Cellular Abnormalities in Pituitary Tumors

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Pituitary cells appear to be programmed to proliferate in response to cyclic adenosine monophosphate (cAMP), leading to tumorigenesis. Stimulatory neurohormones and inhibitory inputs normally act in opposition to control cAMP levels, but receptor/postreceptor alterations may affect their relative effects. Most growth hormone (GH), corticotropin (ACTH)-, prolactin (PRL)-, and gonadotropin-secreting adenomas and nonfunctioning pituitary adenomas (NFPA) possess specific thyrotropin-releasing hormone (TRH) receptors, normally coupled with cytosolic [Ca^{2+}]i increase and diacyl glycerol production. These cells are also sensitive to other peptides such as vasoactive intestinal peptide (VIP) and pituitary adenylyl cyclase–activating peptide (PACAP), which activate adenylyl cyclase in many hormone-secreting adenomas and in all NFPA. The two main inhibitory agents controlling pituitary function are somatostatin (SS) and dopamine (DA), which have been reported to reduce hormone hypersecretion and tumor growth in a variable percentage of patients. Inhibition of adenylyl cyclase activity and cytosolic [Ca^{2+}]i levels is involved in the transduction of DA signals in normal and tumoral mammotrophs, but in GH-secreting adenomas DA receptors are exclusively and defectively coupled only with [Ca^{2+}]i reduction. The abnormal expression of these receptors can amplify stimulatory signals with both secretory and proliferative potential. The availability of specific G proteins may qualify the cell response to inhibitory agents. For example, in a subset of NFPA, SS alone or DA alone causes an abnormal increase in [Ca^{2+}]i levels due to Ca^{2+} mobilization from intracellular stores.

IN RECENT YEARS, in vitro studies, and particularly molecular biological approaches, have provided important insights into the pathogenesis of pituitary tumors, and the activation of cellular processes leading to pituitary tumorigenesis has been clarified, at least in part. In particular, several lines of evidence indicate that the cyclic adenosine monophosphate (cAMP) pathway is involved in the transmission of proliferative signals in the pituitary. In fact, it has been demonstrated that growth hormone–releasing hormone (GHRH) and corticotroph-releasing hormone (CRH) promote in vitro proliferation of somatotrophs and corticotrophs, respectively, with this effect totally depending on cAMP increase induced by the peptides.[1-3] Moreover, targeted expression by cholera toxin, which is known to constitutively activate adenylyl cyclase, has been reported to cause gigantism in transgenic mice.[4] Finally, the identification of oncogenic mutations that constitutively activate adenylyl cyclase and cAMP formation in a subset of pituitary tumor has provided further support for the view that pituitary cells are programmed to proliferate in response to cAMP.[5,6]

In pituitary cells, intracellular cAMP levels are tightly controlled. In fact, the majority of pituitary cell types are sensitive to both stimulatory and inhibitory agents that are effective in dually regulating cAMP production. Therefore, while in a subset of pituitary tumors cAMP production is constitutively activated by the presence of Gs alpha subunit mutations, other cellular abnormalities may prevent the normal regulation of cAMP accumulation in tumors expressing wild-type Gs. In this respect, it is worth noting that receptor/postreceptor alterations occurring in pituitary tumors may cause either increased action of stimulatory neurohormones or defective action of inhibitory inputs, with both events resulting in cAMP dysregulation.

INCREASED ACTION OF STIMULATORY NEUROHORMONES

While the existence of alterations in the central neurotransmission, causing an increased production of stimulatory neurohormones, may only be hypothesized,[7] cellular abnormalities resulting in the amplification of stimulatory neurohormone action are frequently observed in pituitary tumors. The majority of pituitary tumors are extremely sensitive to stimulatory neurohormones.[8,9] Although the cellular alterations responsible for this phenomenon are still unclear, pituitary tumors acquire an enhanced susceptibility to stimulatory inputs by both responding to abnormal stimuli and losing the normal mechanisms of desensitization.

There is general agreement that, during tumoral transformation, along with the persistence of cellular responsiveness to physiological hypothalamic regulators, pituitary tumors frequently express receptors for nonspecific agents. The loss of selectivity in tumor responsiveness seems to be a general rule, particularly when the cellular sensitivity is tested through in vitro experiments.[10-14] In fact, the great majority of growth hormone (GH)-, corticotropin (ACTH)-, prolactin (PRL)-, and gonadotropin-secreting adenomas and nonfunctioning pituitary adenomas (NFPA) possess specific thyrotropin-releasing hormone (TRH) receptors, normally coupled with cytosolic [Ca^{2+}]i increase and diacyl glycerol production. Most importantly, these cells are also sensitive to other agents of the secretin superfamily, such as vasoactive intestinal peptide (VIP) and pituitary adenylyl cyclase–activating peptide (PACAP), which are coupled to the generation of cAMP in target cells. These two peptides seem to be general activators of pituitary cell function, being able to activate adenylyl cyclase in a large proportion of hormone-secreting adenomas and in all NFPA.

