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Convergence of neurotransmissions at synapse on IEG regulation in nucleus

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TABLE OF CONTENTS

1. ABSTRACT

There is no doubt that synaptic activity-regulated expression of immediate early genes (IEGs) contributes to long-lasting changes in neural functions, including learning and memory. Consequently, dysregulation of IEG expression has been involved in the conditions of neural and psychiatric disorders and cognitive dysfunction. This has mainly been demonstrated using genetically modified animal models and neuropharmacological analyses. The regulatory mechanisms of IEG expression have been investigated recently and have re-emphasized the role of IEG expression in plasticity-related processes as well as elucidating molecular mechanisms and drug targets for neurological and psychiatric disorders. This review summarizes recent studies of IEG regulation, including our findings of IEG expression regulated by excitatory and modulatory neurotransmissions. In addition, we propose possible roles for IEG regulation in neurological and psychiatric disorders and long-lasting neural functions. This review improves our understanding of the association between IEG regulation and neural function and diseases, and may promote the discovery of novel drug targets for psychiatric disorders.

2. INTRODUCTION

The brain consists of complicated neural circuits and is the center for acquisition, maintenance, and processing of environmental as well as physiological information to control cognition, emotion, learning, memory, and other physical and physiological functions. Glutamatergic excitatory neurotransmission plays a central role in transmitting information within the brain. Strong synaptic activation evoked by glutamatergic neurotransmission promotes long-lasting synaptic strength termed long-term potentiation (LTP). In contrast, weak synaptic activation elicits long-term depression (LTD). These long-lasting changes in synaptic function underlie synaptic plasticity, which is a cellular mechanism for learning and memory (1). *De novo* mRNA and protein synthesis is required for long-term memory as well as long-lasting changes in synaptic functions (2). The framework is as follows: (i) synaptic activation induces Ca^{2+} influx into neurons via Ca^{2+} channels such as *N*-methyl-D-aspartate (NMDA) receptors (NMDAR), (ii) the increase in intracellular Ca^{2+} triggers biochemical changes in intracellular molecules including protein kinases and phosphatases, (iii) transcriptional regulation of target

genes is controlled by post-translational modifications of transcription factors, and (iv) synaptic structure and function are modified by synaptic activity-regulated gene products (3, 4, 5, 6). Essentially, communication between synapses and the nucleus play an important role in long-lasting changes in neural functions. However, synaptic activity-dependent gene expression has mainly been used to identify active neurons and the role of activity-regulated gene expression in neural functions and diseases has not been fully elucidated.

Modulatory neurotransmissions, which are evoked by neuromodulators including monoamines (e.g., adrenaline, noradrenaline, dopamine, and serotonin), amino acids (e.g., glutamate), numerous hormones, and neuropeptides, also participate in neurotransmissions. Although glutamatergic excitatory neurotransmission is mediated via ionotropic glutamate receptors, neuromodulators exert their functions via metabotropic G protein-coupled receptors (GPCR). Importantly, the function of ionotropic glutamate receptors can be modulated by GPCR-mediated intracellular signaling pathways such as protein kinase A (PKA), protein kinase C (PKC), and Src family kinase (7), as well as direct interaction between these receptors; for example, the dopamine D_1 receptor interacts with the GluN1 subunit of NMDAR (8). The neuromodulation of ionotropic glutamate receptors by GPCRs suggests that simultaneous glutamatergic and modulatory neurotransmissions mediate the response of postsynaptic neurons for long-term plasticity. However, the downstream events of excitatory and modulatory neurotransmissions are not well defined. Fukuchi *et al*. identified a distinctive intracellular signaling pathway that regulated the expression of plasticity-related genes in response to convergent neurotransmissions (9). In this review, we summarize the regulation of gene expression in neurons and describe how the expression of plasticity-related genes is controlled by excitatory and modulatory neurotransmissions. Finally, we discuss the possible role of neuromodulator-regulated gene expression in neural functions and diseases. This review improves our understanding of the molecular mechanisms underlying plasticity-related events as well as neural and psychiatric disorders, and may promote the development of novel therapeutic targets for these diseases.

3. ACTIVITY-DEPENDENT REGULATION OF IEG EXPRESSION

3.1. Regulation of IEG expression in neurons

Immediate early genes (IEGs) are rapidly transcribed by pre-existing transcription factors, originally found in virus-infected cells (10). Currently, rapid inducible genes that respond to a variety of stimuli (including growth/trophic factors, hormones, and cytokines) in mitotic and post-mitotic cells without *de novo* protein synthesis are classified as IEGs (11). In neurons, strong synaptic activation is evoked by glutamatergic excitatory neurotransmission and induces the expression of IEGs encoding factors that modulate synaptic structure and function (From synapse to nucleus) (Figure 1A). These factors then control neural and synaptic properties (From nucleus to synapse) (Figure 1A). This communication between synapse and nucleus plays an important role in long-lasting neural alterations underlying learning and memory (2, 3, 4, 5, 6).

How is synaptic information transferred to the nucleus to regulate IEG expression? Synaptic activation triggers an influx of Ca^{2+} through Ca^{2+} channels such as NMDAR and L-type voltage-dependent Ca^{2+} channels (L-VDCC). Ca^{2+} influx activates intracellular signaling pathways including protein kinases and phosphatases that control transcription factor activity (Figure 1B). Transcription factors such as cAMP-response element (CRE)-binding protein (CREB), serum-response factor (SRF), myocyte enhancer factor 2 (MEF2), and neuronal PAS domain protein 4 (NPAS4), participate in synaptic activity-dependent regulation of IEG expression (12). These transcription factors are believed to modulate brain functions by regulating the expression of target IEGs. The proto-oncogene *c-fos* is a well-described IEG and is rapidly induced by synaptic activity (13). Because the expression of *c-fos* is induced in activated neurons, it has been used to label activated cell populations during the study of memory engrams (14, 15). Genes encoding secretory and synaptic proteins such as brain-derived neurotrophic factor (BDNF) (16) and Homer1A/Vesl1S (17) are also IEGs, indicating that neuronal IEGs also encode functional molecules that positively regulate neural and synaptic functions.

Synaptic activity-regulated IEGs are classified into two main groups: rapid- and slow-response IEGs. Several IEGs encode transcription factors such as *c-fos* and *Npas4* that are rapidly transcribed, while others encode proteins including BDNF and Homer1A that have relatively slow kinetics. The molecular mechanism underlying the activity-regulated transcription of rapid-response IEGs was recently revealed; neuronal activity induces the formation of DNA double strand breaks by topoisomerase IIβ in the promoter region of these IEGs to induce expression (18). This finding supported the concept that the expression of a subset of IEGs, particularly rapid-response transcription factors, is topologically constrained and that these constraints can be resolved in a synaptic activity-dependent manner. Although DNA double strand breaks contribute to activity-dependent IEG expression, they still need to be repaired correctly. Interestingly, more DNA double strand breaks have been reported in neurodegenerative disorders (19, 20), suggesting that unrepaired or incorrectly repaired DNA

