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Novel Medical Therapies for Pituitary Tumors

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Abstract

Despite considerable progress, there is still no medical treatment available for some kinds of pituitary tumors, in particular hormone inactive adenomas and corticotroph pituitary tumors. Surgical removal or at least debulking of the tumor is the only option to treat these kinds of tumors apart from rarely applied radiotherapy. Moreover, treatment resistance is present in a considerable proportion of patients bearing pituitary tumors, for which medical treatment regimens are already available (prolactinomas, somatotroph adenomas). Thus, novel or improved medical treatment strategies would be desirable. Here, we summarize preclinical and clinical findings about the hormone- and growth-suppressive action of various drugs, which will probably lead to novel future medical treatment concepts for pituitary tumors.

Depending on the type of tumors, the primarily aim of medical treatment strategies for pituitary tumors is the normalization of excessive hormone secretion in endocrine-active microadenomas, the reduction of tumor size in nonfunctioning macroadenomas, and the achievement of both in hormone-secreting macroadenomas. Improvement of the medical therapy for pituitary tumors actually follows three directions namely the optimizing of already existing therapeutic strategies, the application of already used drugs in other types of pituitary tumors, and the development of completely new medical treatment concepts. For optimizing existing medical treatment strategies novel somatostatin analogues (e.g. pasireotide) with receptor subtype specificity have been developed as well as chimeric molecules, which target in parallel dopamine and somatostatin receptors. Based on findings about the expression of dopamine and somatostatin receptors in nonfunctioning and corticotroph adenomas, studies have been launched in which the efficacy of old and new somatostatin analogues and dopamine agonists is going to be studied in these kind of tumors. Ongoing

studies of the pathomechanisms of pituitary tumors have led to the detection of novel potential drug targets such as components of intracellular signaling cascades. In the following an overview is given about the state of art of few of these extended or novel medical treatment concepts for pituitary adenomas.

Treatment of Non-Lactotroph Pituitary Tumors with Dopamine Agonists

Treatment of prolactinomas with dopamine agonists (bromocriptine, quinagolide, cabergoline) induces rapid normalization of prolactin levels and shrinkage of the tumors. Only in few patients, prolactinomas have to be removed by surgery due to resistance to dopamine treatment or because of compliance problems [1]. Since dopamine D2 receptors (D2R) have also been detected in the majority of nonfunctioning and corticotroph pituitary adenomas [2–6], the effects of dopamine agonists have been tested in these tumor types. After incomplete resection of nonfunctioning adenomas, subsequent dopamine agonist treatment mostly prevented regrowth or even induced further shrinkage of the remaining inactive tumor tissue [3, 4, 7]. Only in those nonfunctioning adenomas, which had been treated after re-manifestation of clinical symptoms, the efficacy of dopamine agonists was reduced [7, 8]. Thus, adjuvant therapy with dopamine agonist after partial surgical debulking of hormone inactive adenomas seems to be a promising future option in the medical treatment of this kind of tumor. Dopamine agonist treatment of patients with corticotroph adenomas for three months led to normalization of cortisol secretion in about 40% of the patients [5]. Therefore, for a subset of patients with Cushing´s disease medical therapy with dopamine agonists seems to be a future treatment option if other therapeutic approaches fail.

Novel Somatostatin Analogues in Pituitary Tumor Treatment

Pasireotide (SOM230)

Somatostatin has potent antisecretory and antiproliferative effects and therefore it has been a target for vigorous research for drug discovery [9]. Somatostatin analogues are the main medical treatment option for patients with various neuroendocrine tumors including gastroenteropancreatic and acromegaly-associated GH-secreting pituitary tumors. In acromegaly, the commonly used somatostatin analogs octreotide and lanreotide control GH and IGF-I in 50–60% of the cases, respectively, and induce tumor shrinkage in about 40%, indicating that approximately half of acromegaly patients remain uncured [10]. Somatostatin binds to a family of receptors (SSTR1–5), which belong to the seven-transmembrane-domain G-protein-coupled receptors [11]. Octreotide and lanreotide, primarily bind to SSTR2 and with less affinity to SSTR5.

Hence, there was intensive search for metabolically stable analogs mimicking the ability of the native somatostatin-14 to bind several SSTRs, which led to the synthesis of pasireotide (SOM230). Pasireotide binds SSTR1, 2, 3 and 5, displaying lower affinity for SSTR2 compared to octreotide and lanreotide, but higher to SSTR1, 3 and 5 [12]. These features render to pasireotide potent antisecretory and antitumor action in several neuroendocrine tumor models. In acromegalic patients, pasireotide displayed the same extend of GH suppression as octreotide, but it was also active in octreotide-resistant cases indicating that it could be a valuable pharmaceutical mean for the medical treatment of resistant acromegalic tumors [13].

The high affinity of pasireotide for SSTR5 indicated that it could control hormone secretion from corticotrophinomas, which were shown to have high levels of this SSTR but do not generally respond to octreotide or lanreotide. Indeed pasireotide was able to inhibit ACTH secretion in the majority of human corticotrophinomas in primary cell culture [14, 15]. The suppressive effect of pasireotide was not abolished by dexamethasone treatment as happens in the case of octreotide. Detailed investigation has revealed that SSTR2 is downregulated by dexamethasone treatment, while this is not the case with SSTR5 [16]. These in vitro data provide a mechanistic basis for the better suppressive effect of pasireotide on ACTH secretion. Pasireotide is currently in phase II clinical trial for the pharmaceutical treatment of Cushing's disease. The results are promising since it was found to decrease urinary free cortisol levels in most patients after 25 days of treatment [17].

