence of Gd^{3+} in the vicinity of calcium channel, which Gd^{3+} is blocking of calcium channel.

This research is an investigated mechanism model of Ca^{2+} influx influenced by the presence of Gd^{3+}. The simulation is carried out using Monte Carlo method which capable of giving all the probabilities of ion interaction as Ca^{2+}, Gd^{3+}, synaptic vesicle, and ions calcium channel, ion membrane, active membrane, and neurotransmitter. The model simulation also shows the effect of the number of Gd^{3+} and calcium channel density on the speed of calcium channel blocking, duration Ca^{2+} in presynaptic and how much synaptic vesicle can release into the synaptic cleft.

Material and Methods

Monte Carlo Cell simulations were carried out using MCell 3.1 (www.mcell.org) [15,16] running on a Lenovo ThinkPad 2.2. GHz Intel Core i7 (Ubuntu 14.10). Visualization of the synapse consisting of presynaptic, postsynaptic, and boundary of the synapse was made from the output of MCell using blender 2.69, which add-on with Cell-blender.

a. Model Synapse

Figure 1 shows the synapse model representing a presynaptic and postsynaptic with Ca^{2+} and Gd^{3+} around presynaptic. Ca^{2+} and Gd^{3+} diffusions are translated from outside to inside presynaptic through calcium channel because both have radius ion size similar. Gd^{3+} cannot diffuse presynaptic influx as a blocker for Ca^{2+} and the presence of Gd^{3+} has disturbed presynaptic Ca^{2+} diffusion influx.

The synapse design with blender 2.69 consists of three parts, a presynaptic at the top, a postsynaptic at the bottom which in the middle; there are synaptic cleft and boundary as a frame of the synapse. The presynaptic has volume 0.20 μm^3 and surface area 1.85 μm^2, and the postsynaptic has volume 0.21 μm^3

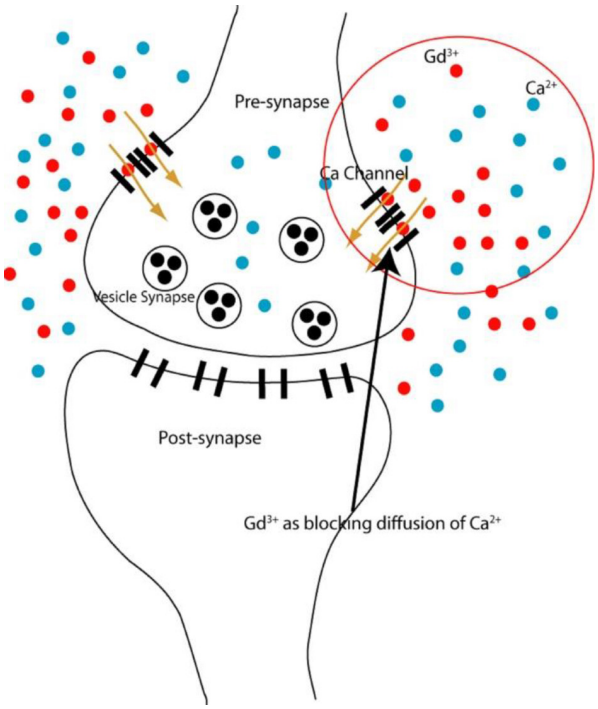

Figure 1: The model of synapse consisting of a presynaptic and a postsynaptic with calcium channel base on Neuroscience [13,17].

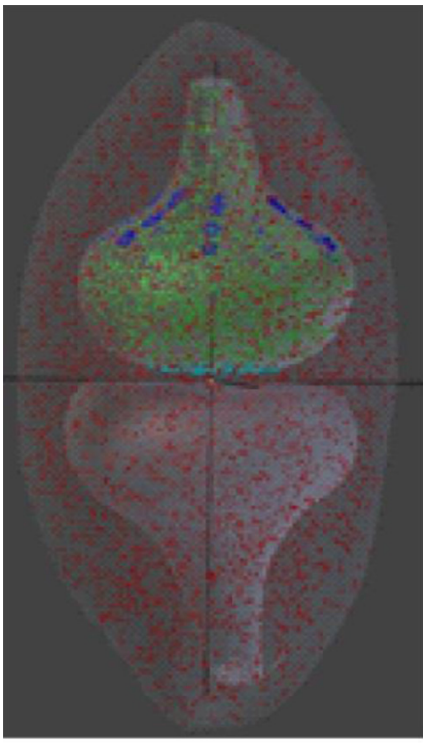

Figure 2: Synapse design use blender 2.69.

