Progesterone-controlled growth hormone overproduction and naturally occurring canine diabetes and acromegaly

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Abstract. Female pet dogs exhibiting either glucose intolerance alone or glucose intolerance and acromegaly were investigated. Some dogs developed the disorder(s) during dioestrus and some animals developed the disorder(s) after they were given medroxyprogesterone acetate (MPA). Elevated fasting plasma glucose levels (12.3 ± 1.9 mM, mean ± SEM) were accompanied by fasting hyperinsulinaemia (144 ± 21 μU/ml, mean ± SEM) and drastic elevation of plasma growth hormone (GH) levels (112.6 ± 45 ng/ml, mean ± SEM). An iv glucose tolerance test (IVGTT) performed on all dogs revealed non-suppressibility of GH levels and glucose intolerance. Plasma concentrations of glucose, insulin and GH during IVGTT in affected dogs differed significantly from the concentrations measured in normal dogs during the same test. MPA withdrawal and/or ovariohysterectomy (OVx-HYx) in affected animals was followed by reversal of GH levels to normal and improved glucose tolerance. Acromegaly associated soft tissue changes were also reversible after MPA withdrawal and/or OVx-HYx when GH levels had dropped. In 5 dogs which had developed diabetes during dioestrus and in which a spontaneous decrease in plasma progesterone occurred during the investigation a concomitant decrease in GH levels was observed. Plasma GH measured at different stages of pregnancy in 45 dogs was found to be elevated in one animal only. The results show that the development of spontaneous diabetes/acromegaly occurring in some female dogs is related to progestagen (progesterone/MPA) exposure and that reversal of the signs is achieved by progesterone/MPA withdrawal. The results suggest that diabetes/acromegaly in the dogs studied was caused by progesterone/MPA-evoked GH elevation. Finally, the findings also suggest that the GH axis normally not appreciably responsive to progestagen elevation in some dogs becomes and/or is paradoxically controlled by physiologic levels of endogenous progesterone or low doses of MPA.

Glucose intolerance is a widespread metabolic disorder, which in general, results from the interaction of genetic and environmental factors. The disease may be precipitated by factors such as nutrition, infection, anti-insulin receptor antibodies, and in man, in rare cases, by hormonal antagonism due to glucocorticoid or growth hormone (GH) excess (Renold et al. 1978).

When factors precipitating naturally occurring diabetes mellitus in the dog are examined, one striking phenomenon is observed: the disease occurs frequently in females of higher age and the disorder becomes manifest during the corpus luteum phase (dioestrus, progesterone phase) (Krook et al. 1960; Wilkinson 1960; Foster 1975) when progesterone synthesis is maximal (Concannon et al. 1977). Despite the constant pattern of initiation, the mechanism leading to the disease at the particular time remains unknown. It this context, it should be noted that dogs, in contrast to most other species, exhibit virtually identical high post-oestrus progesterone concentration changes whether pregnant or not (Concannon et al. 1977).
Moreover, the dog’s reproductive cycles do not cease at older age.

In experimental studies, it has been shown that some of the dogs receiving prolonged treatment with pharmacologic doses of progestagens (chloromadinone acetate) develop diabetes and/or an acromegaly-like condition (Sloan & Oliver 1975). The results would suggest that diabetes in these dogs might have been induced by progestagen-evoked GH overproduction. GH is known to be a powerful diabetogenic agent in the dog (Young 1953; Altszuler 1974; Pierluissi & Campbell 1980). In experimental studies we have shown that medroxyprogesterone acetate (MPA) treatment in some dogs, leads to diabetogenic GH levels (Eigenmann & Rijnberk 1981). The above findings appear important because 1) progestagens are used in the dog for oestrus suppression (pet population control), and 2) endogenous progesterone — as does exogenous MPA — might in some dogs spontaneously induce diabetes and/or acromegaly by inducing GH elevation.

The present studies were undertaken to 1) investigate the possibility that spontaneous, canine diabetes becoming manifest during dioestrus or treatment with MPA is associated with pathologically elevated GH levels, 2) show that acromegaly spontaneously occurs in dogs under progesterone/MPA exposure, and 3) provide indirect evidence that the changes (diabetes/acromegaly) are caused by progesterone/progestagen-evoked GH elevation.

