Kaunia, Vol.XVI, Num.2, October 2020, pp. 29~35
ISSN 1829-5266 (paper), ISSN 2301-8550 (online)
Available online at http://ejournal.uin-suka.ac.id/saintek/kaunia

Analysis of Modification in Synaptic Plasticity STDP (Spike Timing Dependent Plasticity) Model by Changing Intracellular Calcium Concentration

Shella Aisiyah Diva, Anis Yuniati*

Physics Department, Faculty of Science and Technology Sunan Kalijaga State Islamic University Yogyakarta
Correspondency email: anis.yuniati@uin-suka.ac.id*

Abstract

Synapses are a junction between neurons that has a plastic property. Synaptic plasticity can be in the form of long-term potentiation (LTP) and long-term depression (LTD). The changes in intracellular calcium concentration can trigger LTP and LTD. Spike Timing Dependent Plasticity (STDP) is a modification of synapses that depend on the spike timing of pre-synapses and post-synapses neuron. In this study, we analyze the effects of intracellular calcium on the STDP phenomena based on Badoual's model using mechanisms involving parameters such as calcium pumping, AMPA receptors, NMDA receptors, LTP enzymes, and LTD enzymes. In this model, a high calcium concentration will activate the LTP enzyme, while a low calcium concentration will activate the LTD enzyme, each of which will trigger the occurrence of LTP and LTD. The existence of LTP and LTD is the basis for the formation of the STDP. In this model, the parameters can be adjusted to obtain the STDP corresponding to experimental results where LTP is observed in the range between $0 < \Delta t < 50$ms, while LTD is observed at wider intervals between $-150\text{ms} < \Delta t < 0$. These parameters are related to the decay time of the NMDA receptor.

Keywords: *intracellular calcium; LTD; LTP; STDP; synaptic plasticity*

Introduction

Calcium signaling plays a role in many neuron cell processes (Perea et al., 2016) related to protein kinases (Kurniawan et al., 2018), intracellular messenger IP_3, SERCA pumps, AMPA and NMDA agonists (Kurniawan, 2015a), affected the synaptic plasticity in the form of LTD (Kurniawan, 2015b). Changes in synaptic plasticity that are influenced by neurotransmitters, glutamate, and AMPA are associated with seizures and epilepsy (Barker-Haliski & Steve White, 2015; Bonansco & Fuenzalida, 2016; Göl et al., 2019; Guli et al., 2016; Han et al., 2016; Husna & Kurniawan, 2018; Jarero-Basulto et al., 2018; Kryukov et al., 2016; Plasticity et al., 2017; T. Yu Postnikova et al., 2017; T Y Postnikova et al., 2017; Zubareva et al., 2018).

Epilepsy is one of a subject that is still being developed that involves the explanation of the mechanism (Kubena, 1994; Meric-Bernstam & Mills, 2004), treatment techniques (Kurniawan et al., 2018; Pramesti et al., 2017; Spannow, 1998; Zahra et al., 2019), and diagnoses (Approach et al., 2014; Kesahihan & Keandalan, 2015; Lestari et al., 2017; Of et al., 2015; Parameswaran et al., 2019). The study of synaptic plasticity is importantly related to several diseases, especially epilepsy.

Synaptic plasticity is a plastic property that occurs because of synaptic activity between neurons, which allows them to communicate with each other and work to control the effectiveness of communication between two or more neurons. The strength of synaptic plasticity is never static but always experiences strengthening or weakening, which is called long-term potentiation (LTP) or long-term depression (LTD) (Badoual et al., 2006). LTP is a form of synaptic plasticity that is influenced by changes in calcium concentration in the intracellular mechanism (Badoual et al., 2006; J. Lisman, 1989; John Lisman, 1985; Lynch et al., 1983; Malenka et al., 1988). Similarly, LTD has been shown to have a close relationship with the mechanism of intracellular calcium (Badoual et al., 2006; Cooper & Thakur, 2013; Cummings et al., 1996; Hines & Carnevale, 1997).

LTP arises when the pre-synaptic spike time precedes the post-synaptic spike, while LTD arises when the post-synaptic spike time precedes the time of pre-synaptic spike (Caporale & Dan, 2008). The most significant change that occurs in synaptic when there is a small-time difference between the spike of pre-synaptic and post-synaptic, which is accompanied by

a sharp transition from strengthening to weakening, is called STDP (Spike Timing Dependent Plasticity) (Song et al., 2000). STDP is a form of synaptic modification that depends on the difference in the time of pre-synaptic spike and post-synaptic spike, which is a biological process that functions to regulate the strength of connections between neurons in the brain and refers to the process of LTP and LTD (Badoual et al., 2006; Levy, 1983). Based on the calcium hypothesis, the relative similarity of STDP activity patterns that refers to LTP and LTD depends on the concentration of calcium in cells. However, the calcium hypothesis that explains the biophysical mechanisms underlying STDP is still unclear (Badoual et al., 2006; Sjöström & Gerstner, 2010).

