The Potential of Caffeine for Functional Modification from Cortical Synapses to Neuron Networks in the Brain

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Abstract: Structure and function of the brain are use-dependent variables based on "synapse plasticity". Since synapses are driven by chemical transmitters, synaptic functions are liable to be modified by extrinsic chemicals displaying affinities for synaptic receptors or modulators. Caffeine is a widely used chemical substance that can invade synapses, and has several biochemical and metabolic actions on synaptic activities. This review focuses on the actions of caffeine on changes in structure and function in the region of the hippocampal formation and neocortex, which exhibit high synapse plasticity. At the synapse level, various synaptic receptors and channel activities are modulated by caffeine *via* mobilization of intracellular calcium, inhibition of phosphodiesterase, antagonism of adenosine receptors and GABA receptors. These actions of caffeine enable neurons to induce plastic changes in the properties of synaptic activities, such as synaptic transmission efficiency and morphology. At the network level, caffeine has the ability to activate cortical neural oscillators that deliver repetitive *N*-methyl-D-aspartate receptor-dependent signals to surrounding areas, causing strengthening of long-range inter-cortical communications. Caffeine might thus allow reorganization of cortical network functions *via* synaptic mobilizations.

1. INTRODUCTION

The brain is a complex system for information processing. The intellective device requires harmonic and coherent action of the component neuron network units, resulting in consistent and intensive operation of the network systems [23,76]. One prominent property of the brain is that structure and function, such as neural wiring and signal communicating efficiency, remain use-dependent and developmentally variable, allowing the brain to acquire the ability to process various modes of information in accordance with changing circumstances [3,9,13,78]. Mechanisms at the synapse level in local dimensions provide this brain variability. Use-dependent induction of synaptic changes is called "synapse plasticity" [11,19,43,52,53,54,59,75]. In general, induction of the synapse plasticity requires repetitive synaptic experiences. Ionotropic or metabotropic receptor activities elicited by synaptic transmission play important roles in the generation of use-dependent synapse plasticity. Production of the electro-motive forces that drive the network systems is triggered at the synapse level. Synapto-motive forces are generated by presynaptic chemical-transmitter release and postsynaptic receptor activities. Interestingly, various natural and synthetic chemicals in the external environment display affinities for synapse receptors and modulators. When these chemicals invade the synaptic cleft and chemical actions are exerted, synaptic functions are liable to be modified.

Among the natural chemicals in the external environment, caffeine is one of the most well-known chemicals able to invade the synaptic cleft. Caffeine displays affinities for several kinds of receptors embedded in the synaptic membranes and internal calcium store, and also has an affinity for cytoplasmic phosphodiesterases (PDEs), enabling caffeine to modify synaptic activities [31,32,66]. Caffeine thus displays various biochemical and metabolic actions at the synapse level. In general, plastic changes in synaptic transmission efficiency and synaptic architecture are induced according to synaptic activities *via* various kinds of modulation system [6,16,48]. If local synaptic changes are induced systematically and extensively, local changes may develop into network changes. The chemical activity of caffeine might therefore provide the potential for reorganization of brain function from synapse to wide-ranging networks.

Among the various areas of the brain, the hippocampal formation and neocortex exhibit a high susceptibility to the induction of synapse plasticity [11,13,53,75]. The present review focuses attention on these cortical regions, and explores the action of caffeine on plastic changes in structure and function from synapse to cortical network levels.

