p11 (S100A10) — an inducible adaptor protein that modulates neuronal functions

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p11 (S100A10) is a member of the S100 prote in family and forms a heterotetrameric complex with annexin 2. p11 has also been found to interact with a diverse set of proteins that includes several ion channels and the serotonin 5-HT_{1B} receptor. Several factors such as dexamethasone, growth factors, nitric oxide and antidepressant therapies regulate the expression of p11. Furthermore, studies using mutant mouse models, RNA interference and antisense constructs have implicated p11 in several biological processes; in particular, there is evidence that p11 is involved in the pathophysiology underlying nociception and depression-like states.

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Current Opinion in Pharmacology 2007, **7**:27–32

This review comes from a themed issue on
Neurosciences
Edited by Karima Chergui, Bertil Fredholm and Per Svenningsson

Available online 7th November 2006

1471-4892/$ – see front matter

DOI 10.1016/j.coph.2006.10.001

Introduction: p11 is a member of the S100 protein family

P11 (also named S100A10, 42C, calpactin I light chain and annexin II light chain) is a member of the S100 family of proteins [1,2]. S100 proteins are small acidic proteins (10–12 kDa) and constitute the largest subfamily of EF-hand proteins, with at least 25 members [1–3,4•,5]. The chromosomal arrangement of S100 proteins is unusual, as the genes encoding 21 family members (S100A1–S100A18, trichohylin, filaggrin and repetin) are clustered at chromosomal locus 1q21, whereas other S100 proteins are found at chromosomal loci 4p16 (S100P), 5q14 (S100Z), 21q22 (S100B) and Xp22 (S100G) [2,4•]. S100 proteins exist as symmetrical homo- and hetero-dimers, with each monomer containing two EF-hand motifs. The N-terminal EF-hand comprises helix I, calcium-binding site I and helix II, separated by a linker from the C-terminal EF-hand that includes helix III, calcium-binding site II and helix IV. The dimer interface consists of helices I and IV of each monomer arranged in an X-type four-helix bundle [6,7•]. The S100 proteins have 25–65% identity at the amino acid level, with the sequences of the linker region and the C-terminal extension being the most variable among the proteins [1]. A unique feature of p11 is that it contains mutations in both of the calcium-binding sites, making it calcium insensitive [8]. Like other S100 proteins, the majority of p11 is found intracellularly in the cytosol or at the inner surface of the plasma membrane [1,9]. However, p11 is also present on the extracellular surface of many cells where it binds tissue plasminogen activator (tPA) via its C-terminal lysines [10,11]. Carboxypeptidases cleave the carboxyl-terminal lysines of S100A10, resulting in a loss of extracellular binding to tPA.

Here, we review protein–protein interactions involving p11, the regulation of p11 expression, and the current knowledge of the functions of p11 with an emphasis on its role in the nervous system.

Multiple proteins interact with p11

More than 20 years ago, it was shown that p11 could be co-purified as a heterotetramer with annexin 2 [12•]. It has since been found that the translocation of annexin A2 to the cell surface is p11 dependent [13]. Moreover, the heterotetrameric p11/annexin 2 complex organizes lipid microdomains [14], bundles F-actin filaments [15] and has been shown to be involved in membrane–cytoskeleton linkage, membrane trafficking and endocytosis [9].

The p11/annexin 2 complex was the first three-dimensional structure of an S100 complex to be determined [6]. Helices III and IV of p11 interact with the N terminus of the annexin 2 molecule [16]. The locations of the interactions between annexin 2 and p11 are similar to those identified for annexin 2 and S100A11. In addition to annexin 2, p11 has recently been shown to interact with numerous additional proteins (Table 1). These interactions are all calcium independent [7•]. Currently, knowledge of the domains through which p11 interacts with proteins other than annexin 2 is still limited. In the cases where the domains have been examined, it has been found that the C-terminal portion of p11 is involved. However, whereas the domain of interaction between p11 and annexin 2 involves both helices III and IV, the interaction site with NaV1.8 channels resides within helix III [17] and the interactions with tPA [11] and other S100 proteins involve solely helix IV [18]. For most of these protein–protein interactions, it is not known whether p11 is the only S100 protein member that can act as an

Table 1

Proteins that have been shown to interact with p11 and the functional role of p11 in these interactions.