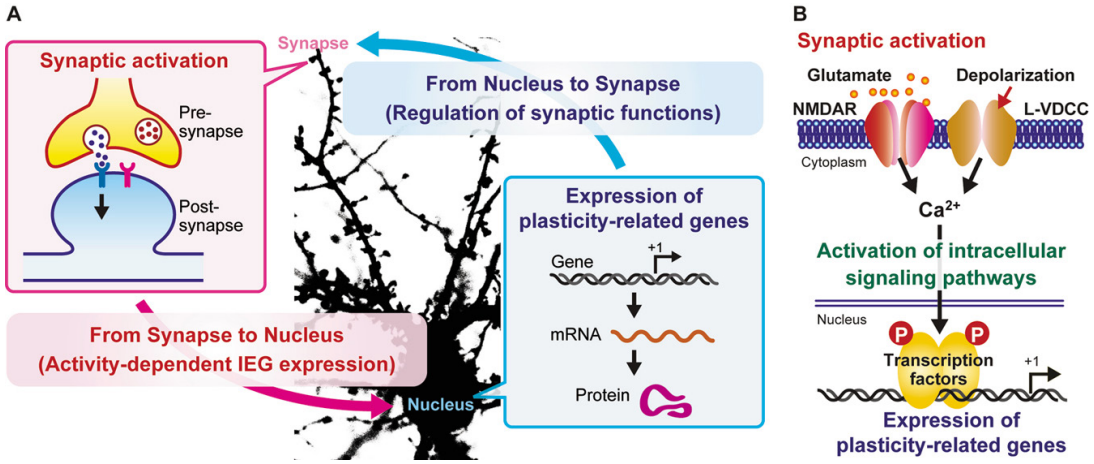

Figure 1. Scheme of synaptic activity-regulated expression of plasticity-related genes. (A) Strong synaptic activation activates intracellular signaling pathways resulting in transcriptional regulation of plasticity-related genes in the nucleus. The molecules that are up-regulated in response to synaptic activation then modulate the structure and function of synapses. (B) A simplified scheme of activity-dependent gene expression in neurons.

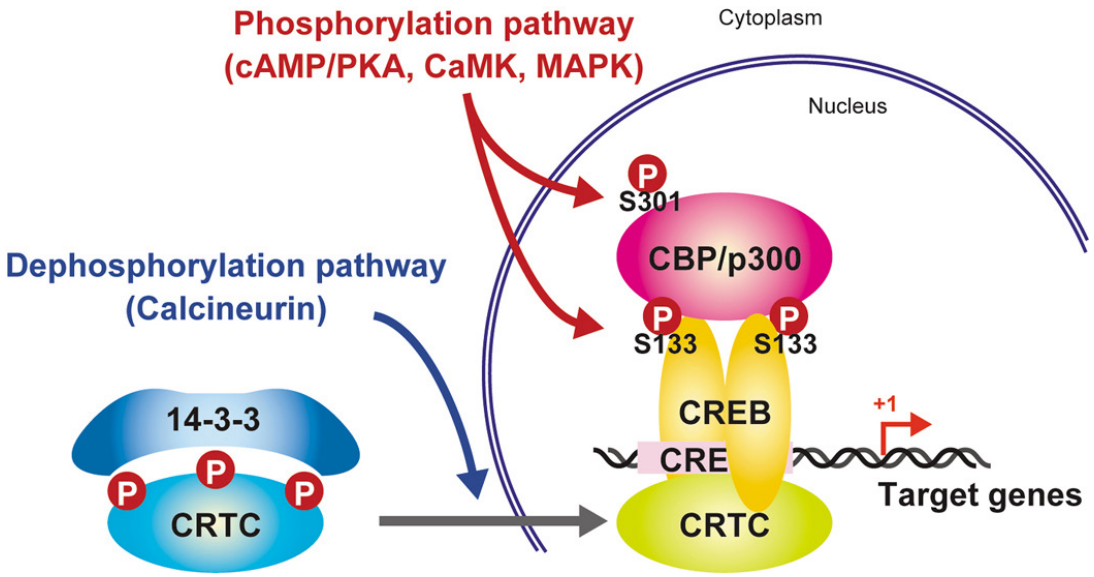

Figure 2. CREB-regulated transcription. CREB regulates transcriptional activation of its target genes in a phosphorylation-dependent or -independent manner. Phosphorylation-dependent and -independent transcriptional activation is mediated by the coactivators CBP/p300 and CRTCs.

may be associated with these disorders. In support of this, it has been shown that amyloid-β exacerbates DNA double strand breaks (21). How synaptic activity regulates the formation of DNA double strand breaks remains to be elucidated.

3.2. CREB: a memory-enhancing transcription factor

The transcription factor CREB was first identified as a nuclear protein that bound to CRE in the somatostatin gene (22). CREB is a master regulator of synaptic activity-dependent IEG expression (23). Transcriptional activation of target genes by CREB is controlled in a CREB phosphorylation-dependent or -independent manner (Figure 2). CREB phosphorylation is a well-known regulatory mechanism of CREB-regulated transcriptional activation. Several kinases such as PKA, mitogen-activated protein kinase (MAPK), and Ca^{2+}/calmodulin-dependent protein kinase (CaMK), phosphorylate CREB at Ser133, which is positioned in the kinase-inducible domain (KID). CREB phosphorylation promotes interaction of the KID with the KIX domain of CREB-binding protein (CBP)/p300 (24, 25). CBP/p300 is a histone acetyltransferase (HAT), and activates transcription of relaxing chromatin structure (26). CBP itself is also regulated by CaMKIV-mediated phosphorylation (27). Transcription of CREB-target genes is also controlled by CREB-regulated

transcription coactivators (CRTCs). In contrast to CBP/p300, CRTC-mediated CREB-dependent transcription is independent of CREB phosphorylation (28, 29, 30, 31). Phosphorylated CRTCs are captured by the scaffold protein 14-3-3 and localize mainly in the cytoplasm. When dephosphorylated by calcineurin, CRTCs translocate to the nucleus and interact with the basic leucine zipper (bZIP) domain of CREB to recruit basic transcription factors. There are three CRTC isoforms (CRTC1, CRTC2, and CRTC3) and CRTC1 is the most abundantly expressed in the central nervous system (32). Although CBP/p300 and CRTCs control CREB-regulated transcription independently, the coordination of CREB, CBP, and CRTC may contribute to enhancing CREB-dependent transcription (33, 34).

CREB was shown to play an important role in memory formation by two research groups in 1994, using gene manipulation strategies. Yin *et al*. disrupted CREB function in *Drosophila* by inducible transgenic overexpression of dominant-negative CREB. With this approach, they demonstrated that CREB is necessary for long-term memory formation (35). Bourtchuladze *et al*. performed targeted disruption of CREB in mice by inserting a neomycin resistance gene into exon 2 of the *Creb* gene, deleting two CREB isoforms. The authors demonstrated a role for CREB in long-term memory in these mice (36). These findings strongly suggested that enhanced CREB activity facilitates long-term memory formation and CREB dysfunction causes memory loss. In support, mice expressing dominant active forms of CREB exhibited enhanced long-term memory (37). CREB activity is controlled by phosphorylation, therefore activators of CREB phosphorylation-related pathways should improve memory impairment. One candidate is a phosphodiesterase (PDE) inhibitor, which hydrolyzes cyclic nucleotides including cAMP and activates PKA, inducing CREB phosphorylation. Pharmacological studies have revealed a number of PDE inhibitors with beneficial effects in mouse models of neurodegenerative disorders such as Alzheimer's disease (38), Huntington's disease (39), chronic stress-induced cognitive decline (40), and aging-associated memory impairment (41). These reports indicate that CREB represents a potent drug target for treating these diseases.