2. BASIC NEUROPHARMACOLOGICAL EFFECTS OF CAFFEINE

2.1. Effects of Caffeine on Adenosine A1 and A2A Receptors

Purines such as adenosine triphosphate (ATP) and adenosine play central roles in energy metabolism for all cells, and purinergic receptors are located on the cell surface and hence bind purines in the extracellular space [14,31,34]. Interestingly, xanthines such as caffeine block adenosine receptors, but not ATP receptors [20,31]. Adenosine receptors are coupled with G-protein, and can be divided into subtypes A1, A2A, A2B and A3 [20,22,24,31,32,34,69]. Among these subtypes, caffeine blocks A1 receptors that inhibit adenylyl cyclase (AC), in addition to A2A receptors that activate AC [22,24,31,32,34]. In neurons, A1 and A2A receptors are expressed at presynaptic terminals. A1 receptors negatively influence transmitter release from presynaptic terminals, whereas A2A receptors positively influence transmitter release [32]. While A1 receptors are widely distributed

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throughout the brain, A1 receptors are expressed at the highest level in the hippocampus and neocortex, where glutamate is used as an excitatory transmitter. Conversely, A2A receptors are not distributed widely, but are distributed locally at the highest level in the striatum and nucleus accumbens [22,24,32]. A2A receptors are expressed in dopamine-rich regions, and are co-expressed with dopamine D2 receptors [28,29,35,49,80]. A2A receptors are thus dominantly linked with the dopaminergic system, whereas A1 receptors in the hippocampus and neocortex are dominantly linked with the glutamatergic system. In addition, in hippocampal CA3 neurons, A1 receptor-selective blockade induces bursting activities, but not A2A receptor-selective blockade [82]. Caffeine is therefore considered to act predominantly on A1 receptors in the cortical regions, and positively influence presynaptic transmitter release *via* blockade of A1 receptors.

2.2. Effects of Caffeine on PDEs

The cyclic AMP (cAMP) cascade is one of the most important intracellular signaling pathways, playing a key role in the expression and modulation of neural function in the central nervous system (CNS) [8]. Activation of membrane receptors coupled to a specific G protein, Gs, such as β-adrenergic receptors or specific metabotropic glutamate (mGlu) receptors, initiates the operation of membrane-bound AC and production of cAMP as a second messenger. Protein phosphorylation or gene expression is finally induced by way of cAMP-dependent protein kinase (PKA) or cAMP response element-binding (CREB) proteins [18,55,85]. These cAMP cascades are negatively controlled by PDEs that breakdown cAMP and turn off the cAMP signaling pathways [4,30,79]. Caffeine depresses PDE activity, and intracellular cAMP is accumulated, resulting in the enhancement of cAMP signaling pathways [5,15,32].

2.3. Effects of Caffeine on Ryanodine Receptors

Calcium signaling pathways play an important role in regulating various brain functions [7]. In particular, increases in cytoplasmic calcium triggers down-stream of the intracellular calcium-dependent cascades. There are extra- and intracellular sources of calcium. Neurons include endoplasmic reticulum (ER) to store high concentrations of calcium. Calcium-release channels called ryanodine receptors are expressed in the membrane of the ER. When extracellular calcium enters the endoplasm through voltage- or receptor-operated calcium channels, ryanodine receptor channels are opened by the binding of calcium with the ryanodine receptors, and calcium is then released from the calcium store into the cytoplasm as a calcium-induced calcium release (CICR) [7,26]. Concentrations of endoplasmic calcium are thus amplified, and intracellular calcium signaling pathways are activated in a feed-forward manner. Caffeine permeating into the cell through the cell membrane combines with ryanodine receptors. This results in activation of the ryanodine receptors, reducing the threshold of the CICR and resulting in intense facilitation of CICR [25,32,36,61]. In rat hippocampal CA3 neurons, caffeine promotes epileptic discharges *via* enhancement of the CICR [56], and caffeine enhances action potential-triggered CICR in rat hippocampal CA1 neurons [71]. Amplification of intracellular calcium is thus positively controlled by caffeine through ryanodine receptors.