Materials and Methods

The data were derived from the study of 21 privately owned female dogs of various breeds presented with typical signs of diabetes or acromegaly. Their mean age was 8.5 ± 0.5 years (mean ± SEM). Ten animals were presented during a natural progesterone phase (dioestrus) and 11 during treatment with low doses of medroxyprogesterone acetate (MPA). The latter animals had received 50 mg MPA (Depo-Provera) twice a year for oestrus prevention. Those animals treated with insulin received insulin Lente (Novo Industries, Copenhagen). The insulin dosage was adjusted according to blood glucose measurements performed 7 h after the injection. Values ranging from 4 to 6 mmol/l were considered ideal and insulin dosage was adjusted accordingly.

Twelve other diabetic dogs (males, castrated females) which had developed the disease independently of progesterone/MPA exposure were used in order to assess the influence of hyperglycaemia on GH levels.

Normal dogs were of various breeds and aged from 5 to 12 years. Growth hormone studies in pregnant dogs were performed in 45 Beagle dogs kept in a breeding colony.

Blood samples were obtained by jugular venipuncture after an overnight fast, transferred into EDTA-coated tubes, centrifuged immediately and plasma was stored at −25°C. Glucose was determined in a Beckman glucose analyzer. Insulin was determined in a double antibody radioimmunoassay (RIA) (Hales & Randle 1963) using canine insulin (22.3 U/mg, Novo Industries, Copenhagen) as standard. GH was determined in a homologous, specific RIA (Eigenmann & Eigenmann 1981a). Progesterone was determined according to Dieleman & Schoenmakers (1979) and medroxyprogesterone acetate (MPA) according to Cornette et al. (1971).

iv) Glucose tolerance tests (IVGTT; 1 g glucose/kg body weight, 50% solution) were performed in dogs not treated with insulin. All tests and blood samplings were performed in conscious dogs between 8 and 11 a.m. The glucose disappearance coefficient (K) was calculated according to \( K = 69.3/\Delta t \) glucose = % elimination rate/min (Lundbaek 1962).

The diagnosis of acromegaly was based on the combined occurrence of 1) the owner’s history of a recent increase in soft tissue mass, 2) the finding of excessive soft tissue (skin folds, enlarged abdomen, diffuse soft tissue mass in the oropharyngeal/orolinguinal region) and 3) elevated GH levels. If available, pictures taken of the dogs at a time when they were still normal were compared with pictures taken when the dogs had developed acromegaly. In many dogs the clinical suspicion of an increased soft tissue mass in the orolingual/oropharyngeal region was evaluated and confirmed radiographically.

In some diabetic dogs, pancreas biopsies (uncinated process) were obtained. The tissue was fixed in buffered formaline, embedded in paraffin and stained with haematoxylin-eosin. For statistical analysis, Student's t-test and repeated measures analysis of variance (Jennrich et al. 1981) was employed.

Results

Twenty-one animals exhibiting hyperglycaemia and some exhibiting acromegaly in addition were investigated. In all animals, signs of diabetes developed shortly after oestrus or MPA administration. Also in acromegalic animals there was a consistent relation to the last oestrus or last MPA administration. Some of the acromegalic animals developed noticeable signs for the first time, and in some the history revealed that signs had been present earlier. In all the latter animals, however, the reappearance or worsening of the acromegalic signs
could be related to a period shortly after oestrus or to a period shortly after the last MPA administration.

Ten animals developed the signs during dioestrus (progesterone phase). The time elapsed between the last oestrus and the time of presentation for investigation ranged from 3 to 5 weeks (average 3.5 weeks). Six of these animals exhibited fasting hyperglycaemia greater than 10 mM and one of these 6 dogs showed acromegalic signs. The remaining 4 animals showed fasting hyperglycaemia ranging from 5.7 to 7.2 mM. All these dogs exhibited acromegalic signs.

Eleven dogs had been repeatedly treated with MPA. The time elapsed between the last MPA administration and the investigation ranged from 6 to 12 weeks (average: 7.5 weeks). Four dogs had fasting hyperglycaemia greater than 10 mM and one among these dogs showed acromegalic signs. Fasting hyperglycaemia in the remaining 7 dogs ranged from 5.4 to 7.7 mM. All these dogs exhibited acromegalic signs.

Four dogs which had developed the signs during dioestrus and 4 dogs which developed the signs during MPA treatment were treated with insulin.