CREB coactivators also contribute to neural functions. CBP deficient mice have memory deficits (42, 43, 44), and represent a mouse model of Rubinstein-Taybi syndrome, which is a genetic disease characterized by mental retardation and physical abnormalities (45). Hirano *et al*. demonstrated the role of CREB coactivators CBP and CRTC in two different types of memory in Drosophila. CBP was involved in long-term memory formation after multiple rounds of spaced training, whereas CRTC was participated in appetite-related long-term memory formation after single training (46). CRTC1 is also involved in long-term memory in mice (47, 48). Conversely, CRTC1-mediated transcriptional regulation is disrupted in Alzheimer's disease (49, 50, 51). Therefore, dysfunction of CREB and its coactivators triggers neural dysfunction resulting in neurological disorders.

3.3. *Bdnf*: an activity-regulated IEG encoding a master regulator of neural function

The gene encoding BDNF, which plays a fundamental role in a variety of functions in the nervous systems, is one of IEGs. BDNF was identified in the pig brain in 1982 (52), as a member of the neurotrophin family, which includes nerve growth factor (NGF), neurotrophin-3 (NT-3), and NT-4/5 (53). BDNF regulates neural development and function, including development of neural circuits, spinogenesis, and synaptogenesis, as well as controlling synaptic properties. For example, hippocampal LTP was impaired in mice lacking BDNF (54), and this impairment was rescued by exogenous addition of BDNF (55). In conditional *Bdnf* knockout mice, the growth of dendrites and spines was impaired in striatal neurons (56) and spine density was reduced in cortical pyramidal cells (57). Similar findings have been reported in conditional *TrkB* knockout mice (58, 59). Taken together, these reports indicate that the BDNF-TrkB pathway regulates synaptic structure and functions, both of which underlie long-lasting synaptic plasticity. The specific functions of BDNF have been also reviewed previously (e.g., 60, 61, 62).

The expression of BDNF gene (*Bdnf*) is controlled by transcriptional and post-transcriptional mechanisms. Mouse and rat *Bdnf* consist of eight untranslated exons (exon I, II, III, IV, V, VI, VII, and VIII) and exon IX, which contains the coding sequence for preproBDNF protein (Figure 3A) (63). Alternative *Bdnf* promoters are located upstream of each exon and control the transcription of downstream genes. The *Bdnf* promoter I, IV, and IX were reported to be activated in a neuronal activity-dependent manner (64, 65, 66, 67, 68, 69). The activity-dependent activation of these promoters is controlled by the activity-dependent transcription factors CREB and NPAS4 (69) (Figure 3D). Other transcription factors involved in *Bdnf* transcription were briefly described in our recent review (70). The primary transcripts of *Bdnf* are alternatively spliced. There are multiple splicing donor sites located at 3' end of each exon and a single splicing acceptor site in exon IX. These generate characteristic *Bdnf* transcripts, which have distinct 5'-specific exons but contain a common coding sequence (63, 70) (Figure 3A, B). Moreover, neuronal activity increases the stability (71) and dendritic targeting (72) of *Bdnf* mRNA (Figure 3D), the latter of which was rarely detected in neurons (73). Thus, the activity-dependent expression of *Bdnf* is controlled by transcriptional and post-transcriptional machineries (Figure 3D). Although *Bdnf*

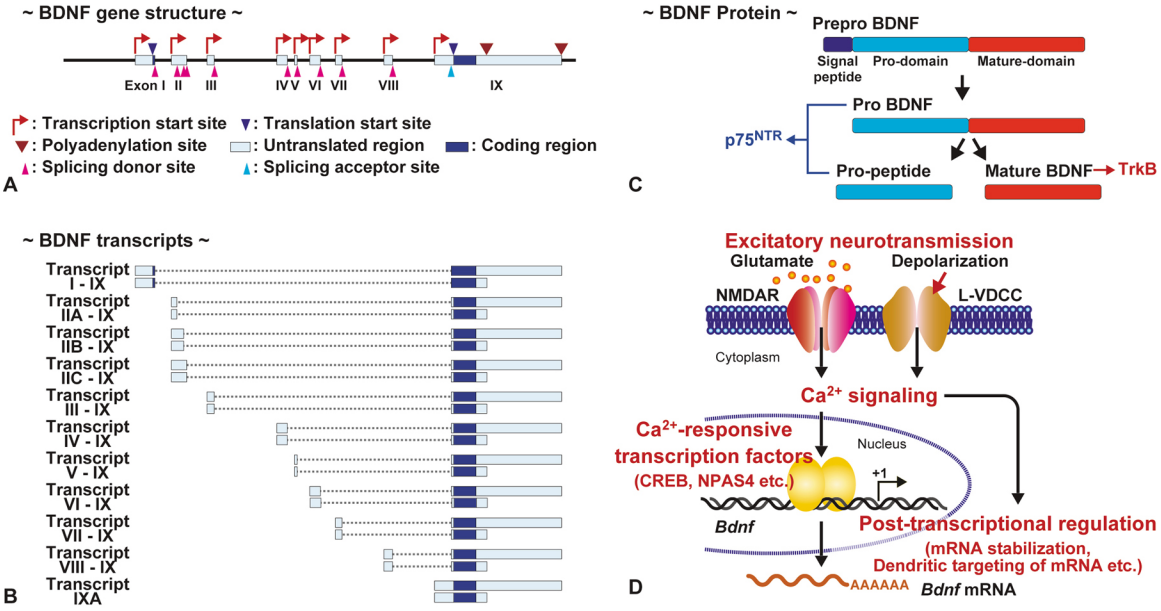

Figure 3. Structures of *Bdnf* gene, *Bdnf* transcripts, and BDNF protein, and regulation of activity-dependent *Bdnf* expression in neurons. (A) Structure of mouse and rat *Bdnf*. (B) Because of alternative *Bdnf* promoters, multiple splicing donor sites but a single acceptor site, and polyadenylation signals (A), *Bdnf* transcripts with a short or long 3'-untranslated region are generated. (C) After signal peptide removal, proBDNF is processed by several processing enzymes, resulting in production of mature BDNF as well as pro-peptide. Mature BDNF exerts its neurotrophic actions via TrkB while proBDNF and pro-peptide enhance LTD via p75 neurotrophin receptor ($p75^{NTR}$). (D) Ca^{2+} signals evoked by excitatory neurotransmissions control transcriptional and post-transcriptional regulation of *Bdnf*.

mRNA possesses a common coding region, another functional translation start site was found in exon I (63) (Figure 3B). Interestingly, the translation efficacy of mRNA containing exon I is higher (74). This was the first report showing functional differences among alternative *Bdnf* transcripts.

After preproBDNF protein synthesis and signal peptide removal, proBDNF is cleaved by processing enzymes (intracellularly by pro-protein convertases and furin, or extracellularly by tissue-type plasminogen activator/plasmin system), to generate mature BDNF protein (75) (Figure 3C). Mature BDNF has potent physiological and neurotrophic effects including neuronal survival and synaptogenesis (60). ProBDNF has biological functions that are distinct from mature BDNF. For example, mature BDNF and proBDNF enhances LTP and LTD, respectively, which are distinct types of synaptic plasticity (54, 76). After proBDNF protein processing, not only mature BDNF but also another peptide possessing the pro-domain of proBDNF should be also produced (Figure 3C). Recently, Mizui *et al*. confirmed the existence of this pro-domain peptide (termed pro-peptide) in neurons and showed that it functions as an enhancer of LTD (77). Guo *et al*. also reported that the BDNF pro-peptide negatively regulates dendritic spines via caspase-3 (78). Thus, *Bdnf* encodes multi-functional proteins that may play coordinating roles in fine-tuning synaptic properties (79) (Figure 3C). The expression of preproBDNF, proBDNF, and BDNF pro-peptide was altered in a rat model of depression (80), suggesting that perturbation of BDNF expression and that of its related peptides may trigger psychiatric disorders.

