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Angiotensinogen: Hormonal regulation and relative importance in the generation of angiotensin II

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Angiotensinogen: Hormonal regulation and relative importance in the generation of angiotensin II. The production of angiotensinogen is controlled mainly by hormones that affect the concentration of its mRNA in tissues. Accordingly, hormones that act upon gene transcription play a prominent role. However, other factors may modulate the transcriptional effects of hormones, and these should be considered to appreciate the final effects of hormones on the secretion of angiotensinogen. The most important role played by hormones in the regulation of angiotensinogen may be to maintain its production in the face of rapid consumption by high levels of renin. However, elevated levels of angiotensinogen may become a risk factor in situations where the normal feedback regulation of renin does not operate normally. Finally, the synthesis of angiotensinogen in tissues may be regulated differentially than that in liver, although the exact importance of these observations is still poorly understood.

Angiotensin II (Ang II) is a vasoactive peptide that plays important roles in the control of blood pressure and in the pathogenesis of a variety of cardiovascular diseases, including hypertension, cardiac hypertrophy and cellular proliferation after myointimal injury. The two factors that limit the rate of production of Ang II are: (1) angiotensinogen (AOG), the glycoprotein precursor to angiotensins, and (2) renin, the enzyme that processes AOG. All available evidence indicates that AOG is secreted only constitutively and cannot be stored within secretory granules [1]. This implies that the production of AOG is controlled mostly at the level of synthesis, instead of secretion. In agreement with this requirement, the hepatic production of AOG is affected primarily by hormones that act at the genomic level, that is, steroids and thyroid hormones. However, other factors may affect how hormones act upon the AOG gene.

Endocrine regulation of liver angiotensinogen

Glucocorticoids (GC) are arguably the regulators of liver AOG that have been studied in greatest detail. They greatly increase the abundance of AOG mRNA both in liver (when administered *in vivo* to experimental rodents) and in hepatoma cell lines (when administered *in vitro*) [2]. Several studies have shown that this effect is the consequence of an increase in transcription of the AOG gene [3]. However, we have observed that GC had much smaller effects on AOG secretion than on AOG mRNA concentration, both *in vivo* and *in vitro* [2]. This observation suggests that GC, despite their strong effect on transcription of the AOG gene, may have opposite effects on translation of its mRNA. In addition, most previous studies testing the effects of GC *in vivo* have used doses that were about 100 times higher than that which is required to induce hypercorticism. We have verified that chronic administration of corticosterone at doses that (although moderate) induced clear signs of hypercorticism did not stimulate plasma AOG. These data make it unlikely that GC will serve as primary regulators of AOG. Rather, their main function may be to serve as permissive factors for the actions of other agents such as interleukins [4].

Liver AOG production has been shown to be controlled by estrogens and thyroid hormones as well. In contrast to glucocorticoids, these two types of hormones affect both AOG secretion and liver AOG mRNA concentration to a comparable extent. However, other factors appear to be important in determining the importance of their overall effect. For instance, the effect of estrogens on liver AOG production was greater in female than in male rats [5]. Likewise, estrogens did not stimulate liver AOG in hypophysectomized rats, but responsiveness was restored by pretreating these animals with prolactin. These data indicate that pituitary hormones may control the responsiveness of liver AOG to estrogens by controlling the abundance of estrogen receptors in liver cells.

The mechanism by which GC and estrogens increase transcription of the AOG gene appears to derive from a direct interaction between the 5′-flanking region of the gene and the DNA-binding domains of their cognate receptors. In contrast, the action of thyroid hormones appears to be dependent on the induction of secondary genes, since their effect on AOG mRNA on hepatoma cells in blocked by cycloheximide, a blocker of protein synthesis [3]. This mechanism may explain why thyroid hormones induce AOG secretion in subconfluent hepatoma cells but not in confluent cultures, whereas no differences in the abundance of thyroid hormone receptors could be detected in these two types of cultures [6]. Finally, some hormones might affect AOG mRNA concentration without affecting gene transcription. Thus, it has been shown recently that Ang II increases the synthesis of AOG in hepatocytes by stabilizing its mRNA transcript [7]. This effect results from an inhibition of ribonucleases following an Ang II-mediated decrease in intracellular cAMP.

These data indicate that, despite its the central role, gene transcription is not the only factor that will determine the response of AOG-secreting cells to a given hormone. This complex interplay of hormones in the regulation of AOG mRNA is summarized in Figure 1.

