Proteinases as hormone-like signal messengers

Proteinase-activated receptors and the pathophysiology of inflammation, pain, cardiovascular disease and cancer

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Summary

Proteinases like thrombin and trypsin, long known for their ability to activate the coagulation cascade or to act as hormone-processing enzymes, are now recognised as hormone-like regulators of cell function. These serine proteinases activate cell signalling by triggering a novel four-member family of G-protein-coupled receptors, termed Proteinase-Activated Receptors (PARs). This review article summarises historically the discovery of PARs as well as their unique mechanism of activation and outlines a number of different pathophysiological settings in which PARs can act to regulate cell and tissue function. PARs can be seen to play a role in pathophysiological processes ranging from inflammation and pain to cardiovascular disease and cancer. Apart from activating PARs to cause their physiological effects in tissues, proteinases can also mediate cell signalling via a number of other mechanisms, including the activation of growth factor receptors, like the one for insulin. Therefore, this article also describes the non-PAR mechanisms whereby proteinases can have hormone-like actions in cells and tissues.

Key words: hormone; information; PAR; protease; proteinase; receptor; signal transduction; thrombin

Introduction

The serine proteinase thrombin is well recognised for its role in the coagulation cascade. In addition to its ability to act as a clotting factor, thrombin has long been known to trigger signalling pathways in platelets and endothelial cells. For more than forty years, in addition to their ability to convert inactive pro-hormone precursors to their active forms (eg, pro-insulin to insulin), other serine proteinases, such as trypsin, have also been known to stimulate cellular hormone-like responses. For instance, work by the Riesers in the mid-1960s documented the insulin-like actions of proteinases like pepsin and chymotrypsin in a rat diaphragm preparation [1, 2]. Subsequent work in the early 1970s showed that like insulin, trypsin, can both stimulate glucose oxidation and inhibit lipolysis in isolated adipocyte preparations [3]. Over the past fifteen years or so, the mechanisms responsible for the cellular actions of proteinases have come into focus. In large part, the physiological actions of serine proteinases can be seen to be mediated by a novel family of G-protein-coupled receptors: the Proteinase-Activated Receptors (PARs). Other mechanisms that mediate the actions of proteinases will also be discussed below.

Thrombin, platelet activation and the discovery of proteinase-activated receptors

The search for the receptor on human platelets and hamster lung fibroblasts responsible for the ability of thrombin to initiate platelet aggregation and to stimulate fibroblast mitogenesis resulted in the cloning of a receptor that turned out to be a member of the G-protein-coupled receptor super-family [4–9]. It was discovered that the unique mechanism of activation of this receptor involves the proteolytic unmasking of an N-terminal receptor

Abbreviations:

Cha: cyclohexylalanine
Cit: Citrulline
IUPHAR: International Union of Pharmacology
PAR: Proteinase-Activated Receptor
PAR-AP: PAR-Activating Peptide
SAR: Structure-Activity Relationship
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sequence that becomes a tethered ligand, which binds to the extracellular receptor domains to trigger receptor signalling [5] (figure 1). Based on this mechanism of activation, the receptor for thrombin has been referred to as a “Proteinase-Activated Receptor” and assigned the acronym “PAR” by the International Union of Pharmacology [8]. The first PAR found to be a target for thrombin has now been designated as PAR1.

Remarkably, it was also discovered that synthetic peptides with sequences matching that of the exposed tethered ligand can also activate the receptor in the absence of proteolysis [5]. Thus, a synthetic peptide, beginning with the sequence of human PAR1, SFLLRN…, was found to be a surrogate activator of the receptor for thrombin in a variety of settings. These peptides (initially termed Thrombin Receptor-Activating Peptides or TRAPs, which mimic the ability of thrombin to activate PAR1, soon revealed that in certain cells,

