Corticotroph adenoma in the dog: Pathogenesis and new therapeutic possibilities

V.A. Castillo a,*, M.F. Gallego b

a Área Clínica Médica Pequeños Animales, U. Endocrinología, Universidad de Buenos Aires. Av. Chorroarín 280, 1427 Ciudad Autónoma de Buenos Aires, Argentina
b UBACyT Grant Scholar, Htal. Escuela de Medicina Veterinaria, Facultad de Ciencias Veterinarias, Universidad de Buenos Aires. Av. Chorroarín 280, 1427 Ciudad Autónoma de Buenos Aires, Argentina

ARTICLE INFO

Article history:
Accepted 16 July 2009

Keywords:
Corticotroph adenoma
Corticotrophinoma
Pituitary dependent hypercortisolism
Cushing’s disease
Pituitary adenoma
Dog

ABSTRACT

The corticotrophinoma, causing pituitary dependent hypercortisolism, represents the highest percentage of pituitary tumours in the dog. The mechanism by which it develops is currently unknown and two theories are postulated: the hypothalamic and the monoclonal. It is not clear either what factors are involved in the tumour genesis; nevertheless, firm candidates are the Rb1 gene, proteins p27, p21 and p16, as are also defects in the glucocorticoid receptor and Nur77/Nurr1. The role of BMPs remains to be evaluated in greater depth. Although at present the chosen treatment in human is surgical, there are various pharmacological treatments already in use that have favourable results and others, still under research, also showing promising results.

© 2009 Elsevier Ltd. All rights reserved.

1. Introduction

The corticotroph adenoma or corticotrophinoma, causing Cushing’s disease (CD) or Pituitary dependent hypercortisolism (PDH) in humans represents 6% of pituitary Tumours (Gsponer et al., 1999; Chanson and Salenave, 2004). On the other hand, this pituitary tumour is observed frequently in the dog, with other types of pituitary adenomas being rare (Fracassi et al., 2007). It has a high morbidity rate, both in human and dogs, because of the adverse effects of the excess of cortisol due to adrenal hyperstimulation and the effect the tumour mass has on the brain (Orth and Kovacs, 1998; Reichlin, 1998). To understand the pathogenesis and further development of this tumour, one has to take into account the embryological origin of the corticotroph area. Like the rest of the adenohypophysis, it originates in the Rathke pouch coming from the lingual ectoderm, differing from the other adenohypophysis cells because of the expression of other transcription factors, particularly Ptx-1 and Tpit, LIF (Leukaemia inhibiting factor) and the corticotroph releasing factor (CRH) (Akita et al., 1995; Dasen et al., 1999; Lamolet et al., 2004; Lanctôt et al., 1999; Ooi et al., 2004; Savage et al., 2003; Suh et al., 2002; Treier et al., 1998). In the dog, corticotroph cells are not only found in the anterior lobe of the pituitary but also in the pars intermedia, with the latter being innervated by dopaminergic axons which regulate the synthesis of pro-opiomelanocortin (POMC) and its peptide derivatives. The increase in dopaminergic tone results in the inhibition of the synthesis of this macromolecule in the pars intermedia and in the anterior lobe (Tanaka, 2003; Colao et al., 2000). Biosynthesis and secretion of adrenocorticotrophin (ACTH) is co-ordinately controlled by different transcription factors at the level of the POMC gene promoter, such as CRH, vasopresin (VP) and LIF. CRH induces the expression of c-fos and the nerve growth factor induced gene-B (NGF-B or Nur77/Nurr1); it also induces Nur77/Nurr1 transcriptional activity (necessary for POMC synthesis) and that of AP-1 and CREB (Phillips et al., 1997; Savage et al., 2003; Seaholtz, 2000). Inhibition is mainly determined by glucocorticoids (GC) through the glucocorticoid receptor (GR). Martens et al. (2005) propose that GC antagonize Nur77 activity, thus inhibiting POMC synthesis. There would seem to be other inhibiting factors interacting (Engler et al., 1999).