2.4. Effects of Caffeine on GABA Receptors

Neuron network activities are based on excitatory and inhibitory synaptic activities. The GABAergic network plays important roles in the stabilization of overall network activities. A recent study revealed that caffeine can modulate the GABAergic system. In ganglion cells of the turtle retina, caffeine depresses the activities of GABA-A receptors. This depression is mediated by caffeine facilitating CICR [1]. Similarly, in dentate gyrus cells of the hippocampus, CICR elicited by caffeine depresses the activities of GABA-A receptors [21]. In neonatal hippocampal neurons, mobilization of Ca^{2+} from caffeine-ryanodine-sensitive stores facilitates GABA release, while caffeine simultaneously depresses the activities of postsynaptic GABA-A receptors [72]. Caffeine thus affects GABA-A receptor activities by way of facilitating CICR. Conversely, although the mechanisms remain unclear, Ca^{2+}-independent inhibition of GABA-A receptor activities by caffeine occurs in hippocampal neurons [81].

3. NEUROPHARMACOLOGICAL EFFECTS OF CAFFEINE AT CORTICAL SYNAPSES

At the synapses, local synaptic potentials are generated by synaptic inputs. As local synaptic potentials are summated spatio-temporally, neurons have the ability to integrate various input signals. In addition, synapses can display changes in the efficiency of synaptic transmissions and induce morphological changes according to activity. The basic targets of caffeine mentioned above are concentrated at the synapses (Fig. **1**). Synapses are therefore considered to represent the dominant targets of caffeine.

3.1. Effects of Caffeine on Presynaptic Sites

Release of excitatory transmitter is more strongly inhibited by adenosine than release of inhibitory neurotransmitters [33]. Blockade of adenosine receptors by caffeine can thus occasionally generate overactivity at excitatory synapses [2,47]. In hippocampal CA3 in guinea pigs, blockade of A1 receptors by caffeine generates paroxysmal depolarizing shifts, and the underlying mechanisms may be increased by intracellular cAMP and Ca^{2+} influxes [62,63]. In hippocampal CA1 neurons, caffeine enhances excitatory postsynaptic potentials (EPSPs), which are mediated by antagonism of presynaptic adenosine receptors [37].

In both glutamatergic and cholinergic neurons, caffeine affects presynaptic sites. In rat hippocampal neurons, caffeine enhances acetylcholine (Ach) release from presynaptic terminals *via* blockade of A1 receptors [17].

Changes in the probability of transmitter release induced by caffeine have been investigated by focusing miniature excitatory postsynaptic currents (EPSCs) [74]. The study proposed that in rat barrel cortex, caffeine enhances glutamate release from presynaptic terminals *via* calcium release from ryanodine-sensitive internal Ca^{2+} stores.

3.2. Effects of Caffeine on Postsynaptic Sites

Postsynaptic activities can be divided into two categories: direct synaptic transmission, and indirect synaptic trans-