and surface area 2.07 μm^2.There are 23 calcium channels on the presynaptic with density 10^{-4}μm^2 and membrane-active with a function to release neurotransmitter at the bottom surface. The number of calcium channels represents an average open calcium channel for each potential action. Figure 2 displays the visual result of synapse design. Each ion has a different color to distinguish each other.

b. Kinematic Schemes

This study used four reaction models to describe the mechanism of Ca^{2+} diffusion from outside presynaptic to neurotransmitter release in the synaptic cleft and that reaction expressed:

$$A + b_1 \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} b_1 + A'$$

$$D + b_1 \xrightarrow{k_2} E$$

$$A' + b_2 \xrightarrow{k_3} b_2 + b_3$$

$$B + b_3 \xrightarrow{k_4} C$$

The first reaction was Ca^{2+} diffusion that presented outside of presynaptic (A) into the presynaptic (A') through the calcium channel (b_1) with the reversible process. The second reaction, Gd^{3+} (D) and calcium channel as a reactant, produced a product (E) that works as blocking in calcium channel [18]. The next response was the outcome of the first reaction that Ca^{2+} in presynaptic and membrane at the bottom of presynaptic (b_2) produced an active layer (b_3) to synaptic vesicle docking. The last response was synaptic vesicle (B), and active membrane as reactant generated a neurotransmitter (C) released to the synaptic cleft. Simulations were carried out using a set of standard parameter values in Table 1.

c. Diffusion

The diffusion of calcium, gadolinium, synaptic vesicle, and neurotransmitter can be

Table 1: The standard value of parameters used in this simulation.

Parameter	Standard Value
Forward rate k_1	1 x 10^8 $M^{-1}s^{-1}$
Backward rate k_{-1}	1 x 10^7 s^{-1}
Forward rate k_2	1 x10^8 $M^{-1}s^{-1}$
Forward rate k_3	1 x 10^7 $M^{-1}s^{-1}$
Forward rate k_4	1 x 10^7 $M^{-1}s^{-1}$
Diffusion coefficient Ca^{2+} outside presynaptic	6 x 10^{-6} cm^2 s^{-1} [15,17]
Diffusion coefficient Ca^{2+} inside presynaptic	6 x 10^{-6} cm^2 s^{-1}
Diffusion coefficient Gd^{3+}	1 x 10^{-6} cm^2 s^{-1}
Diffusion coefficient ion membrane b_1,b_2, b_3	0 cm^2 s^{-1}
Diffusion coefficient Synaptic Vesicle	1.2 x 10^{-6} cm^2 s^{-1}
Diffusion coefficient Neurotransmitter	1 x 10^{-6} cm^2 s^{-1}
Calcium channel density	10^{-4} μm² [19]

described mathematically using a Fick's first law, obtain:

$$J_r = -D\frac{\partial C}{\partial r} \qquad (1)$$

The Fick's first law has a relation with the diffusive flux to the concentration in steady states condition. The flux goes from high to low level, with a magnitude that is proportional to the slope of the concentration function and the constant of proportionality is $-D$. The negative sign indicates the particle concentration will decrease as a function of position, whereas the diffusion coefficient D depends on the diffused particle and the medium it passed [20]. The presynaptic model is built using a spherical base form and considers a spherical absorber of radius one in the medium. Every ion reached the surface of the spherical and absorbed the concentration at the spherical surface was 0, and infinity level was C_0. With these boundary conditions with spherical symmetry has the solution:

$$C(r) = C_0\left(1-\frac{a}{r}\right) \qquad (2)$$

Moreover, the flux is:

$$J_r(r) = -DC_0\frac{a}{r^2} \qquad (3)$$

The net migration of ions through a spherical surface at a rate equal to the area, $4\pi a^2$, time the incoming flux, $-J_r(a)$:

$$I = 4DNsC_0 \qquad (4)$$

Where D is a diffusion coefficient, s is the surface area of a disk, N is the number of discs, C_0 is initial concentration [20,21]. The diffusion current has linear proportional to a total of the disk surface. In terms of the disk number increases, then-current diffusion will decrease and vice versa.