Nudi et al. (2005) suggested that the bone morphogenetic protein-4 (BMP4) acts inhibiting POMC gene expression through Small mothers against decapentaplegic homolog (SMADs), particularly SMAD1, interfering with Ptx1 and Tpit activity, as well as taking part in the embryologic development of the hypophysis (Ooi et al., 2004; Savage et al., 2003). It is thought that BMP-4 has an autocrine and paracrine role in corticotrophs and maintains the balance between the different pituitary cell lines (Nudi et al., 2005). Embryologic and functional characteristics of corticotroph cells have been the basis for explaining the reasons corticotrophinomas appear. Regarding treatment, the first choice in humans is pituitary surgery, with radiotherapy being proposed for children and adolescents (Boscaro et al., 2001; Brada, 1993). In veterinary medicine, surgery has been largely developed by the group at...
Utrecht University, obtaining good results (post surgical survival of 3 years in 79% of the cases), with a low recurrence index (15%) similar to that in human medicine (Mammalam et al., 1988; Simmons et al., 2001). However both surgery and subsequent medical treatment are complex (Meij, 2001; Meij et al., 2002; Hanson et al., 2005, 2007) therefore unfortunately they are not indicated in the majority of hospital-university establishments of other countries. Post surgical morbidity in intensive care and at long term must also be considered (Meij et al., 1997, 2002) as well as those cases in which surgery is contraindicated. In cases where radiotherapy is indicated, the risks are the collateral effects on the area in the vicinity of the tumour (Boscaro et al., 2001).

Different drugs have been proposed for medically treating CD in dog and human with varying success. Dopaminergic drugs (bromocriptin and selegylin) and serotoninergic drugs have been used to try to control ACTH secretion and tumour growth (Braddock et al., 2004; Petrossians et al., 2000; Reusch et al., 1999). Therapies with drugs acting on the adrenal gland are indicated in certain cases (such as prior to surgery, no tumour being found, surgical contraindication). These drugs act by inhibiting cortisol biosynthesis, for example ketoconazole, triostane and aminoglutetimide (Barker et al., 2005; Castillo et al., 1996; Engelhardt and Weber, 1994; Sieber-Ruckstuhl et al., 2006); or by antagonizing glucocorticoid receptors, for example mefepristone (Agarwal, 1996) or by provoking necrosis of the adrenal cortex, for example Op-DDD (Kintzer and Peterson, 1991; den Hertog et al., 1999). The aim of this manuscript is to explain the theories and causes proposed for the appearance and development of the corticotrophinoma and new therapeutic alternatives that can be used in the treatment of this tumour.

2. Corticotrophinoma pathogenesis: hypothalamus vs. hypophysis

Two theories have been put forward to explain the development of the corticotrophinoma. One is the hypothalamic theory. On the one hand, the hypothalamus would exert excess stimulation on the corticotroph area through a greater secretion of CRH (Colao et al., 2000; de Bruin et al., 2004; Reusch et al., 1999) therefore an increase in POMC synthesis and in CRH. On the other hand, dopaminergic neurodegeneration in aged individuals (Bruyette, 1995; Hereñú et al., 2006a,b) or a decreased expression of the D2 dopaminergic receptor in the corticotroph cells could result in a lower inhibition on the corticotroph area (Colao et al., 2000; de Bruin et al., 2008; Pivone et al., 2004) thus producing hyperplasia. The adenoma would then evolve because of a somatic mutation of a hyperplasic cell. This line of thought is reinforced by the recurrence in 80% of the cases and, what is more important: the characterization of a monoclonal state in the majority of the adenomas studied (Dahia and Grossman, 1999; Levy and Lightman, 2003). Taking into account micro and macroadenomas, the existence of a variety of corticotrophinomas is suggested. Macroadenomas can display from a limited growth and benign behaviour, to an aggressive behaviour as in Nelson’s case (Assa and Ezzat, 1998).