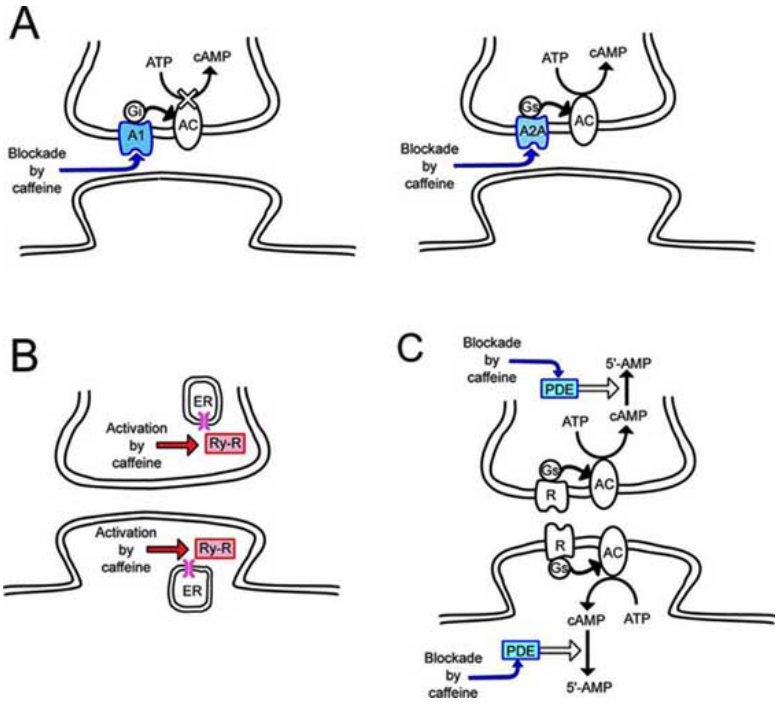

Fig. (1). Basic actions of caffeine at synapses.

(A) Presynaptic A1 receptors inhibit adenylyl cyclase (AC), resulting in decreased levels of intracellular cAMP, whereas presynaptic A2A receptors stimulate AC, increasing intracellular cAMP levels. Caffeine blocks both A1 and A2 receptors, resulting in increased and decreased intracellular cAMP levels, respectively. (B) Intracellular calcium stores are present for both pre- and postsynaptic sites. Ryanodine-sensitive calcium release channels are expressed on the calcium stores. Caffeine activates ryanodine receptor channels, reducing the threshold for calcium-induced calcium-release (CICR). (C) Intracellular phosphodiesterases (PDEs) breakdown intracellular cAMP at both pre- and postsynaptic sites. Caffeine blocks PDEs, increasing intracellular cAMP levels.

mission. Direct synaptic transmission is mediated by ligand-gated ionic channel-coupled receptors. Electro-motive force at the synapse is produced by ligand-gated ionic channel-coupled receptors. In general, two types of ionotropic glutamate receptors produce EPSPs: *N*-methyl-D-aspartate (NMDA) receptors, and non-NMDA receptors. NMDA receptors are postsynaptic activity-dependent calcium permeable channels, and play a central role in the induction of synapse plasticity, as mentioned below.

In rat hippocampal CA3 neurons, caffeine enhances both NMDA and non-NMDA receptor activities, inducing high-frequency oscillations [39]. In rat visual and parietal cortices, caffeine also enhances both NMDA and non-NMDA receptor activities, inducing α-range oscillations [89,90,92,93]. Caffeine-enhanced synaptic activities are triggered by activation of both receptors, in turn causing enhancement of the receptor activities themselves. Since adequate repetitive synaptic inputs are required for caffeine-dependent enhancement of synaptic activities, this enhancement is considered use-dependent.

Indirect synaptic transmission is mediated by G-protein-coupled metabotropic receptors. Expressed at both pre- and postsynaptic sites, mGlu receptors are involved in modulation of synaptic activities by activation of a second messenger system. Generation of a transient increase in intracellular Ca^{2+} to switch on the Ca^{2+}-signaling second messenger pathway is one of the principal roles of mGlu receptors [68]. In hippocampal CA1 neurons, the Ca^{2+} transient induced by postsynaptic mGlu receptor activation is blocked by caffeine [10]. Caffeine thus acts on mGlu receptor activities at postsynaptic sites.

GABA receptors are concerned with generation of inhibitory postsynaptic potentials, so GABA receptors negatively influence synaptic activities. In hippocampal dentate gyrus neurons, elevation of intracellular calcium levels by caffeine depresses postsynaptic ionotropic GABA-A receptor activities, showing that depression of GABA-A receptors by caffeine is dependent on intracellular calcium elevation [21, 72]. In contrast, caffeine depresses GABA-A receptor activities in hippocampal CA3 neurons, which are independent of intracellular calcium elevations [81].