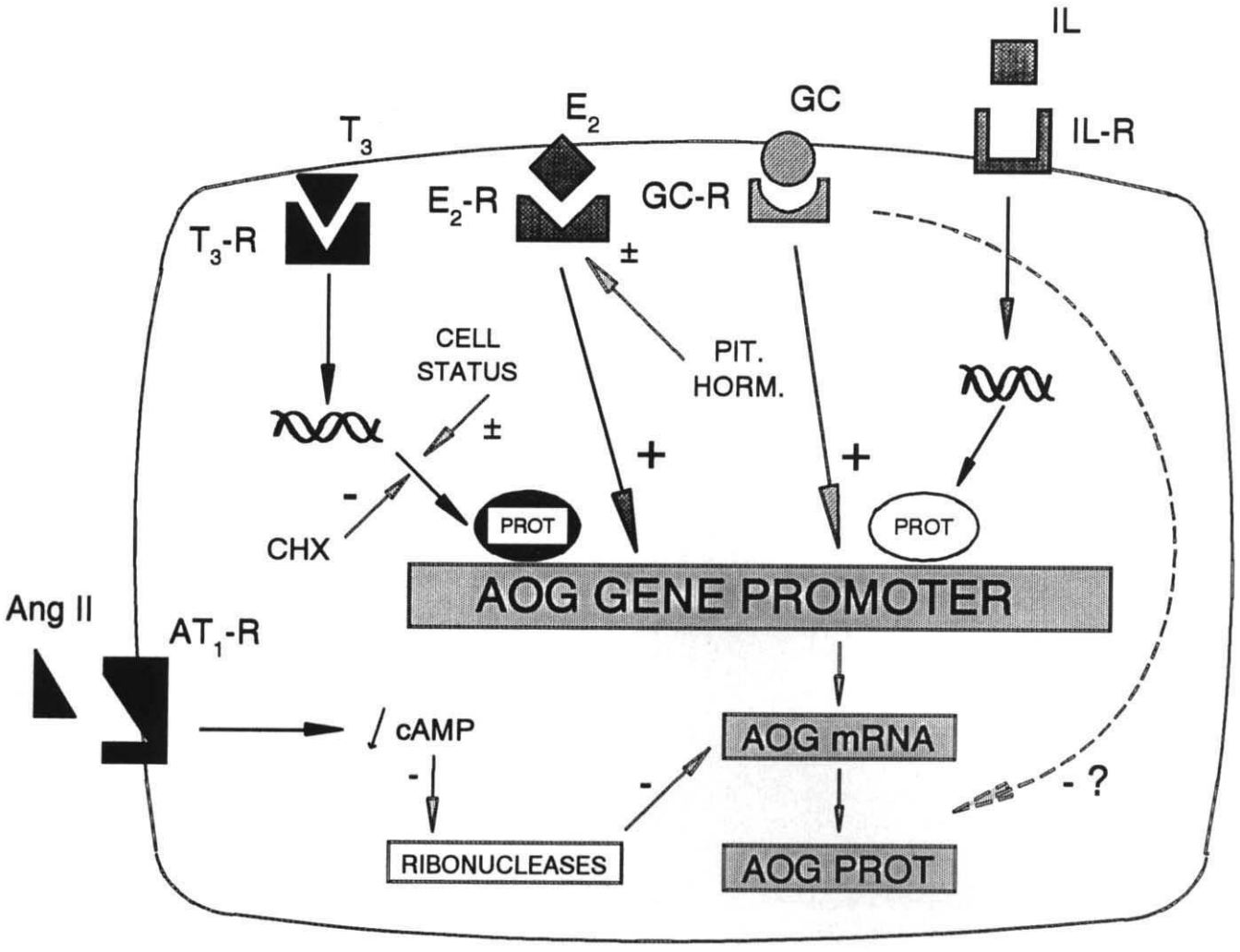

Fig. 1. *Schematic representation summarizing the effects of various hormones on the production of angiotensinogen by a liver cell.* The effects of hormones are represented by arrows, accompanied by the +, − or ± sign to indicate the nature of the effect. The ? sign means that the effect is still speculative. Abbreviations are: AOG, angiotensinogen; T3, triiodothyronine; E2, estradiol; GC, glucocorticoids; IL, interleukins; -R, receptor; pit. horm., pituitary hormones; prot, protein; CHX, cycloheximide; cAMP, cyclic adenosine monophosphate.