3. Proposed factors involved in the appearance of the corticotrophinoma

3.1. Proto-oncogenes

Studies carried out on c-Erb B2/neu, c-MYC and PKC, RET, c-FOS, c-MYB and RAS oncogenes have not shown abnormalities that would suggest their participation in the development of the corticotrophinoma (Dahia and Grossman, 1999). What has been found over-expressed is the tyrosine kinase c-MYC proto-oncogene (Evans et al., 2001). The pituitary tumour transforming gene (PTTG) which is expressed in proliferating cells (controlling chromatin separation) has been proposed in the development of various pituitary adenomas (Zhang et al., 1999; Melmed, 2003). A 50% increase in PTTG was found in only 1 corticotrophinoma of a series of various human pituitary tumours (Zhang et al., 1999). It is not yet clear whether over-expression of PTTG has any role in pituitary tumour formation and/or its subsequent growth (Heaney et al., 2002a; Levy and Lightman, 2003).

3.2. Suppressors tumour genes (proteins associated to the cell cycle)

Protein p53 (which blocks progression of the cell cycle as from G1) was inconsistently found by immunohistochemistry in the corticotrophinomas and in invasive pituitary adenomas (Buckley et al., 1995). Although there is no evidence of the existence of a mutation of this protein that would induced the appearance of the corticotrophinoma, it has been proposed that p53 would have a role in the aggressive behaviour of the tumour (Dahia and Grossman, 1999; Levy and Lightman, 2003). The family of cell cycle inhibitory proteins (p21, p27 and p16) as well as the retinoblastoma gene (Rb1, in its de-phosphorylated form which inhibits
progression of phase G1 to S) have been studied in corticotrophinomas. Knock-out mice for Rb1 and p27 genes have been described to develop tumours in the pars intermedia (Jacks et al., 1999; Nakayama et al., 1996), indicating that both proteins play an important role in tumour pathogenesis. Decreased levels of p27 have been described in various corticotrophinomas, which suggests that post transcriptional mechanisms of inactivation could be possible (Levy and Lightman, 2003; Lidhar et al., 1999).

3.3. Receptor modulation

It has been observed that receptors for CRH (CRHR) and VP (subtype V3, VP3R) are over expressed in corticotrophinomas (Dahia and Grossman, 1999; Melmed, 2003; Zeugswetter et al., 2008). VP3R was also found to be increased under certain stressful conditions (Sonino et al., 1993). While chronic stress is associated with a decrease in the number of CRHR the opposite occurs for VP3R, where the proliferative signal is increased (Thibonnier et al., 1997). This chronic stimulation of the corticotrop area would lead to or aid clonal growth of the corticotrop cell. CRHR are over expressed in corticotrophinomas; nevertheless, it is not clear whether this is provoked by a greater transcription of the receptors, reflecting an abnormal response from the tumour, or if it is due to a defective processing at the post transcriptional level (Levy and Lightman, 2003; Dieterich et al., 1998). LIF involvement in corticotrophinoma pathogenesis has not been established (Levy and Lightman, 2003). Nevertheless, Yano et al. (1998) described corticotropic hyperplasia and Cushing-like characteristics in transgenic mice as a consequence of the expression of this cytokine.

ACTH secreting tumour resistance to GC has been widely communicated (Karl et al., 1996a,b; Lamberts, 2002). As mentioned in the introduction, resistance to GC precedes the appearance of the corticotrophinoma owing to a dominant-negative mutation. Nevertheless, GR mutation is not a common event (Levy and Lightman, 2003). It is feasible that certain types of corticotrophinoma are associated with the defects described in the receptor, while these events are irrelevant in others (Lamberts, 2002; Levy and Lightman, 2003). Recently Teshima et al. (2009b) have suggested an alteration of GR in dogs with corticotrophinomas, affecting the expression of 11 beta hydroxysteroid dehydrogenase type-1 and alteration of GR in dogs with corticotrophinoma, affecting the progression of phase G1 to S) have been studied in corticotrophinomas. Knock-out mice for Rb1 and p27 genes have been described to develop tumours in the pars intermedia (Jacks et al., 1999; Nakayama et al., 1996), indicating that both proteins play an important role in tumour pathogenesis. Decreased levels of p27 have been described in various corticotrophinomas, which suggests that post transcriptional mechanisms of inactivation could be possible (Levy and Lightman, 2003; Lidhar et al., 1999).

