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Review Article

Platelet-activating factor: a new target site for the development of nootropic agents

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CONTENTS

Summary

Long-term potentation (LTP) is a neurophysiological process of memory formation in which brief high-frequency stimulation of afferent fibers increases the calcium-dependent biosynthesis of platelet-activating factor (PAF) in postsynaptic neurons. PAF, a retrograde messenger, enhances the synaptic exocytosis of glutamate. Glutamate activates the postsynaptic Ca^{2+} cascade and the Ras mitogen-activated protein (MAP) kinase (MAPK) system to modulate the expression of immediate early and late response genes, which may be responsible for the formation of short- and long-term memory. Excessive release of PAF produces neurodegeneration, which can be prevented by PAF antagonists such as BN-52021. PAF analogs and PAF acetylhydrolase inhibitors may prove to be potential agents for facilitating the memory process in patients suffering from dementia.

Introduction

Learning is an experience-dependent process of obtaining knowledge about the world (1) and memory is a faculty by which sensations, impressions and ideas are stored and recalled. Various parts of the brain, especially the hippocampus, cerebral cortex, amygdala and neocortex, are responsible for memory processes. Long-term potentiation is considered to be the major molecular basis of learning and memory, whereby stimulation of afferent fibers increases the postsynaptic biosynthesis of the retrograde messenger, which in turn increases the release of glutamate from presynaptic neurons and the expression of early and late response genes, which are responsible for the formation of short- and long-term memory.

Neurobiology of memory

Memory can be classified into declarative (explicit) memory, stored in the medial temporal lobe (especially the hippocampus) (2-5) and diencephalon, and non-declarative (implicit) memory, stored in the striatum (6), neocortex (7), amygadala (8) and cerebellum (9). Three basic processes are required to acquire new memory, *i.e.*, registration, consolidation and retrieval of information (10). Registration of information forms the sensory memory (SM), or short-term memory (STM), consolidation entails the transfer of registered SM/STM to long-term memory (LTM) (11, 12) and the recall of information from the SM/STM/LTM when required is known as retrieval (11). The brain stores the information by changing the efficacy of synapses (1, 13). Coincidence activity (14), the modulatory neuron, or third neuron (15), and LTP (16) are reported to produce synaptic strengthening (17). Various experiments on LTP have supported Hebb's hypothesis, which implicates the involvement of synaptic plasticity in memory (16, 18-21). Brief high-frequency stimulation of afferent fibers of hippocampal neurons induces LTP. Such stimulation releases glutamate from presynaptic neurons and activates postsynaptic glutamate receptors (22), such as AMPA receptors (23, 24), NMDA receptors (25, 26) and metabotropic glutamate receptors (27). Persistent activation of AMPA receptors by glutamate produces sufficient postsynaptic depolarization to overcome Mg^{2+} blockade and allow influx of Ca^{2+} through pores of NMDA receptors (28). Elevated Ca^{2+} ions bind with calmodulin to form the Ca^{2+}/calmodulin complex (29) which activates nitric oxide synthase (NOS), especially the endothelial isoform eNOS, to form nitric oxide (NO) (30). The backward diffusion of several endogenous substances formed in postsynaptic neurons, such as NO (31), carbon monoxide (CO) (32), arachidonic acid (AA) (33, 34) and PAF (35-37), is known as the retrograde phenomenon, and these agents are called retrograde messengers. These retrograde messengers activate

presynaptic neurons to release neurotransmitters such as glutamate. The Ca^{2+}/calmodulin complex activates post-synaptic calmodulin kinase II (29), protein kinase C (PKC) (38, 39), protein kinase A (PKA) and tyrosine kinase, which in turn activate the Ras signaling system (28, 40). Ras-GTP and PKA subsequently activate the MAPK/ERK cascade system to generate retrograde signals and induce the expression of the immediate early response gene and late response gene responsible for short-term and long-term memory, respectively (11, 40). Rac and Raf, as components of the Ras signaling system, activate the transcription of jun by activation of stress-activated protein kinases (SAPKs) and of ternary complex factors (TCFs) through activation of MAPKs, respectively (41). MAPK is translocated to the nucleus to activate two parallel signaling pathways in the fos promoter, *i.e.*, the MAPK/ERK (extracellular signal-regulated kinase)-TCF pathway targeting serum response element (SRE) and the MAPK/ERK-CREB (cAMP response element-binding protein) pathway targeting CRE. The c-Jun N-terminal kinases (JNKs) and p38 (members of SAPKs) phosphorylate activating factor transcription element-2 (ATF2). The JNKs also phosphorylate c-jun. A heterodimer consisting of c-jun and ATF2 activates the AP-1 site in the c-jun promoter and consequently increases the expression of c-jun. The final result of the concerted activity of these transcription modulators is to increase the concentration of the jun-fos dimer, which will activate an unknown target gene (40), bring about alterations in synaptic structure and induce formation of new synapses (42, 43). Induction of the late response modulates the formation of various enzyme proteins responsible for the development of long-term memory. Activation of post-synaptic PKC has been reported to activate silent AMPA receptors (30). The calmodulin kinase II translocates to the postsynaptic density (PSD) and interacts with NMDA receptors to prolong their activated state (28).