In some previous computational models, post-synaptic calcium concentration was used as a signal to distinguish the sequence and time of spike in pre-synaptic and post-synaptic, wherein the model concluded that high post-synaptic calcium concentration would cause LTP. In contrast, low calcium concentration would cause LTD (Abarbanel et al., 2002; Karmarkar & Buonomano, 2002; Shouval et al., 2002). In other computational models, the calcium hypothesis testing is based solely on observing post-synaptic spikes at calcium levels. They show that the results of experiments using the triplet spike of pre-synaptic and post-synaptic indicate that the spike of pre-synaptic that precedes the spike of post-synaptic then followed by the spike of pre-synaptic does not result in any change in the plasticity. Conversely, when a post-synaptic spike precedes a pre-synaptic spike and then followed by a pre-synaptic spike, it triggers LTP (Rubin et al., 2005). In this study, the modeling that was built to explain the biophysical mechanism in the STDP model related to the concentration of calcium in cells will be analyzed through the process of LTP and LTD based on the spike time of pre-synaptic and post-synaptic on the spine of neuronal cells. The computational modeling in this research involves parameters that include pumping of calcium which is influenced by AMPA receptors, NMDA receptors, LTP and LTD enzymes, which is based on the time pair of spikes in pre-synaptic and post-synaptic.

Methodology

The kinetic model used in this research follows the research of Mathilde Badoual et al. (Badoual et al., 2006), where each parameter is written using the NMODL (Model Description League) programming language, which is saved as a .mod file extension. The files then are inputted using the NEURON simulator. The kinetic model of each parameter is as follows:

1. Calcium Pumping

The calcium pumping process is carried out in the dendrite spine and dendrite, leading to the dendrite spine. Equation (1) is a comparison of pumping of calcium that occurs in the spine (Badoual et al., 2006; Sabatini et al., 2002).

$$\frac{d[C_a]_i}{dt} = -\frac{I_{ca}}{2Fd\times 18} + \frac{(C_{a_\infty} - [C_a]_i)}{\tau_r} \quad (1)$$

$[C_a]_i$ is the concentration of calcium in the spine, I_{ca} is the calcium current in the spine, *F* is the Faraday constant, C_{a_∞}= 5x10^{-7}mM is the concentration of calcium in the spine at rest, τ_r is decay time constant equal to 15 ms, and *d* is the depth of the submembrane framework used in this equation, with the value equal to 1/4 of the spine diameter. Equation (2) is the equation of pumping calcium from the dendrite to the spine.

$$-D([C_a]_i - [C_a]_d)\frac{S_{neck}}{L_{neck}V_{spine}} \quad (2)$$

C_{a_d} is the concentration of calcium in dendrites, S_{neck} is the cross section of the neck ($S_{neck} = 0{,}0078\ \mu m^2$), while V_{spine} is the volume in the spine ($V_{spine} = 0{,}065\ \mu m^3$). These values are following with the morphological measurements carried out by Harris and Kater in 1994 (Harris, 1994).

2. AMPA receptor

Calculation of AMPA receptor conductance values is shown in equation (3) as follows (Badoual et al., 2006; A Destexhe et al., 1994)

$$\frac{dm}{dt} = \alpha T(1-m) - \beta m \quad (3)$$

m represents the receptor fraction in the open state, *α* and *β* are forward and backward rate constants, *T* is the concentration of glutamate in the synaptic cleft. Conductance value is given by $g_{AMPA} = \bar{g}_{AMPA}m$ where $\bar{g}_{AMPA} = 0{,}5\mathrm{nS}$ is the maximum conductance value of synapses.

3. NMDA receptor

Calculation of the value of calcium current at the NMDA receptor is shown in equation (4) below (Badoual et al., 2006; Alain Destexhe et al., 1998; Gardette et al., 1985; Goldman, 1943).

$$I_{Ca} = P_{Ca}B(V)\ m\ G(V, [C_a]_o, [C_a]_i \quad (4)$$

$P_{Ca} = 4{,}6925(\mathrm{cm^3 mV/Cb})$ is the permeability of calcium, *m* represents the fraction when the receptor is open, and *B* (*V*) describes the voltage value that depends on the NMDA receptor current. Calculation of *B (V)* is shown in equation (5) below (Badoual et al., 2006; Jahr & Stevens, 1990)

$$B(V) = \frac{1}{1+\exp(-0{,}062V)[M_g]_o/3{,}57} \quad (5)$$

 ISSN 1829-5266 (paper), ISSN 2301-8550 (online)

$[M_g]_o = 1\text{mM}$ is the external calcium concentration, $G(V,[C_a]_o,[C_a]_i)$ is linear function of voltage and ion concentration with the value is shown in equation (6) below

$$G(V,[C_a]_o,[C_a]_i) = Z^2F^2V/RT \frac{[C_a]_i - [C_a]_o \exp\left(-\frac{ZFV}{RT}\right)}{1-\exp(-ZFV/RT)} \quad (6)$$

Z = 2 is the valence of calcium ions, *F* is the Faraday constant, *R* is the gas constant, *T* is the temperature in Kelvin units, $[C_a]_i$ dan $[C_a]_o = 1{,}5\text{mM}$ is the value of intracellular and extracellular calcium concentrations, $\bar{g}_{NMDA} = 0{,}3\text{nS}$ is the NMDA receptor current value.

