# Homeostatic Synaptic Plasticity: Balanced by COX2-PGE$_2$ System to a New Setpoint

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**THE SETPOINT OF neural activity plays a critical role in maintaining the complex neural circuits into stable activities. Homeostatic synaptic plasticity is a major component of the setpoint theory that dynamically adjusts synaptic strengths. Cyclooxy-genase 2 (COX 2) is rapidly upregulated in inflammatory episodes after nervous injury and its product prostaglandin $E_2$ ($PGE_2$) exerts contrast functions in the nervous system by working on the homeostatic plasticity. New data revealed that COX2-$PGE_2$ system takes an essential part in balancing excitation and inhibition of the synaptic activities at a new setpoint that finally is maintained by the homeostatic synaptic plasticity.**

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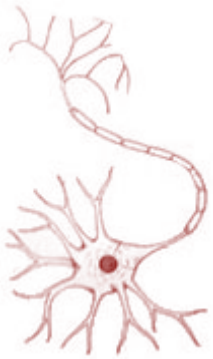
NEURONS are functionally connected with each other to transmit excitatory or inhibitory information produced by internal or external stimulation, which is a crucial property endowed with the neural synaptic transmission. Activity-dependent enhancement or depression in the efficacy of synaptic communication has been proposed to play a critical role in the ability of modifying neural circuitry. Although such activity-associated refinement on synaptic connectivity initially defined as Hebbian assembly is of fundamental importance throughout the brain development, this plasticity tends to destabilize the activity of neural circuits through neuron-to-neuron activation in sequences. In fact, activity-dependent synaptic plasticity occurs physiologically where specific types of neural activity result in changes in neural excitability and synaptic efficacy. However, the so-called "setpoint" of neural activity kept through self-regulating by neurons plays an important role in maintaining the complex circuits into stable activity states in facing the destabilizing stimuli. Homeostatic synaptic plasticity is a major component of the setpoint theory that dynamically adjusts synaptic strengths in the correct direction to promote stability (1). Consistent with homeostatic regulation, excitatory synaptic transmission can be increased after neural activity deprivation in the cultured hippocampal slices, and even leading the hippocampus to generate seizure-like activity (2). While such a consequence of epileptogenesis from homeostatic plasticity is unwanted, it somehow suggests that injury-induced epilepsy may be a state maintained by the homeostatic synaptic plasticity at a new setpoint.

Previous work has long recognized the function of inflammatory mediators in plasticity stability, and suggested they should be treated as neuromodulators in normal or/and injured brain. Cyclooxygenase 2 (COX 2), the inducible isoform of cyclooxygenase is rapidly upregulated in inflammatory episodes after nervous injury, of which consequently

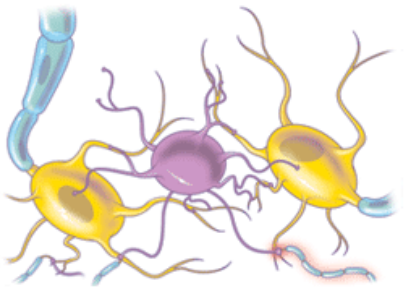
leads to downstream prostaglandins (PGs) production functioning pathologically in promoting further nervous injury. Among the four PGs, $PGE_2$ exerts contrast functions in the nervous system because divergent results obtained in different types of context of nerve injury, during which either neurotoxic or neuroprotective role was observed depending on distinct downstream PG receptor signalings. These seem to be associated with an elevated regulation at a higher-than-normal level by the homeostatic plasticity. This link between $PGE_2$ and homeostatic synaptic plasticity was investigated by Koch et al. (3) using organotypic slices, in which a series of *in vitro* experiments indicated that $PGE_2$ reduces excitatory synaptic transmission and depresses network activity when applied acutely in neocortical slices, but long-term exposure to $PGE_2$ results in a hyperexcitable network state displaying paroxysmal depolarization shifts (PDSs), a result of a homeostatic response that may lead to epileptogenesis.