Results

a. Simulation result

Figure 3 is a simulation result of diffusion time dependence on all ions except Gd^{3+} ion from outside presynaptic to clef synaptic. The black line indicates diffusion of Ca^{2+} from outside to inside presynaptic through the calcium

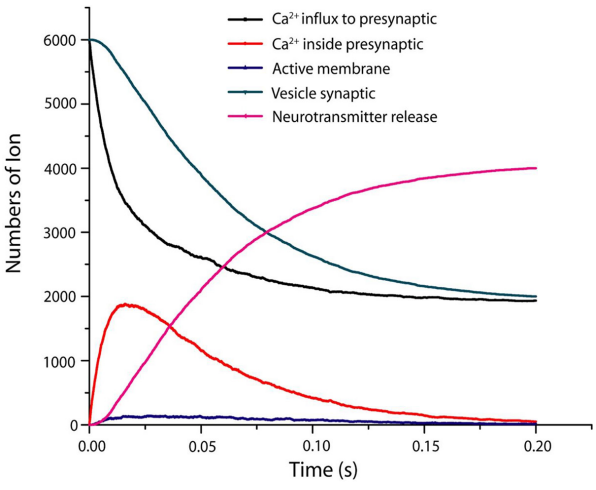

Figure 3: Time dependence of Ca^{2+} diffusion at all part of the synapse. The standard parameters (Table 1) used in this simulation.

channel on the presynaptic surface without blocking of Gd^{3+}. Ca^{2+} in the presynaptic (red line) has two phases, absorption and elimination phase. The absorption phase is from zero to a maximum number of ions, and the elimination phase is from maximum declination to a minimum amount of an ion. During Ca^{2+} diffusion influx presynaptic, Ca^{2+} inside of presynaptic is interacting with ion membrane at the bottom to produce active layer (dark blue line) as docking of a synaptic vesicle (light blue) to release neurotransmitter (pink line) to the synaptic cleft.

b. Diffusion of Ca^{2+} Influx Presynaptic

The presence and absence of Gd^{3+} in presynaptic gives a considerable influence on the Ca^{2+} diffusion process. Ca^{2+} can quickly diffuse influx to presynaptic without Gd^{3+}. On the other hand, the presence of Gd^{3+} impairs diffusion process of Ca^{2+} depending on the number of Gd^{3+} outside presynaptic.

Figure 4 shows the Ca^{2+} diffusion into the presynaptic by varying number of Gd^{3+} at outside presynaptic. The Colour lines show the different ratio between Ca^{2+} and Gd^{3+}, black, red, dark blue, light blue, and pink are 6:0, 6:1, 6:2, 6:4, 6:6, respectively. The black line indicates diffusion of Ca^{2+}, which drops off and then declines gradually and reaches a steady state. More importantly, the black line shows the diffusion of Ca^{2+} with the absence of Gd^{3+} has a half-life ($t_{0.5}$) at 0.028 s. In comparison, the red line as Ca^{2+} diffusion with the presence of Gd^{3+}, which shows the number of Gd^{3+} is one-sixth of Ca^{2+}; time duration declines shorter than the previous result. However, a $t_{0.5}$ of Ca^{2+} is longer than the last result at 0.053 s. Then again, the ratio 6:2, 6:4, and 6:6 lead the number of Ca^{2+} of the total Ca^{2+} diffusion to be 36%, 20%, 13% and that happen at 0.056 s, 0.028 s, and 0.016 s, respectively.

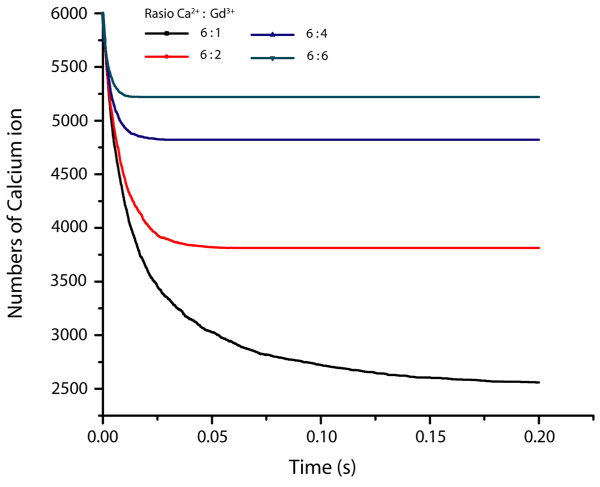

Figure 4: Time dependence of diffusion result of Ca^{2+} from outside to inside presynaptic with different number of Gd^{3+}.