Table 1

<table>
<thead>
<tr>
<th>Receptor designation (IUPHAR)</th>
<th>tethered ligand sequence</th>
<th>comment</th>
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<tbody>
<tr>
<td>PAR1</td>
<td>(h) SFLLRN…</td>
<td>designated: TRAP or PAR1AP</td>
</tr>
<tr>
<td>(r, m) SFLLRN…</td>
<td></td>
<td>SFLLRN… Activates both PAR1 and PAR2; standard PAR1-activating peptide: TFLLR-NH2; standard PAR1-inactive peptide: FTLLR-NH2</td>
</tr>
<tr>
<td>PAR2</td>
<td>(h) SLIGKV…</td>
<td>designated PAR2AP</td>
</tr>
<tr>
<td>(r, m) SLIGRL…</td>
<td></td>
<td>standard PAR2-activating peptide: SLIGRL-NH2; standard PAR2-inactive peptide: LSIGRL-NH2; selectively activates only PAR2; murine and rat sequence more potent than human sequence</td>
</tr>
<tr>
<td>PAR3</td>
<td>(h) TFRGAP…</td>
<td>PAR3 is not activated by PAR-APs</td>
</tr>
<tr>
<td>(m) SFNGGP…</td>
<td></td>
<td>PAR3-derived sequences, eg. TFRGAP… or SFNGGP…, activate both PAR1 and PAR2</td>
</tr>
<tr>
<td>PAR4</td>
<td>(h) GYPGQV…</td>
<td>designated PAR4AP</td>
</tr>
<tr>
<td>(m) GYPGKF…</td>
<td></td>
<td>standard PAR4-activating peptide: AYPGKF-NH2;</td>
</tr>
<tr>
<td>(r) GFPGKP…</td>
<td></td>
<td>standard PAR4-inactive peptide YAPGKF-NH2; PAR4AP sequences do not activate PARs 1 and 2, but are active via non-PAR4 receptors in some bioassays</td>
</tr>
</tbody>
</table>

* Abbreviations: h = human; m = mouse; r = rat; IUPHAR = International Union of Pharmacology; The new N-terminal sequences revealed by serine proteinase cleavage are shown as tethered ligands. These proteolytically revealed sequences activate signalling in PARs 1, 2 and 4, but not in PAR3.

Table 2

<table>
<thead>
<tr>
<th>Feature</th>
<th>comment</th>
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<tbody>
<tr>
<td>Can be proteolytically activated by a number of serine proteinases</td>
<td>multiple circulating or local agonists are possible</td>
</tr>
<tr>
<td>Can be proteolytically cleaved downstream of the tethered ligand sequence thereby preventing receptor activation by agonist serine proteinases</td>
<td>multiple circulating or secreted enzymes, like neutrophil elastase can act as antagonists by disarming PARs</td>
</tr>
<tr>
<td>Susceptibility to proteinase activation can be modulated by receptor glycosylation near the tethered ligand cleavage site</td>
<td>tryptase does not activate fully glycosylated human PAR3; receptors other than PARs may be activated, even by PAR-selective PAR-APs that do not activate other PARs</td>
</tr>
<tr>
<td>PAR-APs can mimic proteolytic activation of signalling</td>
<td></td>
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Figure 1

Mechanism of activation of Proteinase-Activated Receptors, as typified by human PARr. The figure illustrates the activation of human PARr, both by the tethered ligand mechanism triggered by thrombin or trypsin (left and centre) and by a PARr-activating peptide (GYPGQV-NH2) with a sequence based on the proteolytically revealed tethered ligand (right).
such as rodent platelets, the PAR2-Activating Peptide (PAR2-AP) did not cause a thrombin response (eg, aggregation) [10]. Other structure-activity studies with peptides based on the SFLRN sequence also pointed to subtypes of the thrombin receptor in rat vascular and gastric tissues [11]. Subsequent to the cloning of the first receptor for thrombin (PAR1), three other members of this intriguing receptor family have been identified (table 1). Each of these G-protein-coupled receptors, designated PARs 1 to 4, has a unique N-terminal tethered ligand sequence that is revealed by serine proteinase action as illustrated for PAR4 in figure 1 and summarised in table 1. PARs 1, 3, and 4 have been found to be targets for thrombin, whereas PAR2, not readily activated by thrombin, can be activated by trypsin, tryptase and by other serine proteinases of the clotting cascade apart from thrombin (eg, tissue factor-VIIa-Xa complex) [6–9, 12]. Although the signalling properties of PARs are unclear, all of PARs 1, 2 and 4 have been found to signal via a G-protein coupled mechanism involving Goi or Goq. Further, based on the revealed tethered ligand sequences of PARs 1, 2 and 4, it has now been possible to design synthetic peptides (PAR-APs) that can selectively activate each receptor. Appropriate standard inactive peptides, incapable of activating the PARs, are also known (table 1).