Organotypic slice preparations have been increasingly used for the study of synaptic plasticity, where the hippocampus is removed after 5 days of postnatal experience and subsequently develops in the total absence of sensory input. Nonetheless, acute slices are prepared from animals with over 2-week postnatal experience mainly because in which development occurred *in vivo* (4). When analyzing spontaneous synaptic activity, tetrodotoxin (TTX), a blocker of the sodium action potentials, is used to inhibit the occurrence of spontaneous action potentials, and thus generating data for all miniature currents, whether carried by glutamate (excitatory postsynaptic currents, mEPSCs) or GABA (inhibitory postsynaptic currents, mIPSCs). In some cases, bicuculline, a blocker of $GABA_A$ receptors, is added to the TTX solution to block GABAergic activity, which finally allows a study of mEPSCs in isolation. Theoretically, changes in the amplitude of mEPSCs display a postsynaptic mechanism, but presynaptic effect can be explained with the changes in the frequency of mEPSCs.

Using acute and organotypic slices, Koch et al. (3) performed three parts of experiment to approve their hypothesis that traumatic brain injury leads to a homeostatic response that constitutes the first step in a process that will eventually result in seizures and epilepsy, during which COX2-$PGE_2$ system may be involved in the activity-dependent regulation on the homeostatic plasticity to excitable or inhibitable responses. First of all, acute effects of $PGE_2$ on synaptic electrophysiological patterns were tested when TTX was added 48 h to produce activity deprivation leading to increase in peak and mean amplitudes of PDSs and mEPSCs in organotypic preparations [Koch et al. (3), their Fig. 2 and 3], and then the effect of $PGE_2$ on extra potassium-induced network bursting activity was observed in acute and organotypic slices [Koch et al. (3), their Fig. 4 and 5]; subsequently, the authors found that $PGE_2$ decreased the amplitudes of excitatory postsynaptic potentials (EPSPs) and/or mEPSCs in both kinds of cultures [Koch et al. (3), their Fig. 6], leading the authors to suggest that $PGE_2$ postsynaptically inhibits excitatory synaptic transmission in acute and organotypic slices.

Following these observations, the authors then investigated the long-term effect of $PGE_2$ on PDSs' up state activity and mEPSCs in organotypic slices, and found $PGE_2$ exposure 48 h increased the amplitude of PDSs and the frequency of mEPSCs [Koch et al. (3), their Fig. 7 and 8]. This appears diverse compared with the acute effect of $PGE_2$ in that a mainly presynaptic effect was produced when the organotypic slices were exposed to $PGE_2$ in a relatively long-term duration. Then the authors examined the possibility that similar homeostatic mechanisms are involved in the $PGE_2$-induced synaptic plasticity through occlusion experiments by exposing organotypic slices to $PGE_2$+TTX up to 48 h. The combined exposure showed distinct forms of homeostatic plasticity expressed as the increase in amplitude and frequency of both the PDSs up state activity and mEPSCs [Koch et al. (3), their Fig. 9 and 10]. Finally, the authors determined the role of TTX or/and $PGE_2$ in apoptosis using immunofluorescence staining for active caspase-3, and found that chronic exposure of organotypic cultures to TTX or $PGE_2$ induced increased apoptosis [Koch et al. (3), their Fig. 11]. Together, these key findings led the authors to come to the conclusion that the hyperexcitable state together with the permanent changes associated with cell apoptosis may contribute to a change in the balance between inhibition and excitation that could eventually become permanently manifested in epileptic patients.



In the light of above interesting findings, Koch et al. (3) provided fundamental data through which a link between homeostatic synaptic plasticity and $PGE_2$ was established, while several concerns on experimental methodology should be acknowledged. Firstly, Koch et al. (3) used isoflurane as anesthetic to their animals. The reasons for putting this forward are as follows: 1) isoflurane possesses anti-epilepsy property; 2) isoflurane inhibits neuronal degeneration; 3) isoflurane inhibits presynaptic R-type calcium channel resulting in inhibition of synaptic transmission; 4) isoflurane enhances $GABA_A$ receptor-dependent excitability, and suppresses glutamate-mediated excitatory currents (for review, see reference 5). Thus deep anesthesia with isoflurane before decapitation is similar to pre-

conditioning that might produce unwanted influence on synaptic plasticity especially in the immature brains used in this study. Secondly, the authors performed experiments using samples from male or female animals. Although sexual hormones might play no significant role in synaptic development at such an early period of the study animals investigated, it still cannot preclude the sex influence on impending *in vitro* study on synaptic electrophysiology because gender difference exists in synaptic density (6) and it is remarkably similar between the *in vitro* and the *in vivo* development of synapses which largely independent of environment when comparing acute slices with organotypic ones (4).