Interactor	Biological function of p11	Reference
Annexin 2	Regulation of endosomal functions	[12•]
5-HT_{1B} receptor	Localization of 5-HT_{1B} receptors at the cell surface	[25••]
NaV1.8 sodium channel	Increase of NaV1.8 channels at the plasma membrane	[21]
TASK-1 potassium channel	Regulation of TASK-1 channels at the plasma membrane	[22,45]
ASIC-1 channels	Increase of ASIC channels at the plasma membrane	[24]
TRPV5/TRPV6 channels	Increase of TRPV5/TRPV6 channels at the plasma membrane	[23]
NS3	Mediation of virus release	[46]
Cytosolic phospholipase A_2	Reduced arachidonic acid release	[26]
BAD	Inhibition of pro-apoptotic effect	[47]
HBV Pol	Inhibition of DNA polymerase activity	[48]
AHNAK	Increase of AHNAK in the cell membrane	[49]
Cathepsin B	Binding of cathepsin B at the cell surface	[28]
PCTAIRE-1	Stimulation of kinase activity	[27]
Plasminogen activator	Stimulation of plasminogen activity	[10]
Transglutaminase	P11 is a transglutaminase substrate	[19]
S100A7		[18]
S100A8		[18]

5-HT, 5-hydroxytryptamine (serotonin); BAD, Bcl2-antagonist of cell death.

'interactor'. For example, both p11 and S100A11 show interactions with annexin 2 and transglutaminase [19]. Recently, a binding motif of the p11/annexin 2 complex in the AHNAK (meaning 'giant' in Hebrew) protein has been described [20].

Some functional consequences of the interactions between p11 and its partners have been reported. Accumulating evidence indicates that p11 plays an important role in the trafficking of transmembrane proteins. It has been demonstrated that p11 regulates the level of Nav1.8, acid-sensing ion channel (ASIC)-1, TWIK-related acid-sensitive K^+ channel (TASK)-1, transient receptor potential vanilloid (TRPV)5/6 channels and 5-HT_{1B} receptors at the cell surface [21–24,25••]. p11 has also been shown to regulate the enzymatic activity of various proteins including phospholipase A_2, PCTAIRE-1, tPA and cathepsin B [11,26–28].

Regulation of p11 levels by various factors

There is accumulating evidence that p11 is an inducible protein, and several transcription factors, including activator protein-1, SP-1 and nuclear factor-κB, have been identified upstream of the *p11* gene [29]. In addition, multiple factors have been shown to regulate p11 levels (Table 2). In studies using epithelial cell lines expressing native p11 (BEAS cells [a human bronchial epithelial cell line], HeLa cells or RGM-1 cells [rat gastric mucosal cell line known to be normal gastric epithelial cells]), it has been found that dexamethasone, transforming growth factor-α, nitric oxide donors, interferon-γ and epidermal growth factor all induce p11 expression [30–34]. These data demonstrate that diverse types of factors can regulate p11 levels, and that multiple physiological stimuli can regulate its levels. Studies using the pheocytochroma cell line PC12 have shown that nerve growth factor (NGF) can also regulate p11 levels [35]. Likewise, using primary

Table 2

Factors that have been shown to regulate p11 expression in biological systems.

Factor	Biological system	Reference
Dexamethasone	BEAS and HeLa cells	[34]
Transforming growth factor-α	RGM-1 cells	[30]
Epidermal growth factor	BEAS and HeLa cells	[31]
Nitric oxide donors	BEAS and HeLa cells	[33]
Interferon-γ	BEAS cells	[32]
Vitamin D	Mouse kidney	[23]
Retinoic acid	BEAS cells	[50]
Nerve growth factor	PC12 cells, rat dorsal root ganglion	[21,35]
Imipramine	Mouse frontal cortex	[25••]
Tranylcypromine	Mouse frontal cortex	[25••]
Electroconvulsive treatment	Rat frontal cortex	[25••]
Sciatic nerve lesion	Rat	[37]
Experimental autoimmune encephalitis	Rat cerebellum	[38]

cultured dorsal root ganglia neurons, it has been found that NGF induces p11 is these cells [21]. Interestingly, increased p11 levels cause proliferation and differentiation of PC12 cell morphology [36]. Several antidepressant treatments, including imipramine (a tricyclic antidepressant), tranylcypromine (a monoamine oxidase inhibitor) and electroconvulsive treatment, have been shown to upregulate p11 levels in the frontal cortex of mice and rats [25••]. Upregulation of p11 also occurs in response to sciatic nerve lesions [37], as well as in Purkinje cells in experimental autoimmune encephalitis, a rat model of multiple sclerosis [38].