3.3. Receptor modulation

It has been observed that receptors for CRH (CRHR) and VP (subtype V3, VP3R) are over expressed in corticotrophinomas (Dahia and Grossman, 1999; Melmed, 2003; Zeugswetter et al., 2008). VP3R was also found to be increased under certain stressful conditions (Sonino et al., 1993). While chronic stress is associated with a decrease in the number of CRHR the opposite occurs for VP3R, where the proliferative signal is increased (Thibonnier et al., 1997). This chronic stimulation of the corticotrop area would lead to or aid clonal growth of the corticotrop cell. CRHR are over expressed in corticotrophinomas; nevertheless, it is not clear whether this is provoked by a greater transcription of the receptors, reflecting an abnormal response from the tumour, or if it is due to a defective processing at the post transcriptional level (Levy and Lightman, 2003; Dieterich et al., 1998). LIF involvement in corticotrophinoma pathogenesis has not been established (Levy and Lightman, 2003). Nevertheless, Yano et al. (1998) described corticotropic hyperplasia and Cushing-like characteristics in transgenic mice as a consequence of the expression of this cytokine.

ACTH secreting tumour resistance to GC has been widely communicated (Karl et al., 1996a,b; Lamberts, 2002). As mentioned in the introduction, resistance to GC precedes the appearance of the corticotrophinoma owing to a dominant-negative mutation. Nevertheless, GR mutation is not a common event (Levy and Lightman, 2003). It is feasible that certain types of corticotrophinoma are associated with the defects described in the receptor, while these events are irrelevant in others (Lamberts, 2002; Levy and Lightman, 2003). Recently Teshima et al. (2009b) have suggested an alteration of GR in dogs with corticotrophinomas, affecting the expression of 11 beta hydroxysteroid dehydrogenase type-1 and type-2 enzymes (decreased and increased expression respectively). They conclude that these changes may have a profound role in the growth of canine corticotroph adenomas and may help to further understand the pathophysiology of dogs with CD.

Nur77/Nurr1, members of the family of receptors for steroid hormones, are the main intermediaries for CRH induced POMC synthesis, blocking the inhibitory signal of GC (Maira et al., 1999; Philips et al., 1997; Savage et al., 2003). CRH acts via calcium, mitogenic protein kinase A (MAPK) to induce and activate Nur77/Nurr1 (Kovalovsky et al., 2002), having a proliferative effect. Based on reports by Martens et al. (1997) and by Kovalovsky et al. (2002), over expression of Nur77/Nurr1 could lead to GC resistance and/or cell proliferation.

3.4. Genes involved in the development and regulation of pituitary growth

Homebox genes: despite their role in the embryogenesis of the pituitary, and of the corticotroph in particular, “homebox genes Ptx” activity in tumour pathogenesis has not been defined (Dahia and Grossman, 1999; Levy and Lightman, 2003). Analyzing TPIT expression in corticotroph cells, Vallette-Kasic et al. (2003) found a greater expression of TPIT in tumour cells with respect to normal cells. These authors also demonstrated that this expression does not occur in other types of pituitary tumours. Nevertheless, in a recent study Hanson et al. (2008) concluded that mutations in the TPIT gene are unlikely to play a major role in the pathogenesis of canine corticotrophinomas.