Determining the mediators of homeostatic synaptic plasticity is of great interest. As Koch et al. (3) presented that acute exposure of $PGE_2$ reduced electrophysiological activity postsynaptically, but long-term stimulation with $PGE_2$ increased presynaptic plasticity. However, the homeostatic plasticity of the nervous system is such complex that the whole molecular or cellular events involved in this process cannot be figured out totally. Synaptic connectivity is a complex network forming through neuron-to-neuron, astrocyte-to-neuron, microglia-to-neuron and neuron-to-effector organs, and the homeostatic plasticity occurs among these patterns of synapse. Although Koch et al. (3) provided evidence of pre- or/and postsynaptic plasticity after $PGE_2$ exposure, they did not present any clue that which kind of synapses were involved in this process. Additionally, the effect of $PGE_2$ on synaptic plasticity, in fact, is an integrative result detected with experimental means, of which may result from the combined influence of afferent neurons, astrocytes, microglia and inhibitory interneurons (Figure 1). Of the four subtypes of $PGE_2$ receptor, $EP_3$ was found to be involved in the regulation of $PGE_2$-associated synaptic plasticity in acute slices (3). Nonetheless, what about the downstream signaling pathways related with $EP_3$-Gi activation is not defined by Koch et al. (3) and needs to be guaranteed by further studies (Figure 1).