**Glucose tolerance and GH studies**

Glucose tolerance tests were performed in all 21 dogs. Very high basal insulin levels did not increase further during the test. Some more moderately elevated basal insulin levels increased, and some did not. In all animals, insulin levels remained high during the entire test. Despite extremely elevated basal insulin levels (144 ± 21 µU/ml, mean ± SEM) and despite even higher levels during the entire IVGTT, glucose tolerance was drastically impaired. The animals exhibited a fasting blood glucose concentration of 12.3 ± 1.9 mM (mean ± SEM) and a mean glucose disappearance coefficient (K) of 0.9 ± 0.1. The mean glucose disappearance coefficient in 20 additionally studied normal dogs was 3.9 ± 0.2 (mean ± SEM, P < 0.05). These dogs exhibited significantly lower fasting glucose, insulin and GH levels. In all diseased animals developing signs during progesterone/MPA exposure, glucose intolerance was accompanied by elevated, non-suppressible growth hormone (GH) levels (112.6 ± 45 ng/ml, mean ± SEM). (Fig. 1A). Statistical analysis (repeated measures analysis of variance) of IVGTT results (Fig. 1A) revealed significant differences between normal and diabetic dogs exhibiting GH elevation for the glucose (P < 0.001), insulin (P < 0.001), and GH levels (P = 0.022). Significant changes over time were found for glucose and insulin levels (P < 0.001) but not for GH levels (P = 0.133). Significant interaction between groups and time was found for the glucose and insulin curves (P < 0.001). This indicates the non-parallel nature of the curves found in the 2 groups. No interaction between groups and time was found for the GH curves (P = 0.216).

When comparing the animals exhibiting a plasma
glucose of less than 10 mM with animals exhibiting a plasma glucose of more than 10 mM, the following was found. The group with a mean plasma glucose of 21.9 ± 2.8 mM had a mean plasma insulin concentration of 183 ± 48.0 µU/ml while the group exhibiting a mean plasma glucose of 6.4 ± 0.2 mM had a lower plasma insulin concentration (121 ± 17.4 µU/ml) (mean ± SEM, P < 0.01 for glucose and P > 0.2 for insulin). However, the insulin/glucose ratio (µU/mmol) was 18.7 ± 2.9 in the group exhibiting a lower plasma glucose while the group exhibiting frank hyperglycaemia had an insulin/glucose ratio of only 8.35 ± 4.27 (mean ± SEM, P < 0.01). GH levels were similar in both groups (107 ± 48 and 115.6 ± 67.6 ng/ml; mean ± SEM, P > 0.5).

In order to assess the effect of hyperglycaemia and the diabetic state on GH levels, untreated male diabetic animals or female diabetic animals which, however, developed the signs independently of progesterone/MPA exposure were also studied. These dogs exhibited normal GH levels (1.17 ± 0.37 ng/ml, n = 12, mean ± SEM).

Eight of the 10 animals exhibiting hyperglycaemia greater than 10 mM were treated with insulin. These animals, despite extremely elevated endogenous insulin levels, required a mean insulin dose of 4.9 ± 2.52 U/kg x day⁻¹ (mean ± SEM) in order to control their diabetic condition adequately while dogs exhibiting diabetes not associated with GH elevation require insulin doses of 1–2 U/kg x day⁻¹. Ovariohysterectomy (OVx-HYx) performed in animals exhibiting elevated GH levels was followed by a drop in GH and, in general, resulted in reversal of the diabetic condition.

Fourteen of the initially studied 21 animals were

![Fig. 2.](Image)

Photomicrograph of pancreatic tissue (uncinate process) from a diabetic dog (natural progesterone phase; the dog recovered from diabetes after ovariohysterectomy. HE stain, 290 x. Note: Hydropic degeneration of β-cells, hydropic changes in intercalated ducts (white arrows), unaffected acinar tissue.)
available for a second IVGTT after OVx-HYx when GH levels had dropped and when previously given insulin treatment had been stopped. Two animals were not made available by the owners, 2 were euthanized on the owner's request, 1 animal died and 2 animals did not recover from diabetes despite exogenous insulin had been given. The latter 2 dogs exhibited GH levels of 93 and 40.5 ng/ml.

Among the 14 available, 4 dogs had been on exogenous insulin for periods ranging from 20 to 40 days. IVGTT's were performed no earlier than 3 days after insulin withdrawal. At this stage, glucose was tolerated significantly better ($K_{\text{before}} = 0.9 \pm 0.1$, $K_{\text{after}} = 2.9 \pm 0.2$, n = 14, mean ± SEM, $P < 0.05$, t-test) in spite of weak and less protracted insulin response to glucose (Fig. 1B). One acromegalic dog who had a plasma GH concentration of 918 ng/ml and died for unknown reasons did not become available for a second IVGTT, thus explaining why the mean GH level was appreciably higher in group A than in group B.