3.5. Other factors involved in the genesis of corticotroph tumours

Sugawara et al. (1995) described the expression of the retinoid (RXR) and retinoic acid receptor (RAR) in the pituitary, where they intervene in cell differentiation and growth regulation (Zhou et al., 1999). According to Merino and Hurlé (2003) retinoic acid interacts with BMP’s, both through the SMADs and MAPK via, having in this way a role in the corticotroph cell growth and in the expression of the POMC promoter gene. The MAPK via would be related to pro-apoptotic and anti-proliferative activity of retinoic acid observed in certain tumours (Chen et al., 2004; Lei and Thé, 2003; Merino and Hurlé, 2003). As has been recently described by Giacomini et al. (2006) defects in RXR/RAR or in BMP’s signalling, would lead to the loss of the corticotroph cell regulation and could be a factor promoting the development of the ACTH producing adenoma. Peroxisome proliferator-activated receptor gamma (PPAR-γ) is expressed in corticotroph cells, both from normal pituitaries and from those with tumours in mice and humans (Heaney et al., 2003). PPAR-γ is restricted to and localized in cells that secrete ACTH in the pars distalis of the pituitary (it is not expressed in the pars intermedia of mice). PPAR-γ was abundantly expressed in all of 6 evaluated corticotrophinomas (Heaney et al., 2002b) (Fig. 1). PPAR-γ function in corticotroph cells (and in the pituitary in general) is as a transcription factor of ligands dependent on the synthesis process of mRNA, therefore regulating POMC synthesis stimulated by CRH and acting in the cell cycle regulating its mitogenic effect (Heaney et al., 2002b, 2003; Lovekamp-Swan and Chaffin, 2005).

4. Conventional and current therapies

Conventional and current therapies have been mentioned in the introduction. The ones that act on the pituitary are generally ineffective. In human patients with PDH, antiserotonnergic drugs, such as cyproheptadine, ritanserin and ketanserin haven’t shown good results (Sonino et al., 2000; Arnaldi et al., 2007). In dogs, seleglidine, a monoamine oxidase-B inhibitor, could not control the disease satisfactorily (Reusch et al., 1999; Braddock et al., 2004).

Drugs acting on the adrenal gland have been extensively studied and seem to be useful in the treatment of PDH in dogs (den Hertog et al., 1999; Ruckstuhl et al., 2002; Wenger et al., 2004; Barker et al., 2005; Reine, 2007; Sieber-Ruckstuhl et al., 2008). On the other hand, although they solve the hypercortisolism or its effects, trilostane therapy, tumour growth can progress (Teshima et al., 2009a).

5. Future therapies for treating the corticotorphinoma

Three new therapies, which either have been or are currently under study, will now be described.

5.1. Tiazolindindiones (TZD)

Studies with TZD have been started keeping in mind the PPAR-γ expression previously described and the effects on cell regulation (Lei and Thé, 2003; Lovekamp-Swan and Chaffin, 2005). Heaney et al. (2002b) studied the effect of rosiglitazone (Ros) both in vitro, in cell culture with AtT20 tumour corticotrophs, and in vivo, in nude female mice (nu/nu); this being the first work...
carried out on the use of Ros in PDH. The authors observed the arrest of the cell cycle in G0/G1 when administering Ros in vitro (preventing the phosphorylation of Rb1, they increased p21 and p27), the induction of corticotroph apoptosis (anti-apoptotic protein Bcl-2 decreases and pro-apoptotic Bax increases) and a decrease in the synthesis of POMC and ACTH. In cells treated with Ros, as the rate of cell proliferation decreases, a lower expression of the PTTG gene is also described.

In vivo studies, carried out inoculating a group of five mice with AtT20, showed Ros preventing tumour development in four of the five treated mice while all controls showed tumour growth after 4 weeks. ACTH and cortisol concentration was significantly greater in controls when compared to the treated animals. To know if Ros blocked previously inoculated untreated tumours, they allowed tumour growth in five mice and then administered Ros (and compared results to controls without Ros). Although growth continued in both groups, growth was lower than that of controls in three out of five mice treated with Ros. PTTg mRNA expression decreased 80% with respect to the controls, and approximately 60% POMC mRNA expression decreased, confirming in vitro observations. ACTH concentration was 75% lower and corticosterone showed a 96% reduction in Ros treated mice with respect to the controls and, contrary to the controls, treated mice did not present clinical signs of the disease. Based on these findings, the authors conclude that TZDs show a potential use in patients with CD (Ambrosi et al., 2004). Similar results have been observed with pioglitazone (Suri and Weiss, 2005).

