CONTROL OF THYROID GROWTH

J.E. Dumont

Institut de Recherche Interdisciplinaire
Faculté de Médecine, Hôpital Erasme, Université Libre de Bruxelles,
Campus Erasme, 808 route de Lennik, B-1070 Bruxelles, Belgium

In adults, the thyroid maintains its size with a slow cell turnover, it retains the capacity to grow by cell hypertrophy and proliferation in response to a stimulus (Dumont et al., 1992). The size and function of the thyroid are controlled by a physiological negative feedback mechanism: the thyroid cell secretes thyroid hormones which inhibit the secretion by pituitary thyrotrophs of thyrotropin (TSH), the thyroid stimulating hormone. Whenever thyroid hormone secretion decreases as in iodine metabolism defects, iodine deficiency or after goitrogen or antithyroid drug administration, TSH secretion increases, causing an activation of thyroid function and growth (Doniach, 1960; Dumont et al., 1989; Dumont, 1971; Larsen, 1982). Iodine supply negatively modulates the action of TSH in iodine deficiency the thyroid is more responsive to TSH and conversely.

Growth hormone, perhaps through IGF1 as an intermediate (Bachrach et al., 1988) induces thyroid growth but does not markedly enhance function as demonstrated in acromegaly (Geelhoed-Duijvestijn et al., 1989; Lamberg et al., 1976; Miyakawa et al., 1988) although some degree of autonomy in the goitrous acromegalic has been reported (Reuse et al., 1990).

Human chorionic gonadotropin and thus LH, at high concentrations activates the cAMP cascade and consequently proliferation in FRTL-5 cells (Davies and Platzer, 1986; Yoshimura et al., 1990; Yoshimura et al., 1991) and human thyroid cells (Pekonen et al., 1988). As these effects are inhibited by TSH receptor blocking antibodies they are mediated by this receptor (Yoshikawa et al., 1990). The concentrations reached in patients with trophoblastic tumors or even in pregnancy (Pekonen et al., 1988; Yoshimura et al., 1991) are sufficient to activate the human thyroid (Hershman et al., 1988; Kasagi et al., 1989; Yoshikawa et al., 1989).

Other plasma signals appear only in disease, such as the autoimmune immunoglobulins directed against thyroid cell membrane receptors. TSAb (thyroid stimulating antibodies) and TBAbs (thyroid blocking antibodies) bind to the adenylate cyclase coupled TSH receptor. TSAb activate (Adams, 1980), TBAbs block the stimulation by this receptor of function and growth. TSAbs are responsible for Graves’ disease hyperthyroidism; TBAbs for some idiopathic myxoedemas (Lu et al., 1990; Zakarija and McKenzie, 1990).

Thyrocytes, as other cells, also respond in vitro to a number of paracrine factors, i.e. factors secreted by neighboring cells. Some of these factors are also synthesized and secreted by the thyrocytes themselves (autocrine secretion). Several growth factors have been shown to be mitogenic or comitogenic (permissive) for thyrocytes (Brandi et al., 1987; Emoto et al., 1991; Errick et al., 1986; Fayet and Hovsepian, 1985; Gérard et al., 1989; Kasai et al., 1987; Maciel et al., 1988; Ollis et al., 1986; Roger and Dumont, 1984; Roger et al., 1982a; Roger et al., 1983; Roger et al., 1987; Roger et al., 1988;
Roger et al. 1985; Roger and Dumont, 1982b; Smith and Wyndford-Thomas, 1986; Tramontano et al., 1986a; Tramontano et al., 1986b; Tramontano et al., 1988a; Tramontano et al., 1988b; Westermark et al., 1983; Westermark and Westermark, 1982; Williams et al., 1988): epidermal growth factor (EGF), fibroblast growth factor (FGF), insulin like growth factor I (IGF1) the secondary factor secreted in response to growth hormone, IGF-2 and insulin, even at physiological concentrations. IGF1 is produced by sheep thyroid (Bachrach et al., 1988) and IGF-2 by FRTL-5 cells (Maciel et al., 1988) and FGF by porcine thyrocytes (Emoto et al., 1991; Greil et al., 1989). A possible role of insulin and/or IGF1 in modulating thyroid growth response in vivo is known since a long time (Jolin et al., 1970).