Statistical analysis of the results from IVGTT studies obtained in these dogs (Fig. 1B) before and after GH correction (repeated measures analysis of variance) revealed 1) significant differences for glucose ($P < 0.001$), insulin ($P < 0.001$) and GH.
levels over time for glucose and insulin \((P < 0.001)\), but not for GH \((P = 0.425)\), and 3) significant interaction between time and groups for the insulin and glucose curves \((P < 0.001)\) demonstrating non-parallelism of these curves. No significant interaction between groups and time was found for GH \((P = 0.084)\). While all animals exhibiting frank fasting hyperglycaemia exhibited elevated GH levels, there was no correlation between the degree of GH elevation and the degree of hyperglycaemia \((P > 0.05)\).

**Pancreatic biopsies**

Pancreatic biopsies were obtained from some diabetic dogs. Hypoplasia and vacuolization of the islets was usually seen. Also, islets still exhibiting normal size showed typical vacuolization (Fig. 2).

**Acromegalic signs**

Acromegalic signs were noted in 5 dogs presented during dioestrus and in 8 dogs with a history of MPA treatment. Fig. 3, upper row depicts the appearance of a severe case of acromegaly occurring during dioestrus. Three months after removal of the ovaries, the increase of soft tissue mass had reversed (Fig. 3, lower row).

**Progesterone-GH-relationship in diseased and in pregnant animals**

Dogs exhibiting signs of acromegaly/hyperglycaemia during a natural progesterone phase (dioestrus) showed progesterone levels within the normal range \((30.4 \pm 4.9 \text{ ng/ml}, \text{mean} \pm \text{SEM}, n = 10)\); progesterone levels in normal dogs ascertained by the employed method reach maximum concentrations ranging from 35 to 60 ng/ml 20 days after the first day of pro-oestrus). In animals developing signs during dioestrus, ovariohysterectomy or when, if spontaneous reduction of progesterone levels could be observed, drop in progesterone was followed by invariable but delayed drop in GH levels (Fig. 4). (Only a limited number of dogs

![Fig. 4.](image)

Time course of plasma GH levels following ovariohysterectomy or spontaneous decrease of progesterone levels (†) in 9 dogs exhibiting GH overproduction and glucose intolerance during dioestrus, left panel. Time course of plasma GH levels during a spontaneous decrease of plasma progesterone levels in 5 out of the 9 dogs shown on the left. The corresponding progesterone concentrations \((= (P)\text{ in ng/ml})\) are indicated in the figure on the right of each corresponding GH concentration; †† = ovariohysterectomy, right panel.
became available for the study of spontaneous drop in progesterone and drop in GH levels. However, in all animals studied, drop in progesterone was followed by drop in GH levels). In dogs receiving MPA, plasma levels of the compound had a mean of 3.1±0.6 ng/ml (± SEM, n = 11).

In order to assess whether GH elevation could occur during a natural progesterone phase, pregnant dogs were also studied. GH was measured in samples obtained from three different groups of 15 dogs: group 1 during the interval of 1–20 days, group 2 during the interval of 21–40 days, and group 3 during the interval of 41–60 days after conception. (Average duration of normal canine pregnancy is 63 days). From each dog, three independent samples were obtained and assayed for GH. Among these 45 dogs, only one exhibited elevated GH levels (21, 25.6, and 36.2 ng/ml).

Discussion

The finding that hyperglycaemia (glucose intolerance) was accompanied by hyperinsulinaemia points to insulin resistance as the factor responsible for hyperglycaemia and glucose intolerance observed in our dogs. This is further supported by the fact that the insulin requirement of dogs having GH elevation, despite elevated endogeneous insulin levels, was appreciably higher than the insulin requirement of diabetic dogs not having GH elevation.

Our findings are compatible with GH-induced diabetes. GH appears to cause glucose intolerance mainly by inducing insulin resistance (Altszuler 1974). As opposed to other species such as the rat, carnivores (dogs, cats) appear to be particularly sensitive to the diabetogenic action of GH (Young 1945, 1953; Pierluissi & Campbell 1980; Altszuler 1974). Administration of GH to the dog, within a matter of days, can lead to a diabetic stage which initially is characterized by hyperinsulinaemia. If exposure to high GH levels persists, hypoinsulinæmia and exhaustion of pancreatic β-cells might ensue (Pierluissi & Campbell 1980).