4. LTP Enzyme

The activation of the LTP enzyme during the kinetic scheme shown in equation (7) follows (Badoual et al., 2006)

$$K + 4{C_a}^{2+} \underset{b_k}{\overset{a_k}{\rightleftarrows}} K^* \quad (7)$$

K is the non-activated LTP enzyme form and *K* * is the activated LTP enzyme form. The value of a_k and b_k is constant.

5. LTD Enzyme

The enzyme activation of LTD during the kinetic scheme shown in equation (8) - (10) follows (Badoual et al., 2006)

$$m + {C_a}^{2+} \underset{b_m}{\overset{a_m}{\rightleftarrows}} m^* \quad (8)$$

$$h + T \underset{b_h}{\overset{a_h}{\rightleftarrows}} h^* \quad (9)$$

$$m^* + h^* + P_h \rightarrow {P_h}^* \quad (10)$$

m is an enzyme activated by calcium, *h* is an enzyme activated by glutamate, *m** and *h** are forms of activation used to activate the LTD enzyme, whereas P_h, a_m, b_m, a_h, and b_h are constant.

Results and Discussion

1. The relation of LTP, LTD and intracellular calcium concentration

Long Term Potentiation/LTP is triggered by activation of calcium autophosphorylation or protein-dependent calmodulin (CaMKII). Activation of protein kinase-dependent CaMKII involves four calcium ions for each calmodulin molecule in the LTP enzyme. The LTP enzyme will be activated when the concentration of calcium in the cell is high, or the peak of the LTP enzyme will also be high. However, when the concentration of calcium in cells is low, the LTP enzyme will not be activated, or the LTP enzyme peak is low. The calcium concentration for positive value of tpost-tpre (tpost-tpre = 130 ms) is shown in Figure 1. The figure shows the calcium concentration is high at the time 300 ms, indicated by sharp peak with the value of calcium concentration equal to 0.012 μM.

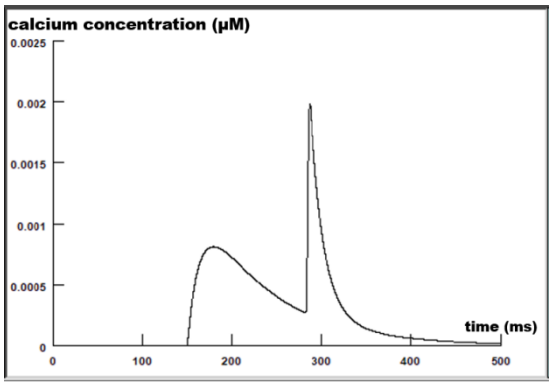

Figure 1. Calcium concentration for tpost-tpre 130 ms.

LTP enzyme signals represented by %*K** in Figure 2. Comparing with the result shown in Figure 1, when the calcium concentration is high, the LTP enzyme will be activated. Meanwhile, when the calcium concentration is low, the value of LTP enzyme also low. As shown by a sharp peak in Figure 2 at the time close to 300 ms, the value of LTP enzyme is 0.04 μM.

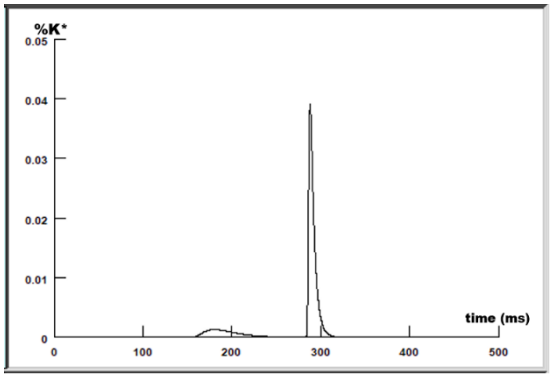

Figure 2. LTP enzyme for tpost-tpre 130 ms.

The strengthening of the calcium signal in the biophysical mechanism in the STDP model depends on the interaction of Backpropagating Action Potential (BAP) and Excitatory Postsynaptic Potential (EPSP) which increases the calcium permeability that is affected by NMDA receptors and is voltage-dependent. BAP is a phenomenon when the action potential makes a voltage spike at the end of the axon and returns to the dendrite. The interaction between BAP

and EPSP can cause many things (Caporale & Dan, 2008), for example, that it can strengthen the calcium signal when the NMDA receptors are opened with three to four times larger in the dendrite (Magee & Johnston, 1997).