Although PARs can be activated by a variety of serine proteinases using the tethered-ligand mechanism outlined in Figure 1, it is also the case that the cleavage of a PAR N-terminal sequence downstream of the tethered ligand portion would disarm the receptor, thus preventing its subsequent activation by a proteinase. For instance, the elastase secreted by Pseudomonas aeruginosa, a complicating pathogen in the setting of cystic fibrosis, can cleave and remove the tethered ligand sequence from PAR2, thereby disabling the receptor on lung epithelial cells [13]. The disabling of PAR2 in this setting may contribute to the pathophysiology of lung inflammation in this disease. Thus, PARs can be said to have a variety of circulating agonists (ie, serine proteinases that reveal the tethered ligand) as well as circulating functional antagonists that can disarm them downstream of their tethered ligands, thereby silencing the receptors. That said, the proteolytically disarmed receptors would still be sensitive to activation by the PAR-APs that do not depend on the tethered ligand sequence for receptor activation.

The unique features of PARs are summarised in table 2. One of the key features of these receptors is their ability to be activated by receptor-selective PAR-APs. These PAR-APs have proved to be of considerable utility to determine the potential consequences of activating PARs in bioassay systems in vitro or in inflammatory or other animal models in vivo. As summarised in the following sections, PARs have been found to play an important role in the pathophysiology of diseases ranging from inflammation and pain to cardiovascular disease and cancer. For a comprehensive collection of articles dealing with PARs and their potential impact on physiological function, the reader is invited to access the special issues of Drug Development Research (volumes 59 [4] and 60 [1]) to be found on the following website: http://www.inflammation-calgary.com.

**Discovering pathophysiological roles for PARs: a pharmacological approach**

**PAR-APs trigger both PAR and non-PAR responses in target tissues: use of structure-activity studies**

As alluded to above, Structure-Activity Relationship (SAR) studies using peptides with sequences based on human PAR1 revealed the presence of a receptor other than PAR1 in an endothelium-dependent rat aorta relaxation assay [11]. That receptor, unknown at the time, turned out to be PAR2 [14, 15]. The principle that led to the discovery of functional PAR2 in the rat vascular endothelium was outlined some time ago by Ahlquist [16] in defining the pharmacology of alpha- and beta-adrenoceptors. In essence, with only minor exceptions, a receptor can be typified for distinct responses in different tissues by the relative potencies (EC50s or IC50s) of a series of chemically related agonists and antagonists. The presence of distinct SAR relationships for the same set of compounds (eg, agonists) in different tissue assays points to the existence of distinct receptors. This principle has been used to advantage in studying potential PAR-mediated responses in different bioassay systems, employing, for example, a series of PAR1 and PAR2APs. Thus, for PAR2-mediated calcium signalling in a PAR2-expressing KNRK cell line, the relative potencies of the PAR2-selective agonist peptides, SLIGRL-NH2, trans-cinnamoyl-LIGRLO-NH2, 2-furoyl-LIGRO-NH2 and of a potent PAR2-selective PAR2AP, AparafluoroFrChaChaCitY-NH2 would be: 2-furoyl-LIGRO-NH2 >> trans-cinnamoyl-LIGRLO-NH2 ≈ SLIGRL-NH2 >>> AparafluoroFr-RChaChaCitY-NH2 [17, 18]. A completely reversed SAR would be expected of a PAR1-mediated response, in which the three PAR2-activating peptides would be essentially inactive. Surprisingly, the SAR relationship for these PAR2 agonists observed in a rat jejunal ion transport assay (SLIGRL-NH2 > trans-cinnamoyl-LIGRLO-NH2 > AparafluoroFrChaChaCitY-NH2) was different from the SAR expected of either PAR1 or PAR2 [17]. A plausible conclusion was that the short-circuit current response in the jejunal Ussing chamber due to the
serosal application of the PAR-APs and trypsin was mediated by a receptor different from PAR1 and PAR2. In a similar manner, some recent work with PAR4-derived agonists has been able to verify the presence of PAR4 in rat platelets, using a platelet aggregation assay, while pointing to a non-PAR4-mediated response in a rat gastric longitudinal muscle assay [19].