The exact mechanism whereby GH induces insulin resistance is only insufficiently understood. There is evidence suggesting that the insulin resistance associated with GH excess is mediated at a site on the receptor distal to the insulin-binding site or at one or more of the intracellular reactions important in insulin action (Kahn et al. 1978). Even if the mechanism by which GH induces insulin resistance was known more fully, the question why carnivores are highly susceptible and other species are less susceptible to the diabetogenic action of the hormone would remain open.

It is important to note that in our study there was no correlation between the degree of GH elevation and the degree of hyperglycaemia. This finding would suggest that factors other than GH might have been responsible for hyperglycaemia and insulin resistance. However, even under the most controllable situation when dogs are given comparable amounts of GH, there is wide variation in response. Some dogs do develop overt diabetes and some do not (Young 1945; Campbell & Rastogi 1966). Similarly, the time course and the extent of response in experimentally induced GH-diabetes can vary from experiment to experiment (Campbell et al. 1978). In our study, it is of interest to note that animals having a plasma glucose of less than 10 mM had a higher insulin/glucose ratio than animals exhibiting a plasma glucose of more than 10 mM. Yet, both groups had similar plasma GH concentrations. Less pronounced hyperglycaemia in the not frankly diabetic dogs, therefore, appears to be, at least partly, the result of a relatively higher plasma insulin concentration likely to prevent plasma glucose concentrations from appreciable escape. Further, the degree of hyperglycaemia also depends upon the duration of exposure to GH (Pierluissi & Campbell 1980). Duration of exposure to GH might have been an additional unknown factor influencing the degree of hyperglycaemia in our dogs. Yet, the fact that in almost all dogs investigated glucose tolerance improved once GH levels had dropped, is strong evidence for GH as the major glucose intolerance-precipitating factor.

The fact that in our study GH was elevated in animals exhibiting diabetes during progesterone/MPA exposure, but not in dogs developing diabetes independently of such exposure precludes the possibility that GH elevation might be caused by hyperglycaemia or the diabetic state as such.

Further evidence for GH as a major factor in inducing insulin resistance, glucose intolerance, and acromegaly in our dogs is derived from the following: all the observed endocrine, metabolic and physical changes reflect the result of a persistent elevation of biologically active GH. This is further supported by the almost invariable correc-
tion of GH excess associated changes following GH reduction. The histologic appearance of pancreatic biopsies resembled that found in experimental GH-diabetes (Volk & Lazarus 1962).

It is possible that progesterone or MPA, by virtue of their steroidal (glucocorticoid) nature, are glucose intolerance-inducing factors in our dogs. However, it seems unlikely that these steroids are major contributing factors because 1) progesterone levels were in the normal range and MPA levels were low, 2) when oestadiol-primed, MPA injected dogs which exhibit much higher MPA levels than our dogs do not respond with GH increase, only moderate glucose intolerance and moderately increased insulin response to glucose results (Eigenmann & Rijnberk 1981), and 3) if progesterone were the major cause of severely impaired glucose tolerance, the phenomenon would be expected to occur in a much larger proportion of female dogs. Moreover, MPA administration in the dog leads to decreased rather than increased cortisol levels (Concannon et al. 1980).

An interesting finding is that only 2 out of 10 dogs exhibiting frank diabetes (glucose > 10 mM) showed acromegalic signs, and that among dogs exhibiting mild hyperglycaemia all were consistently acromegalic. These findings would suggest that the opportunity to develop acromegaly might be inversely correlated with the catabolic state (hyperglycaemia) and/or availability of insulin for the animals. However, the situation is more complex because 1) GH displays both anabolic (growth promoting) and catabolic (hyperglycaemic) actions, 2) radioimmunologically measured GH does not always parallel the biological activity of GH (Ellis et al. 1978), and 3) some of the effects of GH appear to be mediated by the GH molecule directly, but the growth-promoting effects of GH appear to be mediated by somatomedins (Baumann & Nissley 1979) or insulin-like growth factors (Zapf et al. 1978). In this context, it should be mentioned that experimentally-induced diabetes in the dog is followed by a drastic drop in concentration of growth factors (insulin-like growth factors, earlier non-suppressible insulin-like activity), and that this activity is restored toward normal by insulin treatment which counteracts the catabolic state (Eigenmann et al. 1977). Determination of insulin-like growth factors in individual samples of our dogs should be helpful in elucidating whether frank hyperglycaemia might be a factor determining the opportunity to develop acromegaly.