EPSP can cause changes in the conductance values in dendrites which cause BAP to return to dendrites, whereas an increase in BAP can cause calcium influx to flow through calcium channels that depend on voltage to increase LTP without any contribution from Ca2 + induced Ca2 + release (CICR). Calcium is mediated by pumping calcium ATPases to the endoplasmic reticulum (SERCA pumps) and by exchanging Na + -Ca2 + on the plasma membrane or Ca2 + -ATPase plasma membrane (Caporale & Dan, 2008; Holthoff & Tsay, 2002). This process can be simplified and represented by the value of the decay time constant τ_r in the calcium pumping equation. A value of τ_r of 15 ms initiated by a current pulse in the initial segment section, while EPSP in the spine is triggered by the action potential in the cells of pre-synaptic. Increased calcium permeability will cause calcium signals to strengthen. The voltage-dependent NMDA receptor in this mechanism is represented by the value of $B(V)$ in the calcium current equation. The value of $B(V)$ in this mechanism plays a role in opening or closing the magnesium block channel contained in the NMDA receptor.

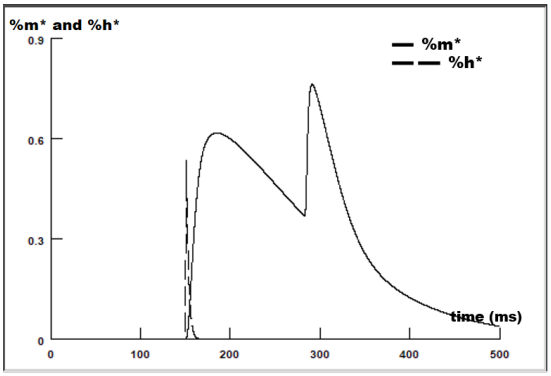

Figure 3. The enzyme activated by calcium *m** and the enzyme activated by glutamate *h** for tpost-tpre 130 ms.

Long Term Depression/LTD is triggered by the activation of protein phosphatase. Activation of protein phosphatase involves the neurotransmitter (glutamate) and also the concentration of calcium in cells. Glutamate will be released to the AMPA receptor when there is an action potential in pre-synaptic cells. The LTD enzyme will not be activated when the calcium concentration in the cell is high, or the LTD enzyme peak is low. Still, when the concentration of calcium in the cell is low, the LTD enzyme will be activated, or the peak enzyme LTD is high. The enzyme activated by calcium *m** and the enzyme activated by glutamate *h**, are shown in Figure 3. The sharp peak at the time close to 300 ms indicate that *m** is high, as the consequence that calcium concentration reach the highest concentration at the same time as shown in Figure 1. The enzyme activated by glutamate *h** is high at the time close to 150 ms as the result that the calcium concentration is start to produce at the same time, as shown in Figure 1. The LTD enzyme is represented by % *Ph** in Figure 4. The sharp peak is shown at the time close to 150 ms, as the consequence that the mechanism for activating LTD enzyme is occur when m^* is low and h^* is high.

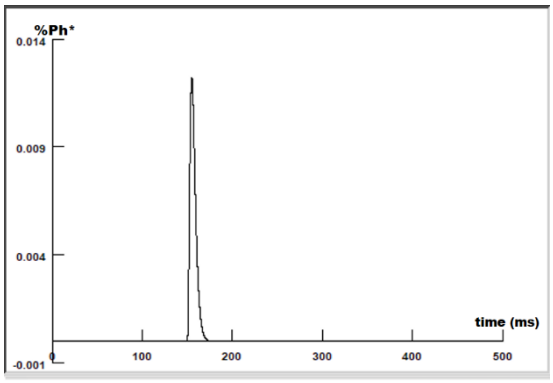

Figure 4. LTD enzyme for tpost-tpre 130 ms.

The glutamate found in the synapses valve will be sent to the receptors on the post-synaptic when there is an action potential in pre-synaptic cells, such as kinetics on AMPA receptors that mediate conductance. The release of glutamate or transmitter (T) through synapses activates the enzyme *h* to *h**. Meanwhile, calcium will activate the enzyme *m* to be *m** while the LTD enzyme activation process from *Ph* to *Ph** is carried out by enzymes *m** and *h**. The mechanism of enzyme activation of LTD occurs when the enzyme peak *m** is low, and the enzyme peak *h** is high, when the enzyme peak *h** is high, the enzyme LTD will be activated from *Ph* to *Ph** and has a high peak. Conversely, when the enzyme peak *m** is high and the enzyme peak *h** is low, the LTD enzyme will still be activated but has a small value.

Simulation results with tpost-tpre has a positive value (tpost-tpre = 130 ms) shows that the LTP enzyme peak has a higher value than the LTD enzyme peak value, where the LTP enzyme peak value is 0.04 μM and the LTD enzyme peak value is 0.012 μM. We concluded based on these results that the positive value of tpost-tpre triggers the occurrence of LTP in cells because of the value of LTP> LTD. When the value of LTP is higher than the value of LTD, synapses activity will experience strengthening. LTP will play an important role in the mechanism of storing information in the brain when the value of LTP is high.