BDNF has a potent neurotrophic effect, therefore BDNF inducers or agonists for BDNF receptor tropomyosin-related kinase B (TrkB) have beneficial effects on neural and psychiatric disorders. Fingolimod is a sphingoshine-1 phosphate receptor modulator that increases BDNF level and ameliorated symptoms of Rett syndrome in a mouse model (81). Fingolimod also improved amyloid-β-induced memory impairment (82) and depression (83) in mice. The hydrophobic dipeptide Leu-Ile induces BDNF expression and repeated administration reduced immobility times induced by repeated forced swimming in mice (84). Interestingly, Leu-Ile has no effect in BDNF (+/-) mice, suggesting that the antidepressant-like effect of Leu-Ile is dependent on the amount of BDNF. In addition, 7,8-hydroxyflavone, which is a selective agonist of TrkB (85), improves memory impairment in stressed rats (86), memory deficits in a mouse model of Alzheimer's disease (87), symptoms in a mouse model of Rett syndrome (88), and cognitive deficits in a rat model of schizophrenia (89). Therefore, BDNF and its receptor are therapeutic targets for neurodegenerative and psychiatric diseases. *Bdnf* is a CREB-target gene (64, 67, 69); therefore, activation of the CREB-*Bdnf* pathway would improve neural dysfunction in diseases.

4. NEUROMODULATOR-REGULATED IEG EXPRESSION

4.1. Excitatory and modulatory neurotransmissions

Glutamatergic excitatory neurotransmission plays a fundamental role in transmitting physiological and environmental information in the nervous systems. Excitatory neurotransmission is mediated by ionotropic receptors such as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor (AMPAR) and NMDAR. Modulatory neurotransmission also regulates diverse and complicated neurotransmissions and is triggered by a number of neuromodulators including monoamines, amino acids, hormones, and other neurotransmitters and neuropeptides. Neuromodulators mainly exert their functions via metabotropic receptors such as GPCRs.

4.2. Modulation of ionotropic glutamate receptors by GPCR-mediated signaling

The activity of ionotropic glutamate receptors can be modulated by GPCR activation. This is mainly controlled by the phosphorylation of glutamate receptor subunits (details are reviewed previously (7, 90, 91)). Changes in the phosphorylation of receptors are controlled by serine-threonine protein kinases including PKA and PKC, and Src family non-receptor tyrosine kinases such as Fyn and Src (7). Phosphorylation of these receptors increases their surface expression and affects interactions between the receptors and postsynaptic density (PSD) proteins in synapses, which modulates the channel properties of NMDAR (90, 91). In addition, several GPCRs, such as mGluR5 (92), dopamine D1 (8), and mu opioid receptor (93), physically interact with NMDAR subunits.

4.3. Regulation of IEG expression by GPCR activation

Long-lasting changes in neural functions such as learning and memory require *de novo* expression of IEGs. Although NMDAR activation by excitatory neurotransmission regulates IEG expression, modulatory neurotransmissions also have an effect. For example, morphine induced *c-fos* expression in the striatum and nucleus accumbens (NAc) through the dopamine D_1 receptor. Interestingly, this induction was prevented by a dopamine D_1 antagonist and an NMDAR antagonist (94). Similarly, stimulation of the dopamine D_1 receptor induced *c-fos* expression via NMDAR (95). These results indicate the involvement of NMDAR in dopamine-induced IEG expression. NMDAR function is modulated by GPCR signaling; therefore activation of dopamine D_1 receptors should induce *c-fos* expression following the influx of Ca^{2+} via NMDAR.

Consistent with the findings that dopamine D_1 induces *c-fos* expression via NMDAR, pituitary adenylate cyclase-activating polypeptide (PACAP) induces IEG expression (including *c-fos* and *Bdnf*) via NMDAR in cortical neurons (96, 97). PACAP is a member of the vasoactive intestinal polypeptide (VIP)/secretin/glucagon neuropeptide family and has a variety of neural functions (98). PACAP has been associated with psychiatric disorders such as schizophrenia (99) and post-traumatic stress disorder (100). The PACAP-specific GPCR, PAC1, is a Gs/q-coupled receptor (98) and PACAP stimulates adenylate cyclase and phospholipase C-mediated intracellular pathways. Activation of PAC1 potentiates NMDAR function via Fyn and Src (101, 102), which strongly suggests that PACAP induces activity-dependent IEG expression via NMDAR activation, similar to dopamine D_1-induced *c-fos* expression via NMDAR (94, 95). However, the mechanism of PACAP-induced IEG expression remains controversial. Yaka *et al*. reported that the PACAP-induced cAMP/PKA pathway dissociates receptor for activated C kinase 1 (RACK1) from NMDAR and Fyn, enhancing the nuclear translocation of RACK1 (101). In the absence of RACK1, Fyn phosphorylated the NMDAR subunit to modulate NMDAR activity. This report showed that RACK1 participated in *Bdnf* transcription in the nucleus. It is likely that nuclear translocation of RACK1, but not NMDAR activation, plays a central role in the induction of *Bdnf* expression. However, Baxter *et al*. proposed a mechanism for PACAP-induced activation of CRE-dependent transcription (103). They reported that the PACAP-induced cAMP/PKA pathway triggers action potential firing, followed by activity-regulated CRTC1/CREB-dependent transcription, which participates in long-lasting neuroprotection.

GPCRs including PAC1 potentiate NMDAR activity (7, 101, 102). NMDAR activation triggers multiple Ca^{2+} signaling pathways including MAPK, CaMK, and calcineurin, to activate *Bdnf* expression (Figure 4B). Therefore, PACAP may induce the expression of IEGs via NMDAR. However, we demonstrated distinct mechanisms of PACAP-induced regulation of IEG expression using cortical neurons by investigating the regulation of a subset of IEGs (9) (Figs. 4 and 5). We found that the calcineurin inhibitor FK506 completely blocked PACAP-induced *Bdnf* expression, while inhibitors of MAPK and CaMK did not have an inhibitory effect (Figure 4A). In contrast, PACAP-induced dual specificity protein phosphatase 5 (*Dusp5*) expression was not dependent upon NMDAR and calcineurin (Figure 4D). Despite of the independence of PACAP-induced *Dusp5* expression on NMDAR, *Dusp5* expression was induced by direct activation of NMDAR by NMDA. However, this induction was not dependent on calcineurin activity (Figure 4E). These observations indicate that expression of calcineurin-regulated genes is induced by PACAP-mediated NMDAR pathways,

