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Stress responses: the contribution of prostaglandin E_2 and its receptors

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Abstract

Stress is a state of physiological or psychological strain caused by adverse stimuli; responses include activation of the sympathetic nervous system, glucocorticoid secretion, and emotional behaviors. Prostaglandin E_2 (PGE_2), through its four receptor subtypes (EP1, EP2, EP3, and EP4), is involved in these stress responses. Studies of EP-selective drugs and mice lacking specific EPs have identified the neuronal pathways regulated by PGE_2. In animals with febrile illnesses, PGE_2 acts on neurons expressing EP3 in the preoptic hypothalamus. In illness-induced activation of the hypothalamic–pituitary–adrenal axis, EP1 and EP3 regulate distinct neuronal pathways that converge at the paraventricular hypothalamus. During psychological stress, EP1 suppresses impulsive behaviors via the midbrain dopaminergic systems. PGE_2 induces illness-induced memory impairment, yet also supports hippocampus-dependent memory formation and synaptic plasticity via EP2 in physiological conditions. In response to illness, PGE_2 is synthesized by enzymes induced in various cell types inside and outside the brain, whereas constitutively expressed enzymes in neurons and/or microglia synthesize PGE_2 in response to psychological stress. Dependent on the type of stress stimuli, PGE_2 released from different cell types activates distinct EP receptors, which mobilize multiple neuronal pathways, resulting in stress responses.

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Competing interests

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Key points

- Prostaglandin (PG) E_2 regulates multiple responses to illness and psychological stress via distinct PGE_2 receptor subtypes
- During illness-induced fever, PGE_2 activates EP3 in neurons in the preoptic hypothalamus, which promotes two independent effector mechanisms: increased metabolism in brown adipose tissue and vasoconstriction of the skin
- In illness-induced activation of the hypothalamic–pituitary–adrenal axis, EP1 and EP3 mediate distinct neuronal pathways that converge on neurons in the paraventricular hypothalamus that contain corticotropin-releasing factor
- Under psychological stress, PGE_2–EP1 signaling regulates impulsive behaviors via the midbrain dopaminergic system
- PGE_2 regulates illness-induced impairment of memory formation, but under physiological conditions (without illness), it supports hippocampus-dependent memory formation and synaptic plasticity via EP2
- PGE_2 is synthesized by enzymes induced inside and outside the brain in response to illness and by constitutive enzymes in neurons and/or microglia in response to psychological stress

Introduction

Stress is a state of physical and psychological stain caused by adverse stimuli (physical, mental, or emotional), and evokes common biological responses including fever, glucocorticoid secretion, activation of the sympathetic nervous system and emotional behaviors (Box 1).[1] While these stress responses can promote our well-being and survival, excessive or abnormal responses to stress can precipitate the development of psychiatric disorders, such as depression.[1] One of the physical stimuli that induces stress is a systemic inflammatory challenge, which induces illness-related stress responses (also called sickness behaviors or sickness syndrome) including fever, lethargy, hypersomnia, anorexia, and hyperalgesia.[2,3] Administration of NSAIDs (Box 2), which inhibit prostanoid synthesis, can treat some of these illness-related stress responses. The involvement of prostanoids in stress responses induced by illness have been studied extensively.[4–7]

The best-studied prostanoid, prostaglandin E_2 (PGE_2), is produced abundantly in the brain in response to illness and mimics stress responses when injected. PGE_2 is a bioactive lipid derived from arachidonic acid that binds to four cognate G-protein-coupled receptor subtypes (EP1, EP2, EP3, and EP4) and is involved in various aspects of inflammation and immunity (Figure 1, Box 2).[8] As each receptor subtype has a specific tissue distribution and induces a specific intracellular signaling cascade, the receptors each have distinct functions (some functional redundancy might exist between EP2 and EP4, as both are involved in the activation of adenylate cyclase). All the EP receptor subtypes have been identified and cloned, and mice lacking each EP subtype and drugs selective to each subtype are now available (Figure 1, Box 2).[8] These tools have been used to confirm the involvement of PGE_2 in stress responses, and to reveal the identity and action of the EP subtype in various illness-related behaviors.[8] Such studies have uncovered unforeseen functions for PGE_2 under conditions of psychological stress.[9] In this Review, we will examine these findings, and describe how PGE_2 orchestrates a range of stress responses via the EPs.

Stress responses to illness

In animal models, administration of lipopolysaccharide (a component of Gram-negative bacterial cell walls that act as an endotoxin) and proinflammatory cytokines, such as IL-1β, can reproduce various illness-related stress behaviors, such as fever, activation of the HPA axis, anorexia, lethargy and hypersomnia.[2-7] Suppression of some of these responses by NSAIDs and the effects of injecting various prostaglandins and their analogs into the brain suggest that PGE_2 is involved in illness-related stress responses in the brain, especially in the

hypothalamus.[10,11,34,35] Studies in EP-knockout mice and with EP-selective drugs have verified these roles and identified their neural mechanisms downstream of PGE_2.[13,14,18,38,73]

PGE_2 synthesis during illness

The brain

Since PGE_2 is synthesized in the brain (especially in the hypothalamus) and is a crucial mediator of responses to illness, the site and mode of its synthesis are of intense interest. During the first stage of PGE_2 synthesis, arachidonic acid is released from membrane phospholipids by phospholipase A_2 activity. The role of phospholipase A_2 in illness-induced fever has rarely been analyzed, except with regard to the upregulation of several phospholipase A_2 isoforms inside and outside the brain following administration of lipopolysaccharide.[57] The phospholipase A_2 isoform(s) involved in illness-induced fever remain to be clarified.

PGE_2 is produced from arachidonic acid by sequential actions of cyclo-oxygenase (COX) enzymes and prostaglandin E synthases (Figure 1a). The involvement of COX2 and microsomal prostaglandin E synthase 1 (mPGES1) in responses to illness[29,58–63] and the upregulation of expression of these enzymes by illness-related stimuli are well established.[57,64–69] For example, many studies have shown that lipopolysaccharide and/or interleukin (IL)-1β induce the expression of COX2 and mPGES1 in the brain vasculature.[64–69] However, whether endothelial cells of the brain vasculature or perivascular macrophages, or both, express these enzymes in response to illness is an area of controversy.[64–69] Whereas one group of studies reported that COX2 and mPGES1 are expressed exclusively in endothelial cells,[64,66] others showed that COX2 is induced in perivascular macrophages, but not in endothelial cells.[65]

The findings that lipopolysaccharide and/or IL-1β induce expression of COX2 and mPGES1 in the brain vasculature led to the proposal that blood-borne cytokines could stimulate the release of PGE_2 from brain vasculature, which in turn acts upon EPs in the brain parenchyma (Figure 2a). Since the IL-1 type 1 receptor is predominantly expressed in brain endothelial cells,[71,72] this proposal was tested in an animal model, in which knockdown of the IL-1 type 1 receptor in endothelial cells was achieved by inducible expression of an antisense RNA molecule.[70] In this model, induction of COX2 expression was completely abolished and almost no febrile response occurred following intravenous injection of IL-1β.[70] Furthermore, a partial decrease was observed in the febrile response following intraperitoneal injection of IL-1β.[70] This study thus supports the importance of COX2 induction in brain endothelial cells

in the stress response to illness-related stimuli.

The receptor activator of nuclear factor κB (RANK) and its ligand, RANKL, have an intermediary role in febrile response to illness stimuli—represented by intraperitoneal administration of lipopolysaccharide, IL-1β and TNF.[73] Gene-deletion studies in astrocytes showed that RANK is required for both the febrile response and for IL-1β-induced PGE_2 production.[73] Injection of RANKL into the central nervous system also induces production of COX2 in astrocytes.[73] Thus, current studies in animal models have revealed the brain vasculature and astrocytes to be potential sites of PGE_2 production during illness (Figure 2a). However, COX2 induction in astrocytes as a response to illness-related stress should be demonstrated *in vivo*, and selective deletion of COX2 in cell types suspected to be involved in this response should be carried out to verify the role of these cells in responses to illness-related stress.