The work with the PAR4-derived peptides illustrates that a judicious choice of standard PAR-APs as well as a standard PAR-inactive peptide is required to establish whether or not a given response can be attributed to a given PAR. For responses thought to be mediated by PAR1, use can be made of receptor antagonists (eg, RWJ66110 or SCH79797) [20, 21]. Although not yet available for PAR2, antagonists have been developed for PARs [22, 23]. That said, although the peptide PAR4 antagonists are suitable for antagonizing the receptor in platelets, these antagonists can cause responses via receptors other than PAR1 in tissue assays [19]. To resolve such discrepancies, PAR-deficient mice have been used to demonstrate unequivocally the PAR-related actions of PAR-APs and to prove that a proteinase-triggered response may be due to the activation of one or more of the PARs (below). The essence of these findings with the PAR-APs is that it is now possible with reasonable confidence to use these receptor probes to assess the potential impact that PAR activation might have in a variety of physiological and pathological settings.

PARs, inflammation, neuronal responses and nociception
Although PARs 1 and 4 were discovered primarily due to the search for the target of thrombin on mammalian platelets, the potential physiological role for PAR2 was not known at the time of its discovery [24]. However, the use of selective PAR2-APs as probes for PAR2 function quickly revealed a potential role for this receptor in regulating vascular and gastric smooth muscle tension [14, 15]. It came as a surprise, however, that the administration of small doses of either a PAR or a PAR4-AP caused marked swelling and leukocyte infiltration in a rat paw oedema model of inflammation [25, 26]. At that time, it was also observed that functional PAR2 as well as PAR1 could be localised on neuronal elements [27]. Putting these two sets of observations together, it has become evident that the inflammatory response triggered by PARs 1 and 2 is mediated via a neurogenic mechanism [28, 29]. The administration of a PAR4-AP also causes the formation of oedema and leukocyte recruitment in a rat paw model of inflammation [19, unpublished results]. However, in contrast with PARs 1 and 2, these PAR4-mediated events are not dependent on a neurogenic mechanism [19]. It has also become clear that in addition to triggering the inflammatory response, PARs also play a role in sensing pain [30–33]. Given the widespread distribution of PARs on neurons and their associated cells, such as astrocytes, both in the central and peripheral nervous systems, it is to be expected that neuronal PARs may play a widespread physiological role. As an example, one can point to an up-regulation of PAR1 in the central nervous system in the setting of HIV encephalitis [34]. Further, PAR2 would appear to play a neuroprotective role in the setting of HIV infection [35]. The overarching working hypothesis that can be put forward is that PARs play a key role in the body’s innate defense, as a primary trigger of the inflammatory response and pain sensation due to tissue injury or remodeling caused by pathogenic processes. This hypothesis is strongly supported by the striking resistance of PAR2-deficient mice to adjuvant-induced arthritis [36].

PARs and cardiovascular function
An isolated rat aorta tissue preparation provided one of the first bioassay systems that enabled us to predict a role for PARs in regulating vascular function [14, 15, 37]. Using the same approach, it was possible to document the ability of PARs as well as

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**Figure 2**

Vasorelaxation of rat aorta from normal and streptozotocin diabetic rats following PAR2 activation. Male Sprague-Dawley rats (about 200 g) were either treated or not with streptozotocin (SZT), to render treated animals diabetic. One week after streptozotocin treatment, with hyperglycaemia established, animals were sacrificed and endothelium-intact aorta rings were monitored for PAR2-mediated vasodilatation as described previously [14], using SLIGRL-NH$_2$ (SL-NH$_2$) as a receptor agonist. Relaxation in the normal (●) or SZT-diabetic (+) aorta rings by increasing concentrations of SL-NH$_2$ was expressed as a percentage of the relaxation caused in the same preparation by 10 µM acetylcholine (% Ach). Values showing the shift to the left in sensitivity of the SZT-diabetic tissues represent the averages (± sem) for measurements done with three independent tissue preparations. (Saifeddine and Hollenberg, unpublished)
PAR1 to activate an endothelium-dependent, nitric oxide (NO)-mediated vasorelaxation. In contrast with PAR2 which does not appear to regulate vascular smooth muscle function directly, PAR1, activated by either a PAR1-selective AP such as TFLLR-NH₂ or by thrombin, causes a prompt vasoconstriction. In the setting of renal function, both PARs 1 and 2 can have an effect on perfusion, with PAR1 activation causing a profound decrease in flow similar to angiotensin and with PAR2 acting as a vasodilator to increase flow [38]. Thus, in certain settings, PARs 1 and 2 may play a bi-directional role. Although in conduit vessels like the aorta PAR activation leads primarily to an NO-mediated relaxation, in resistance vessels or in renal afferent arterioles, vasodilatation caused by PAR activation is mediated not only by NO, but also by as yet unidentified endothelium-derived relaxing factors (EDHFs) [39, 40]. The impact of PAR1 activation on vascular function is not yet clear, except for its ability to play a potential role for endothelium-leukocyte interactions [41].