The fact that GH levels dropped after ovariectomy/progestagen withdrawal is evidence for an ovarian/progestagen-GH interrelationship. Moreover, the observation that spontaneous drop of progesterone was followed by spontaneous drop in GH levels and that almost all pregnant dogs had normal GH levels suggests that GH in some dogs becomes and/or is paradoxically controlled by natural levels of progesterone. It is interesting to find that there was a correlation between progesterone and GH levels in individual dogs. When, however, progesterone and GH levels from different dogs are compared, there appears to be no correlation (Fig. 4). Since most normal dogs, however, during their progesterone phase despite elevated progesterone concentrations do not have elevated GH levels, a similar non-quantitative relationship has to be expected when dogs which show GH elevation are compared with each other. This view is in keeping with findings from experimental studies in dogs. MPA given to dogs can lead to elevation of GH levels. Yet, the extent of GH elevation, despite similar MPA levels being reached, varies substantially from dog to dog (Eigenmann & Rijnberk 1981; Eigenmann & Eigenmann 1981b).

A common feature of sex steroids is their ability to induce tissue differentiation and protein synthesis. When sex steroids are withdrawn, several days are usually required before protein synthesis in sex steroid targets returns to pre-stimulatory values (Palmiter & Schimke 1973). The time course of GH levels following removal of the ovaries or following spontaneous reduction of progesterone levels resembles the time course of protein synthesis observed in sex steroid targets following steroid withdrawal. Yet, the mechanism whereby the GH axis becomes responsive to progesterone remains unknown. This disorder might be present at birth or develop later in life. It is possible that the dogs studied exhibited GH elevation during progestosterone exposure at a young age. However, the fact 1) that GH levels in some cases were elevated to an extent certainly sufficient to induce diabetes earlier in life and 2) that the animals did not develop diabetes sooner would suggest that the condition, for some unknown reason, develops at an older age. In this context, it is important to know that dogs, in contrast to other species, exhibit virtually identical high post-oestrus progesterone concentration changes whether pregnant or not (Concannon et al. 1977). Additionally, dogs' reproductive cycles do not cease at old age. Whether such
lifelong exposure to 'pregnancy progesterone levels' contributes to or provides the necessary environment for the development of the disorder is unknown but remains an interesting possibility.

The dogs studied when receiving MPA were injected with 50 mg MPA twice a year. This is a very low dose in comparison to the pharmacologic dosages employed in experimental studies concerned with progestagen exposure associated diabetes (Sloan & Oliver 1975) or the development of mammary tumours (Concannon et al. 1980). In these studies, chlormadinone acetate was given orally at a dose of 0.6 mg/kg body weight daily for one year (Sloan & Oliver 1975) or MPA was administered at a dose of 75 mg/kg body weight every third months for 17 months (Concannon et al. 1980). Experimental dogs treated repeatedly with extremely high doses of medroxyprogesterone acetate (MPA) showed acromegalic signs and elevated growth hormone levels (Concannon et al. 1980). Yet, administration of physiologic doses of natural progesterone failed to provoke increased GH levels (Concannon et al. 1980) and in another study high doses even led to a reduction in the number of pituitary GH cells (Attia & Zayed 1979). These findings could suggest that increased plasma GH and acromegaly are exclusively, experimentally induced by pharmacologic doses of synthetic progesterone derivatives, but not by natural progesterone. From our findings, however, it appears that the abnormal response of the GH axis to progestagen exposure also occurs under physiologic circumstances (e.g., progesterone phase).

From this study the following conclusions can be drawn:

1) Diabetes/acromegaly developing in older female dogs during dioestrus or MPA exposure appears to be induced by progesterone/MPA-evoked GH overproduction.

2) In general, progesterone exposure (pregnancy) in dogs does not lead to significant GH elevation; in some dogs, paradoxically, GH levels appear to be positively controlled by physiologic levels of progesterone or low doses of MPA.

Additional studies are necessary to determine the primary event (change) leading to the altered response of the GH axis to progesterone. Such studies might provide fundamental insight into normal and abnormal steroid-neuroendocrine interaction.

GH displays several incompletely understood biological actions. These include the hyperglycaemic, hyperinsulinaemic effects and the generation of somatomedin or insulin-like growth factors (IGF). Progesterone-induced canine GH overproduction should be a useful tool for clarifying some of the questions pertinent to the multiple intriguing actions of GH. The possibility of manipulating plasma GH by progesterone in order to study the natural regulation of IGF or other actions of GH in an experimental model represents a unique opportunity.

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