The contribution of COX1 has been reassessed with regard to early responses to illness, especially activation of the hypothalamic–pituitary–adrenal (HPA) axis.[62,74,75] Studies in mice deficient in either COX1 or COX2 showed that COX1 is involved in early (1 h) responses whereas COX2 is involved in late (6 h) responses, specifically the rise in plasma corticosterone concentrations following treatment with lipopolysaccharide.[62,75] This action of COX1 seems to be located in the brain, as injection of the COX1 inhibitor SC-560 into the central nervous system suppressed the early release of adrenocorticotropic hormone (ACTH).[74] COX1 is constitutively expressed in microglia in the brain,[76] and its expression is induced in endothelial cells and microglia during illness-related stress.[74] In contrast to activation of the HPA axis, studies of COX1-deficient mice indicated that COX1 is not involved in any phase of illness-induced fever.[58,59,77] These findings suggest that in the early phases of illness-related stress, febrile and neuroendocrine responses occur via distinct mechanisms. In contrast, in the late phase of illness-induced responses, COX2, but not COX1, is involved in both fever and activation of the HPA axis.[58,59,62,74,75,77] As described above, COX2 is induced in various cell types inside and outside the brain during illness. Whether both fever and activation of the HPA axis utilize PGE_2 from the same cell type remains to be examined.

The periphery

Studies using peripheral injection of an anti-PGE_2 antibody have suggested a crucial role for circulating PGE_2 during the initial febrile response (Figure 2a).[78] Thus, neutralizing circulating PGE_2 with an anti-PGE_2 antibody delayed and attenuated

lipopolysaccharide-induced fever.[78] Systemic lipopolysaccharide injection causes an immediate increase in blood levels of PGE_2,[78] and intravascular injection of PGE_2 can rapidly induce fever.[79] COX2 can be upregulated within 1 h of a stress stimulus in macrophages from the lung and the liver, but not those from the brain; therefore, pulmonary and hepatic macrophages might be the peripheral origin of PGE_2 for the initial febrile response.[78] However, the mechanism by which circulating PGE_2 elicits fever remains unknown. The febrile pathway in the brain is probably involved, as inactivation of the raphe region prevented fever from being induced by intravascular injection of PGE_2.[80] The vagus nerve is involved in mediation of the febrile response caused by small doses of lipopolysaccharide[81] or IL-1β;[82] however, vagotomy did not affect the fever induced by intravenous injection of PGE_2.[80] Exogenously applied PGE_2 can enter the brain during illness-related stress,[83] but whether PGE_2 synthesized peripherally can act directly on the central febrile pathway via the systemic circulation remains to be examined.

Action of PGE_2 during illness

Fever

Fever can be generated by various autonomic (e.g. increase in brown adipose tissue metabolism, skin vasoconstriction, shivering) and behavioral (e.g. thermal preference, postural change) thermoeffector responses.[19] PGE_2 regulates at least two of the autonomic mechanisms, namely brown adipose tissue metabolism and skin vasoconstriction. These mechanisms are activated by sympathetic premotor neurons in the intermediolateral cell column of the spinal cord.[20]

Microinjection of PGE_2 and NSAIDs into various regions of the brain and monitoring local concentrations of endogenous PGE_2 in the brain revealed that PGE_2 is synthesized in the preoptic area (POA) and induces the febrile response.[10–12] However, this central PGE_2 action was not directly corroborated and its mechanism remained unknown for many years. In mouse models of EP deficiency, only EP3-deficient mice did not show a febrile response to illness stimuli—systemic injection of lipopolysaccharide and/or IL-1β or injection of PGE_2 into the central nervous system.[13] When data on the febrile responses of these EP-knockout mice were re-examined, the primary role of EP3 in lipopolysaccharide-induced febrile response across various doses of lipopolysaccharide was confirmed.[14] The results of pharmacological experiments suggest that EP1 is also involved in illness-induced febrile responses.[15] EP1-deficient mice show an impairment in the febrile response only following intraperitoneal injection of a limited dose of lipopolysaccharide, and this impairment in the

febrile response was much milder than that of EP3-deficient mice under the same conditions.[14] As EP1-deficient mice show a normal febrile response to injection of PGE_2 into the central nervous system,[13] this EP1 action might be exerted outside the brain.

Consistent with the febrile response to injection of PGE_2 into the POA, EP3 is expressed in neurons in this brain region.[16,17] Selective deletion of EP3 in POA neurons in conditional-knockout mice showed that expression of EP3 in POA neurons is required for lipopolysaccharide-induced fever.[18] Identification of EP3 in POA neurons has facilitated identification of the downstream neural pathway involved in fever generation.[21,23-26]

The raphe pallidus nucleus (RPa) could have a crucial role in illness-induced febrile responses, as pharmacological inhibition of RPa neurons blocked the fever induced by PGE_2 injected into the POA.[21] Injection of PGE_2 into the POA induced expression of c-fos, a marker of neuronal activation, in neurons of the rostral RPa.[21] Indeed, RPa neurons are connected directly to the sympathetic premotor neurons in the intermediolateral cell column of the spinal cord.[22] POA neurons that express EP3 are GAD67-positive, putative inhibitory neurons using γ-aminobutyric acid (GABA) as a neurotransmitter, and directly project to RPa neurons.[21] On the basis of these findings, PGE_2 was proposed to generate a febrile response by suppressing POA neurons that express EP3 (thus disinhibiting RPa neurons).[21] Further studies have shown that EP3-expressing POA neurons regulate brown adipose tissue metabolism and skin vasoconstriction via separate pathways.[21,23–26] Notably, pharmacological inhibition of neurons in the dorsomedial hypothalamus blocked thermogenesis in brown adipose tissue but not skin vasoconstriction following injection of PGE_2 into the POA.[23,24,26] Two groups of neurons in the POA that both express EP3 directly project to the dorsomedial hypothalamus and the RPa, respectively.[25] Currently, POA neurons that express EP3 are thought to control skin vasoconstriction through direct projection to the RPa and to control brown adipose tissue metabolism through indirect projection to the RPa via the dorsomedial hypothalamus (Figure 3a). Whether the role of EP3 in the POA is applicable to other effector mechanisms, such as shivering, for illness-induced fever remains unknown.

Hyperthermia

The POA is not involved in every type of illness-induced fever.[27] For example, animals given lipopolysaccharide can develop hyperthermia by selecting warmer environments owing to a rise in the set point of their body temperature. This hyperthermia induced by thermal preference does not involve the POA, as it was not eliminated by POA lesions.[27] Whether EP3 is involved in this type of hyperthermia remains unknown.

Psychological stress can also induce hyperthermia, but EP3 does not seem to be involved in this response.[13,14] Thus, different mechanisms, at least in part, underlie psychological-stress-induced hyperthermia and illness-induced fever (Box 3).

Hypothermia

High doses of lipopolysaccharide, such as an intraperitoneal injection of 1 mg/kg, might cause hypothermia instead of fever.[28] Results from pharmacological studies suggest that prostanoids are also involved in this hypothermic response.[29,30] Injection of ONO-AE1-329, a selective EP4 agonist, into the central nervous system induced hypothermia, which suggests that EP4 might regulate this response.[31] EP4 is expressed in various hypothalamic nuclei implicated in thermoregulation.[17,32] For example, EP4 is expressed in POA neurons as EP3, and lipopolysaccharide activates these EP4-expressing neurons.[17] As stimulation of EP3 and EP4 elicits opposite signaling actions—typically decreasing and increasing cyclic AMP (cAMP) production, respectively[8]—the presence of these two receptors in the POA could exert opposite actions in thermoregulation. Studies in EP4-deficient mice are warranted, to establish the role of EP4 in illness-induced hypothermia.

Activation of the HPA axis

The HPA axis is the neuroendocrine system by which corticotropin-releasing factor (CRF) from neurons in the paraventricular hypothalamus (PVH) induces ACTH release from the pituitary gland, which in turn stimulates glucocorticoid production in and secretion from the adrenal cortex.[33] Systemic injection of NSAIDs blocks activation of the HPA axis induced by illness-related stimuli, although the effect is often partial.[5] Thus, illness-induced activation of the HPA axis seems to have prostaglandin-dependent and prostaglandin-independent components. Results from studies using microinjection of PGE_2, its analogs and NSAIDs into the brain suggest that PGE_2 synthesized in the POA is also critical for activation of the HPA axis in response to illness-related stressors.[34,35] Microinjection of PGE_2 into the PVH or the median eminence (through which CRF-containing PVH neurons secrete CRF from their axon terminals) also activates the HPA axis.[36,37]

An examination of ACTH release following lipopolysaccharide injection in mice deficient in various EPs revealed the mechanism of PGE_2 action in the HPA-axis response to illness.[38] Consistent with previous findings, indomethacin-sensitive and indomethacin-insensitive components of ACTH release were identified in studies of intraperitoneal lipopolysaccharide injection.[38] Mice deficient in either EP1 or EP3 had impaired ACTH release. Both EP1

deletion and EP3 deletion suppressed ACTH release to the same extent as administration of indomethacin did. This finding suggests that both EP1 and EP3 are required for prostaglandin-dependent ACTH release.