3.3. Effects of Caffeine on Long-Term Potentiation and Long-Term Depression

At many cortical synapses, repetitive synaptic activities can produce long-term changes in synaptic efficiency [11,12, 59]. According to the patterns of temporal coincidence, location and intensity of pre- and potsynaptic activities, synaptic efficiency is potentiated or depressed over the long term, and termed long-term potentiation (LTP) or long-

term depression (LTD) respectively. Various kinds of LTP, LTD and associated mechanisms have been investigated and summarized in many reviews [43,48,52,53,54,59, 75]. Considering the mechanisms of LTP and LTD, whether LTP and LTD are NMDA receptor-dependent represents a central issue, since induction of activity-dependent synapse plasticity is deeply affected by NMDA receptor activities [16,43,50,73,75]. Activities of postsynaptic NMDA receptors are blocked by extracellular Mg^{2+}, and reduction of this Mg^{2+} block requires postsynaptic depolarization, allowing NMDA receptors to function as important detectors of coincident pre- and postsynaptic activities [60,67]. The coincidence between pre- and postsynaptic activities is deeply involved in the induction of synapse plasticity [40].

In general, LTP in hippocampal CA1 neurons requires both postsynaptic NMDA receptors and increased levels of intracellular Ca^{2+} by way of NMDA receptors. In contrast, caffeine induces another form of LTP in hippocampal CA1 neurons. Caffeine-dependent LTP requires neither postsynaptic NMDA receptors nor increased intracellular Ca^{2+} by way of NMDA receptors, but does require the interaction of caffeine with P1 adenosine receptors, P2 prinoreceptors and ryanodine receptors, indicating that caffeine-dependent CA1 LTP is caused by increases in presynaptic transmitter release [57, 58]. Another presynaptically induced caffeine-dependent LTP in hippocampal CA1 has been reported. In rat hippocampal CA1 neurons, caffeine promotes forskolin-induced LTP, where adenosine A1 receptor antagonism underlies the effects of caffeine [51]. Caffeine thus increases susceptibility to the induction of cAMP-dependent LTP, *via* enhancement of presynaptic cAMP accumulation. Actions of caffeine at presynaptic sites may be sufficient to induce such cAMP-dependent NMDA receptor-independent LTP.

As for LTD, postsynaptically induced caffeine-dependent LTD has been reported. Caffeine-dependent LTD in hippocampal CA neurons is postsynaptically induced in a stimulation frequency-dependent manner. LTD requires both NMDA receptor activities and calcium release from internal calcium store [65].

3.4. Effects of Caffeine on Morphological Changes in Synapses

The morphology of dendritic spines exerts a substantial effect on important aspects of synaptic activities, such as synaptic transmission and integration of synaptic information [41,73,77,87,95,96]. In dendritic spines, calcium dynamics play an important role in the expression of those synaptic functions, by way of various calcium-dependent biochemical processes. Particularly in hippocampal CA1 neurons, individual spines play an important role in detecting temporal coincidence between pre- and postsynaptic activities *via* NMDA receptors [96].

In cultured hippocampal neurons, application of caffeine causes a transient rise in intracellular calcium levels *via* ryanodine receptors in dendrites and spines, resulting in increased size of excitatory dendritic spines and changes in spine shapes [44,45]. Calcium from internal stores elicited by caffeine can thus modify dendritic spine shape [38]. Dynamics of intracellular calcium increases differently between short- and long-neck dendritic spines, suggesting that control of spatio-temporal calcium increases is provided by the shape of dendritic spines [84]. Since changes in spine structure contribute to changes in brain function [64,95], caffeine might modulate brain function *via* increases in intracellular Ca^{2+} level [38].

4. NEUROPHARMACOLOGICAL EFFECTS OF CAFFEINE ON CORTICO-CORTICAL SIGNAL INTERACTIONS

Local synaptic changes may in turn induce reorganization of cortical network function. However, this might require strong and long-range synchronization of synaptic activities or firing between neuron clusters [27,46,70,76]. In this respect, a strong relationship may exist between neural oscillations and synapse plasticity [27,83]. To understand the mechanisms of neural oscillation, several network oscillation models have been proposed [27]. Theoretically, synchronization as a non-local event is convenient for induction of synapse plasticity between long-range discrete cortical areas. Even if synchronization is a local event, however, synapse plasticity is inducible between long-range discrete areas, on the condition that the propagating system is strong and stable.