5.2. Retinoic acid (RA)

RA has been studied in various types of tumours (Lei and Thé, 2003; Páez-Pereda et al., 2000). It inhibits cell proliferation, growth and invasion and induces cell apoptosis and differentiation (Merino and Hurlé, 2003). Some of these effects are due to inhibition of AP-1 and of the orphan Nur77 receptor (Kang, 2000). Based on these effects of RA and on its activity in the corticotroph cell (see introduction) Páez-Pareda et al. (2001) examined the effects RA would have on the ACTH secreting tumour cell. In AtT-20 cell cultures, RA only inhibits transcriptional activity of AP-1 and Nur77/Nurr1, thus inhibiting POMC and ACTH synthesis. In human corticotroph cells, obtained from ACTH secreting tumours and from different cell populations of normal pituitaries, ACTH biosynthesis was only inhibited in tumour corticotroph cells, while normal cells were unaffected. Neither was the synthesis of prolactin and growth hormone affected. With regard to RA pro-apoptotic activity, they describe an increase in caspase-3 activity in AtT-20 cells, decreasing their viability and function.

RA has been shown to have a variety of effects on cells, including inhibition of proliferation, induction of apoptosis, and differentiation. In the context of corticotroph tumours, RA has been shown to inhibit the transcriptional activity of AP-1 and Nur77/Nurr1, which results in the inhibition of POMC and ACTH synthesis. This effect was observed in both human and rodent corticotroph cells. Furthermore, RA has been shown to induce apoptosis in these cells, as evidenced by an increase in caspase-3 activity. These findings suggest that RA may have therapeutic potential for the treatment of corticotroph tumours.
proliferation. It has been observed in in vivo studies in nu/nu mice that if AtT-20 cells were treated with RA before implantation, the corticotrophinoma did not develop and no changes were seen in ACTH and cortisol concentrations of the mice. The opposite happened in those that were inoculated with untreated cells. Studying the effect of RA on previously formed tumours, it was observed that tumour growth was inhibited in mice under RA treatment, showing focal signs of cell death on histopathological examination. Both ACTH and corticosterone had lower concentrations than that of controls. The authors conclusion is that RA inhibits ACTH synthesis by inhibiting POMC transcription because of its activity on AP-1 and Nur77/Nurr1, and reduces the proliferation and survival of the corticotrophinoma; thus having potential therapeutic use in CD. The report by Páez-Pareda et al. (2001) was verified in a recent study carried out in 22 dogs with PDH. Dogs treated with RA-9 cis (2 mg/kg/day) showed clinical improvement (decrease of liquids and solid food intake; oestrous cycle recovery, longer survival). Likewise, magnetic resonance imaging (MRI) revealed a reduction in tumour size; and the decrease in ACTH and plasma α-MSH and in the urinary cortisol/creatinine ratio was also evident (Fig. 2) (Castillo et al., 2006).

5.3. Cabergoline (Cbg)

Dopamine exerts an inhibitory effect on the adenohypophysis and pars intermedia through its union with D2 type receptors (D2R). Dopaminergic agonists can be used in corticotrophinoma treatment as 80% express these receptors, and cabergoline, being the most efficient of these agonists is proposed to be useful in 40% of the corticotrophinomas (Colao et al., 2000; Pivonello et al., 2004). We have recently communicated that 42% (17/40) of dogs treated with cabergoline (0.07 mg/kg) every 48 h not only improve clinical signs (decrease of liquids and solid food intake; oestrous cycle recovery, reduction in abdomen size, longer survival) but also show a decline in tumour size as well as a decrease in plasma ACTH and α-MSH concentrations and in the cortisol/creatinine ratio in urine (Fig. 3) (Castillo et al., 2008).