Biology of PAF

PAF, 1-*O*-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine, constitutes a component of all cells. PAF was discovered by Henson (44) as a soluble factor released from leukocytes to produce platelet aggregation, and was named by Benveniste *et al.* (45). Muirhead (46) described APRL (antihypertensive polar renal lipid) produced by interstitial cells of the renal medulla, which was found to be identical to PAF (47-49).

1-*O*-Alkyl-2-acylglycerophosphocholine, a precursor of PAF found in high concentrations in the membranes of many types of cells (50, 51), is converted to an inactive intermediate, lyso-PAF, by active phospholipase A_2 (PLA_2) (52). Lyso-PAF is further transacetylated by acetyl-coenzyme A in a reaction catalyzed by lyso-PAF acetyltransferase to yield PAF (53). Both phospholipase and acetyltransferase are Ca^{2+}-dependent enzymes and therefore PAF synthesis is regulated by the availability of Ca^{2+} (53-55). Within the cell, part of newly synthesized PAF is inactivated back to lyso-PAF by PAF acetylhydrolase. Lyso-PAF is further converted to 1-*O*-alkyl-2-acyl-glycerophosphocholine by an acyltransferase (56), which is inhibited by Ca^{2+} ions (57). Alternative pathways of PAF synthesis, such as CoA-independent transacylase and the *de novo* route of synthesis, are not yet clear.

Lyso-PAF is present (active form) in many areas of the brain (58-62). Tiberghien et al. (63), using a competitive radioreceptor binding assay (RIA), reported that PAF is present in the cortex (0-16 ng/g wet tissue), hippocampus and midbrain (62), whereas lyso-PAF is found in high concentrations in the hippocampus (7 μg/g wet tissue), hypothalamus (2.5 μg/g wet tissue), medulla oblongata and corpus striatum, and in low concentrations in the cortex (0.7 μg/g wet tissue) and cerebellum. Bito *et al.* (59) confirmed the presence of PAF in rat brain.

PAF and neurodegeneration

PAF at physiological concentrations acts as a retrograde messenger and modulates the release of neurotransmitters (such as glutamate) to facilitate learning and memory. On the other hand, high concentrations of PAF produce neurodegeneration (64). Brain injury due to cerebral hypoxia or brain trauma activates PLA_2, which in turn increases the biosynthesis of PAF in postsynaptic neurons (52, 53, 65). The increased release of PAF from postsynaptic neurons enhances the releases of glutamate by exocytosis, and activates glutamate receptors and consequently elevates intracellular calcium in target cells. Increases in intracellular calcium enhance the expression of the cyclooxygenase type 2 (COX-2) gene, which may produce neurodegeneration through an unknown mechanism (67, 68).

PAF antagonists and neurodegenetration

BN-50730, a potent intracellular PAF antagonist (69), has been reported to inhibit COX-2 gene induction and provide neuroprotection (53, 68, 70). BN-52021, a membrane PAF receptor antagonist (58), provides neuroprotection by inhibiting the PAF-induced release of glutamate and induction of the COX-2 gene (67, 70).

Cognitive impairment is the most common neurological complication of advanced HIV-1 infection. Excessive release of PAF produces neuronal injury, which further leads to cognitive impairment in HIV patients (71). Lexipafant, the first PAF antagonist, is used to improve cognitive dysfunction in HIV-infected subjects. Lexipafant produced significant improvement in cognition at the well-tolerated dose of 500 mg/kg in HIV-infected subjects (72). *Ginkgo biloba* extract, containing ginkgolide B (a PAF antagonist), other ginkgolides and free radical scavengers, has been shown to produce a neuroprotective effect during seizure activity and hypoxia/ischemia-induced neurodegeneration (73). Recent evidence has suggested that the neuroprotective effect of *Ginkgo*

biloba extract may be due to its direct effects on the cholinergic system (74, 75). This contention is further supported by clinical trials conducted with a special *Ginkgo biloba* extract (EGb-761) (76, 77).