Although the sites of action of EP1 and EP3 remain to be determined, these two receptors seem to stimulate the HPA axis via distinct neural pathways that ultimately converge.[38] Studies of c-fos mapping suggest that EP1, but not EP3, is involved in the activation of neurons in the central nucleus of the amygdala, and that both EP1-mediated and EP3-mediated neural pathways are involved in activation of PVH neurons.[38] Illness-related stressors increase levels of PGE_2 in the PVH as well as in the POA[12] and EP1 is localized at synaptic structures on PVH neurons.[38] In hypothalamic slices, PGE_2 depolarizes CRF-containing PVH neurons,[39] and injection of PGE_2 into the PVH promotes ACTH release.[37] These results indicate that EP1 probably facilitates neurotransmitter release from the axon terminals that are formed on CRF-containing neurons in the PVH. However, which neurotransmitter(s) EP1 regulates is currently unknown. In addition, since EP1 is expressed in the presynaptic terminal on neurons in the central nucleus of the amygdala,[38] this same receptor could also act in the latter brain region to activate PVH and induce release of ACTH. Neurons in the central nucleus of the amygdala indirectly project to the PVH via the bed nucleus of the stria terminalis.[33] One report suggested that lesions in the central nucleus of the amygdala resulted in considerably reduced IL-1β-induced ACTH release.[40] These findings suggest that EP1 could act in the PVH both directly and indirectly (through the central nucleus of the amygdala).

In addition to the PVH, the POA is involved in the effect of PGE_2 on activation of the HPA axis.[34,35] EP3 has a critical role in illness-induced fever; therefore, EP3 might activate the HPA axis in a similar manner to its action in fever, because GABAergic neurons in the POA are thought to project directly to the PVH.[33] As PGE_2 probably suppresses EP3-expressing POA neurons to produce a febrile response,[21] PVH neurons could also be disinhibited to enable the activation of the HPA axis.

Alternatively, EP3 is expressed in various catecholaminergic neuron groups,[41] and one such site, the rostral ventrolateral medulla, has been proposed to mediate illness-induced activation of the HPA axis.[42] EP3 might, therefore, have a role in activating neurons in this site. Collectively, these findings suggest that EP1 and EP3 activate distinct pathways in response to illness, and that these pathways converge on CRF-expressing PVH neurons (Figure 3b).

Anorexia

In addition to febrile and neuroendocrine responses, illness-related stress also induces other behavioral changes, such as anorexia.[2,3,7] Studies using COX inhibitors and knockout mice suggest that prostanoids are involved in illness-induced anorexia.[43–45] As administration of COX inhibitors or COX2 deletion only partially reverses illness-induced anorexia,[43-45] both prostaglandin-dependent and prostaglandin-independent mechanisms for the development of anorexia seem to exist.

Two research groups have reported that mice lacking mPGES1 did not develop anorexia when they were injected intraperitoneally with IL-1β, unlike their wild-type counterparts.[46,47] These findings clearly show that PGE_2 signaling has a role in illness-induced anorexia. However, mPGES1 is not involved in anorexia induced by administration of lipopolysaccharide.[46] By contrast, NSAIDs reduced the severity of anorexia induced by various illness-related stressors, including IL-1β and lipopolysaccharide.[43–45] Thus, mPGES1-independent prostanoid synthesis could mediate lipopolysaccharide-induced anorexia.

One report indicates that EP4 can induce anorexia.[48] Administration of ONO-AE1-329, a selective EP4 agonist, to the central nervous system induced anorexia, mimicking the action of PGE_2.[48] The anorexic effects of PGE_2 and ONO-AE1-329 were blocked by ONO-AE3-208, a selective EP4 antagonist, but not by selective antagonists of the other EPs. Although no studies have examined illness-induced anorexia in EP4-deficient mice, one report using EP1-knockout and EP3-knockout mice showed that neither of these receptor subtypes is involved in tumor-induced anorexia.[49]

A primary neuronal circuit that controls feeding behavior is located in the hypothalamus (Figure 3c).[50] The arcuate nucleus of the hypothalamus senses peripheral hormonal signals, such as insulin and leptin, and its neurons project to other hypothalamic areas (mainly the dorsomedial hypothalamus, the ventromedial hypothalamus, PVH, and the lateral hypothalamic area) involved in the metabolic regulation of feeding.[50] The nucleus tractus solitarius receives peripheral satiety signals via vagal afferent fibers and has reciprocal connections with the PVH. [50] EP4 is expressed in both the PVH and the nucleus tractus solitarius.[32] EP4 is also expressed in the bed nucleus of the stria terminalis, which together with the PVH has been implicated in anorexia induced by CRF, a stress-related molecule.[51] EP4 is dramatically upregulated in these areas in response to illness-related stress.[32]

Another possible connection between EP4 and feeding control is histamine. EP4 is expressed in histaminergic neurons in the tuberomammillary nucleus of the hypothalamus,

and ONO-AE1-329, a selective EP4 agonist, stimulated histamine release to induce wakefulness.[52] Histamine is also an anorectic substance,[53] and seems to be involved in illness-induced anorexia: central injection of α-fluoromethylhistidine, a blocker of histamine synthesis, attenuated the anorexia induced by IL-1β.[54] Thus, EP4 could cause anorexia via inducing histamine release. In summary, EP4 seems to be a good candidate for central regulation of feeding, although PGE_2 is probably also involved in peripheral regulation of anorexia.[55]

Suppression of social behavior

Administration of indomethacin abrogates the reduction in social behaviors, such as sniffing and grooming, induced by IL-1β.[56] Prostaglandins could be involved in this mechanism.[56] The identity and neural mechanism of this presumed prostaglandin-mediated action remain unknown.

Impaired learning and memory formation

Illness-related stress impairs memory formation via the effects of cytokines and prostanoids.[7] Systemic injection of lipopolysaccharide and IL-1β impairs memory formation in various behavioral models.[95,96] Hippocampus-dependent memory formation is especially impaired.[95,96] COX inhibitors can attenuate illness-induced memory impairment, which suggests that prostanoids might be involved in this process.[97–100] Notably, microinjection of naproxen, a COX inhibitor, into the hippocampus reverses the impairment in hippocampus-dependent memory following injection of IL-1β into the hippocampus.[100] Furthermore, injection of PGE_2 into the hippocampus mimics the memory-impairing effect of IL-1β injection.[98,100] The results of these studies suggest that PGE_2 acts downstream of IL-1β in the hippocampus, and causes illness-induced memory impairment. The role of prostanoids in illness-induced memory impairment has been characterized using a transgenic mouse model, in which chronically raised levels of IL-1β could be induced with spatiotemporal specificity.[101] In this model, a chronic increase in levels of IL-1β in the hippocampus impairs long-term contextual and spatial memory.[102,103] This IL-1β overexpression induced the expression of COX1 and mPGES1 and enhanced PGE_2 production.[103,104] Many COX1-positive cells are microglia.[104] Importantly, deletion of the gene encoding COX1 eliminated the memory impairment induced by IL-1β overexpression in the hippocampus.[104] Deletion of this gene also reversed IL-1β-induced increase in levels of PGE_2, but not the increases in levels of various cytokines (such as TNF and IL-6) and chemokines (such as

CC-chemokine ligand 2 and CXC-chemokine ligand 2).[104] These findings suggest that a COX1-derived prostanoid, perhaps PGE_2, induces memory impairment independent of other cytokines.

Which EP subtype is involved in memory impairment has not been fully examined. EP2 is a plausible candidate, as systemic injection of lipopolysaccharide increases expression of EP2 and EP4 in the brain, and EP2 is expressed in the hippocampus.[32] As described in detail below, EP2 is involved in various forms of long-term synaptic plasticity in the hippocampus.[105–108] EP3 is another candidate, as injection of IL-1β into the central nervous system raised expression of EP3 in the hippocampus,[109] and EP3 mediates suppression of long-term potentiation in the visual cortex.[106]

Responses to psychological stress

Impulsive behavior

A study in EP1-deficient mice discovered that PGE_2 signaling is crucial for regulating impulsive behaviors related to acute psychological stress.[84] Thus, EP1-deficient mice showed impulsive aggression and deficits in social behavior in response to psychological stress. EP1-deficient mice also showed impaired cliff avoidance and an exaggerated startle response to acoustic stimuli.[84] Some of these behaviors can be mimicked by administration of ONO-8713, a selective antagonist of EP1, to wild-type mice.[84] Collectively, EP1 deficiency or antagonism seem to induce 'emotional impulsivity' after Soubrié's definition, a tendency of disinhibiting otherwise restrained bhavior.[REFa] The central injection of ONO-DI-004, a selective EP1 agonist, suppressed aggressive behavior, which suggests that this EP1 action occurs in the brain.[84] Further studies have demonstrated that EP1 acts, at least in part, on the dopaminergic system to exert such actions (Figure 4, Box 4).[84,85] Impulsive behaviors of EP1-deficient mice were suppressed when they were given dopamine receptor antagonists.[84] In addition, results from biochemical and microdialysis experiments showed that the basal level of dopamine release is increased in EP1-deficient mice compared with wild-type mice.[84,85] Results from slice electrophysiology studies suggest stimulation of EP1 by ONO-DI-004, an EP1 agonist, augments GABAergic inputs to dopaminergic neurons in the substantia nigra pars compacta.[85] EP1 is consistently localized at the GABAergic terminals on these neurons, which are at least in part derived from neuronal projections in the striatum.[85,86] These results suggest that PGE_2–EP1 signaling augments the negative feedback to midbrain dopamine neurons in a direct pathway from the striatum.