Moreover, with increasing Gd^{3+} ratio, the number of Ca^{2+} influx to presynaptic will decrease and $t_{0.5}$ never achieved, and this happens for a ratio 6:2, 6:4, 6:6, respectively. Hence, the difference in the number of Gd^{3+} has a different effect on the speed of diffusion and the amount of Ca^{2+} diffusion. The Gd^{3+}presence has been competing with Ca^{2+}, which has a significant role in chemical transmission.

c. Blocking of Gd3+

Ca^{2+} and Gd^{3+} are at the same location that is outside of presynaptic. Each ion will surely move randomly and migrate from high to the low concentration; in this case, it will move from outside to the inside of presynaptic. Ca^{2+} migration to the presynaptic through calcium channel happens, while Gd^{3+} will suspend on the surface of calcium channel. Ca^{2+} and Gd^{3+} compete to reach on the calcium channel surface. However, the presence of Gd^{3+} on the calcium channel surface becomes an impair Ca^{2+} diffusion, and the amount of Gd^{3+} will affect the speed block of calcium channel.

At t = 0.200 s, the Gd^{3+} blocks all calcium channels surface that amounts of Ca^{2+} and Gd^{3+} were as ratio 6:1. Similarly, Gd^{3+} totally blocks calcium channel with variety amount of Gd^{3+}, t = 0.060 s, 0.284 s, and 0.019 s with ratio 6:2, 6:4, 6:6, respectively, Figure 5. At initial state to 40% blocked, the speed of blocking calcium

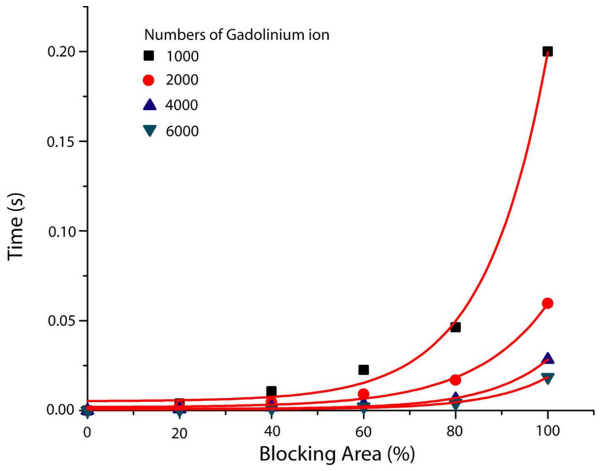

Figure 5: The Gd^{3+} blocking calcium channel at variety ratio Ca^{2+} and Gd^{3+} stepwise 20% blocking.

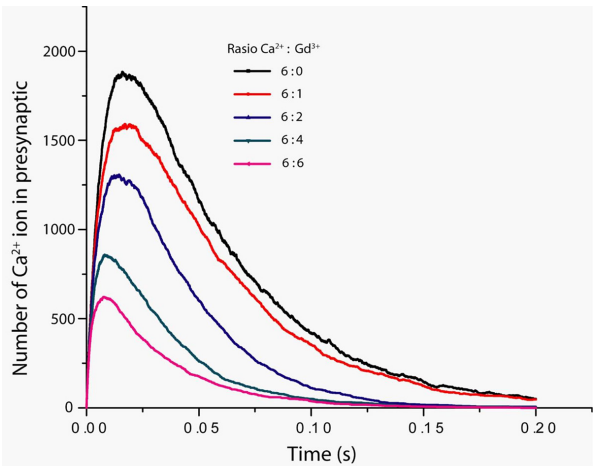

Figure 6: Time-dependent of Ca^{2+} in presynaptic with the variation amount of Gd^{3+}.

channel is linear then follows an exponential function. The fastest blocking is the one with the greatest Gd^{3+}. In terms of the number of Gd^{3+} blocking, the calcium channel is extensive. Besides, the increasing number of Gd^{3+} attached to the calcium channel, the area of the calcium channel reduced so that the Ca^{2+} current will be proportional to the calcium channel extent.

d. The amount, half-life, and Duration of Ca^{2+} in presynaptic

Figure 6 shows the amount of Ca^{2+} present in presynaptic after diffusion from the outside presynaptic. The amount of Ca^{2+} that influx to the presynaptic greatly influenced by the amount of Gd^{3+} present outside the presynaptic. The black line shows an amount of Ca^{2+} in the absence of Gd^{3+} while red, dark blue, light blue, and pink lines indicate Ca^{2+} in presynaptic due to Gd^{3+} with ratio 6:1, 6:2, 6:4, 6:6, respectively. Each line has two phases; the first phase indicates the absorption phase from the initial state to the maximum amount, and the second phase indicates the elimination phase from the maximum amount to the minimum amount. Furthermore, the increasing amount of Gd^{3+} that exists outside presynaptic influences the amount of Ca^{2+} influx to the presynaptic.