 ISSN 1829-5266 (paper), ISSN 2301-8550 (online)

2. The relation of STDP phenomenon and intracellular calcium concentration

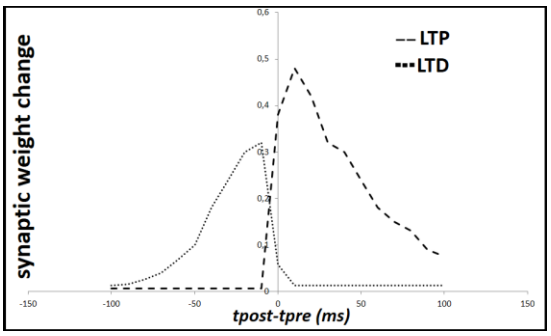

Figure 5. LTP and LTD curve for tpost-tpre from -100 to 100 ms.

The synaptic plasticity of the STDP model is based on measuring synaptic weights through spike time pairs of pre-synaptic and post-synaptic, with Δt (the time difference between the post-synaptic spike and pre-synaptic spike) < 0 will give a negative value of synaptic weight change, whereas Δt > 0 will give a value of positive synaptic weight change.

Changes in synaptic weights that are positive will cause plasticity to strengthen. Meanwhile, changes in synaptic weights that are negative will weaken plasticity. The curve of the change in synaptic weight value is described in Figure 5, where the total value of the synaptic weight change is the value of LTP-LTD. Meanwhile, in the previous analysis, it has been explained that changes in intracellular calcium concentration values can cause the onset of strengthening (LTP) and weakening (LTD). From these results, it can be concluded that the synaptic plasticity of the STDP model is related or influenced by changes in intracellular calcium concentration values. In other words, changes in intracellular calcium concentration affect the changes in this model through the mechanism of LTP and LTD. Based on the time difference between the relative pre-synaptic and post-synaptic, the curves of the STDP model, is shown in Figure 6. The STDP curve is obtained from LTP curve – LTD curve.

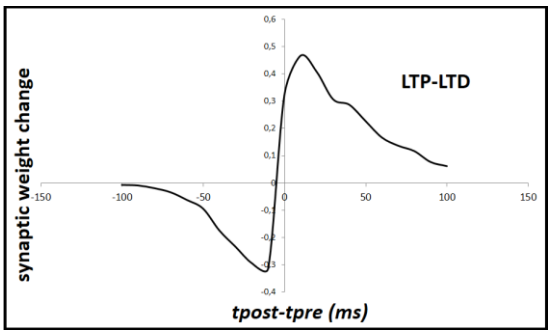

Figure 6. STDP curve for tpost-tpre from -100 to 100 ms.

Through variations in the kinetics of NMDA receptors, which are related to the time of decay, when the decay occurs faster, the LTP curve window looks narrower. Another related parameter is calcium diffusion. Calcium diffusion can occur from the dendrite to the spine, where this diffusion is inversely proportional to the length of the spine's neck.

Several studies have shown that BAP calcium signaling has a faster decay time in the spine and has a slower decay time in the dendrite. However, this cannot be seen in more detail through the diffusion of calcium in the dendrites and spines, which have almost the same decay time of 20 ms in the dendrites and 15 ms in the spine. In several other cases, the dendrite and spine decay kinetics look very different.

For example, calcium decay due to BAP must involve two exponential values, the fast decay time constant reflects the calcium decay time in the spine, while the slow decay constant reflects the calcium decay in dendrites. Therefore, to examine the effect of calcium diffusion, the value of the pumping time constant in the dendrite is set much larger 70 ms than in the spine. Through the variation of decay time at NMDA receptors with τ_r = 10 ms, a realistic STDP curve model is obtained according to the experimental results, as shown in Figure 7.

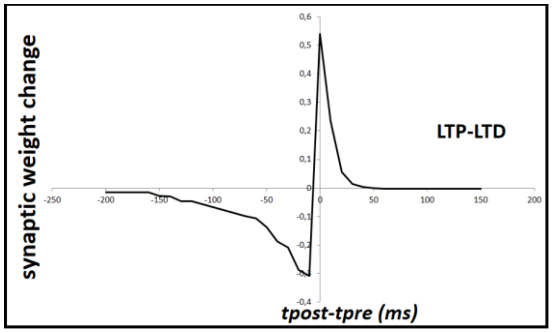

Figure 7. STDP curve for tpost-tpre from -200 to 150 ms with τ_r = 10 ms

The decay time τ_r = 10 ms with tpost-tpre values at intervals of -200 ms to +150 ms gives the simulation results of realistic STDP model curve that close to the results of experiments conducted by Bi and Poo, where the LTP window is observed in the time interval $0<\Delta t<50$ms, and the LTD window is observed in the time interval of $-150<\Delta t<0$ ms.