Dopaminergic disinhibition associated with EP1 deficiency should cause behavioral

impulsivity through some dopaminoceptive area(s). Although this issue remains to be examined, several dopaminoceptive areas, such as the prefrontal cortex and the amygdala, are critical for impulsivity.[88] Alternatively, dopamine in the nucleus accumbens suppresses and enhances excitatory inputs from the prefrontal cortex and the hippocampus, respectively.[89] Enhanced dopamine release in EP1-deficient mice could disengage the nucleus accumbens from the top-down signal from the prefrontal cortex, a pathway that negatively regulates impulsivity in animals.[90] These possibilities remain to be explored.

Since the above EP1-mediated response takes place immediately upon psychological stress, the release of PGE_2 for this EP1 action should involve the constitutive COX–prostaglandin E synthase pathway. COX1 and COX2 are constitutively expressed in microglia and neurons, respectively.[76] Various psychological stressors, such as forced swim and restraint, increase COX2 expression in cortical pyramidal neurons.[91,REFb] At the same time, psychological stress alters gene expression profiles and morphology of microglia.[92,93] Thus, both neurons and microglia could participate in activating EP1 under conditions of psychological stress (Figure 2b).

Hyperlocomotion

Interestingly, despite the presence of a hyperdopaminergic state, EP1 deficiency did not cause hyperlocomotion,[84] a phenotype of raised dopamine levels in the striatum.[87] This discrepancy could be explained by impairment of another EP1 action that facilitates dopamine receptor signaling in the striatum.[86] EP1 is expressed in the cell bodies of spiny striatal projection neurons, and augments both dopamine D1 and D2 receptor signaling in an agonist-dependent manner. Dependent on where and when PGE_2 is produced, therefore, PGE_2–EP1 signaling can regulate the outcome of the dopaminergic activity in either direction. The lack of hyperlocomotion in EP1-deficient mice suggests that these two EP1 actions are normally balanced in the striatum.

Alterations in learning and memory (level 2 subheading)

Illness-related stress and psychological stress alter the ability of animals to learn in a complicated manner. Acute and chronic psychological stress either facilitates or suppresses memory formation, effects often linked to the actions of glucocorticoids.[1,94] However, results from several studies have indicated that cytokines and prostanoids are also involved in learning and memory under conditions of psychological stress.[107,108,110-115,117]

Many behavioral tasks used to evaluate learning and memory employ stimuli that are

psychologically aversive for rodents, such as water immersion in the Morris maze and foot shock in fear conditioning. These tasks can potentially be used to evaluate memory formation under psychological stress, although the exact effects of psychological stress should be identified by comparing the findings obtained using these behavioral tasks to those obtained in situations without aversive stimuli, such as reward-oriented spatial learning. Using the Morris water maze and context-dependent fear conditioning, involvement of IL-1β and PGE_2 in memory formation *per se* in these tasks has been revealed.[110–115] For example, mice that lack the IL-1 receptor show deficits in contextual fear conditioning and in the spatial memory.[111] Results from previous studies also suggest that prostaglandins are involved in hippocampus-dependent spatial memory.[108,112-115] Thus, COX inhibitors impaired the acquisition and retention of spatial memory in the Morris water maze task.[112,113] Similarly, injection of celecoxib, a selective inhibitor of COX2, into the hippocampus blocked spatial memory in the Morris water maze task,[114,115] indicating that prostaglandins might be involved in the hippocampus.

Consistent with these effects of COX inhibitors and the actions of EP2 in synaptic plasticity described below, EP2-deficient mice show various memory disturbances.[107,108] For example, EP2-deficient mice had impaired spatial memory during the Morris water maze task.[108] EP2-deficient mice also showed a deficit in prepulse inhibition (suppression of sensory-evoked motor response due to a prior weak sensory stimulus) and heightened anxiety.[107] This latter EP2 action might be attributable to areas of the brain other than the hippocampus, as EP2 is also expressed in other areas, including the amygdala.[32] Another study examined the role of IL-1 in a particular type of psychological stress on hippocampus-dependent memory. [117] Social isolation, a type of psychological stress, impairs context-dependent fear conditioning.[116] Injection of an IL-1 receptor antagonist into the central nervous system eliminated this effect of social isolation, which indicates that IL-1 signaling has a role in the brain.[117] However, the function of prostanoid signaling in this model has not yet been examined.

PGE_2 signaling in synaptic plasticity

Consistent with above behavioral findings under illness-related and psychological stress, results from electrophysiological studies have demonstrated that PGE_2 is involved in excitatory synaptic transmission and long-term plasticity (Figure 5).[105–108,113,118–121] For example, the addition of COX inhibitors to a hippocampus slice blocks the induction of long-term potentiation at the perforant path–dentate gyrus (PP–DG) excitatory synapse,

deficits that are reversed by exogenous application of PGE_2.[113,118,119] Long-term potentiation at this synapse was consistently impaired in EP2-deficient mice.[108] Thus, PGE_2–EP2 signaling seems to be crucial in long-term potentiation at the PP–DG synapse in the hippocampus. Furthermore, expression-knockdown experiments using RNA interference showed that PGE_2–EP2 signaling is also necessary in long-term potentiation at the layer IV–layer II–III excitatory synapse in the visual cortex.[106] In contrast to EP2, EP3 knockdown by RNA interference augmented long-term potentiation at this synapse in the visual cortex, which indicates that EP3 is inhibitory.[106]

Although EP2 is involved in long-term potentiation at both the PP–DG synapse in the hippocampus and the layer IV–layer II–III synapse in the visual cortex, different subcellular localizations of EP2 have been shown at these two synapses.[105,106] Immunostaining suggests that EP2 is localized at the presynaptic structure of primary neurons in the hippocampus and at postsynaptic structures of neurons in the visual cortex,[105,106] although EP2 localization *in vivo* has not been examined. Ca^{2+} influx through the *N*-methyl D-aspartate-type glutamate receptor activates PGE_2 production by COX2,[122] and COX2 is located at postsynaptic structures in various types of neurons.[105,106] On the basis of these findings, PGE_2 released from the postsynaptic site was proposed to act on presynaptic EP2 as a retrograde messenger, which mediates signaling from a postsynaptic structure to an adjacent presynaptic structure, in the PP–DG synapse,[105] and postsynaptically released PGE_2 acts on postsynaptic EP2 in the layer IV–layer II–III synapse.[106]

Long-term potentiation at the Schaffer collateral–CA1 synapse was not impaired in hippocampal slices from EP2-deficient mice, which suggests that EP2 is not involved in all kinds of long-term potentiation.[107] Rather, EP2 deficiency impaired long-term depression at this synapse.[107] Prostaglandins also seem to mediate long-term depression at the PP–DG synapse, given that NS-398, a COX2 inhibitor, blocked long-term depression as well as long-term potentiation at this synapse.[120] Long-term depression at the parallel fiber–Purkinje cell synapse in the cerebellum also seems to depend on prostanoid signaling.[121] Several COX2 inhibitors, such as NS-398 and DUP 697, suppressed long-term depression at this synapse, and this blockade was reversed by exogenously applied prostaglandin D_2 or PGE_2.[121] However, the receptor subtype involved in this form of long-term depression remains unidentified.