The maximum amount of Ca^{2+} diffusing into the presynaptic in the presence of Gd^{3+} is 1592, 1308, 831, and 622 Ca^{2+} ions and it occurs at t = 0.017 s, 0.015 s, 0.013 s, and 0.007 s, respectively. This data shows that the presence of Gd^{3+} has reduced the maximum number of diffused Ca^{2+}. The decreases in the amount of Ca^{2+} caused the total number of Ca^{2+} and diffused reductions of the Area under the Curve (AUC) of the graph.

Then again, the half-life of Ca^{2+} of the highest to the lowest presence of Gd^{3+} in the elimination phase is $t_{0.5}$ = 0.062 s, 0.047 s, 0.038 s, and 0.032 s, respectively. The indicates that a high amount of Ca^{2+} in the presynaptic has a longer half-life of Ca^{2+}. This advantage is the high Ca^{2+} amount in presynaptic which provides an opportunity for the formation of an active membrane for the synaptic vesicle docking.

The duration of Ca^{2+} in the presynaptic is another important factor because the longer Ca^{2+} due to the large amount in the presynaptic means the opportunities of the synaptic vesicle docked in the active membrane increases. The meaning of duration, in this case, is from the

onset time to half-life. Thus, the duration of Ca^{2+} for each presence Gd^{3+} from higher to lower is Δt = 0.059 s, 0.045 s, 0.036 s, and 0.031 s.

e. Calcium Channel Density

To sum up, this interference in the rate-limiting steps supported by a simulation in which the density of calcium channel decreased. The $t_{0.5}$ values plotted as Figure 7 showed and summarised the result of simulation using the different density of calcium channel that is 0.5 to 2 × 10^4 μm^2 stepwise 0.5 × 10^4 μm^2 with the $t_{0.5}$ = 0.0457 s, 0.0068 s, 0.0076 s, and 0.0083 s, respectively.

According to the shape of the curve, a particular moment will experience saturation. Thus, the increase in density after saturation did not change the equilibrium time. With faster the equilibrium time, ion migration time shortened. It has shown that calcium channel density has a vital role in ion migration from higher to lower concentration.

f. Active Membrane

The active membrane is the membrane at the bottom of the presynaptic place for synaptic vesicle docking. It provides a location of the synaptic vesicle to be able to release neurotransmitter. An active layer formed due to the interaction between membrane ions and Ca^{2+}. Figure 8 shows the number of active membranes occurs based on the amount of Ca^{2+} in the presynaptic, where the amount of Ca^{2+} depends on the ration Ca^{2+} and Gd^{3+} in the initial state. The formation of the active membrane is higher, too. Because of the higher amount of Ca^{2+} in the presynaptic, the probability of Ca^{2+} interaction with the membrane ion is higher. It can seen from the simulation result that the color sequence of the black line is the lowest Gd^{3+}. It shows the highest number of the active membrane followed by red, dark blue and light blue lines, respectively.

g. Neurotransmitter Release

Neurotransmitters are stored in a synaptic vesicle. Furthermore, neurotransmitter release is comparable to the amount of synaptic vesicle docking in the active membrane. The active layer is formed due to the role of calcium in the presynaptic. Therefore, Figure 9 shows

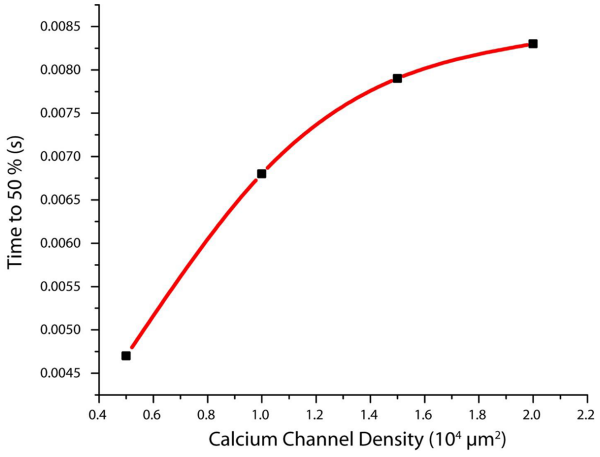

Figure 7: The effect of calcium channel density on surface presynaptic. Parameters are the same as shown in Table 1 except for calcium channel density. Amount of gd^{3+} is equal in 2000.

