The long goodbye to glycine-extended peptide hormones

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“Endocrine oncology has for decades had considerable interest in α -amidated peptide hormones.”

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Even for Raymond Chandler’s sharp and experienced private eye, Philip Marlowe, an apparently simple murder story may in the long run turn out to be entirely different from what it looked like at first sight [1]. Similar experience in science is not uncommon. Obvious and immediate explanations for new phenomena and molecular mechanisms may often require a devious scrutiny that in the end leads to rejection of the original explanation.

Endocrine oncology has for decades had considerable interest in α -amidated peptide hormones. These hormones constitute more than half of all known hormonal peptides. Some of the hormones also promote cellular growth, and many are in addition promiscuously expressed in cancers. These hormones are, in other words, also acting as tumor growth factors. Around 1980, we learned that the immediate biosynthetic precursor of α -amidated hormone is a glycine-extended precursor peptide, where the glycyl residue constitutes the amide donor for α -amidation of the C-terminus of the hormone [2,3]. Moreover, it was shown that the glycine-extended precursor

is often released together with the mature α -amidated hormone [4], also when the cells of origin are neoplastic tumor cells [5]. The corelease happens because α -amidation is the last of a row of post-translational modifications and it occurs within the secretory granules that mature along the secretory pathway of the cell. And the secretory granules empty their content of peptides, chaperones and pro-hormone convertases into the surrounding capillary bed. Therefore, much interest was given to the report from 1994 [6], which suggested glycine-extended gastrin itself to be a tumor growth factor that targeted its own receptor in tumor cell membranes, a receptor different from the known receptor for α -amidated gastrins [7]. The suggestion was based on growth studies of a cell line from a rat pancreatic cancer, ARH-2J [6]. The report stimulated studies of the growth effect of mainly glycine-extended gastrin and its homolog, the glycine-extended cholecystokinin (CCK; for review, see [8]). But the initial enthusiasm turned after some years into widespread scepticism, because several laboratories,

KEYWORDS

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including a number of experienced receptor laboratories, could not demonstrate specific receptors or receptor mechanisms for glycine-extended gastrins and CCKs. And as often happens with negative results, the failure to identify a specific receptor has not been published, and the discussion therefore skewed and unbalanced. A sort of exception among the negative receptor result was, however, found for glycine-extended adrenomedullin, which is α -amidated after release from its cells of origin. Consequently, the amidated adrenomedullin targets the known receptor for adrenomedullin [9]. But this finding in fact also corroborates the impression that glycine-extended hormone precursors do not have their own specific receptors.

Four years ago, the editors of the present journal asked for a review article addressing the question: ‘Do glycine-extended hormone precursors have clinical significance?’ The review [8] – called ‘Management Perspective’ – stated first that nobody questions the biosynthetic significance of glycine-extended peptides as important intracellular-processing intermediates in the cellular synthesis of α -amidated peptide hormones, and second that neither does anyone question the fact that glycine-extended precursors are often released extracellularly following endocrine, paracrine or autocrine routes of secretion. The amount of released glycine-extended peptides varies considerably, however, depending on hormone system, on its anatomical location, its phylo- and onto-genetic development and of course on the nature and magnitude of the secretory stimulus. What the review did question, however, was the clinical significance of extracellularly released glycine-extended peptides as such – meaning whether extracellular glycine-extended peptides had bioactivity exerted via specific receptors or receptor mechanisms different from the known receptors for the corresponding α -amidated hormones. In other words, the review questioned whether glycine-extended peptides could be considered as separate hormones or hormonal growth factors, and consequently whether they deserved further clinical interest.

There are two major arguments behind the growing scepticism. First, after nearly a quarter of a century of quite intensive research, there is still no convincing evidence of specific high-affinity receptors for glycine-extended peptides. Second, beyond gastrin, CCK and adrenomedullin, there has not been particular endocrine or oncological interest in extracellular

glycine-extended precursors among the many other α -amidated hormones [8]. In addition, a bibliometric evaluation of publications about glycine-extended peptides in the period from 1983 to 2013 showed that the interest in later years was dwindling [8]. Thus, further research in the area was apparently not to be encouraged.

According to the editorial office, the review about glycine-extended precursors [8] has nevertheless aroused interest to a degree that it has become “*one of our most highly read articles in recent years*” (personal letter from the Editor). So, the question now is whether the apparent decline in publications from 2006 to 2013 has continued, or whether new discoveries after 2013 have brought glycine-extended hormone precursors back into clinical focus. In order to answer that question, a new PubMed search of articles published since 2014 has been performed in which glycine-extended peptide has been a keyword. The search addressed not least glycine-extended gastrin, CCK and adrenomedullin.

The result as of May 2017 is that PubMed since 2013 has registered seven original articles of which four were published in 2014 [10–13], two in 2015 [14,15] and one in 2016 [16]. None of the recent publications describes or identifies specific receptors or receptor mechanisms for glycine-extended peptide hormones. Thus, the situation has not changed since 2013. Consequently, what remains to be understood is the possible reasons why some laboratories did observe biological effects of glycine-extended peptide hormones. As earlier mentioned [8], there may have been tiny impurities of α -amidated bioactive peptides in some of the synthetic preparations of glycine-extended hormones. Another possibility is that some of the glycine-extended peptides in circulation could have been activated/degraded to α -amidated peptides as suggested for adrenomedullin [9]. And such activation may potentially occur, because PAM (the amidation–enzyme complex) also is released from secretory granules to blood together with the peptides [17,18]. Pharmacokinetic infusion and clearance studies comparing glycine-extended gastrin-17 with amidated gastrin-17 in man, however, do not support such contention [19].

After balanced evaluation of the pros and cons, it may be justified here in mid-2017 to conclude that the time has come to say a definitive goodbye to the idea about an independent extracellular growth-promoting role of glycine-extended hormone precursors. An interesting journey in

peptide research has come to its end, and the goodbye has indeed been long with abundant time to find and identify appropriate receptors.

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