Conclusions

The development of EP-knockout mice and EP-selective drugs has enabled the identification

of multiple adaptive functions of PGE_2 under illness-related stress, each of which is mediated by a distinct EP subtype.[8,9,13,14,18,31,38,73] These molecular tools have also provided evidence that PGE_2 signaling has unexpected actions under conditions of psychological stress and in physiological brain functions, such as the role of EP1 in suppressing impulsive behaviors via the dopaminergic system and that of EP2 in hippocampus-dependent learning and synaptic plasticity.[84-86,105-108] Dependent on the type of stressor present, PGE_2 is released from various cell types, and acts in the vicinity of its synthesis. Upon illness-related stress, blood-borne cytokines (such as IL-1β) induce the production of COX2 and mPGES1 in several types of cells inside and outside the brain, and these enzymes, in turn, synthesize PGE_2.[57,64-70,73,78] Cooperative actions of PGE_2 and cytokines are also key features in the immune system and bone metabolism.[8] By contrast, psychological stimuli are perceived as stress through neuronal connections, which in turn affects neuronal pathways involved in behavioral outcomes.[1] Although both IL-1 and PGE_2 clearly have roles in responses to psychological stress, the mechanisms to explain how these two molecules are released and their involvement in the neural cascades from stressful stimuli to behavioral responses remain elusive. Results from clinical studies have shown the relevance of prostanoids in patients with schizophrenia or major depression.[123] As chronic psychological stress precipitates psychiatric disorders, the number of studies on the role of prostanoids in animal models of chronic stress is increasing.[124–126] Whether and how the PGE_2-dependent mechanisms involved in responses to stress contribute to mental illnesses is also an exciting question.

Review criteria

A search for original articles published between 1998 and April of 2010 and focusing on neural functions of prostaglandin E_2 in stress responses was performed in PubMed. The search terms used were “prostaglandin” and “brain”, and relevant articles were manually selected from the resultant list. We also searched the reference lists of identified articles for relevant papers.

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Author contributions

Both authors contributed equally to all aspects of this Review.

Figure legends

Figure 1. PGE_2 synthesis, prostaglandin receptor subtypes and subtype-selective compounds. a | PGE_2 is synthesized by sequential catalysis involving COX1, COX2 and PGESs. NSAIDs, including aspirin and indomethacin, suppress prostaglandin production by inhibiting COX. b | The four subtypes of prostaglandin E receptors (EP1–EP4) are encoded by different genes. These receptors are divided into three groups according to their major signaling pathways: EP1 is linked to increases in levels of intracellular Ca^{2+}, EP2 and EP4 are linked to increases in levels of cAMP via $G_s\alpha$, and EP3 is linked to decreases in levels of cAMP via $G_i\alpha$. c | Some EP-subtype-selective agents. Only representative compounds are shown. Abbreviations: COX, cyclo-oxygenase; $G_i\alpha$, inhibitory G-protein subunit; $G_s\alpha$, stimulatory G-protein subunit; PGES, prostaglandin E synthase.

Figure 2. Proposed sites of PGE_2 production during illness and psychological stress. a | Various studies have shown that illness-related stressors, such as lipopolysaccharide and IL-1β, induce expression of COX2 in endothelial cells and/or perivascular macrophages in the brain, which in turn induces synthesis of PGE_2. RANKL–RANK signaling can also mediate IL-1β-induced production of PGE_2 in the hypothalamus and COX2 induction in astrocytes. The major site of PGE_2 production in the brain involved in stress responses to illness remains to be elucidated. Furthermore, PGE_2 from peripheral macrophages in the lungs and liver mediates the initial febrile response (within 1 h) to illness. b | COX1 and COX2 are constitutively expressed in microglia and cortical pyramidal neurons, respectively. Under conditions of psychological stress, one or both of these constitutively expressed COX isoforms could conceivably be responsible for PGE_2 production. Abbreviations: COX, cyclo-oxygenase; IL, interleukin; PGE_2, prostaglandin E_2.

Figure 3. Neuronal pathways involved in stress responses to illness. a | Pathways for autonomic mechanisms involved in the febrile response. EP3 localizations are shown in red. The neural pathway for shivering (another critical thermoeffector) is not shown, as the role of PGE_2 in this response remains unknown. b | Pathways for the hypothalamus–pituitary–adrenal response. Putative localizations of EP1 and EP3 receptors in these pathways are shown in yellow and red, respectively. c | Pathways involved in anorexia. Putative EP4 localizations are

shown in green. In a | and b | excitatory and inhibitory neurons involved in each pathway are shown in purple and blue, respectively. The use of these specific colors does not, however, exclude the presence of other neuron types in a given area. Abbreviations: ACTH, adrenocorticotropic hormone; ARC, arcuate nucleus of the hypothalamus; BNST, bed nucleus of the stria terminalis; CeA, central nucleus of the amygdala; CRF, corticotropin-releasing factor; DMH, dorsomedial hypothalamus; His, histamine; LHA, lateral hypothalamic area; ME, median eminence; POA, preoptic area; NA, noradrenaline; NTS, nucleus tractus solitarius; PVH, paraventricular hypothalamus; RPa, raphe pallidus nucleus; RVLM, rostral ventrolateral medulla; TMN, tuberomammillary nucleus; VMH, ventromedial hypothalamus.

Figure 4. EP1-mediated regulation of dopaminergic systems under psychological stress. a | Dopaminergic neurons in the SNc and the VTA and their projections are shown in green. Circuits from striatal neurons that express dopamine receptors D1 and D2 are shown in black. EP1 localizations are shown in yellow. b | Psychological stress seems to induce PGE_2 production in the SNc and striatum. In the SNc, PGE_2-mediated EP1 activation occurs at the GABAergic presynaptic terminals on dopaminergic neurons, and augments GABA release that negatively modulates the activity of these neurons. In the striatum, PGE_2 activates EP1, which is expressed on both D1-expressing neurons and D2-expressing neurons, and facilitates signaling of both dopamine receptors. Abbreviations: CPu, caudate putamen; EP, PGE_2 receptor; GABA, γ-aminobutyric acid; GPe, external globus pallidus; GPi, internal globus pallidus; NAc, nucleus accumbens; PFC, prefrontal cortex; PGE_2, prostaglandin E_2; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; VTA, ventral tegmental area.

Figure 5. Proposed mechanisms in EP2-mediated control of synaptic plasticity. a | In the hippocampus, EP2 is suggested to function at the PP–DG synapse for long-term potentiation and at the SC–CA1 synapse for long-term depression of responses. b | Proposed mechanisms for EP2 actions on long-term potentiation of neuronal circuits. Ca^{2+} influx through NMDA receptor (NR) during synaptic inputs evokes PGE_2 production from arachidonic acid (AA) via COX-2 and PGES activity at the postsynaptic structure. PGE_2 released is suggested to act on either presynaptic structure (in the hippocampus) or postsynaptic structure (in the visual cortex) via EP2. To cause long-term potentiation, cAMP increase downstream of EP2 could increase the probability of neurotransmitter release and/or the trafficking of AMPA-type glutamate receptor (AMPA-R). Abbreviations: AA, arachidonic acid; AMPA-R, AMPA-type

glutamate receptor; CA, cornus ammonis; DG, dentate gyrus; EC, entorhinal cortex; EP, prostaglandin E_2 receptor; NR, *N*-methyl-D-aspartate-type glutamate receptor; PGES, prostaglandin E synthase; PP, perforant path; sub, subiculum; SC, Schaffer collateral; TA, temporoammonic path.

Figure 1.

