Antiproliferative effects of somatostatin analogs in endocrine tumours

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Abstract

Somatostatin has been discovered as a somatotroph release inhibitory factor (SRIF), and it has been demonstrated that SRIF and its analogs can inhibit hormone secretion and control the neoplastic bulk of several endocrine tumours. In vitro studies have contributed to the current knowledge of the mechanisms by which SRIF and its analogs may influence endocrine tumour proliferation, opening the way to new possible therapeutic strategies. Here, we focus on the studies concerning the antiproliferative effects of SRIF and its analogs that provide the basis for future investigations, both at basic and clinical levels, into the application of SRIF analogs in the endocrine field.

Introduction and context

On the basis of the antisecretory and antiproliferative effects of somatostatin [somatotroph release inhibitory factor (SRIF)] and its analogs on normal and neoplastic endocrine cells, these compounds have been widely used in the medical field. Many studies have demonstrated that they activate several intracellular pathways, depending on receptor subtype and target cells [1], with highly variable effects depending on the tissue [2]. Currently available SRIF analogs (such as octreotide and lanreotide) are indeed capable of normalizing growth hormone and insulin-like growth factor 1 (IGF-1) levels and of controlling tumour growth in a substantial portion of acromegalic patients. They can also be effective in patients with gastroenteropancreatic endocrine tumours, where they can effectively suppress the production of bioactive peptides and hormones by the tumour cells, and in some cases may display antiproliferative effects. It has been indicated that the inhibitory effects of SRIF and its analogs depend on tissue SRIF receptor (SSTR) expression pattern, agonist-binding profile, and SSTR effector coupling [3]. The clinically available SRIF analogs do indeed display slight differences in SSTR affinity profile; octreotide shows higher affinity for SSTR5 as compared with lanreotide and exhibits some SSTR3 affinity.

Moreover, the two compounds have different pharmacokinetic profiles depending on the formulation, which might influence the antitumoural effects [4]. There is also evidence indicating that inhibition of cell proliferation may occur independently of the effects on hormone secretion [5-7], possibly providing an explanation for resistance to somatostatin analogs [8]. In the field of pituitary adenomas, predictive indices for response to SRIF analogs are a decrease in hormone levels after short-term SRIF analog treatment, a positive octreoscan [9], and previous radiotherapy [10]. However, these parameters do not reliably predict antiproliferative effects of somatostatin analogs and do not seem applicable for neuroendocrine tumours [11].

Recent advances

Several studies to elucidate SSTR expression pattern in endocrine tumours have been performed recently. Besides pituitary adenomas [3,12], other endocrine tumours display a variable SSTR expression pattern: thyroid tumours deriving from follicular [13] and parafollicular [14,15] cells, adrenocortical tumours [16], and bronchial [17] and gastroenteropancreatic [18,19] neuroendocrine tumours. Most of these studies correlate SSTR expression pattern with functional data.
demonstrating the inhibitory effects of SRIF analogs in specific endocrine tumour subsets, linking the efficacy of these drugs to their affinity for SSTR2. Indeed, it has been indicated that SSTR2 expression level might be a critical factor affecting both tumour progression and SRIF analog treatment outcome [20] since SSTR2 re-expression by gene transfer is able to improve sensitivity toward SSTR2-interacting drugs [21]. The mechanism by which SRIF inhibits endocrine cell proliferation has been widely investigated in immortalized cell lines as well as in endocrine tumour primary cultures, demonstrating the involvement of tyrosine phosphatases [22] that might trigger apoptotic changes [23,24]. Moreover, SRIF and its analogs can cause decreases in cell proliferation [25,26], cell cycle inhibition [27], and growth arrest [23], also acting through the PI3K/Akt signaling pathway [28]. These results confirm that SSTR2 is an important receptor subtype in transducing the antiproliferative signals of SRIF, but they also indicate that more than one SSTR is able to induce antiproliferative effects. Multiple subtypes may indeed cooperate to induce growth arrest since these receptors can homo- and hetero-dimerize with other G protein-coupled receptors [29]. Besides the direct actions on endocrine neoplastic cells, SRIF and its analogs can indirectly influence cell proliferation by inhibiting production and secretion of many angiogenic factors [30]. Moreover, it was recently demonstrated that SRIF analog treatment might result in biochemical/neuroradiological disease remission in a subset of acromegalic patients [31], suggesting that medical therapy might actually cure acromegaly in selected patients.

Implications for clinical practice

The studies performed so far indicate that the antiproliferative effect of SRIF analogs on endocrine tumours depends on tissue SSTR expression pattern (mainly SSTR2), as well as on the different binding profiles of the various agonists, and SSTR-effector coupling. Therefore, the employment of SRIF analogs for ‘oncologic’ purposes should be based on both clinical and molecular tumour characterization of each patient in order to perform a really tailored targeted therapy. This implies a strict collaboration among endocrinologists, oncologists, nuclear medicine experts, surgeons, pathologists, and molecular biologists in order to provide correct indications for the therapeutical use of SRIF analogs. In vivo and in vitro data do indeed indicate that currently available SRIF analogs and new upcoming compounds can achieve significant results in terms of tumour volume control in endocrine tumours, especially pituitary adenomas [32,33], but further clinical and basic studies are needed to confirm this effect.

Abbreviations

IGF-1, insulin-like growth factor 1; SRIF, somatotroph release inhibitory factor; SSTR, somatostatin receptor.

Competing interests

The author declares that she has no competing interests.

References


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