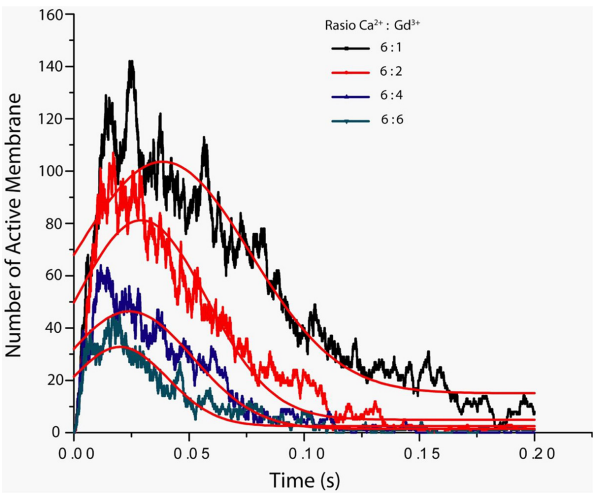

Figure 8: Time dependence of active membrane creates by interaction with calcium in presynaptic

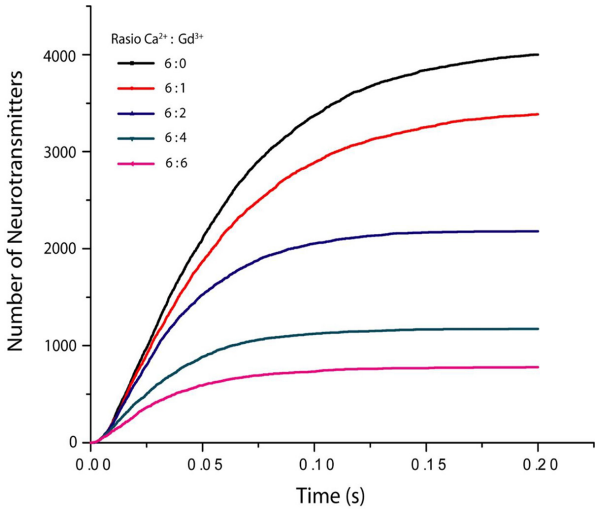

Figure 9: Time dependence of neurotransmitter release to synaptic cleft due to the influence of the number of Gd^{3+}.

the results of neurotransmitter release based on the amount of synaptic vesicle. It can be seen that each color has a different amount of presence Gd^{3+} from the initial state. According to the result, the increase in the amount of Gd^{3+} causes different effects for the amount of synaptic vesicle docking and then releases neurotransmitter into the synaptic cleft. All lines show the same patterns that neurotransmitters released are not abrupt. The length of the time gap depends on the amount of Gd^{3+}in the initial state. The black line shows Gd^{3+} absence with a steep slope. It means the speed of synaptic vesicles to release neurotransmitters is high and saturated in the vast amount. The pink line shows the highest presence Gd^{3+} on the initial state with a gentle slope. It has proved that the degree of the slope indicates the level of Gd^{3+} presence at the initial state. The presence of Gd^{3+} in the presynaptic inhibits the docking process of a synaptic vesicle, causing a slow release of neurotransmitters by synaptic vesicles. Complementary, the first 0.05 second for each ratio Ca^{2+} and G^{3+} from lowest to the highest presence of Gd^{3+} indicates different numbers of neurotransmitters that are 2098, 1868, 1525,884, and 590, respectively.

Discussion

Patients can receive repeated Gd^{3+} injections for diagnostic MRI, and the results show high signal intensity [8, 9]. High signal intensity has indicated that contrast material cannot be all released the patient's body. The presence of Gd^{3+} in the patient's body raises serious problems because Gd^{3+} is toxic and has the potential for blocking calcium channels [6, 11]. The closure of calcium channels by Gd^{3+} can disrupt the signal system in the patient's body.

Calcium is an essential ion in the signal system body, especially in the synapse. The calcium influence the number of neurotransmitters released into the synaptic cleft [22]. The action potential causes the calcium channel to open, and the higher the action potential causes the calcium channel to open to increase. The number of calcium channels strongly influences the amount of calcium that enters the presynaptic.