A potential role for PAR2 in the setting of cardiovascular disease may occur in the setting of ischaemia-reperfusion in which case there can be an up-regulation of PAR2 to promote vasodilatation [42]. It has also been found that PAR2 is increased in human coronary atherosclerotic lesions [43]. Moreover, a preliminary assessment of aorta tissue derived from rats rendered diabetic by streptozotocin treatment indicates an increased sensitivity to the vasodilatory actions of PAR2 (Figure 2). The distinct effects on blood pressure and heart rate upon activating either PAR1 (both hypotension and tachycardia) or PAR2 (hypotension only, without an effect on heart rate) have been established unequivocally with the use of mice deficient in either PAR1 or PAR2 [44]. Thus, a generalised role for the PARs in the setting of cardiovascular pathophysiology would appear to be plausible.

**PARs, cancer and metastasis**

Since the mid 1990s, it has been suggested that the coagulation system in general and thrombin specifically may play an important role in tumour growth and metastasis [45, 46]. Not only might thrombin facilitate the ability of tumour cells to migrate through the basement membrane, but the enzyme itself has been known for some time to be a particularly potent mitogen for normal as well as tumour-derived cells, presumably acting via PAR1. A clear link has been made between the expression of PAR1 in mammary tumour-derived cells and the ability of the cells to migrate in culture through a reconstituted basement membrane [47]. The ability of PAR1 to subserve a role in tumour metastasis and invasion is underlined by the ability of tumour-derived matrix metalloproteinase-1 to activate the receptor and drive the process of migration and metastasis of breast carcinoma cells in a xenograft model [48]. A comparable role for PAR2 in the setting of cancer would not be unexpected [49]. Given the information provided in the previous sections, it is clear that in addition to contributing to the growth and metastasis of tumour cells, PARs can potentially play a role in a wide variety of pathophysiological processes, as summarised in Table 3.

### Table 3

<table>
<thead>
<tr>
<th>Potential physiological roles for PARs.</th>
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<tbody>
<tr>
<td><strong>Potential role</strong></td>
<td><strong>comment</strong></td>
</tr>
<tr>
<td>Platelet activation, haemostasis: Thrombin-activated receptors (PARs 1, 3, 4)</td>
<td>PARs regulate both secretion and aggregation; PARs 1 and 4 can play separate roles</td>
</tr>
<tr>
<td>Endothelial cell function: (PARs 1, 2 and 4)</td>
<td>release of NO, von Willebrand factor; increased neutrophil adherence; cell migration</td>
</tr>
<tr>
<td>Vascular smooth muscle function</td>
<td>activation of contractility; angiogenesis?</td>
</tr>
<tr>
<td>Intestinal function: (PARs 1, 2 and 4)</td>
<td>regulation of motility (GI smooth muscle) and secretion (GI epithelial cell)</td>
</tr>
<tr>
<td>Myenteric neuron function</td>
<td>also affects GI motility and inflammatory response</td>
</tr>
<tr>
<td>Renal vascular function</td>
<td>regulation of flow and afferent arteriolar function</td>
</tr>
<tr>
<td>CNS neuronal and astrocyte function</td>
<td>up-regulation of PARs in the setting of CNS inflammation</td>
</tr>
<tr>
<td>Response to joint injury</td>
<td>key role for PAR2 in arthritis</td>
</tr>
<tr>
<td>Tumour cell growth and metastasis</td>
<td>both PARs 1 and 2 may play roles, activated by tumour-derived serine proteinases and Matrix metalloproteinases (eg, MMP-1)</td>
</tr>
</tbody>
</table>