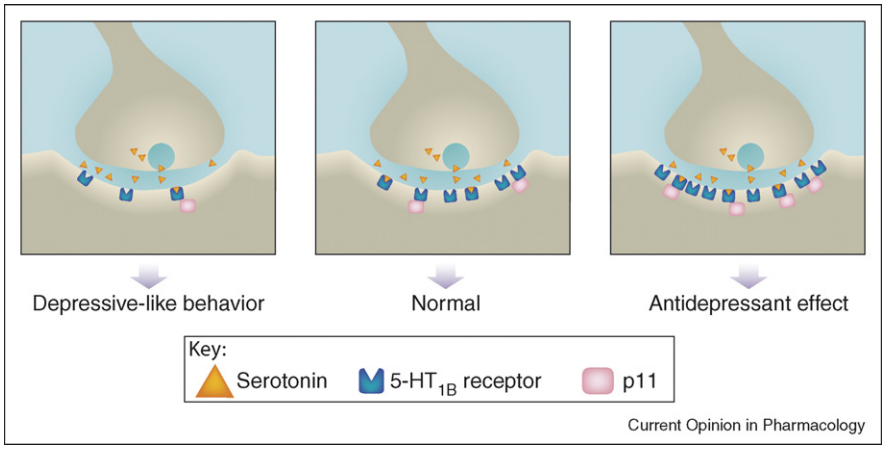
Involvement of p11 in neuronal function

p11 is widely distributed in the body and has been detected in the brain, heart, gastrointestinal tract, kidney, liver, lung, spleen, testes, epidermis, aorta and thymus [4•,39]. Within the brain, p11 is expressed in several regions, including the cerebral cortex, hippocampus, hypothalamus and raphe nuclei [25••]; however, a detailed study of its distribution remains to be performed. By virtue of its interactions with 5-HT_{1B} receptors and NaV1.8/ASIC-1 channels, the involvement of p11 in the regulation of depression-like states [25••] and nociception [21,24] has been investigated. As mentioned above, p11 expression is increased in the rodent brain following several types of antidepressant therapy (Figure 1). Interestingly, the levels of p11 are decreased in a mouse model of depression and in brain tissue from unipolar depressed patients. Overexpression of p11 in the forebrain leads to increased motor activity, thigmotaxis and reduced immobility in the tail suspension test — a test commonly used to evaluate antidepressant drug efficacy. Conversely, p11 knockout mice have significantly reduced responsiveness to stimulation of 5-HT_{1B} receptors in biochemical, electrophysiological and behavioural tests, as well as to the behavioral action of imipramine in the tail suspension test. These experiments have provided strong evidence to suggest that the interaction between p11 and 5-HT_{1B} receptors plays a role in the pathophysiology of depression-like states. In this context, it is interesting to note that studies in cell lines have shown that p11 levels are stimulated by dexamethasone and neurotrophic factors.

It is commonly believed that stressful life events can precipitate depression [40], and hippocampal atrophy has been found in depressed individuals and in patients suffering from Cushing''s disease, a condition involving hypercortisolemia [40]. Animal studies have shown that stress-induced dendritic atrophy can be counteracted by some antidepressant treatments [40]. Our data indicate that decreased levels of p11 correlate with the susceptibility to depression. It is therefore paradoxical that dexamethasone stimulates the levels of p11. However, the relationships between cortisol, stress, depression and p11 are likely to be complex and require detailed investigation. Neurotrophic factors are potent regulators of plasticity and survival of adult neurons and glia. The neurotrophic hypothesis of depression states that a deficiency in neurotrophic support contributes to hippocampal pathology in depression, and that reversal of this deficiency by antidepressants can contribute to the treatment of depression [41]. However, recent studies have shown that decreased levels of neurotrophins in some brain regions correlate with antidepressant actions; as a result, there is an ongoing revision of the neurotrophin hypothesis of depression.