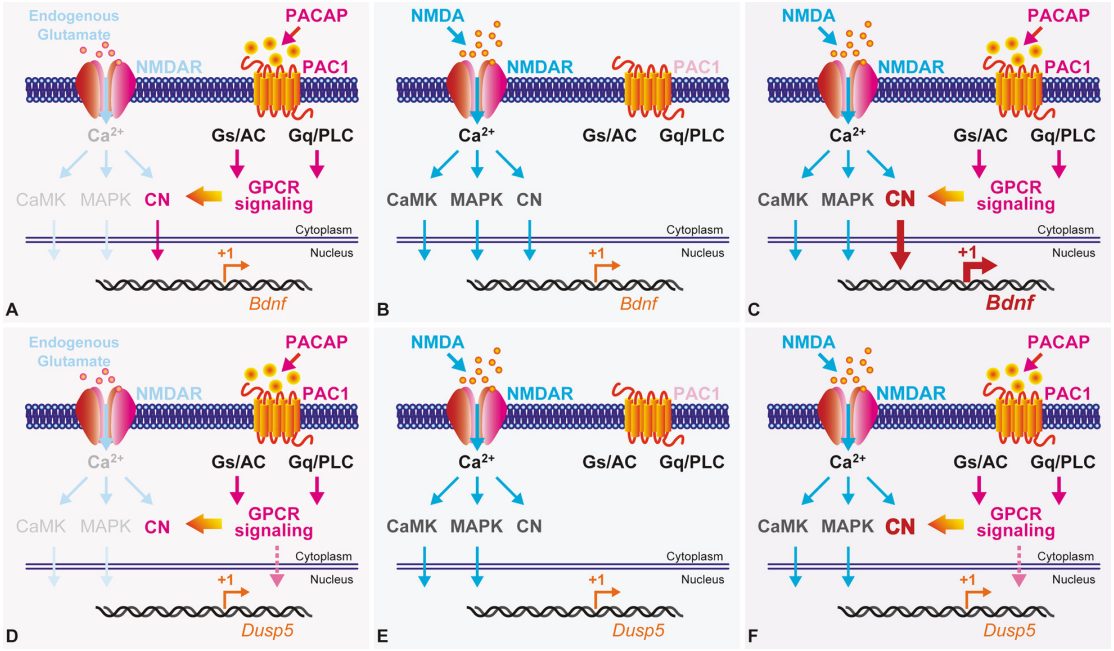

Figure 4. Summary of *Bdnf* and *Dusp5* induction upon PAC1 and/or NMDAR stimulation. PAC1 stimulation-induced expression of *Bdnf* is completely dependent on NMDAR and calcineurin (A), whereas NMDAR stimulation-induced expression is dependent on several Ca^{2+} signaling pathways (B). In contrast, PAC1 stimulation-induced expression of *Dusp5* is independent of NMDAR and calcineurin, but dependent on GPCR-mediated signaling pathways such as PKA, PKC, and MAPK (D). However, NMDAR stimulation increases the expression of *Dusp5*, independent of calcineurin (E). Because of calcineurin dependence, the expression of *Bdnf* is synergistically induced by simultaneous stimulation of PAC1 and NMDAR (C), whereas *Dusp5* is not (F).

while genes that are not regulated by calcineurin are induced by PACAP without NMDA activity (Figure 4A, D). Importantly, the differences in induction of *Bdnf* and *Dusp5* expression further support the idea that PACAP-induced *Bdnf* expression is not caused by the direct (or indirect) activation of NMDAR by PACAP/PAC1 signaling, in contrast to previous reports (101, 102). If PACAP directly (or indirectly) activates NMDAR to induce *Bdnf* expression, PACAP-induced *Dusp5* expression should be inhibited by an NMDAR antagonist because *Dusp5* expression is induced by NMDAR activation (Figure 4E).

Further analysis indicated a correlation between the dependence of PACAP-induced IEG expression on NMDAR and calcineurin. The expression of several IEGs that encode plasticity-related molecules, as well as BDNF, was also regulated by an NMDAR/calcineurin-mediated pathway (9) (Figure 5). For example, the NMDAR/calcineurin pathway completely or partially contributed to PACAP-induced expression of activity-regulated cytoskeleton-associated protein (*Arc*), *Nr4a1*, *Nr4a2*, *Homer1a*, tissue-type plasminogen activator (*Plat*), and proprotein convertase subtilisin/kexin type 1 (*Pcsk1*) (9) (Figure 5). Nuclear receptor Nr4a family Nr4a1 and Nr4a2 participate in long-term memory (104, 105). Homer1A and Arc are postsynaptic proteins that control synaptic functions as synaptic tag molecules (106, 107). PCSK1 converts proBDNF to mature form (108). PLAT also contributes to BDNF processing and is involved in LTP (109). Together, PCSK1 and PLAT are probably important for controlling neural functions by converting proBDNF to mature BDNF.

The expression of *Bdnf* and other NMDAR/calcineurin-dependent IEGs is synergistically induced by the simultaneous activation of NMDAR and PAC1 (9) (Figure 4C) and this synergistic induction is prevented by a calcineurin inhibitor, suggesting that PACAP/PAC1 signaling selectively activates the calcineurin pathway to induce *Bdnf* and NMDAR/calcineurin-dependent IEG expression (9). Selective activation of the calcineurin pathway by PACAP/PAC1-mediated signaling is also supported by the observation that neither synergistic nor additive induction of *Dusp5* and other NMDAR/calcineurin-independent genes is observed upon simultaneous activation of NMDAR and PAC1 (9) (Figure 4F).

These observations have raised other important questions. We used the GPCR agonist PACAP to demonstrate the intracellular mechanism of neuromodulator-induced IEG expression. However, there are many Gs/q-coupled GPCRs in the nervous systems; therefore, other GPCR ligands could also induce the expression of *Bdnf* and NMDAR/calcineurin-regulated IEGs. We found that agonists for

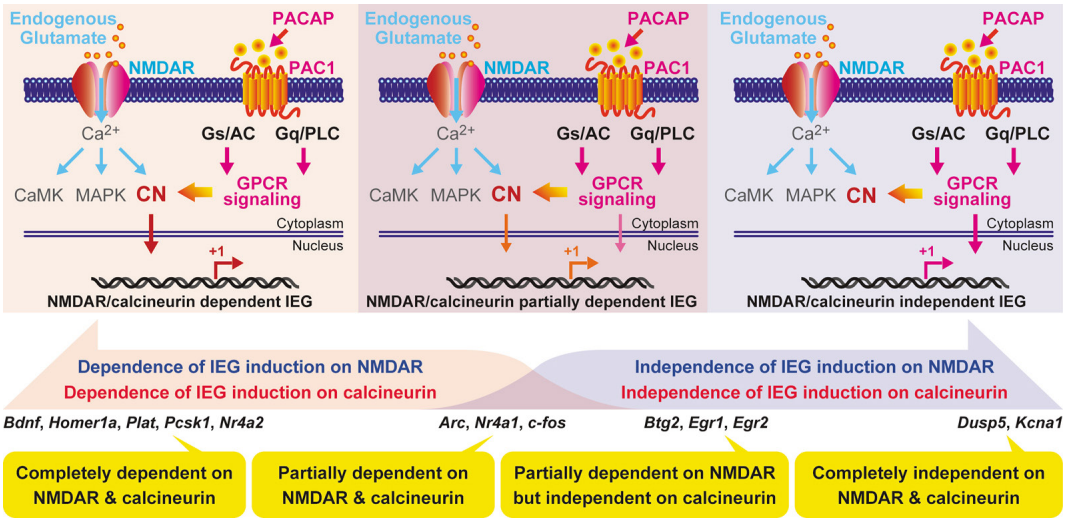

Figure 5. NMDAR/calcineurin-dependent and independent regulation of PACAP-induced IEG expression.PACAP-induced expression of *Homer1a*, *Plat*, *Pcsk1*, and *Nr4a2*, as well as *Bdnf*, is completely dependent on NMDAR and calcineurin (left), while the expression of *Dusp5* and *Kcna1* is completely independent on NMDAR and calcineurin (right). PACAP-induced expression of a subset of IEGs including *Arc*, *Nr4a1*, and *c-fos* is strongly dependent on NMDAR but only partially dependent on calcineurin (middle). However, the induction of other IEGs such as *Btg2*, *Egr1*, and *Egr2* is partially dependent on NMDAR but independent on calcineurin. Therefore, the dependence of IEG induction on NMDAR is correlated to dependence on calcineurin. *Arc*, *c-fos*, *Egr2*, and *Dusp5*) and experimental information were described previously (9).