Recently, a protocol for inducing synchronized membrane potential oscillation at a frequency of 8-10 Hz in the visual cortex has been developed, by applying caffeine to rat brain slices [90,92,93]. The start of oscillation requires a trigger input, and oscillation comprises several propagating wavelets. Oscillation induction requires low-frequency activation of input fibers in conjunction with caffeine application, suggesting that use-dependent mechanisms underlie oscillation induction. Notably, induction of oscillation requires both NMDA receptor activation and the release of intracellular calcium from the internal calcium store, suggesting that functional coupling between NMDA and ryanodine receptors underlies caffeine-dependent oscillation [92,93]. In the absence of caffeine, the strength of functional coupling between NMDA and ryanodine receptors in hippocampal neurons depends on the magnitude of NMDA receptor activation [42]. In the presence of caffeine, caffeine activates ryanodine receptors and potentiates presynaptic glutamate release, resulting in an increased likelihood of functional coupling between NMDA and ryanodine receptors.

Strictly speaking, caffeine-dependent oscillation comprises initial propagating components and subsequent oscillatory components. These subsequent oscillatory components emerge from the local area in the visual cortex, showing that the oscillator is localized. Although synchrony is a local event, the neural oscillator delivers NMDA receptor-dependent signals to the surrounding areas [90,94]. These signal deliveries finally cause strengthening of non-NMDA receptor-dependent inter-cortical functional connections between long-range discrete areas [94]. The oscillators are separately located in the medial and lateral secondary visual cortices. Horizontal connections in layer II/III between the primary and secondary visual cortices are strengthened after repetitive NMDA receptor-dependent signal delivery originating from the oscillators.

Another study revealed that the oscillator is also located outside the visual cortex. The retrosplenial cortex is located

at a critical position between the visual cortex and hippocampal formation. In the area of the retrosplenial cortex, the oscillator is present in the retrosplenial granular a cortex (RSGa). Activation of oscillators in both the secondary visual cortex and RSGa under application of caffeine finally opens functional connections from primary visual cortex to the postsubiculum [91]. Hence, in the presence of caffeine, an oscillator with local synchronization can induce spatially wide-ranging synapse plasticity from the visual cortex to the hippocampal formation.

These studies resulted in the "oscillator-dependent plasticity hypothesis" [90,91,94]. This hypothesis is illustrated in Fig. **2**, showing the induction of plastic changes in the visual cortex in the presence of caffeine. Caffeine, in combination with low-frequency electrical stimulation, promotes the voltage oscillator delivering NMDA receptor-dependent signals at a frequency of 8-10 Hz from the secondary visual cortex to surrounding cortical areas. This induces opening and strengthening of non-NMDA receptor-dependent signal pathways. Repetitive activities of an NMDA receptor-dependent voltage oscillator thus induce use-dependent network plasticity in the cortical regions.

The same mechanism is present between the gustatory insular cortex and somatosensory parietal cortex. In these areas, the oscillator that delivers NMDA receptor-dependent signals is located in the parietal cortex, and is driven under application of caffeine by repetitive low-frequency stimulation. Oscillatory NMDA receptor-dependent signal delivery causes strengthening of functional connections between the insular and parietal cortices [88,89].

Theoretical investigation has demonstrated that oscillation-dependent mechanisms underlie the establishment of working memory. The study showed that NMDA receptor-mediated synaptic transmission at a frequency of 8 Hz is required to sustain persistent network activities of the prefrontal cortex [86]. Results collected by experimental and theoretical studies thus suggest that NMDA receptor-mediated α-range signal delivery plays a critical role in the generation and stabilization of functional networks *via* plastic changes from synapses to networks.