Gd^{3+} around presynaptic has potential as a barrier to calcium channels, and then calcium cannot diffuse into the presynaptic. Gd^{3+} enters the presynaptic through calcium channel and interact with the wall then it called side binding. Gd^{3+} sticking to the wall of calcium channel causing calcium diffusion is blocked into the presynaptic [23].

The calcium channel is blocked by Gd^{3+}, causing interference of calcium diffusion. The disorder is the amount of calcium can enter the presynaptic reduced. The presence of Gd^{3+} in the signal system occurs because of the accumulation of the patient's body. This pattern is shown in Figure 4; the diffusion of calcium from outside the presynaptic to the inside of the presynaptic is disrupted by the increasing number of Gd^{3+} outside the presynaptic. The increased amount of Gd^{3+} outside the presynaptic causes the amount of calcium that diffuses into the presynaptic to decrease, as shown in Figure 6. A large amount of Gd^{3+} around the presynaptic causes the amount of calcium present in the presynaptic to decrease. The amount of calcium decreases affects the number of docking synaptic vesicles. Another

condition, the half-life of calcium in the presynaptic becomes shorter, which means the docking process occurs in a shorter time. This situation sequentially causes the number of neurotransmitters released into the synaptic gap to decrease, as shown in Figure 9 and the signal process to disrupted.

The number of neurotransmitters released into cleft decreases, causing the action potential at the next synapse to decrease, so the weaker the signal that can be transmitted. The presence of Gd^{3+} around the synapse due to the effect of repeated injections greatly influences signaling in the body. Therefore it is necessary to get serious attention in handling patients using Gd^{3+} contrast both the number of doses given and the number of repetitions.

Conclusion

Gadolinium is a substance that is injected into the body which has the advantage of enhancement images of MRI. Gadolinium can differentiate between healthy and unhealthy tissues. In the beginning, the benefit of gadolinium has caused a new problem in the mechanism of chemical synapses. The presence of gadolinium around synapse has affected the amount of calcium diffusion into presynaptic, which the existence of calcium is significant to synaptic vesicle released neurotransmitter as chemical messengers. Gadolinium and calcium compete with each other across of calcium channel. However, gadolinium is attached to the calcium channel surface as calcium blocker. The presence of gadolinium has caused a chain effect for signal transmission at chemical synapse, which reduces the amount of active membrane, synaptic vesicle docking, and neurotransmitter release.

Acknowledgment

The authors gratefully acknowledgment to the Ministry of Research, Technology and Higher Education and this Grand support of PTUPT 2018.

Conflict of Interest

None

References

1. Lohrke J, Frenzel T, Endrikat J, Alves FC, Grist TM, Law M, et al. 25 Years of Contrast-Enhanced MRI: Developments, Current Challenges and Future Perspectives. *Adv Ther*. 2016;**33**:1-28. doi: 10.1007/s12325-015-0275-4. PubMed PMID: 26809251. PubMed PMCID: PMC4735235.
2. Aime S, Caravan P. Biodistribution of gadolinium-based contrast agents, including gadolinium deposition. *J Magn Reson Imaging*. 2009;**30**:1259-67. doi: 10.1002/jmri.21969. PubMed PMID: 19938038. PubMed PMCID: PMC2822463.
3. Morcos S. Extracellular gadolinium contrast agents: differences in stability. *Eur J Radiol.* 2008;**66**:175-9. doi: 10.1016/j.ejrad.2008.01.025.
4. Kanda T, Oba H, Toyoda K, Kitajima K, Furui S. Brain gadolinium deposition after administration of gadolinium-based contrast agents. *Jpn J Radiol.* 2016;**34**:3-9. doi: 10.1007/s11604-015-0503-5. PubMed PMID: 26608061.
5. Wiginton CD, Kelly B, Oto A, Jesse M, Aristimuno P, Ernst R, et al. Gadolinium-based contrast exposure, nephrogenic systemic fibrosis, and gadolinium detection in tissue. *AJR Am J Roentgenol.* 2008;**190**:1060-8. doi: 10.2214/AJR.07.2822. PubMed PMID: 18356456.
6. Bourne G, Trifaro J. The gadolinium ion: a potent blocker of calcium channels and catecholamine release from cultured chromaffin cells. *Neuroscience*. 1982;**7**:1615-22. doi: 10.1016/0306-4522(82)90019-7.
7. Hasebroock KM, Serkova NJ. Toxicity of MRI and CT contrast agents. *Expert Opin Drug Metab Toxicol.* 2009;**5**:403-16. doi: 10.1517/17425250902873796. PubMed PMID: 19368492.
8. Kanda T, Ishii K, Kawaguchi H, Kitajima K, Takenaka D. High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: relationship with increasing cumulative dose of a gadolinium-based contrast material. *Radiology*. 2014;**270**:834-41. doi: 10.1148/radiol.13131669. PubMed PMID: 24475844.
9. Kanda T, Oba H, Toyoda K, Kitajima K, Furui S. Brain gadolinium deposition after administration of gadolinium-based contrast agents. *Jpn J Radiol.* 2016;**34**:3-9. doi: 10.1007/s11604-015-0503-5. PubMed PMID: 26608061.