Conclusion

Based on the results and studies, it can be concluded that the occurrence of LTP and LTD is influenced by the large concentration of calcium in neuron cells through the mechanism of activation of the LTP and

LTD enzymes. High calcium concentration causes LTP, and low calcium concentration causes LTD. The time of pre-synaptic spike that precedes the time of post-synaptic spike (tpost-tpre is positive) gives rise to LTP, while the time of post-synaptic spike which precedes the time of pre-synaptic spike (tpost-tpre is negative) gives an LTD. The STDP model curve based on the tpost-tpre value shows the LTP and LTD processes that are influenced by the large calcium concentration in neuron cells. The STDP curves are consistent with experimental results where LTP is observed in the range between $0 < \Delta t < 50$ms, while LTD is observed at wider intervals between -150ms $< \Delta t < 0$. In the future study, the parameters need to be varied to be compared with the results from experimental research in various organism.

References

Abarbanel, H. D. I., Huerta, R., & Rabinovich, M. I. (2002). Dynamical model of long-term synaptic plasticity. *Proceedings of the National Academy of Sciences of the United States of America*, *99*(15), 10132–10137. https://doi.org/10.1073/pnas.132651299

Approach, D., Absence, I. N., Epileptic, V., With, S., & Seizure, A. (2014). *PENDEKATAN DIAGNOSIS BANGKITAN ABSANS DAN*. *31*(4).

Badoual, M., Zou, Q., Davison, A. P., Rudolph, M., Bal, T., Frégnac, Y., & Destexhe, A. (2006). Biophysical and phenomenological models of multiple spike interactions in spike-timing dependent plasticity. *International Journal of Neural Systems*, *16*(2), 79–97. https://doi.org/10.1142/S0129065706000524

Barker-Haliski, M., & Steve White, H. (2015). Glutamatergic mechanisms associated with seizures and epilepsy. *Cold Spring Harbor Perspectives in Medicine*, *5*(8), 1–15. https://doi.org/10.1101/cshperspect.a022863

Bonansco, C., & Fuenzalida, M. (2016). Plasticity of hippocampal excitatory-inhibitory balance: Missing the synaptic control in the epileptic brain. *Neural Plasticity*, *2016*. https://doi.org/10.1155/2016/8607038

Caporale, N., & Dan, Y. (2008). Spike Timing–Dependent Plasticity: A Hebbian Learning Rule. *Annual Review of Neuroscience*, *31*(1), 25–46. https://doi.org/10.1146/annurev.neuro.31.060407.125639

Cooper, A. F., & Thakur, R. (2013). The group of twenty (G20). In *The Group of Twenty (G20)* (pp. 1–194). https://doi.org/10.4324/9780203071236

Cummings, J. A., Mulkey, R. M., Nicoll, R. A., & Malenka, R. C. (1996). Ca2+ signaling requirements for long-term depression in the hippocampus. *Neuron*, *16*(4), 825–833. https://doi.org/10.1016/S0896-6273(00)80102-6

Destexhe, A, Mainen, Z. F., & Sejnowski, T. J. (1994). *Destexhe Mainen Sejnowski 1994*. 3–6.

Destexhe, Alain, Mainen, Z. F., & Sejnowski, T. J. (1998). Kinetic models of synaptic transmission. *Methods in Neuronal Modeling*, *January 1998*, 1–25. http://cns.iaf.cnrs-gif.fr/abstracts/KSchap96.html

Gardette, R., Debono, M., Dupont, J. L., & Crepel, F. (1985). Electrophysiological studies on the postnatal development of intracerebellar nuclei neurons in rat cerebellar slices maintained in vitro. II. Membrane conductances. *Developmental Brain Research*, *20*(1), 97–106. https://doi.org/10.1016/0165-3806(85)90091-4

Göl, M. F., Erdoğan, F. F., Bayramov, K. K., Mehmetbeyoğlu, E., & Özkul, Y. (2019). Assessment of genes involved in behavior, learning, memory, and synaptic plasticity following status epilepticus in rats. *Epilepsy and Behavior*, *98*, 101–109. https://doi.org/10.1016/j.yebeh.2019.06.023

Goldman, B. Y. D. E. (1943). *IN MEMBRANES (From the Department of] Physiology , College of Physicians and Surgeons , Columbia University , New York)*. 37–60.

Guli, X., Tokay, T., Kirschstein, T., & Köhling, R. (2016). Status Epilepticus Enhances Depotentiation after Fully Established LTP in an NMDAR-Dependent but GluN2B-Independent Manner. *Neural Plasticity*, *2016*(1). https://doi.org/10.1155/2016/6592038

Han, T., Qin, Y., Mou, C., Wang, M., Jiang, M., & Liu, B. (2016). *SZ induced synaptic plasticity alternation in hippo is mediated by IL-1B receptor throtugh PI3K-Akt pathway 2016 Han Liu AmJTranslRes*. *8*(10), 4499–4509.

Harris, K. M. (1994). *Harris_1994_DS_Flexibility*.