Studies in cell lines have shown that overexpression of p11 leads to an enhanced number of 5-HT_{1B} receptors at the cell surface (Figure 1) [25••]. A reduced number of

Figure 1



Schematic drawings of the hypothetical relationship between p11, serotonin 5-HT_{1B} receptors and depression-like states. p11 recruits 5-HT_{1B} receptors to the plasma membrane, thereby regulating the efficacy of serotonergic neurotransmission. Left-hand side: decreased p11 expression correlates with a reduced number of 5-HT_{1B} receptors at the cell surface, decreasing serotonergic neurotransmission and leading to depression-like symptomatology. Right-hand side: conversely, increased p11 expression (e.g. induced by antidepressant therapies) upregulates the number of 5-HT_{1B} receptors at the cell membrane, increasing serotonergic neurotransmission and producing antidepressant effects.

binding sites for 5-HT_{1B} receptor ligands has been demonstrated in p11 knockout mice. These effects could be mediated by multiple mechanisms, such as altered recruitment of the receptors to the cell membrane or disturbed endosomal recycling and/or degradation of the receptor. There is indeed evidence that p11, together with annexin 2, is involved in intracellular positioning of early recycling endosomes [9,42]. It is also noteworthy that antidepressants not only increase the brain content of p11 but also stimulate the production of S100B [43]. As p11 appears to be expressed in both neurons and glia, whereas S100B is more abundant in glia, S100 proteins might be important in determining the region and cell specificity of antidepressant mechanisms.

P11 levels have been shown to increase in response to sciatic nerve lesions, indicating that p11 is involved in nociceptive processes [37]. At least two channels interacting with p11, NaV1.8 and ASIC-1 are involved in nociception [21,24]. In both instances, p11 increases the expression of these channels at the cell membrane in cell lines. Studies investigating the functional importance of the interaction between p11 and these channels have been performed in dorsal root ganglia, a neuronal population that expresses high levels of both types of channels [21,24]. Using an antisense construct against p11, loss of a tetrodotoxin-resistent NaV1.8 current density was found [21]. An involvement of p11 in peripheral pain pathways was recently found in mice lacking p11 in dorsal root ganglia (see also Update).

P11 can also regulate neuronal functions by virtue of its interaction with tPA. Most cases of stroke are caused by sudden blood vessel occlusion, and the primary treatment for this condition is systemic administration of tPA, which stimulates plasmin-dependent thrombolysis. As mentioned above, the carboxyl-terminal lysines of p11 bind tPA, resulting in the stimulation of tPA-dependent plasmin production [11]. Interestingly, plasmin can also bind to p11, and the formation of the p11/tPA/plasmin complex stimulates highly localized plasmin activity at the cell surface. These data indicate that p11 plays a role in regulating the severity of stroke and the treatment response towards tPA. Moreover, as tPA/plasmin is also known to cleave pro-brain-derived neurotrophic factor (BDNF) to BDNF [44], it is possible that the p11/tPA/plasmin complex might regulate BDNF synthesis that, in turn, could modulate, for example, emotions and mood state.

Conclusions

There is accumulating evidence that p11 interacts with a diverse set of target proteins and regulates various biological functions in different cellular compartments. Additional work is required to determine the extent to which p11 can interact with multiple target proteins simultaneously. As the expression of p11 is inducible, it is likely that the cell specificity of these interactions differs between normal and disease states. p11 has been shown to be implicated in depression-like states and nociception, and future work should clarify whether p11 is implicated in additional diseases states. The availability of p11 knockout mice [25••] will facilitate efforts to understand the role of p11 under physiological and pathophysiological conditions. The development of pharmacological agents, such as peptides or small molecules, which can interfere with the interactions between p11 and target proteins, should allow novel approaches to the treatment of disease states including depression and anxiety.

Update

A recent study [51•] evaluated the role of p11 in peripheral pain pathways. Using mice lacking p11 specifically in dorsal root ganglia, it was found that noxious coding in wide-dynamic-range neurons in the dorsal horn was markedly compromised. Pain behavior was attenuated in certain models of acute and neuropathic pain. However, given the fact that pro-inflammatory NGF and interferon-γ upregulate p11 levels, it was surprising that no deficits in inflammatory pain were observed. Nonetheless, this study confirms a modulatory role for p11 in pain pathways.

Acknowledgements

We would like to thank Vetenskapsrådet, Hjärnfonden, US Public Health Service grants MH40899 and DA10044 for financial support.

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