10. Barbieri S, Schroeder C, Froehlich JM, Pasch A, Thoeny HC. High signal intensity in dentate nucleus and globus pallidus on unenhanced T1-weighted MR images in three patients with impaired renal function and vascular calcification. *Contrast Media Mol Imaging.* 2016;**11**:245-50. doi: 10.1002/cmmi.1683. PubMed PMID: 26929131. PubMed PMCID: PMC5066707.
11. Yang XC, Sachs F. Block of stretch-activated ion channels in Xenopus oocytes by gadolinium and calcium ions. *Science*. 1989;**243**:1068-71. doi: 10.1126/science.2466333. PubMed PMID: 2466333.
12. Sudhof TC. Calcium control of neurotransmitter release. *Cold Spring Harb Perspect Biol.* 2012;**4**:a011353. doi: 10.1101/cshperspect.a011353. PubMed PMID: 22068972. PubMed PMCID: PMC3249630.
13. Purves D, Augustine G, Fitzpatrick D, Hall W, LaMantia A, McNamara J, et al. Neurosciences. 3th ed. Sunderland: Sinauer Associates Inc. 2004. p. 93.
14. Tarr TB, Wipf P, Meriney SD. Synaptic Pathophysiology and Treatment of Lambert-Eaton Myasthenic Syndrome. *Mol Neurobiol.* 2015;**52**:456-63. doi: 10.1007/s12035-014-8887-2. PubMed PMID: 25195700. PubMed PMCID: PMC4362862.
15. Bartol Jr TM, Land BR, Salpeter EE, Salpeter MM. Monte Carlo simulation of miniature endplate current generation in the vertebrate neuromuscular junction. *Biophys J.* 1991;**59**:1290-307. doi: 10.1016/S0006-3495(91)82344-X. PubMed PMID: 1873466. PubMed PMCID: PMC1281209.
16. Dilger JP. Monte Carlo simulation of buffered diffusion into and out of a model synapse. *Biophys J.* 2010;**98**:959-67. doi: 10.1016/j.bpj.2009.11.034. PubMed PMID: 20303853. PubMed PMCID: PMC2849082.
17. Sutresno A, Haryanto F, Viridi S, Arif I, editors. Diffusion and Interaction between ion Ca2+ and ion Gd3+ in a Model Synapse: A Monte Carlo Study. Journal of Physics: Conference Series; IOP Publishing; 2019. doi: 10.1088/1742-6596/1127/1/012006.
18. Donahue BS, Abercrombie RF. Free diffusion coefficient of ionic calcium in cytoplasm. *Cell Calcium*. 1987;**8**:437-48. doi: 10.1016/0143-4160(87)90027-3. PubMed PMID: 3435913.
19. Ermakov YA, Kamaraju K, Sengupta K, Sukharev S. Gadolinium ions block mechanosensitive channels by altering the packing and lateral pressure of anionic lipids. *Biophys J.* 2010;**98**:1018-27. doi: 10.1016/j.bpj.2009.11.044. PubMed PMID: 20303859. PubMed PMCID: PMC2849073.
20. Berg HC. Random walks in biology. Princeton University Press; 1993.
21. Crank J. The mathematics of diffusion. 2nd ed. Oxford: Oxford university press; 1975. p. 42.
22. Rusakov DA. Ca2+-dependent mechanisms of presynaptic control at central synapses. *Neuroscientist.* 2006;**12**(4):317-326. doi: 10.1177/1073858405284672.
23. Malasics A, Boda D, Valisko M, Henderson D, Gillespie D. Simulations of calcium channel block by trivalent cations: Gd3+ competes with permeant ions for the selectivity filter. *BBA – Biomembranes.* 2010;**1798**(11):2013-2021. doi: 10.1016/j.bbamem.2010.08.001.