Hines, M. L., & Carnevale, N. T. (1997). The NEURON Simulation Environment. *Neural Computation*, *9*(6), 1179–1209. https://doi.org/10.1162/neco.1997.9.6.1179

Holthoff, K., & Tsay, D. (2002). Dynamic Confocal Imaging of Living Brain Calcium dynamics in spines : link to synaptic plasticity Experimental Physiology : Experimental Physiology : *Experimental Physiology*, *87*(6), 725--731.

Husna, M., & Kurniawan, S. N. (2018). Mekanisme Kerja Obat Anti Epilepsi Secara Biomolekuler. *Mnj, 4*(3), 38–45.

Jahr, C. E., & Stevens, C. F. (1990). Voltage Dependence of NMDA-Activated Predicted by Single-Channel Kinetics. *Journal of Neuroscience*, *10*(9), 3178–3182.

Jarero-Basulto, J. J., Gasca-Martínez, Y., Rivera-Cervantes, M. C., Ureña-Guerrero, M. E., Feria-Velasco, A. I., & Beas-Zarate, C. (2018). Interactions between epilepsy and plasticity. *Pharmaceuticals*, *11*(1), 1–18. https://doi.org/10.3390/ph11010017

Karmarkar, U. R., & Buonomano, D. V. (2002). A model of spike-timing dependent plasticity: One or two coincidence detectors? *Journal of Neurophysiology*, *88*(1), 507–513. https://doi.org/10.1152/jn.2002.88.1.507

Kesahihan, U. J. I., & Keandalan, D. A. N. (2015). *(Qolie-31) Versi Bahasa Indonesia Validation and Reliability Test of the Indonesian Version of*. *32*(3).

Kryukov, K. A., Kim, K. K., Magazanik, L. G., & Zaitsev, A. V. (2016). Status epilepticus alters hippocampal long-term synaptic potentiation in a rat lithium-pilocarpine model. *NeuroReport*, *27*(16), 1191–1195. https://doi.org/10.1097/WNR.0000000000000656

Kubena, K. S. (1994). The role of magnesium in immunity. *Journal of Nutritional Immunology*, *2*(3), 107–126. https://doi.org/10.1300/J053v02n03_07

Kurniawan, S. N. (2015a). INTRACELLULAR Ca2+ HOMEOSTASIS. *MNJ (Malang Neurology Journal)*, *1*(1), 36–45. https://doi.org/10.21776/ub.mnj.2015.001.01.7

Kurniawan, S. N. (2015b). *Sinyal Neuron Neuronal Signaling*. *1*(2), 86–96. https://doi.org/10.21776

Kurniawan, S. N., Utomo, D. H., Rudijanto, A., Rahayu, M., & Aulanni'am, A. (2018). Nuclear Factor Erythroid 2 activation mediated by PRKCA in increasing Ca2+ intracellular in diabetic condition. *International Journal Bioautomation*, *22*(2), 159–168. https://doi.org/10.7546/ijba.2018.22.2.159-168

Lestari, N. D., Mutiawati, E., Rahmawati, E., Octaviana, F., & Bachtiar, A. (2017). *Analisis Properti Psikometri Internalized Stigma of Epilepsy Versi Indonesia*. *34*(2).

Levy, W. B. (1983). in the Hippocampus. *Neuroscience*, *8*(4).

Lisman, J. (1989). A mechanism for the Hebb and the anti-Hebb processes underlying learning and memory. *Proceedings of the National Academy of Sciences of the United States of America*, *86*(23), 9574–9578. https://doi.org/10.1073/pnas.86.23.9574

Lisman, John. (1985). A mechanism for memory storage insensitive to molecular turnover. *Proceedings of the National Academy of Sciences of the United States of America*, *82*(May), 3055–3057. https://www.pnas.org/content/pnas/82/9/3055.full.pdf

Lynch, G., Larson, J., Kelso, S., Barrionuevo, G., & Schottler, F. (1983). Intracellular injections of EGTA block induction of hippocampal long-term potentiation. *Nature*, *305*(5936), 719–721. https://doi.org/10.1038/305719a0

Magee, J. C., & Johnston, D. (1997). A synaptically controlled, associative signal for Hebbian plasticity in hippocampal neurons. *Science*, *275*(5297), 209–213. https://doi.org/10.1126/science.275.5297.209

Malenka, R. C., Kauer, J. A., Zucker, R. S., & Nicoll, R. A. (1988). Postsynaptic calcium is sufficient for potentiation of hippocampal synaptic transmission. *Science*, *242*(4875), 81–84. https://doi.org/10.1126/science.2845577

Meric-Bernstam, F., & Mills, G. B. (2004). Mammalian target of rapamycin. *Seminars in Oncology*, *31*(SUPPL. 16), 10–17. https://doi.org/10.1053/j.seminoncol.2004.10.013

Of, C., Mri, Q., Magnetization, I., Ratio, T., Intelligence, W., In, Q., Temporal, M., & Epilepsy, L. (2015). *KORELASI MAGNETIZATION TRANSFER RATIO INTERIKTAL DENGAN INTELLIGENCE QUOTIENT PADA EPILEPSI LOBUS TEMPORAL MESIAL RESISTEN OBAT TRANSFER RATIO WITH INTELLIGENCE QUOTIENT IN DRUG-RESISTANT*. *32*(2).