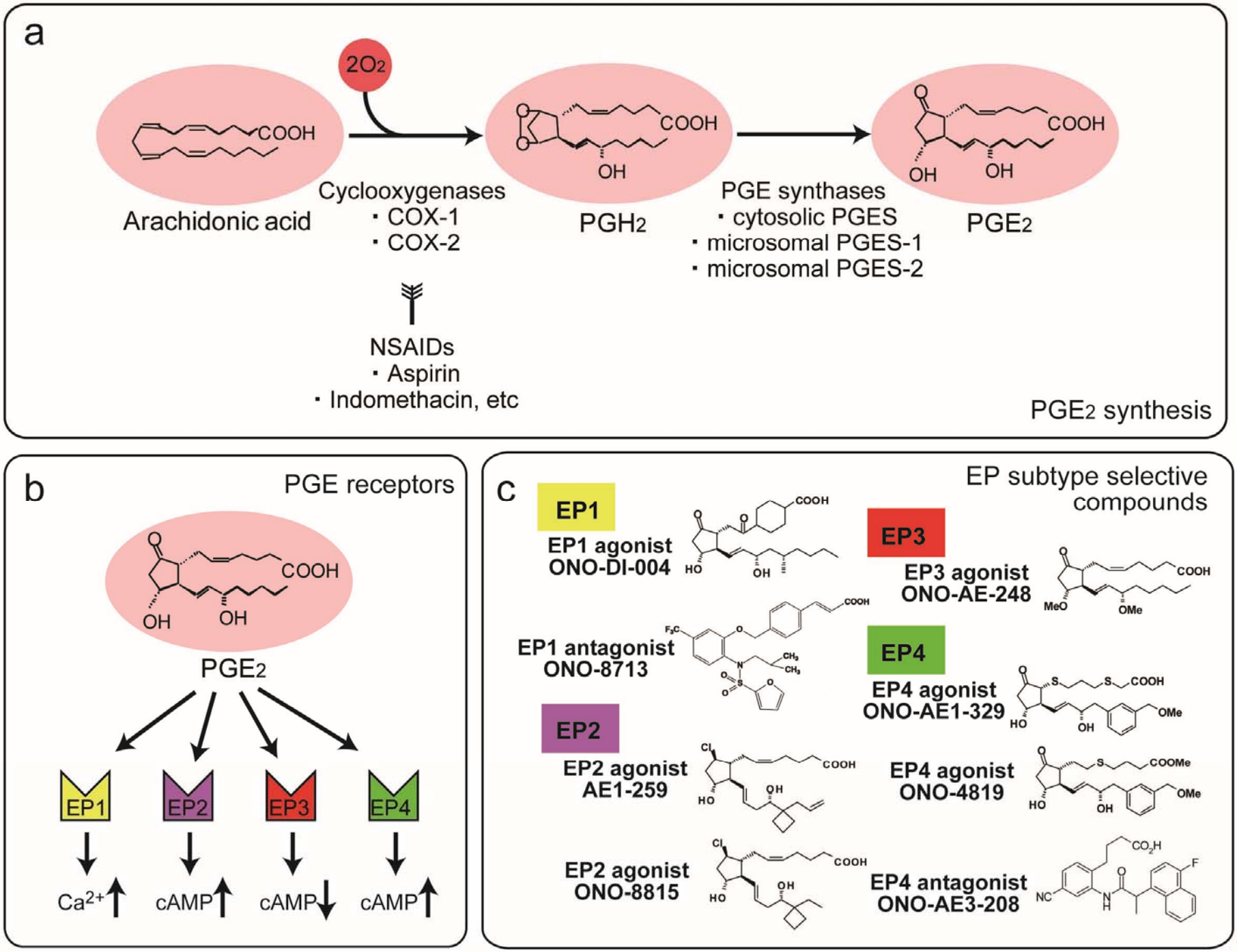

a
2O2
COOH
Arachidonic acid
Cyclooxygenases
・COX-1
・COX-2
COOH
OH
PGH2
PGE synthases
・cytosolic PGES
・microsomal PGES-1
・microsomal PGES-2
COOH
OH
OH
PGE2
NSAIDs
・Aspirin
・Indomethacin, etc
PGE2 synthesis
b
PGE receptors
COOH
OH
OH
PGE2
EP1
EP2
EP3
EP4
Ca2+
cAMP
cAMP
cAMP
c
EP subtype selective compounds
EP1
EP1 agonist
ONO-DI-004
EP1 antagonist
ONO-8713
EP2
EP2 agonist
AE1-259
EP2 agonist
ONO-8815
EP3
EP3 agonist
ONO-AE-248
EP4
EP4 agonist
ONO-AE1-329
EP4 agonist
ONO-4819
EP4 antagonist
ONO-AE3-208

Figure 2.

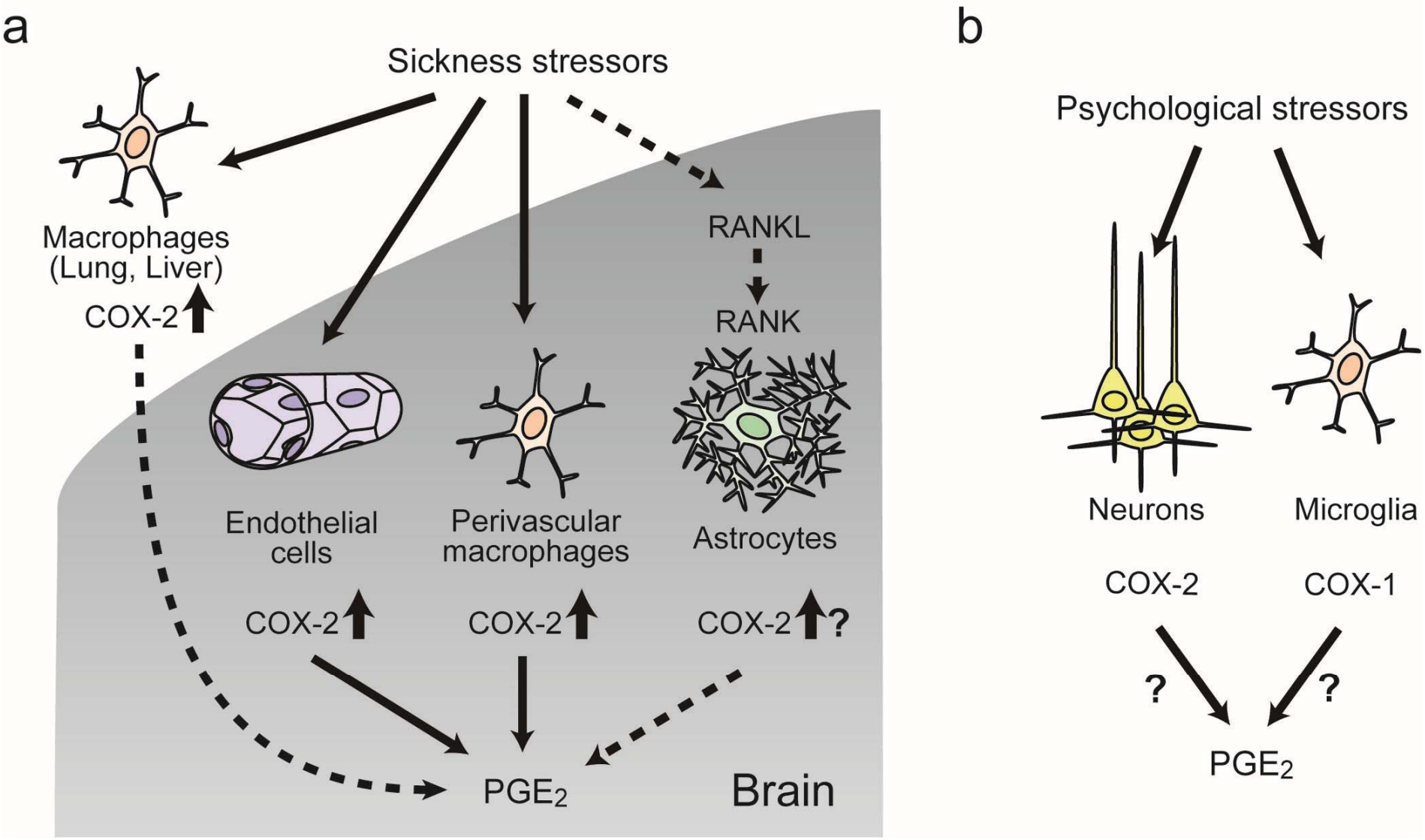

a
Sickness stressors
Macrophages
(Lung, Liver)
COX-2
RANKL
RANK
Endothelial
cells
Perivascular
macrophages
Astrocytes
COX-2
COX-2
COX-2 ?
PGE2
Brain
b
Psychological stressors
Neurons
Microglia
COX-2
COX-1
?
?
PGE2

Figure 3.

