New Insights into the Adrenocortical Accumulation of Lipofuscin

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Introduction

Adrenocortical zona reticularis of aged rats accumulates lipofuscin granules, but the mechanism of the formation has not been established. ACTH stimulation is a major factor that affects the accumulation.

Discussion

Rat adrenal cortex comprises three zones of steroidogenic tissues: glomerulosa (ZG), fasciculata (ZF) and reticularis (ZR). The ZG synthesizes mineralocorticoid (aldosterone) in response to low Na+ or high K+ in circulation. In parallel, the ZF and ZR synthesize glucocorticoid (corticosterone) responding to stimulation by the pituitary hormone ACTH. Prolonged ACTH-stimulation of rats induces transformation of ZG-cells to ZF-like cells to maximize the production of corticosterone [1].

The morphological appearance of the three adrenocortical zones has been theorized by a centripetal migration of glomerular cells. Diderholm and Hellman [2] studied 3H-thymidine labeled cells (at the S-phase) in rat adrenals and found that four hours after the thymidine injection, the labeled cells were first localized to the capsule, ZG, and the outer parts of the ZF. After two months, the labeled cells were found within the ZR. Furthermore, the labeled cells reach the ZR where they ultimately become apoptotic. The loss of ZR cells is considered as a prerequisite of the centripetal migration theory for renewal of adrenocortical cells [3]. Zajicek et al. [4] and Huang et al. [5] proposed that the cell migration is derived from sub-capsular and capsular stem cells. Using a 'lineage-tracing technique', Freedman et al. [6] demonstrated that, mouse adrenocortical zonation occurs when differentiated G-cells undergo centripetal migration and lineage conversion into F-like cells during postnatal development. The migration is a slow process which takes weeks to months, and the lineage conversion process is Steroidogenic Factor 1 (SF-1)-dependent. However, following SF-1-knockout, fully functional F-cells are still maintained. This observation demonstrates that a G-cell independent mechanism also exists, perhaps through an activation process of progenitor cells in ZF under the circumstance. Our recent findings [7] indicate that ACTH stimulation can accelerate the rat centripetal migration process. This is based on the observation that the immunostains of aldosterone synthase were originally concentrated in the rat adrenocortical ZG, but became scattering in the ZR after ACTH stimulation for four consecutive days.

Adrenal steroid hormones are derived from cholesterol. Thus, adrenocortical cells develop effective mechanisms with which cholesterol is taken up from plasma lipoproteins for steroidogenesis, and excessive cholesterol is either stored in cytosolic lipid droplets or released back to circulation via an ATP-binding cassette (ABC) transporter-mediated process, commonly referred as "cholesterol efflux." Rat adrenal cortex expresses liver-X-receptor (LXR) [8] and retinoid-X-receptors (RXR) α and β [9]. LXR/RXR heterodimer enhances the expression of ABCA1 and ABCG1 [10]. We have found that ACTH-stimulation affectsthe male Wistar rat adrenal ABCA1 and ABCG1 protein levels and their glandular distributions (unpublished observations).

In this context, the pathogenic mechanism of the human Stargardt Disease is believed to be associated with the disorder of ABOCR (ABCA4) in the discs of the outer rod segments which consequently leads to the formation of A2E (a pyridinium bisretinoid) [11]. A2E is a major component of lipofuscin and is toxic to retinal pigment epithelium (RPE). The accumulation of A2E causes RPE cell apoptosis, thereby explaining age-related macular degeneration and macular degeneration characteristic of Stargardt Disease. However, Crouch et al. [12] recently reported that the accumulation of A2E is not responsible for the increase in lipofuscin fluorescence observed in the central RPE with aging in humans, but is correlated well in all the mouse models.

Aged rat adrenocortical ZR accumulates a large amount of lipofuscin. We have reported that aging in the male F344 rats is
accompanied by accumulations of cholesterol esters [13] and retinyl stearate [14] in addition to lipofuscin in the adrenal glands. Prolonged stimulation of the rats with ACTH for seven days causes reduced adrenocortical accumulations of retinyl stearate fluorescence [14] and lipofuscin accumulation [15]. These facts collectively indicate that adrenocortical accumulation of lipofuscin in the aged rat (never been experimentally stimulated) may be a result of lacking ACTH stimulation during the captivity.

**Conclusion**

The accumulation of lipofuscin granules in the adrenocortical zona reticularis of unstimulated aged rats is likely associated with “lacking of ACTH stimulation” during their captivities.

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