Parameswaran, S., Vijayamma, A. K. T., & Pillai, A. M. (2019). Efficacy of Short Term Video Eeg in Detecting Psychogenic Non-Epileptic Seizures. *MNJ (Malang Neurology Journal)*, *5*(2), 65–67. https://doi.org/10.21776/ub.mnj.2019.005.02.3

Perea, G., Gómez, R., Mederos, S., Covelo, A., Ballesteros, J. J., Schlosser, L., Hernández-Vivanco, A., Martín-Fernández, M., Quintana, R., Rayan, A., Díez, A., Fuenzalida, M., Agarwal, A., Bergles, D. E., Bettler, B., Manahan-Vaughan, D., Martín, E. D., Kirchhoff, F., & Araque, A. (2016). Activity-dependent switch of gabaergic inhibition into glutamatergic excitation in astrocyte-neuron networks. *ELife*, *5*(DECEMBER2016), 1–26. https://doi.org/10.7554/eLife.20362

Plasticity, A., Dentate, O. F. A., In, C., Model, A. R. A. T., Mesial, O. F., & Lobe, T. (2017). *CELLS IN A RAT MODEL OF MESIAL TEMPORAL LOBE*. *734*, 187–196. https://doi.org/10.1016/j.nbd.2015.11.024.AXONAL

Postnikova, T. Yu, Trofimova, A. M., Zaitsev, A. V., & Magazanik, L. G. (2017). Status epilepticus induced by pentylenetetrazole increases short-term synaptic facilitation in the hippocampus of juvenile rats. *Doklady Biological Sciences*, *477*(1), 207–209. https://doi.org/10.1134/S0012496617060102

Postnikova, T Y, Zubareva, O. E., Kovalenko, A. A., Kim, K. K., Magazanik, L. G., & Zaitsev, A. V. (2017). *Epileptic seizures in patients with temporal*. *82*(3), 282–290. https://doi.org/10.1134/S0006297917030063

Pramesti, F. A., Husna, M., Kurniawan, S. N., Rahayu, M., Neurologi, L., Kedokteran, F., & Brawijaya, U. (2017). Diagnosis and Management of Nonconvulsive Status Epilepticus (NCSE). *Diagnosis and Management of Nonconvulsive Status Epilepticus (NCSE)*, *Vol.03*, *No*, 30–38.

Rubin, J. E., Gerkin, R. C., Bi, G. Q., & Chow, C. C. (2005). Calcium time course as a signal for spike-timing-dependent plasticity. *Journal of Neurophysiology*, *93*(5), 2600–2613. https://doi.org/10.1152/jn.00803.2004

Sabatini, B. L., Oertner, T. G., & Svoboda, K. (2002). The life cycle of Ca2+ ions in dendritic spines. *Neuron*, *33*(3), 439–452. https://doi.org/10.1016/S0896-6273(02)00573-1

Shouval, H. Z., Bear, M. F., & Cooper, L. N. (2002). A unified model of NMDA receptor-dependent bidirectional synaptic plasticity. *Proceedings of the National Academy of Sciences of the United States of America*, *99*(16), 10831–10836. https://doi.org/10.1073/pnas.152343099

Sjöström, J., & Gerstner, W. (2010). {S}pike-timing dependent plasticity. *Scholarpedia*, *5*(2), 1362. https://doi.org/10.4249/scholarpedia.1362

Song, S., Miller, K. D., & Abbott, L. F. (2000). Competitive Hebbian learning through spike-timing-dependent synaptic plasticity. *Nature Neuroscience*, *3*(9), 919–926. https://doi.org/10.1038/78829

Spannow, K. E. (1998). Research Article. *Nordic Studies on Alcohol and Drugs*, *15*(1), 3–4. https://doi.org/10.1177/145507259801500104

Zahra, F. A., Islamiyah, W. R., & Budiono, B. (2019). Profile of Subjective Sleep Disturbance in Patient With Antiepileptic Drugs. *MNJ (Malang Neurology Journal)*, *5*(2), 61–64. https://doi.org/10.21776/ub.mnj.2019.005.02.2

Zubareva, O. E., Kovalenko, A. A., Karyakin, V. B., Kalemenev, S. V., Lavrent'eva, V. V., Magazanik, L. G., & Zaitsev, A. V. (2018). Changes in the Expression of Genes of the Glutamate Transporter and Subunits of the NMDA and AMPA Receptors in the Rat Amygdala in the Lithium–Pilocarpine Model of Epilepsy. *Neurochemical Journal*, *12*(3), 222–227. https://doi.org/10.1134/s1819712418030170

THIS PAGE INTENTIONALLY LEFT BLANK