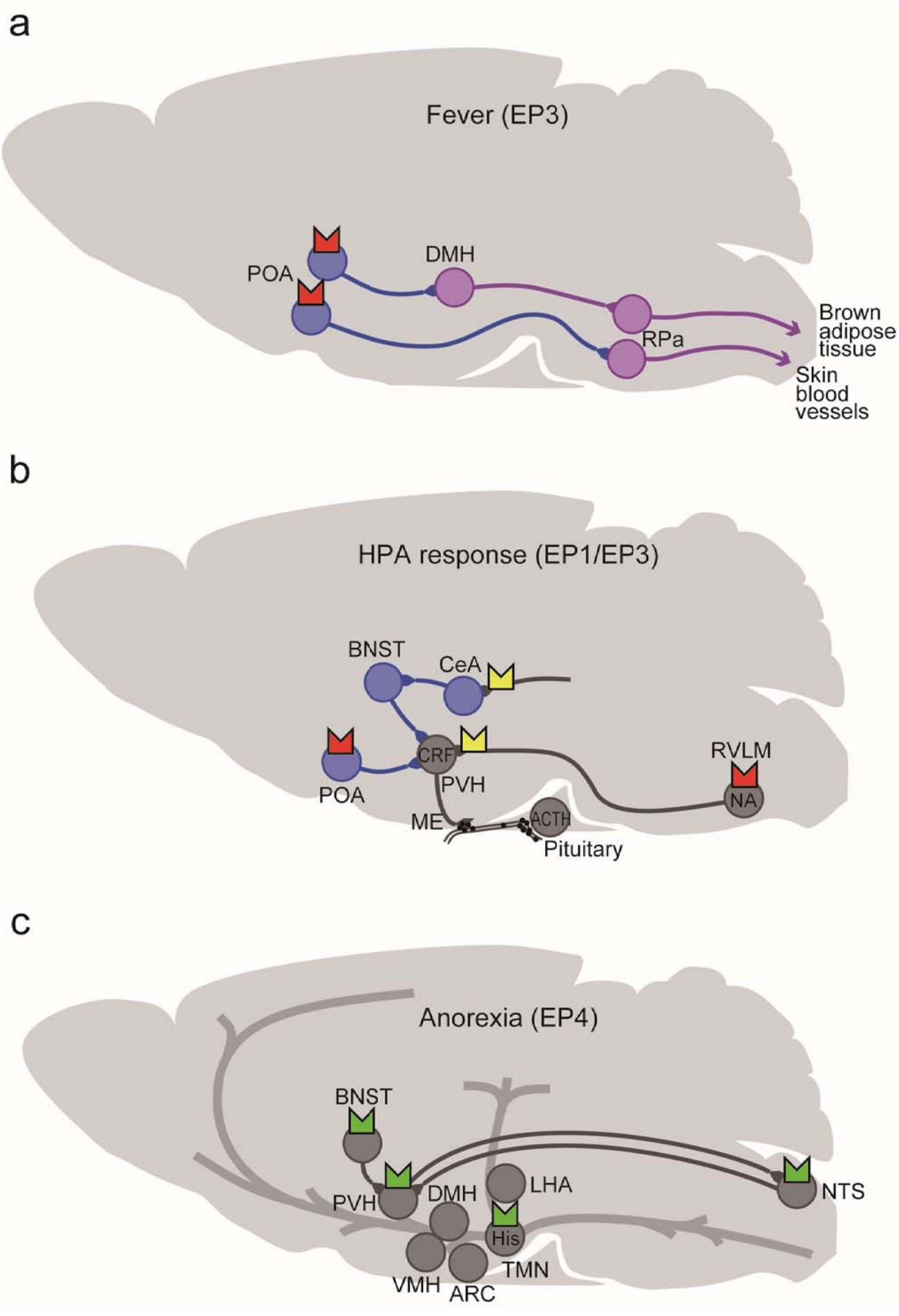

a
Fever (EP3)
POA
DMH
RPa
Brown adipose tissue
Skin blood vessels
b
HPA response (EP1/EP3)
BNST
CeA
CRF
PVH
POA
ME
ACTH
Pituitary
RVLM
NA
c
Anorexia (EP4)
BNST
PVH
DMH
LHA
His
TMN
VMH
ARC
NTS

Figure 4.

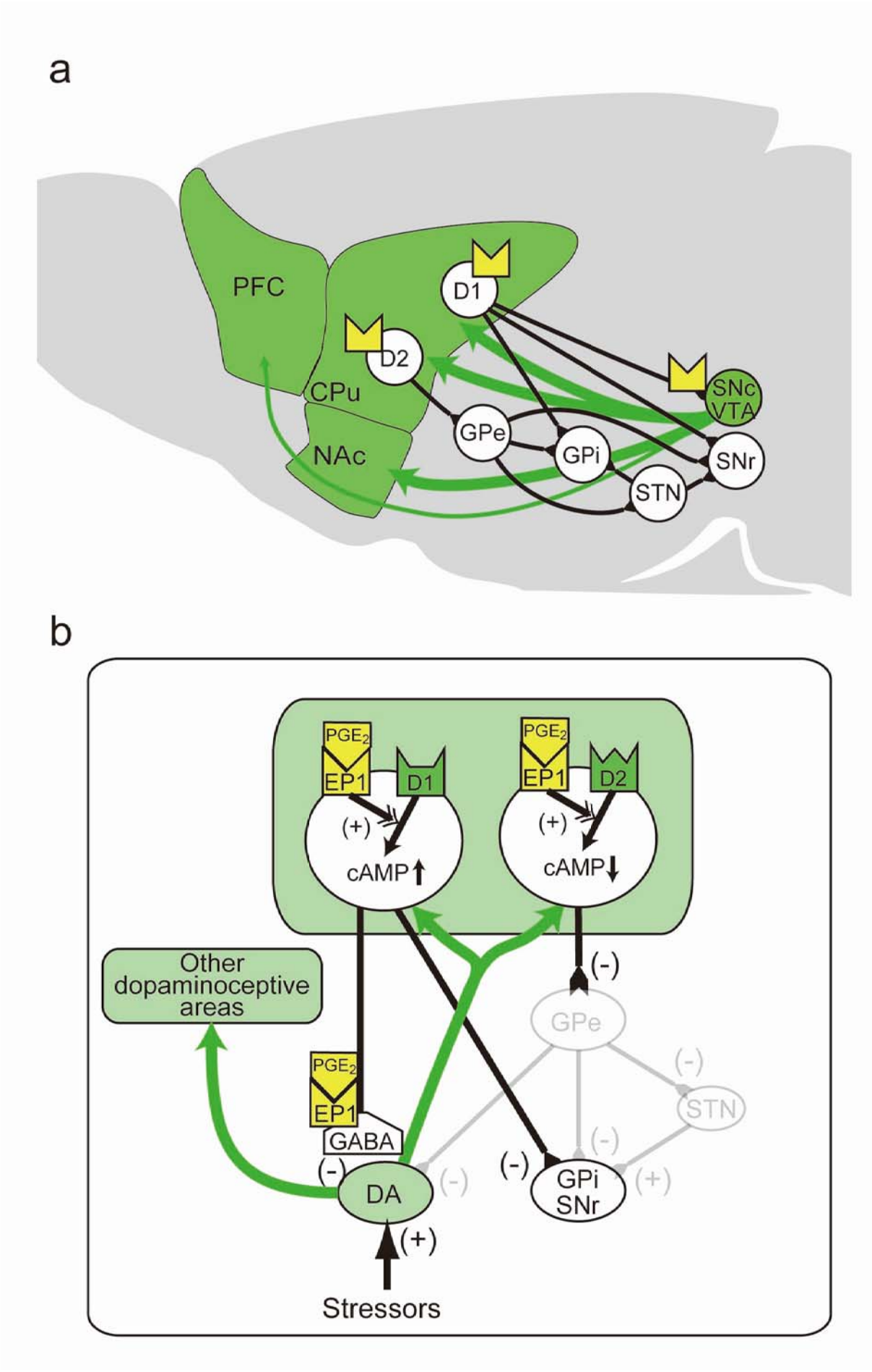
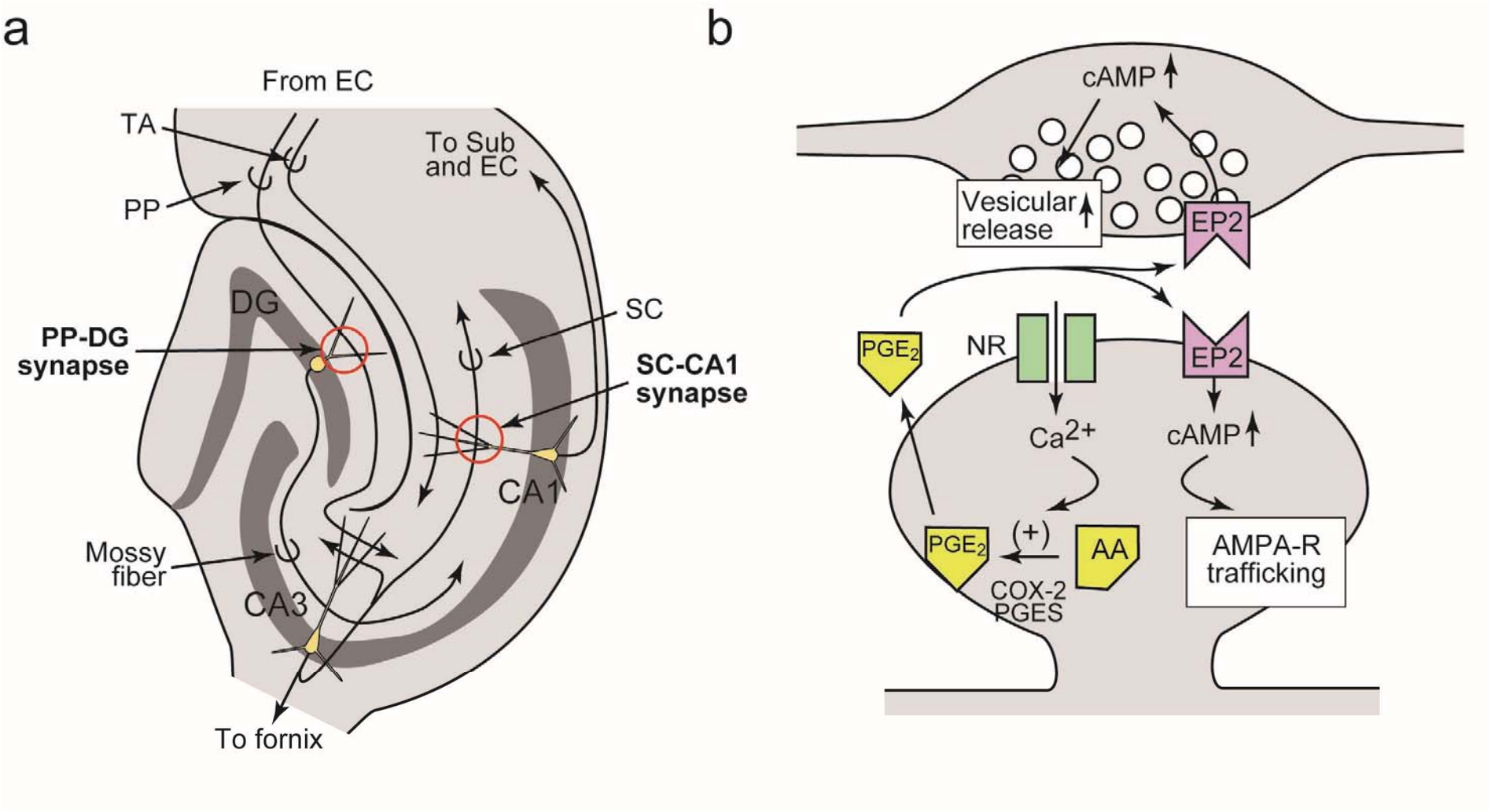

