The pituitary is the target of different neurohormones that have a crucial role in the control of cell differentiation, cell proliferation and hormone secretion by recognizing specific receptors belonging to the G Protein-Coupled Receptor super-family (GPCR). Evidence from in vitro studies and naturally occurring human diseases indicate that several endocrine cells, and particularly somatotrophs, recognize cAMP as a growth factor. Accordingly, mutations of the alpha subunit of the stimulatory G protein gene (GNAS) leading to the constitutive activation of adenylyl cyclase (i.e. gsp oncogene) have been recognized in a significant proportion of GH-secreting pituitary adenomas. The role of cAMP in the control of cell proliferation in selected cell types and in particular in somatotroph cells has been further confirmed by identification of genetics defect affecting the regulatory subunit IA of PKA. The role of cAMP in the control of cell proliferation as well as the crosstalk with different intracellular signalling pathways will be discussed.

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so called gsp oncogene) have been found in about 30–40% of GH-secreting pituitary adenomas, in 5–10% of pituitary tumors of different type, in other endocrine neoplasia and in the McCune-Albright syndrome [3]. GNAS1 mutations stimulate both growth and specialized functions and are generally associated with a benign phenotype. The limited oncogenic potential of these mutants may be related to the induction of multiple counter-regulatory events, such as cAMP-dependent activation of phosphodiesterase enzymes, upregulation of inductive early cAMP-repressor (ICER) gene transcription, monoallelic expression of GNAS1 gene or the instability of the mutant Gsa protein [4].

The role of cAMP in the control of cell proliferation in selected cell types and in particular in somatotroph cells has been further confirmed by identification of genetics defect affecting the regulatory subunit IA of PKA. Inactivating mutations of the gene encoding the PKA regulatory subunit type IA (PRKAR1A) have been identified in patients with Carney complex, a familial multiple neoplasia syndrome including also hyperfunctioning tumors affecting different organs the pituitary. All these features are reminiscent of the McCune-Albright phenotype and are consistent with the activation of the cAMP cascade [5]. According to this working hypothesis, we demonstrated a reduced RI expression at the protein level in sporadic GH-secreting tumors, this phenomenon being due to an increased RI proteasome-mediated degradation. By RIA RNA silencing technology and by RII selective activation we have also demonstrated that this unbalanced RI/RII ratio promotes cell growth, consistent with the hypothesis that the activation of the cAMP/PKA pathway by either activating GNAS1 mutations or reduced RIA expression may favour proliferation of somatotroph cells [6].

However, it is still unknown whether the cAMP/PKA pathway may have a similar mitogenic effect in lactotroph, corticotroph and thyrotroph cells. In fact, what observed in the somatotroph cells can not be transferred to all the pituitary cyto-
types. In this respect, we observed that the activation of the cAMP cascade in tumourous cells of gonadotroph origin that constitute the so called non-functioning pituitary tumors (NFPA) do not represent a proliferative signal in this cell type [2]. On the contrary, in a subgroup of these tumors the increase in intracellular cAMP levels as well as the modification of RI/RII ratio reduced the expression of cell cycle proteins such as cyclin D1 [2].

It is still unknown why the cAMP cascade may have either a proliferative role in some cells (i.e. somatotrophs) or an antiproliferative effect in others (i.e. gonadotrophs). In particular, it has been proposed that in certain cell types the activation of cAMP and protein kinase A (PKA) interacts with the extra-
cellular signal-regulated kinases (ERKs) pathway via specific activation of Ras and Rap1, this dialogue being crucial for the control of hormonal [1,7].

The pituitary is target of neurohormones that exert inhibitory action on hormone secretion and cell proliferation, such as dopamine and somatostatin. It is of interest that somatostatin receptors SST1-5 and dopaminergic D2 receptors are GPCR coupled to the Gi protein that causes inhibition of adenylcyclase activity and cAMP production [8,9]. Therefore, it is further confirmed that modulation of intracellular cAMP is crucial for the control of pituitary cell proliferation, although signalling generated by somatostatin and dopamine is more complex and involves different cascades, such as JNK, ERK and PKB/AKT pathways [8,9]. Long acting somatostatin analogs and dopaminergic agonists are effective in controlling the disease in the majority of GH-, TSH- and PRL- secreting adenomas, respectively, while they are ineffective in ACTH-secreting adenomas and NFPA. The mechanism responsible for the resistance to these agents are unknown. In particular, inactivating mutations of SST1-5 and D2R genes are a rare event, a mutation affecting SST5 having been described in a single acromegalic patient resistant to medical treatment. Subsequent studies demonstrated that SST5 carrying the R240W mutation as well as other mutations in the third intracellular loop maintained the ability to inhibit intracellular cAMP levels similarly to the wild-type but failed to mediate the inhibition of intracellular calcium levels, GH release and cell proliferation [10,11]. Preliminary studies seem to suggest that mutant R240W SST5 maintain the ability to activate all Gi and GoA, but not GoC, this G protein possibly being implicated in inhibiting both GH secretion and ERK1/2 phosphorylation. As mentioned before, since inactivating mutations of SST1-5 and D2R genes are a rare event, non definitive data on the mechanisms possible involved in the reduc-
tion of receptor expression are so far available. In this respect, we recently observed a reduced expression of both D2R and Filamin A (FLNA), a cytoskeleton protein with scaffolding properties, in DA-resistant tumors. Subsequent studies showed that FLNA silencing in DA-sensitive prolactinomas resulted in 60% reduction of D2R expression and abrogation of DA-induced inhibition of prolactin release and antiproliferative signals. Interestingly, FLNA overexpression in DA-resistant prolacti-
nomas restored D2R expression and prolactin responsiveness to DA [12].

Further studies are in progress to determine whether resistance to somatostatin analogues in acromegalic patients might be due to a cytoskeleton-related reduction in SST2-5 expression.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