6. Discussion

Diverse and multiple associated factors take part in the origin of the corticotrophinoma, with the monoclonal theory being the most widely accepted (Assa and Ezzat, 1998; Clayton and Farrell, 2001; Herman et al., 1990; Levy and Lightman, 2003; Melmed, 2003). An hypothalamic desregulation initiating the tumour process from a first phase of hyperplasia should not be totally discarded (Dahia and Grossman, 1999; Hereñú et al., 2006a,b; Otte et al., 2005; Teshima et al., 2009b). Although Van Wijk et al. (1992) did not observe correlation between CRH concentration in cerebrospinal fluid and ACTH plasma concentration in dogs with PDH, the study was carried out in animals of up to 11 years of age with corticotrophinoma and does not take into account older dogs, where dopaminergic neurodegeneration would be an important factor. Also, the fact that these dogs already had an ACTH secreting tumour makes it impossible to totally discard the previous action of CRH, at least in some of the cases, as CRH could have been inhibited by the ACTH and cortisol increase. On the other hand, LOH, mutation or defects in factors controlling the cell cycle would lead to tumour growth commencing with the affected cell (clone) (Dahia and Grossman, 1999; Levy and Lightman, 2003). Firm candidates for this process are the Rb1 gene, proteins p27, p21 and p16 (Dahia and Grossman,
1999; Levy and Lightman, 2003; Lidhar et al., 1999) and defects in GR, Nur77/Nur1 and 11 beta hydroxysteroid dehydrogenase (Kang, 2000; Kovalovsky et al., 2002; Lambert, 2002; Levy and Lightman, 2003; Martens et al., 2005; Teshima et al., 2009b). More studies are necessary to know if BMPs have a role in tumour pathogenesis, given their interaction with "home-box" Ptx-1 and Tpit genes and with RXR/RAR activity (Merino and Hurlé, 2003; Nudi et al., 2005; Vallette-Kasic et al., 2003; Giacomini et al., 2006). Light shed from studies by Kovalovsky et al. (2002) and Páez-Pareda et al. (2001) on Nur77/Nur1 make it evident that the greater expression of its promoter gene would lead to an amplification of CRH activity with an increased synthesis of POMC and trophic effects on this peptide. It remains to be seen if this greater expression, similar to that of the PPAR-γ, is due to mutations or LOH inducing tumour genesis. These therapeutic alternatives open up an interesting field of new options. Due to the scarce adverse effects they have demonstrated, these therapies would be of great use. They could be indicated as the initial treatment in cases where surgery is contraindicated or as a therapeutic aid to surgery (post surgical indication) or pituitary radiotherapy.

Acknowledgements

This study was funded by UBACyT (V045 and V006). We specially thank Dr Eduardo Arzt, from Facultad de Ciencias Exactas y Naturales-IFBM, UBA, for his critical revision and advice.

References

Goponer, J., De Trambolet, N., Deuraz, J.P., Acker, J., Uske, A., Mirimanoff, R.O., 1997. Expression of its promoter gene would lead to an amplification of CRH activity with an increased synthesis of POMC and trophic effects they have demonstrated, these therapies would be of great use. They could be indicated as the initial treatment in cases where surgery is contraindicated or as a therapeutic aid to surgery (post surgical indication) or pituitary radiotherapy.
Orth, D.N., Kovacs, W., 1998. The adrenal cortex. In: Williams Textbooks of
Nakayama, K., Ishida, N., Shirane, M., Inomata, A., Inoue, T., Shishido, N., Horii, I., Loh,
Maira, M., Martens, C., Philips, A., Drouin, J., 1999. Heterodimerization between
Kovalovsky, D., Refojo, D., Liberman, A.C., Hochbaum, D., Paez Pereda, M., Coso, O.A.,
Kovalsky, D., Rebrov, N., Valdes Socín, H., Kalife, A., Stevenaert, B., Bloch, T., Tabarin, A.,