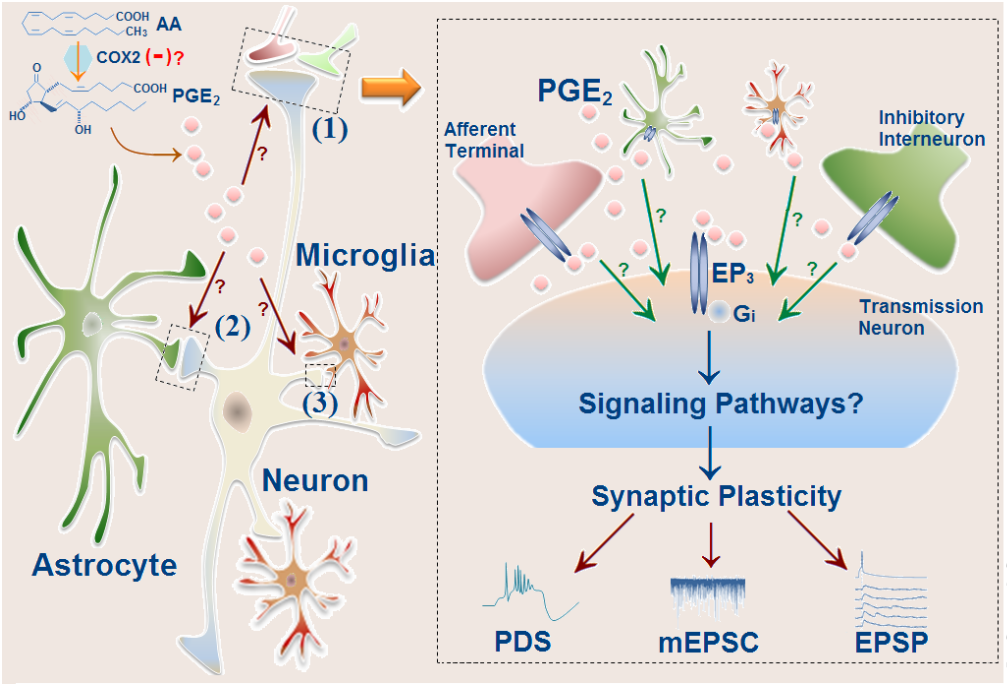



**Figure 1. Schematic of COX2-$PGE_2$ system in neural synaptic plasticity.** Arachidonic acid (AA) is converted to prostaglandin $E_2$ ($PGE_2$) by cyclooxygenase 2 (COX2) physiologically, and pathologically increased after nervous injury evoked by following inflammatory responses, and the secreted $PGE_2$ involves in the regulation of synaptic plasticity at sites of neuron-to-neuron (1), astrocyte-to-neuron (2), and microglia-to-neuron (3) connections. On micrographic display at neuron-to-neuron synapse, $PGE_2$ exerts function through binding to its subtype receptor $EP_3$, one type of G protein coupled receptor, lying within the membrane of afferent terminal, inhibitory interneuron, transmission neuron, astrocyte and microglial cell, which results in activation of unknown downstream signaling pathways and, finally displays with synaptic plasticity including changes in paroxysmal depolarization shift (PDS), miniature excitatory postsynaptic current (mEPSC) and/or excitatory postsynaptic potential (EPSP). In the light of role for $PGE_2$ in synaptic plasticity, the upstream enzyme COX2 possesses therapeutic potential by using corresponding inhibitors. Question mark (?) refers to untested or uncertained effects as indicated.

Although the study from Koch et al. (3) suggests a therapeutic potential for $PGE_2$ in epileptic patients, dissatisfactory results reported when the $PGE_2$ upstream enzyme COX2 was focused on as therapeutic target (7). Therefore, the data from Koch et al. (3), on another side, may reveal a role for COX2-$PGE_2$ system in balancing excitation and inhibition of the synaptic activities at a new setpoint that finally is maintained by the homeostatic synaptic plasticity.■

## Acknowledgements

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## Conflict of Interests

None

## References

1. Turrigiano GG, Nelson SB. Homeostatic plasticity in the developing nervous system. Nat Rev Neurosci 2004; 5: 97-107.
2. Trasande CA, Ramirez JM. Activity deprivation leads to seizures in hippocampal slice cultures: is epilepsy the consequence of homeostatic plasticity? J Clin Neurophysiol 2007; 24: 154-64.
3. Koch H, Huh SE, Elsen FP, Carroll MS, Hodge RD, Bedogni F, Turner MS, Hevner RF, Ramirez JM. Prostaglandin E2-induced synaptic plasticity in neocortical networks of organotypic slice cultures. J Neurosci 2010; 30: 11678-87.

4. De Simoni A, Griesinger CB, Edwards FA. Development of rat CA1 neurones in acute versus organotypic slices: role of experience in synaptic morphology and activity. J Physiol 2003; 550: 135-47.
5. Larsen M, Langmoen IA. The effect of volatile anaesthetics on synaptic release and uptake of glutamate. Toxicol Lett 1998; 100-101: 59-64.
6. Alonso-Nanclares L, Gonzalez-Soriano J, Rodriguez JR, DeFelipe J. Gender differences in human cortical synaptic density. Proc Natl Acad Sci USA 2008; 105: 14615-9.
7. Holtman L, van Vliet EA, Edelbroek PM, Aronica E, Gorter JA. Cox-2 inhibition can lead to adverse effects in a rat model for temporal lobe epilepsy. Epilepsy Res 2010; 91: 49-56.

## *Paper Discussed in This Journal Club*

Koch H, Huh SE, Elsen FP, Carroll MS, Hodge RD, Bedogni F, Turner MS, Hevner RF, Ramirez JM. Prostaglandin E2-induced synaptic plasticity in neocortical networks of organotypic slice cultures. J Neurosci 2010; 30:11678-87.

## PICTURE STATION

By **Frei Cristovao de Lisboa** in the 17th Century (1625-1631), Brazil. He draws birds, mammals and plants while he was in Brazil as a missionary. The original drawings, in pencil and covered in ink, are part of a manuscript "Historia dos animais e árvores de Maranhao" that is kept in an archive in Portugal. This is a Yellow-rumpled Cacique, *Cacicus Cela* (a passerine bird) and a *Crimson-crested Woodpecker* (Campephilus Melanoleucos).