Pathophysiological importance of AOG regulation

The importance of maintaining adequate levels of AOG is underscored by the fact that its concentration in circulating plasma is close to the K_m of the proteolytic activity of renin. As a consequence, the amounts of Ang I generated by a fixed amount of renin are directly proportional to the amounts of available substrate. However, changes in plasma AOG are usually accompanied by inversely proportional changes in renin secretion. It follows that hormonally-induced changes in plasma AOG are usually not accompanied by any change in plasma renin activity or Ang II concentration. In addition, it take several hours before obtaining increases in AOG secretion following stimulation by hormones that act at the genomic level. Because of these idiosyncrasies, it has been hard to pinpoint how exactly changes in the levels of plasma angiotensinogen could affect blood pressure and/or Ang II generation. Nevertheless, blood pressure is increased in people who have genetic elevations in plasma AOG [8] or in transgenic mice carrying the AOG gene [9]. Thus, it is important to gain insights about how exactly AOG could affect blood pressure.

To understand the role of AOG, it is important to keep in mind that hypertension is a disease, and that it develops in a background that might be different from that of a healthy individual. In particular, one should consider the consequence of changes of plasma AOG when the normal feedback mechanism on renin secretion does not function normally. This particular question has been investigated recently by J.E. Sealey and collaborators. This group had previously demonstrated that in Dahl salt-sensitive rats, there was a paradoxical increase in renin secretion after six weeks of salt-loading which appeared to be secondary to the appearance of renal vascular lesions [10]. In those animals where renin was paradoxically elevated (and apparently not under normal control), there was a strong correlation between blood pressure and plasma angiotensinogen, but no correlation with plasma renin concentration [11]. These data provide a framework to understand the possible link that exists between angiotensinogen and blood

pressure. Angiotensinogen is not a primary determinant in the control of plasma Ang II, but may amplify the consequences of an alteration of the normal regulatory mechanisms of renin secretion. In that sense, it may literally function as a "risk factor." A similar mechanism may explain why hypertension develops in certain women undergoing estrogen therapy.

In nonhypertensive individuals, the role of regulators of AOG is not to induce primary elevations, but to maintain its production in the face of rapid consumption. Thus, important elevations in renin induce a proportional depletion in AOG, which impairs the ability of renin to generate angiotensins. One such situation is hemorrhage, where a stimulation of AOG has been shown to be essential in order to allow renin to mount an efficient response [12]. In this context, it is fitting that Ang II can stimulate AOG, since it is the only hormone that can act in a relatively short period of time. Other hormones (including interleukins and GC) will contribute to sustain the response over extended periods of time.

Tissue angiotensinogen

Lastly, AOG is produced in many other tissues but liver, including brain, adipose tissue and kidney. We have examined the effects of various hormones on at least one of these tissues, the brain. Diencephalon AOG mRNA concentration was significantly decreased after adrenalectomy, but increased only marginally after acute administration of dexamethasone [13]. Similarly, diencephalon AOG mRNA concentration was decreased in hypothyroid rats, but did not increase in hyperthyroid rats [6]. Thus, the main contributions of GC and thyroid hormones to the synthesis of AOG in the brain appear to be confined to the maintenance of basal levels of production. The effect of estrogens was more variable. Thus, the amplitude, direction and time course of their effect differed greatly between brain regions, indicating that cell-specific factors modulated the effect of these hormones in brain cells [5]. All together, these data indicate that regulation of the AOG gene in extrahepatic tissues may be different from that in the liver.

Conceivably, the production of AOG in tissues may be one factor fostering the local production of angiotensins, especially if (in contrast to kidney renin) there is no negative feedback mechanism of Ang II on the production of renin (or renin-like enzymes) in tissues. However, there is still no convincing evidence to date demonstrating that alterations in the local concentration of AOG in tissues induce corresponding changes in the local concentration of Ang II. Before such data are available, it will be hard to interpret the significance of regulation of angiotensinogen in tissues. This difficulty is compounded by the fact that it is still not clear how AOG can be converted into Ang II in tissues. This is particularly puzzling in at least three cell-types where Ang II has been located within secretory granules: in the kidney juxtaglomerular cells, in the pituitary gonadotrophs and in nerve terminals. Indeed, we have shown that AOG cannot be routed from the Golgi to secretory granules [1], so the presence of Ang II within the same secretory granules remains a mystery. One possibility is that these cells internalize AOG from the surrounding extracellular fluid. We are currently conducting experiments to test whether such a mechanism could explain the presence of Ang II within granules of the juxtaglomerular cells.

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