PAF as a retrograde messenger

Brief and high-frequency stimulation of afferent fibers of the hippocampus induces LTP as a result of a sustained increased release of glutamate from presynaptic neurons. Glutamate activates postsynaptic glutamate receptors (22) and consequently increases the postsynaptic intracellular Ca^{2+} level. Elevated intracellular Ca^{2+} levels in postsynaptic neurons will lead to an increase in the biosynthesis of PAF through activation of the enzyme PAF acetytransferase (52, 54, 55). It has been reported that methylcarbamyl-PAF microinjection to postsynaptic cells increased the frequency of miniature excitatory postsynaptic currents for at least 20 minutes, which suggests that postsynaptically generated PAF produces an increase in glutamate release from presynaptic neurons (78, 79). It has been reported that a non-hydrolyzable analog of PAF such as carbamyl-PAF is associated with increased glutamate-mediated excitatory synaptic transmission in cultured hippocampal neurons (78). High-frequency stimulation (HFS) of presynaptic neurons has been reported to produce a ninefold increase in PAF release in the extracellular environment and to induce LTP in neurons. Application of PAF analogs has been found to increase the frequency of miniature excitatory postsynaptic potentials (EPSPs). PAF may diffuse from postsynaptic sites of synthesis to presynaptic sites of action, and act as a retrograde messenger in the induction of LTP (35, 36, 65, 79, 80). PAF activates presynaptic G-protein-coupled PAF receptors and the formation of inositol triphosphate may increase the intracellular Ca^{2+} levels (81). A presynaptic rise in extracellular Ca^{2+} promotes vesicular exocytosis of glutamate from presynaptic neurons (35, 37) and will enhance the glutamate concentrations in the synapse (78, 80). Activation of postsynaptic glutamate receptors and presynaptic PAF receptors in a coordinated fashion to amplify Hebbian synaptic transmission will lead to LTP induction (37). PAF may also play a role in LTP induction through pre- and postsynaptic structural changes (36).

PAF in learning and memory

PAF is a bioactive phospholipid mediator of LTP (18-20, 82, 83), synaptic plasticity and memory formation (84). Intrahippocampal and intra-amygdala infusion of the PAF analog *O*-hexadecyl-2-*N*-methylcarbamyl-*sn*-glycero-3-phosphocholine (mc-PAF) has been shown to facilitate the LTP process (79) and to enhance learning and memory in experimental animals (82). PAF antagonists have been reported to impair learning and memory (67). Intracerebroventricular (i.c.v.) injection of PAF attenuates retrograde amnesia produced by PAF antagonists such as BN-52021 (85). Moreover, BN-52021-induced amnesia is also reversed by a non-selective PAF hydrolase inhibitor (85, 86). Administration of the PAF analog mc-PAF into the hippocampus (10 minutes after training), amygdala (immediately after training) and entorhinal cortex (100 minutes after training) greatly improved retention test performance in a habitual task, and administration of the PAF antagonist BN-52021 as above produced amnesia (58, 82, 87). Moreover, administration of BN-52021 into the intradorsal striataum (caudate putamen) at 2 hours after training produced no effect on retention. However, administration of mc-PAF and BN-52021 immediately after training facilitated and impaired retention, respectively (70, 88). This suggests the time-dependent involvement of PAF in memory processes.

The application of BN-52021 to the CA1 region of the hippocampus, prevented brief tetanus-induced LTP formation (33, 79). Moreover, BN-52021 and BN-50730 induced retrograde amnesia which was attenuated by physostigmine, an acetylcholinesterase (AChE) inhibitor. This may be due to increased concentrations of cerebral acetylcholine and the consequent increase in PAF release (89). The anterograde amnesia produced by alprazolam may be mediated through benzodiazepine receptors, because it is blocked by flumazenil, a selective benzodiazepine receptor antagonist (90). Moreover, benzodiazepine-induced anterograde amnesia is not affected either by PAF nor by cigarette smoke extract (CSE), a PAF acetylhydrolase inhibitor (86), suggesting that anterograde amnesia produced by benzodiazepines is not mediated through PAF receptors (85). Cigarette smoke extract prevents retrograde amnesia induced by triazolam (85) and BN-52021, whereas no such effect is noted on anterograde amnesia induced by diazepam or triazolam. The retrograde amnesia observed with BN-52021 and triazolam may be mediated through PAF receptors because PAF acetylhydrolase inhibitors such as CSE (85) and phenyl methyl sulfony fluoride (PMSF) (87) have been shown to prevent their amnesic effect, possibly by increasing the concentration of PAF. Hence, PAF may play an important role in the development of retrograde amnesia (85, 91, 92).

PAF and development of nootropic agents

Experimental evidence implicates the involvement of PAF in the facilitation of LTP and improvement of learning and memory. Therefore, PAF analogs may provide a good therapeutic alternative to treat patients with memory loss. PAF hydrolase inhibitors such as CSE are reported to improve retention test performance in the Morris water maze task (92). The development of PAF hydrolase inhibitors may equip us with new therapeutic agents to be used in memory loss and learning impairment.

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