The persistent stimulation of the pituitary by hypothalamic releasing hormones blunts the physiological re-

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sponses to subsequent challenge with the same agent.[15] This regulatory mechanism of desensitization may undergo derangement in pituitary tumors; in fact, it has been observed that long-term gonadotropin-releasing hormone (GnRH) analog administration is not effective in reducing gonadotropin levels in patients with gonadotropinoma, while acromegalic subjects continue to release GH after repeated GHRH injection.[16,17] This effect is due to alterations occurring at the tumoral cell level, since the phenomenon is reproducible during in vitro experiments, and it probably involves modifications of either receptor internalization or G-protein uncoupling processes.[17] Collectively, these data suggest that the abnormal expression of functionally operating receptors, as well as the loss of desensitization mechanisms, may result in the amplification of stimulatory signals with both secretory and proliferative potential.

DEFECTIVE ACTION OF INHIBITORY NEUROHORMONES

Two main inhibitory agents are involved in the control of pituitary function: somatostatin (SS) and dopamine (DA). These agents have been reported to reduce hormone hypersecretion and tumor growth in a variable percentage of patients.[18,19] These biological effects are the final result of a complex series of intracellular events leading to the inhibition of both adenylyl cyclase activity and cytosolic $[Ca^{2+}]i$ levels, possibly due to K^+ channel activation and subsequent membrane hyperpolarization. By this mechanism, a single inhibitory hormone may achieve efficient control of cell function by blocking both cAMP- and Ca^{2+}-dependent pathways. In pituitary tumors, defective action of inhibitory signals may arise from either defective receptor/effector coupling or altered G-protein pattern.

A defective coupling of DA receptors is probably present in tumoral somatotrophs. Although DA receptors mediating the inhibition of GH secretion in acromegalic patients during dopaminergic treatment display the pharmacological characteristics of D2 receptors,[20,21] they show a coupling different from that characterising the D2 receptor.[22] In fact, while in mammotrophs DA causes the inhibition of both adenylyl cyclase activity and cytosolic $[Ca^{2+}]i$ levels, in GH-secreting adenomas DA receptors are exclusively coupled with $[Ca^{2+}]i$ reduction.[22] This defective coupling seems to selectively occur in tumoral somatotrophs, since in GH-secreting adenomas mainly constituted by mammosomatotrophs, DA causes the inhibition of both adenylyl cyclase and $[Ca^{2+}]i$ levels. It is therefore tempting to speculate that lowering of $[Ca^{2+}]i$ levels is probably sufficient to cause a reduction of circulating GH levels in acromegalic patients. However, the lack of DA effect on adenylyl cyclase may result in a defective inhibition of the proliferative action of cAMP in tumoral cells, and this defective action may account for the poor therapeutic efficacy of dopaminergic drugs in acromegalic patients.[23]

The intracellular effectors triggered by receptor activation largely depend on the specific G protein involved in the process. In vitro transfection experiments have demonstrated that the same receptor, when transfected in different cell types, may activate different intracellular effectors. It is therefore possible to hypothesize that the availability of certain G proteins may qualify the cell response. This phenomenon has been observed to occur not only during in vitro transfection experiments,[24] but also in pituitary tumors. In a subset of NFPA, it has been found that SS causes an abnormal increase in $[Ca^{2+}]i$ levels due to Ca^{2+} mobilization from intracellular stores.[12] Since the same stimulatory effect is induced by DA in these tumors, it is unlikely that this abnormal action might result from the simultaneous presence of alterations in both SS and DA receptors.[12] This observation suggests that in individual tumors, inhibitory agents can activate different G proteins, with this phenomenon conferring stimulatory properties to inhibitory inputs.

CONCLUSIONS

Several lines of evidence suggest that pituitary tumors might arise as a consequence of structural genetic abnormalities, such as rearrangement, deletion, or mutation resulting in transcriptional activation, although genomic mutations have up to now only been identified in a minority of these tumors. However, promoting agents, such as hypothalamic neurohormones and growth factors, may be required for the selective growth of a cell clone. In this respect, the high susceptibility of tumoral cells to hypothalamic regulators with proliferative potential, as well as the loss of inhibitory control, may have important implications in multistep processes of pituitary tumorigenesis.

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