dopamine D_1 and adrenaline β receptors, and several neuropeptides such as corticotropin-releasing factor (CRF) and neurotensin, also induced the expression of *Bdnf* through the NMDAR and calcineurin pathway. Thus, the expression of *Bdnf* and other NMDAR/calcineurin-dependent IEGs can be induced when Gs- and/or Gq-coupled GPCRs are activated in neurons with active NMDAR (Figure 6). However, we also found that several agonists of Gs- or Gq-coupled GPCRs, which could be functionally expressed in cortical neurons, did not affect the expression of *Bdnf* (unpublished observations). Therefore, the expression of certain endogenous GPCRs may be necessary to induce IEG expression via the NMDAR-mediated pathway. And also, there may be several conditions to induce *Bdnf* expression through the NMDAR and calcineurin pathway; for example, a distribution of NMDAR and GPCR in the same neurons, a direct or indirect interaction between these receptors, or a co-expression of another molecule (such as DARPP-32 and A kinase-anchoring protein (AKAP), as described below) with the receptors. Elucidating the molecular mechanisms that underlie GPCR-induced *Bdnf* expression via the NMDAR and calcineurin pathway will help clarify this issue.

We also demonstrated that activation of the NMDAR/calcineurin pathway by PACAP and other agonists of Gs/q-coupled GPCRs promoted translocation of CRTC1 to the nucleus for *Bdnf* and other NMDAR/calcineurin-dependent IEG transcription via CRE/CREB (9). CRTC1 is localized in synapses and translocated to the nucleus in response to synaptic activity (110). Therefore, simultaneous projection of excitatory and modulatory inputs to the synapse efficiently facilitates calcineurin-dependent dephosphorylation of CRTC1 at the activated synapse. This enhances translocation of CRTC1 to the nucleus in order to regulate *Bdnf* and NMDAR/calcineurin-dependent IEG expression (Figure 7). Becasue CRTC1 localizes to dendritic spines (110), selective activation of the calcineurin pathway by the activation of Gs/q-coupled GPCRs with NMDAR is likely to be important for excitatory and modulatory input-specific regulation of plasticity-related IEG expression in neurons. This may represent a highly efficient machinery for converting these neurotransmissions into the IEG expression, probably due to their contribution to long-lasting plasticity-related events.

Although NMDAR and Gs/q-coupled GPCR activation induced *Bdnf* expression through calcineurin, we could not identify the activator of the NMDAR/calcineurin pathway. One candidate is dopamine- and cAMP-regulated phosphoprotein, Mr 32 kDa (DARPP-32) (111). Dopamine D_1-induced activation of the cAMP/PKA pathway phosphorylates DARPP-32 at Thr-34, which acts as an inhibitor of protein phosphatase-1 (PP-1). DARPP-32 phosphorylation at Thr-34 is dephosphorylated by calcineurin. Therefore, DARPP-32 is likely to be the molecule converging Gs-coupled GPCR-mediated and NMDAR-derived intracellular signaling pathways (PKA and calcineurin, respectively). However, how DARPP-32 contributes to the selective activation of NMDAR/calcineurin pathway for inducing *Bdnf* expression remains unclear. Another candidate is AKAP, which interacts with calcineurin and intracellular kinases downstream of Gs/q-

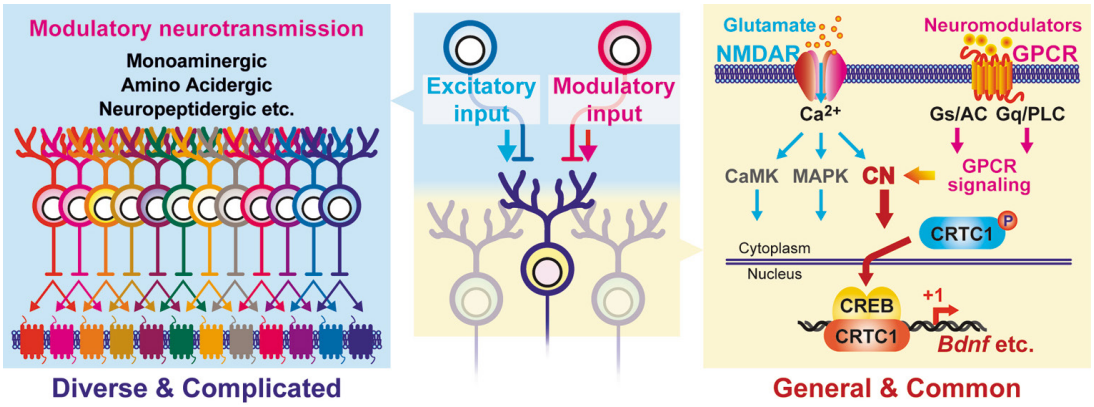

Figure 6. Possible effects of simultaneous projection of excitatory and modulatory inputs on IEG expression in postsynaptic neurons.Downstream pathways of GPCRs are limited, although there are many GPCRs and endogenous ligands. Thus, a common intracellular signaling pathway, which contributes to the efficient induction of *Bdnf* gene, may be operated when Gs/q-coupled GPCRs and NMDAR are simultaneously activated by excitatory and modulatory neurotransmissions.

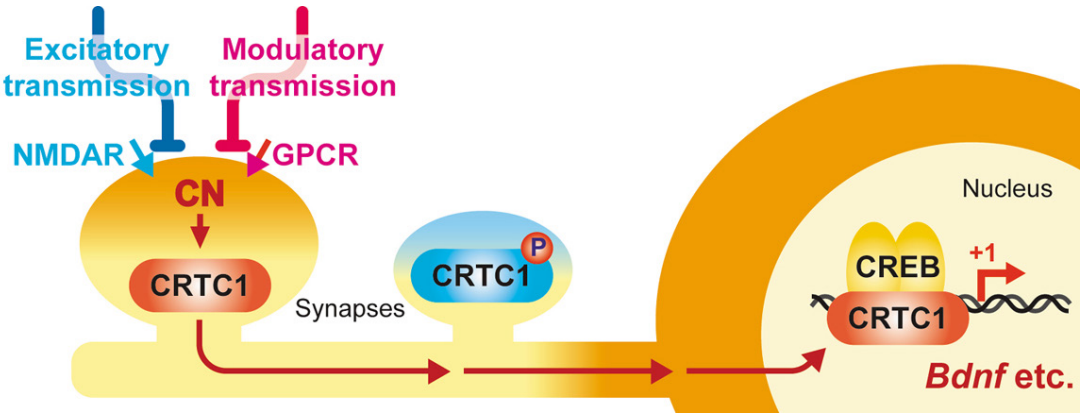

Figure 7. Efficient nuclear localization of CRTC1 upon simultaneous projection of excitatory and modulatory inputs.CRTC1 is found at synapses and translocates to the nucleus in response to synaptic activation, therefore simultaneous projection of glutamatergic excitatory inputs and neuromodulatory inputs to the same spine may induce nuclear translocation of CRTC1. This efficiently induces *Bdnf* and other calcineurin-regulated genes.

coupled GPCRs such as PKA and PKC (112). AKAP5 (AKAP150 in rodents and AKAP79 in humans) is highly expressed in neurons and controls synaptic plasticity (113). Depolarization-induced nuclear translocation of nuclear factor activated T cell (NFAT) is blocked in AKAP150 (-/-) cells without affecting the intracellular Ca^{2+} concentration (114). This phenotype was rescued by AKAP79, but not by mutant AKAP79 that cannot interact with PKA or calcineurin. Nuclear translocation of CRTC1 may be controlled by AKAP5.