Chimeric SSTR/D2R Compounds

Functional interaction of G-protein-coupled receptors from different families was repeatedly observed in several models. Interestingly, SSTR5 was found to heterooligomerize with D2R resulting in enhanced activity in terms of cAMP suppression [18]. This observation paved the way to the development of compounds that can be recognized by one or more SSTR and D2R. One of the first chimeric compounds developed, BIM-23A387, was shown to strongly suppress GH and PRL secretion from human mammosomatotrophinomas in primary cell culture compared to single SSTR2 or D2R analogue treatment [19]. A most recent analog with high affinity for SSTR2, 5 and D2R (BIM-23A760) had a strong antisecretory effect in GH-secreting tumors from patients partially resistant to standard octreotide treatment.

The higher potency of these chimeric compounds suggested that they could be beneficial for the treatment of pituitary tumor types that cannot respond to the classical SSTR2 or D2R analogs. Nonfunctioning pituitary adenomas (NFPA) express SSTR2 [20] and D2R [21], but they do not benefit from their antiproliferative action [21–23]. In an in vitro study involving four centers, BIM-23A760 exerted antiproliferative action in almost 60% of the NFPA in primary cell culture [24]. Because it was

shown that postoperative dopamine agonist treatment in NFPA patients significantly associates with decreased prevalence of residual tumor growth [5], the higher potency of chimeric SSTR/D2R compounds such as BIM-23A760 could be useful as primary or adjunctive treatment option to surgery in NFPA patients.

Novel Treatment Options in Cushing's Disease: Retinoic Acid and Interferon-Gamma

Cushing's disease is a severe clinical condition caused by hypersecretion of corticosteroids due to excessive adrenocorticotrophin (ACTH) secretion from a pituitary adenoma [25]. New findings on the mechanisms, which are responsible for ACTH hypersecretion has enabled the identification of new targets, namely retinoic acid and interferon-γ (IFN-γ), which may be used for future treatment of ACTH-secreting pituitary adenomas.

Retinoic Acid

The biological effects of retinoic acid, broadly used for the prevention and treatment of different human cancers, are mediated by the nuclear receptors RAR (retinoic acid receptor) and RXR (retinoic X receptor) [26, 27]. In AtT-20 pituitary ACTH-secreting tumor cells, retinoic acid decreases ACTH secretion by inhibiting the transcriptional activity of the transcription factors AP1 and Nur on the POMC gene, which encodes ACTH [28]. Treatment of human corticotrophinomas in primary cell culture also resulted in the inhibition of ACTH production. The antiproliferative action and the inhibition of ACTH produced by retinoic acid in vitro were confirmed in vivo in experimental ACTH-secreting tumors in nude mice [28]. Recently, a randomized study using retinoic acid in dogs with Cushing's disease was performed [29]. Dogs were treated with 2 mg/kg body weight/day with isotretinoin *all-trans* retinoic acid for a period of 180 days. The control group received ketoconazole, an established treatment for Cushing's disease in humans and dogs. A significant reduction in plasma ACTH and α-MSH was observed along the time in the retinoic acid treated group. Moreover, the cortisol/creatinine urine ratio and the pituitary adenoma size were also significantly decreased in dogs under retinoic acid treatment. The survival time after initiation of treatment was significantly longer in the retinoid acid group compared to the control group. An improvement in different clinical signs, such as returning to estrus, food intake, skin appearance and hair loss, was observed after the treatment with retinoic acid. Thus, retinoic acid treatment resulted in the resolution of the clinical phenotype observed in Cushing's disease.

Retinoic acid treatment may represent a therapeutic option for the inhibition of ACTH and cortisol production, as well as tumor growth in patients with Cushing's disease.

Interferon-γ

IFN-γ, a cytokine exerting potent antitumorigenic effects in a variety of cancers, was recently shown to inhibit proliferation and ACTH production in tumoral pituitary cells [30]. In AtT-20 pituitary ACTH-secreting tumor cells, IFN-γ acting on its transmembrane receptor activates the receptor-associated Janus kinases (JAK 1 and 2), which allows the recruitment of the signal transducer and activator of transcription STAT1. An activated JAK-STAT1cascade is required for IFN-γ inhibitory action on POMC promoter activity. Moreover, factor-κ B (NF-κB) plays a crucial role in this inhibition. In agreement with the data obtained in AtT-20 cells, IFN-γ inhibits ACTH production in human pituitary adenoma cells from patients with Cushing's disease.

Thus, the development of therapeutic agents that target this novel IFN-γ/JAK-STAT1/NF-κB pathway might provide a valuable approach for treating Cushing's disease.

Conclusion and Perspectives

Progress in medical therapy of pituitary tumors is not only restricted to the improvement or extension of already existing treatment concepts with improved somatostatin analogs or dopamine agonists or the combination of both. Recent studies on drugs targeting intracellular signaling proteins or transcription factors involved in the regulation of hormone production and/or growth have shown promising results in vitro and in animals in vivo suggesting a future role of these compounds in the development of novel medical therapies for pituitary tumors. Other compounds already used in the treatment of different types of tumors such as the polyphenolic substance curcumin or the epidermal growth factor receptor antagonist gefitinib have also shown potent antitumorigenic activities in pituitary tumors in vitro [31, 32]. However, more work is needed to confirm these results in vivo before these drugs can be applied for the medical treatment of pituitary adenomas.

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