At least one local hormone has been shown to inhibit growth: transforming growth factor β (TGFβ) (Grubeck-Loebenstein et al., 1989; Morris et al., 1988; Tsushima et al., 1988; Wyllie et al., 1991) as in other epithelial cells (Lyons et al., 1990).

The TSH effects on the proliferation and differentiation of thyroid cells are mediated by cyclic AMP. The stimulation of proliferation by cyclic AMP is mediated by the activation of cyclic AMP dependent protein kinases. Indeed analogues of cyclic AMP which are selective for the 2 sites of each kinase and for each kinase must be used in the combination which activates these kinases to elicit the mitogenic effects in dog thyroid cells (Van Sande et al., 1989). The inhibitory effect of iodide of thyroid cell proliferation in vivo can also be explained by its well documented inhibition of thyroid adenylate cyclase (Van Sande et al., 1975).

The most compelling argument for the roles of the cyclic AMP cascades in vivo are the effects of TSAb, thyroid stimulating immunoglobulins, in man and of adenosine A2 receptor expression in the thyroids of transgenic mice. TSAb are antibodies against the TSH receptor which activate this receptor. Their chronic stimulatory effects leads to hyperthyroidism (vide infra). At the concentrations reached in vivo these immunoglobulins only activate the cyclic AMP cascade in human thyroid cells (Laurent et al., 1991). The cloned A2 adenosine receptor behaves in transfected cells as a physiologically constitutive activator of adenylate cyclase. In dog thyroid cells its expression is sufficient to elicit DNA synthesis (Maenhaut et al., 1990). When expressed in the thyroids of transgenic mice it induces hyperthyroidism (i.e. hyperfunction) and goiter (i.e. growth). Eventually the mice die from hyperthyroidism and if treated with antithyroid drugs from the consequences of their huge goiter (eg. tracheal compression) (Ledent C. and Dumont J.E., unpublished).

The effects of EGF on dog thyroid cell (proliferation, inhibition of differentiation expression) are mimicked by phorbol esters tumor promoters (Roger et al., 1986). However, these compounds also inhibit EGF action: the effect of phorbol esters which is lower than the effect of EGF is not increased by EGF. In several cell types, EGF, not only activates a tyrosine specific protein kinase, but also induces a rapid rise in cytoplasmic free Ca++ concentration. This rise in Ca++ concentration following EGF stimulation has been linked to an activation of the phosphatidylinositol Ca++ cascade although it has been suggested recently that it might result form an entry of extracellular Ca++ through the plasma membrane. It would therefore be conceivable that EGF action on the thyroid cell might result from an increase in Ca++ entry or from an activation of the phosphatidylinositol Ca++ cascade with generation of diacylglycerol, the action of which is mimicked by phorbol esters. However it should be noted that this activation of the PIP2 cascade by EGF apparently only occurs in cells in which EGF receptors are overexpressed (Levitzki, 1990). EGF induces a rise in intracellular Ca++ and alcalinisation in porcine thyroid cells (Takasu et al., 1990a; Takasu et al., 1988). IGF1 which also enhances the proliferation of these cells activates the PIP2 cascade and raises Ca++ levels in these cells (Takasu et al., 1989; Takasu et al., 1990b), but such an effect, if existent, is minor in dog cells. Moreover carbamylcholine, the most potent activator of the Ca++ phosphatidylinositol cascade in these cells is not mitogenic (Raspe E. and Dumont J.E., unpublished). On the other hand, neither EGF nor phorbol esters enhance cyclic AMP accumulation in dog thyroid cells. It is therefore likely that EGF acts through the phosphorylation of key proteins on tyrosyl residues. In FRTL-5 cells adenosine inhibits TSH cAMP induced thymidine incorporation into DNA while enhancing the effect of the IGF1 protein tyrosine phosphorylation cascade (Moses et al., 1989). The three cascades are therefore fully distinct at the level of their primary intracellular signal and/or of the first signal activated protein kinase (Contor et al., 1988).