5. POSSIBLE ROLES OF IEG REGULATION BY EXCITATORY AND MODULATORY NEUROTRANSMISSIONS

5.1. Neuromodulators and long-term memory

A series of previous reports have supported the concept that neuromodulators actively participate in long-lasting changes in neural functions, such as long-term memory. Here, we give an example of the role of β adrenergic regulation in long-term memory. The locus coeruleus in the brain stem is the source of noradrenaline, and noradrenergic inputs are projected to many brain regions including the hippocampus, a memory center (115). Activation of β adrenergic receptors enhances LTP in hippocampal CA1 region, although contradictory findings have been reported, possibly owing to the time frame of LTP measurement (116). Most studies investigating the molecular mechanisms of β adrenergic-regulated synaptic plasticity have focused on the phosphorylation of ionotropic glutamate receptors subunits such as the AMPAR. Phosphorylation of AMPAR facilitates AMPAR function by increasing synaptic expression and is important for LTP (117). β adrenergic activation triggers phosphorylation of the GluA1 subunit of AMPAR to increase surface expression of AMPAR (118). However, noradrenaline-induced LTP, which requires NMDAR activity, is regulated by epigenetic mechanisms

including histone acetylation and DNA methylation (119). This finding was based on electrophysiology with pharmacological agents, but the contribution of epigenetic regulation to noradrenaline-induced LTP is plausible because IEG expression is required for long-lasting enhancement of synaptic functions. In addition, β adrenergic activation may selectively activate the NMDAR/calcineurin/CRTC1 pathway via Gs-coupled β adrenergic receptors to effectively induce the expression of *Bdnf* and other NMDAR/calcineurin/CRTC1-dependent IEGs. This may contribute to long-lasting changes in neural structure and function.

5.2. Dopamine-related plasticity; reward learning and drug addiction

The mesolimbic dopaminergic circuit controls reward and addiction. The well-characterized circuit in the brain is the dopaminergic projection from the ventral tegmental area (VTA) to the NAc (120). Glutamatergic inputs from many brain areas including the frontal cortex, amygdala, and hippocampus also project to medium spiny neurons in the NAc and dorsal striatum (121). Dendrites and axons of typical medium spiny neurons arborize extensively and contain numerous spines. Striatal neurons receive a number of projections from the VTA, neocortex, and other brain areas. Importantly, dopaminergic and glutamatergic projections converge on striatal neurons. Kelley has discussed that cellular convergence of these two projections on medium spiny neurons activates a series of intracellular signaling pathways and transcription of plasticity-related factors via CREB (121, 122). Kirschmann *et al*. (2014) demonstrated that an appetitive cue activates the ERK/CREB pathway in the NAc via dopamine D_1 and NMDAR (123). Dopaminergic and glutamatergic interaction in medium spiny neurons enhances the formation of the dopamine D_1/NMDAR complex, and disruption of the complex reduced the response to cocaine (124). These findings indicated that the intracellular convergence of D_1 and NMDAR signaling is important for long-lasting changes in neural functions underlying drug addiction and reward learning. This convergence is thought to be regulated by DARPP-32, which is highly expressed in medium spiny neurons. The activity of DARPP-32 is controlled by various kinases, and DARPP-32 itself controls the activity of several kinases and phosphatases including PKA and PP-1 (111). However, our recent findings suggest that simultaneous activation of dopamine D_1 and NMDAR, which is triggered by addictive drugs (121, 122), selectively activates the NMDAR/calcineurin/CRTC1 pathway to induce *Bdnf* expression. Cocaine increased BDNF levels in the NAc and cocaine-induced BDNF signaling is necessary for the development of addictive behaviors (125). BDNF has a potent neurotrophic effect; therefore, addictive drugs may reinforce addictive neural circuits by producing BDNF and other plasticity-related molecules.

5.3. Do antidepressant drugs affect plasticity-related pathways?

Depression is a mood disorder with serious problems such as suicide or suicidal ideation. Pathogenesis of depression has been associated with the imbalance of monoaminergic systems in the brain - the monoamine hypothesis. Commercially available antidepressant drugs control monoamine levels such as serotonin and noradrenaline in the brain. The dysregulation of plasticity-related signaling pathways is likely to underlie the pathogenesis of depression. Stress-induced dysfunction of intracellular molecules involved in neural plasticity, including CREB and BDNF, has been associated with depressive symptoms. In support of this, antidepressants increase CREB phosphorylation, BDNF expression, and neurogenesis in the hippocampal dentate gyrus (126, 127, 128, 129). The serotonin receptor 5-HT_4 is a Gs-coupled GPCR and is expressed in mature granule cells of the dentate gyrus. 5-HT_4 is necessary for the effects of the selective serotonin re-uptake inhibitor (SSRI) fluoxetine (130). These results suggest that SSRIs activate the CREB-BDNF pathway via 5-HT_4 in dentate granule cells to exert their antidepressant effect. Furthermore, CRTC1-KO mice have a severe depressive phenotype and the antidepressant effect of fluoxetine has shown to be lowered in these mice (131). Taken together with our previous findings, this indicates that antidepressants activate the NMDAR/calcineurin/CRTC1 pathway via 5-HT_4 to express *Bdnf* and exert an antidepressant effect. In contrast, NMDAR antagonists rapidly exert their antidepressant effect (132). However, this is mediated by deactivation of eukaryotic elongation factor 2 (eEF2)-mediated up-regulation of BDNF translation (132). Traditional antidepressants increase synaptic serotonin levels and take several weeks to exert their therapeutic effects. Therefore, the mechanisms underlying the antidepressant effects of NMDAR antagonists are different from traditional antidepressants. This may explain the discrepancy between our proposal and the antidepressant effect of NMDAR antagonists.

5.4. Intracellular mechanisms underlying schizophrenia

Schizophrenia is a complex and severe psychiatric disorder. Genetic, epigenetic, and transcriptome analyses have revealed potential risk factors for schizophrenia (133). Interestingly, we found several risk factors of schizophrenia that were involved in GPCR-mediated *Bdnf* expression via NMDAR (9). For example, PACAP-KO mice exhibited hyperactivity, abnormal jumping behaviors, and reduced anxiety (134). In agreement, PACAP and its receptor PAC1 have been associated with schizophrenia (99). Miyakawa *et al*. showed that forebrain-specific calcineurin knockout mice have schizophrenia-related behaviors (135).