a
PFC
CPu
NAc
D1
D2
SNc
VTA
GPe
GPi
SNr
STN
b
PGE2
EP1
D1
(+)
cAMP
PGE2
EP1
D2
(+)
cAMP
Other
dopaminoceptive
areas
(-)
GPe
(-)
STN
PGE2
EP1
GABA
(-)
DA
(-)
(-)
(-)
GPi
SNr
(+)
(+)
Stressors

Figure 5.


a
From EC
TA
PP
To Sub
and EC
DG
SC
PP-DG
synapse
SC-CA1
synapse
CA1
Mossy
fiber
CA3
To fornix
b
cAMP
Vesicular
release
EP2
PGE2
NR
EP2
Ca2+
cAMP
PGE2
(+)
AA
AMPA-R
trafficking
COX-2
PGES

Box 1. Stress, stressors and stress responses

Stress is a concept that was developed to explain the similarity of biological responses to various external and internal stimuli, such as illness and psychological stimuli. Stress is a state of physical and psychological stain caused by adverse stimuli, which results in adaptive responses to restore our bodily status.[1] Stimuli that cause stress are called stressors, and biological responses to these stressors are called stress responses. However, the mechanisms underlying stress responses are still being investigated. The extent to which similar or overlapping mechanisms regulate stress responses across stressors remains unknown.

Illnesses attributable to systemic inflammation are typically associated with a cluster of biological responses. The pattern of responses depends on the severity and time course of the illness.[2,3,127] At the onset of illness (or if illness is mild) active defense mechanisms, such as fever, wakefulness, hypertension, hyperalgesia, and generalized motor agitation, typically occur. By contrast, if illness is severe or prolonged, passive defense mechanisms including lethargy, analgesia and hypersomnia become dominant to avoid further energy expenditure. At this stage, either hyperthermia or hypothermia might occur owing to an increased susceptibility to the ambient temperature.

Acute exposure to fearful or anxiogenic stimuli, such as the presence of a predator or being in an unprotected place, activates a coping strategy called the ‘flight or fight’ response, a preparatory response to facilitate escape and self-defense. This response manifests as activation of the sympathetic nervous system (for example, increased heart and lung action, hyperthermia and pupil dilation) and increased levels of glucocorticoids. Chronic exposure to such stimuli often precipitates exhaustion and depression.[1] Thus, both illness and psychological stimuli result in a dynamic course of adaptive responses, either active or passive, depending on bodily demands.

Box 2. NSAIDs, prostanoids and their receptors

The NSAIDs are drugs with analgesic, antipyretic and anti-inflammatory actions that do not have a steroid backbone. Various NSAIDs, such as aspirin, indomethacin and ibuprofen, have been developed. Their actions are mostly attributable to the blockade of cyclo-oxygenase (COX) enzymes, which are responsible for prostanoid synthesis.[128]

The prostanoids are a family of bioactive lipids produced from C20-unsaturated fatty acids, such as arachidonic acid. They are synthesized throughout the body in response to various noxious stimuli and tissue injuries, and have multiple physiological and pathological roles in inflammation and immunity, cardiovascular homeostasis, bone metabolism and illness-related stress responses. The prostanoids include prostaglandin (PG) PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2 and thromboxane A_2,[8] all of which are formed by the sequential actions of two isoforms of COX (COX1 and COX2) and three isoforms of PGE synthase (PGES): cytosolic PGES, microsomal PGES1 and microsomal PGES2. Expression of COX2 and mPGES1 is induced by illness-related stressors such as lipopolysaccharide and proinflammatory cytokines.

Each prostanoid binds to its cognate G-protein-coupled receptor, for example, PGE_2 has four receptor subtypes (EP1, EP2, EP3 and EP4).[8] These receptors are categorized into three groups according to their major signaling pathways: those coupled to Ca^{2+} increase (EP1), those coupled to cyclic AMP increase (EP2 and EP4), and those coupled to cyclic AMP decrease (EP3). These receptors show distinct tissue expression and cell localization, enabling them to exert specific functions.

Box 3. Stress-induced hyperthermia

Acute psychological stress induces hyperthermia. Some animal studies showed that NSAIDs block the hyperthermia response to psychological stressors, such as exposure to an open field or a cage of another individual, whereas other studies did not show this effect.[129] However, as NSAIDs also exert some prostaglandin-independent effects, these pharmacological studies are not conclusive. Gene-deletion studies do not yet support a role of prostaglandin E_2 signaling in stress-induced hyperthermia. Mice lacking either microsomal prostaglandin E synthase 1 or prostaglandin E_2 receptor (EP) 3 did not develop illness-induced fever, whereas these mice showed a normal hyperthermia response to psychological stress.[13,14,61] EP1-deficient mice also demonstrated a normal stress-induced hyperthermia response.[14] By contrast, stress-induced hyperthermia is specifically sensitive to anxiolytics[129,130] and blockade of the corticotropin-releasing factor receptor in the brain.[131] Thus, the mechanisms of stress-induced hyperthermia and illness-induced fever seem to differ.

Box 4. Midbrain dopaminergic systems

Midbrain dopaminergic neurons are mainly located in the ventral tegmental area and the substantia nigra pars compacta.[132] Dopaminergic neurons in the ventral tegmental area project mostly to the medial prefrontal cortex and the nucleus accumbens. Substantia nigra pars compacta dopaminergic neurons primarily project to the dorsal striatum or the caudate putamen. The dorsal striatum contains two types of projection neurons: those that express the dopamine D1 receptor and the dopamine D2 receptor, respectively. D1-expressing neurons project directly to the internal globus pallidus and the substantia nigra pars reticulata, which in turn project to the thalamus and the superior colliculus. A subset of D1-expressing neurons in the striatum provides negative feedback control of dopaminergic neurons.[132] D2-expressing neurons project to the external globus pallidus, which in turn project to the internal globus pallidus and substantia nigra pars reticulata, mostly via the subthalamic nucleus.

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Shuh Narumiya, MD, PhD, is Professor and Chair of the Department of Pharmacology at Kyoto University Graduate School of Medicine, Kyoto, Japan. He is trained as a biochemist and pharmacologist. Prof. Narumiya's main research interest is the physiological and pathophysiological roles of prostanoid receptors and in the signal transduction and functions of Rho small GTPases. For his outstanding contribution to these research fields through over 370 peer-reviewed publications, he has received numerous domestic and international awards. He also served as the Dean of Kyoto University Graduate School of Medicine (2004–2007) and the President of the Japanese Pharmacological Society (2008–2010).

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