### Which endogenous proteinases regulate PAR activity?

**Thrombin and other serine proteinases**

Given the physiological role established for thrombin as a member of the coagulation cascade, it is clear that this serine proteinase is a key regulator of PARs 1 and 4, with the amplification provided by PAR1 [6]. That said, the tissue-localised proteinases other than thrombin that may regulate PARs, including PARs 2 and 4, which are both potentially activated by trypsin (and presumably other serine proteinases), have yet to be identified. In the
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...it has been suggested that trypsin itself (presumably pancreatic trypsin-I in humans) is responsible for activating PAR2 on the intestinal epithelium [50]. Mast cell tryptase, which in humans might be released in the vicinity of sensory nerves, is another candidate enzyme that may regulate PAR2 [51–53]. Of importance is the potential role that other serine proteinases of the coagulation cascade (Factor VIIa/Xa) may play [12], especially in terms of activating PARs, a receptor that, as outlined above, plays a prominent role in inflammatory and nociceptive settings.

Given that PARs 1 and 2 have been shown to play an important role in models of inflammatory bowel disease [54], a major question to ask is: what intestinal proteinases at the site of inflammation might trigger the inflammatory response? A clue to answering this question has come from a study using a model of murine infectious colitis, in which the infecting organism, C. rodentium, induces the production of PAR2-activating serine proteinases (members of the trypsin family and granzyme A) that in turn activate PAR2 [55]. Significantly, the oral administration of a serine proteinase inhibitor (soya trypsin inhibitor) was able to attenuate the pathogen-induced PAR2-mediated colitis [55]. Thus, the identification of site-produced PAR-activating proteinases and the selective targeting of proteinase inhibitors to individual tissues may provide an interesting therapeutic modality for treating a number of inflammatory disorders that may involve PARs.

Proteinase signalling by mechanisms other than PARs

Regulation of growth factor receptors

As mentioned above, one of the first indications that proteinases can activate cellular signals comparable to those of hormones came from the observations in the early 1960s that trypsin exhibits an insulin-like action in rat diaphragm tissue [1]. This hormone-like action of trypsin in striated muscle and adipocytes [3] cannot be attributed to the activation of PARs, but is rather due to the effect of trypsin on the receptor for insulin. By cleaving at a di-basic residue of the insulin receptor α-subunit, trypsin generates a truncated receptor that has intrinsic signalling activity [56]. In principle, this kind of action of proteinases, either activating or disarming growth factor receptors (eg, at higher concentrations, trypsin can abolish the ability of the insulin receptor to bind insulin: [57]) can modulate cell function in a variety of settings, for example via the IGF-I receptor. Another proteolytic mechanism that can lead to the activation of a growth factor receptor involves the proteolytic generation of a growth factor agonist in the cell environment. For instance, the trans-activation of the EGF receptor can result from the metalloproteinase-mediated release from the cell surface of a receptor agonist (heparin-binding EGF) [58]. In this regard, thrombin, apart from signalling via the PARs can also yield chemotactic-mitogenic peptides from proteolytic processing of its non-catalytic domain [59–61]. These thrombin-derived peptides cause their effects via receptors that are not PARs. Thrombin can also potentially cause its cellular effects via the activation of pro-metallopeptidase [62]. In addition to generating active peptide hormones from recognised pro-hormone precursors (eg, pro-insulin) that in turn activate receptors, novel receptor-activating hormone-like agonists can be generated from precursors in the vicinity of target receptors. For instance, interleukin-beta is generated by the interleukin-beta converting enzyme (ICE), a cysteine proteinase that also plays a role intracellularly in the apoptotic process [63]. Thus, proteinases can play a signalling role not only by receptor modulation and ligand generation, but also by regulating intracellular signalling pathways such as the one responsible for the apoptotic response. Hence, apart from activating or inactivating PARs, proteinases can play hormone-like signalling roles in a variety of cellular settings via non-PAR mechanisms. This diversity of hormone-like roles played by proteinases is exceeded only by the diversity of the proteinase families themselves.

Conclusions

This article has summarised the various hormone-like roles that proteinases can play, not only by activating or silencing members of a unique G-protein-coupled receptors family, the proteinase-activated receptors (PARs), but also by regulating the activity of growth factor receptors, like the one for insulin. Apart from these receptor-mediated signal pathways, proteinases can generate novel receptor-activating agonists and can regulate intracellular signal transduction pathways using mechanisms that can be added to their recognised ability to generate peptide hormones from pro-hormone precursors. These signalling properties of proteinases add a novel dimension to the biological significance of this enzyme superfamily. Thus, the targeting of proteinases with tissue site-selective
References


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