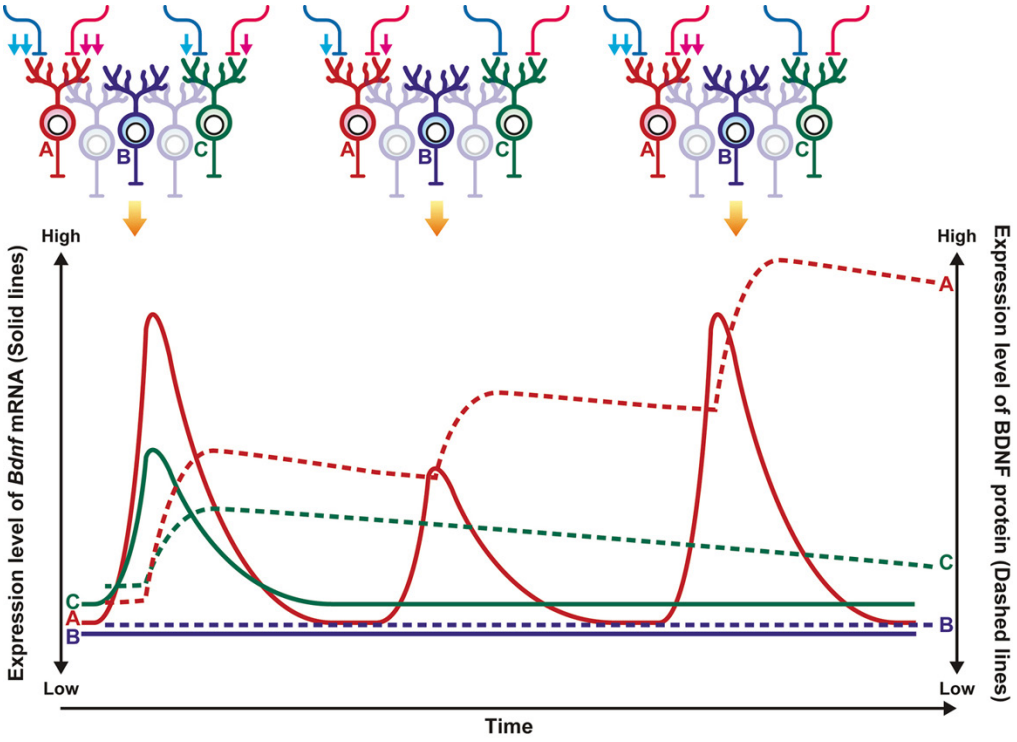

Figure 8. Possible changes in *Bdnf* mRNA and BDNF protein levels in neurons. Although the extent of the increase in the levels of *Bdnf* mRNA would be dependent on the strength of neurotransmissions, these increases would be transient because of its short half-life (solid lines). However, the expression levels of BDNF protein may accumulate because of its stable expression. The content of BDNF protein may be higher in the neurons that were strongly activated in the past (dashed lines). Thus, the history of neurotransmissions might be reflected in the levels of BDNF in the neurons (A >> C > B in this scheme).

Phencyclidine and ketamine are NMDAR antagonists and are schizophrenomimetic drugs (drugs inducing abnormalities related to schizophrenia), supporting "the hypoglutamatergic hypothesis" of schizophrenia (136). Furthermore, CRTC1, CREB, and BDNF, all of which are downstream of the GPCR-mediated selective activation of NMDAR/calcineurin pathway, modulate long-lasting changes in neural functions (Section 3). Therefore, the disruption of GPCR-mediated BDNF expression via the NMDAR/calcineurin/CRTC1/CREB pathway may be associated with the pathogenesis of schizophrenia.

6. SUMMARY AND PERSPECTIVES

Neuromodulators regulate multiple, diverse, and complicated neurotransmissions by modulating glutamatergic excitatory neurotransmission. These neuromodulatory effects have been investigated in neuronal membranes, such as changes in electrophysiological property, phosphorylation, and synaptic localization of glutamate receptors. In this review, we focused on the excitatory and modulatory neurotransmissions that control the expression of plasticity-related IEGs (Figure 6). Coordinated neurotransmissions efficiently induce the expression of *Bdnf*, which is important because BDNF plays a fundamental role in long-lasting changes in neural functions such as memory consolidation. Danzer and McNamara reported that BDNF protein content was similar in mossy fiber boutons of the same axon in dentate granule cells, and conversely, different in the boutons of close but different axons (137). They suggested that BDNF protein levels in mossy fiber boutons reflect the history of granule cell activity; cells that were strongly activated may store more BDNF protein. Our preliminary observations showed stable BDNF expression in cultured cortical cells (unpublished observations), whereas the half-life of *Bdnf* mRNA was short (approximately 1 h) (71). These findings indicate that previous excitatory and modulatory neurotransmissions may influence the levels of BDNF protein in neurons (Figure 8). Therefore, GPCR and NMDAR are activated by excitatory and modulatory neurotransmissions, respectively, and regulate induction and storage of BDNF in neurons. The regulated secretion of BDNF is enhanced in an activity-dependent manner (138). Thus, once the neurons are re-activated, they may efficiently secrete BDNF protein (Figure 9). Furthermore, coordinated neurotransmissions are likely to be important for the induction of other plasticity-related IEGs such as *Arc*, *Nr4a2*, and *Homer1a*. Simultaneous activation of GPCR and NMDAR induce BDNF and other plasticity-

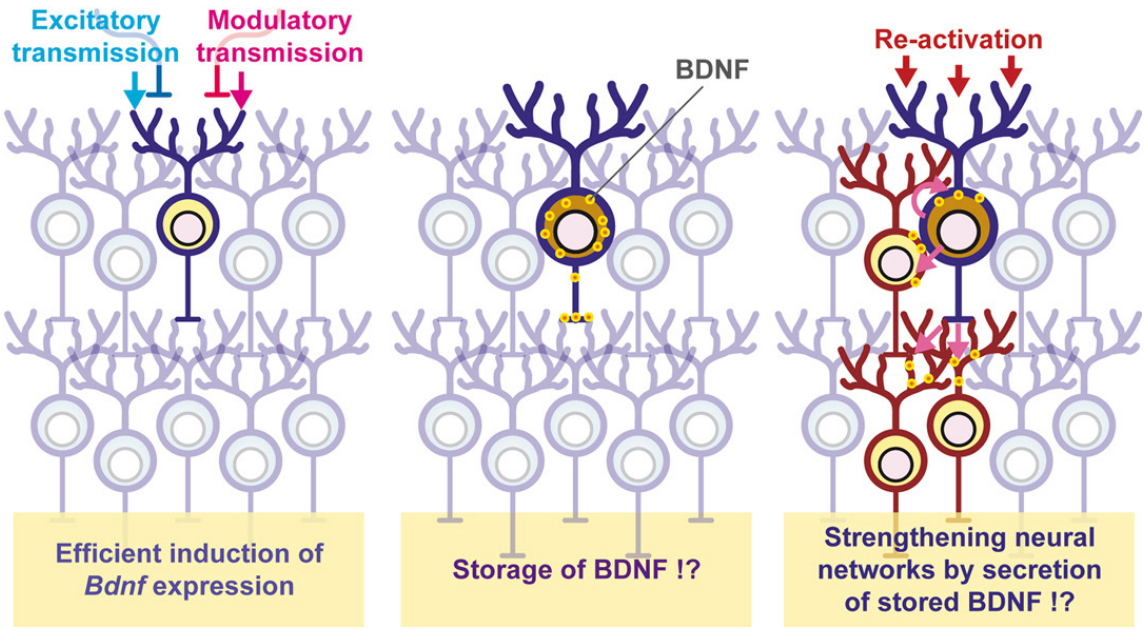

Figure 9. Schematic of BDNF storage under coordinated projection of excitatory and modulatory inputs.After *Bdnf* induction by simultaneous projection of excitatory and modulatory inputs, previous activation may be reflected in the BDNF protein content (Figure 8). When re-activated, the neuron might efficiently release BDNF protein, reinforcing neural networks and synaptic functions.

related molecules in neurons, probably refining the neural networks and synaptic functions around the neurons. It is likely that the coordinated excitatory and modulatory neurotransmissions promote long-lasting plasticity by regulating IEG expression. Taken together, we believe that IEG expression is regulated by excitatory and modulatory neurotransmissions for plasticity-related events. Dysregulation of IEG expression may be associated with the pathogenesis of neural and psychiatric disorders including depression, addiction, and schizophrenia. In addition, molecules controlling IEG expression may represent drug targets for these diseases.

7. ACKNOWLEDGMENTS

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