5. CONCLUSION

Caffeine displays various general pharmacological actions: 1) blockade of presynaptic A1 and A2A receptors, resulting in modulation of transmitter release; 2) activation of internal ryanodine receptors, resulting in reduction of CICR threshold; 3) blockade of PDEs, resulting in intracellular cAMP accumulation; and 4) blockade of GABA-A receptors, resulting in depression of inhibitory synaptic activities. In the brain, these general actions of caffeine are liable to take place at the synapses, as the targets of caffeine and its effects are concentrated at the synapses. Particularly in the regions of the hippocampal formation and neocortex, where use-dependent synapse plasticity is liable to be established, caffeine is able to enhance synaptic NMDA receptor activities and intracellular calcium signaling pathways, through which plastic changes in synaptic morphology and transmission efficiency are induced. In cortical neuron networks, the actions of caffeine in combination with adequate input fiber activation produce opening and strengthening of long-rage inter-cortical signal

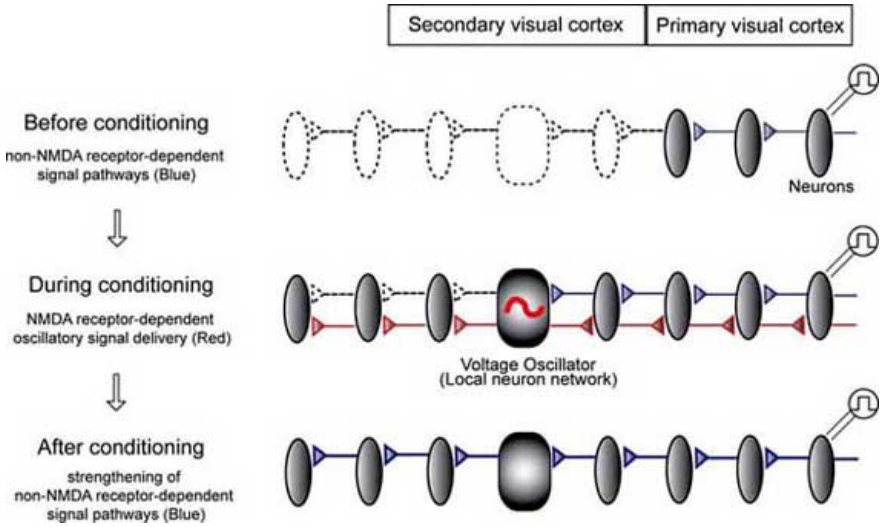

Fig. (2). Oscillator-dependent plasticity hypothesis.

Each ellipse indicates a postsynaptic neuron or neuron cluster, and small triangles indicate presynaptic terminals. In the presence of caffeine, low-frequency electrical stimulation is applied to the primary visual cortex as "conditioning". Horizontal pathways in blue represent non-NMDA receptor-dependent pathways. A voltage oscillator comprising local neuron networks is equipped in the secondary visual cortex, and horizontal pathways in red represent *N*-methyl-D-aspartate (NMDA) receptor-dependent pathways. (Upper) Before conditioning, signals elicited by the primary visual cortex stimulation propagate within a short distance. (Middle) During conditioning, non-NMDA receptor-dependent signals switch on the oscillator that delivers NMDA receptor-dependent oscillatory signals back and forth. (Lower) After conditioning, non-NMDA receptor-dependent pathways are strengthened, and signals propagate a long distance. Note that when NMDA receptor activities are blocked from the beginning, strengthening of non-NMDA receptor-dependent pathways is not induced [90,91,94].

communications *via* activation of cortical neural oscillators that deliver NMDA receptor-dependent signals to surrounding areas. The actions of caffeine at a synapse level thus cause plastic changes at the cortical network level.

Most of the experimental evidence has been collected from basic studies using peculiar conditions *in vitro*. However, these basic studies have elicited the potential of caffeine, and the evidence indicates that caffeine exerts profound actions from synapse to neuron networks in the cortical regions. Caffeine might thus provide the potential for use-dependent reorganization of brain function.

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