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Adrenal

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Sublethal Hyperthermia Decreases Cellular Proliferation and Transiently Disrupts Steroidogenesis in Adrenal Cells

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Introduction: Primary Aldosteronism is the most common cause of secondary hypertension. First-line treatment; adrenalectomy resects adrenal nodules and adjacent normal tissue, limiting suitability to those who present with unilateral disease. Use of thermal ablation represents an emerging approach as a possible minimally invasive therapy for unilateral and bilateral disease, to target and disrupt hypersecreting aldosterone producing adenomas, while preserving adjacent normal adrenal cortex. Ablation involves heating tissue >50°C to induce cellular necrosis. Outside the core ablation zone, the transitional zone is an area exposed to variable temperatures between 37°C – 50°C. To understand the feasibility of precision ablation in the adrenal gland, we examined the effect of applying these temperatures to adrenocortical cells to identify i) the required temperature to effectively ablate adrenal cells ii) the extent of damage that may occur to surrounding healthy adrenal cells with exposure to transitional zone temperatures.

Methods: Steroidogenic adrenocortical cell lines, H295R and HAC15, were treated with hyperthermia (high precision water bath) at temperatures of 37, 42, 45, 48 and 50° C and steroidogenesis was subsequently stimulated using forskolin (10μM) and angiotensin II (10nM). Cell death (Propidium iodide staining by flow cytometry), proliferation (xCELLigence real-time cell analysis), protein expression (Western blot/qRT-PCR), and steroid secretion (HPLC-Mass spectrometry) were analysed immediately and 7-days post-treatment.

Results: Cell death occurred at 48°C and 50°C ($p<0.05$ vs 37°C control), but not 45°C, or 42°C. Sublethal hyperthermia (42°C and 45°C for 30 minutes) induced a heat shock response demonstrated by upregulation of HSP70 and HSP90. Proliferation was subsequently reduced over 7-days alongside a decrease in aldosterone and cortisol secretion ($p<0.05$), and reduced expression of steroidogenic enzymes (CYP11B1, CYP11B2, CYP11A1) 18-hours post treatment ($p<0.05$). Following 7-days sublethal hyperthermia, steroid secretion and steroidogenic enzymatic expression returned to baseline levels.

Conclusion: Hyperthermia at 48°C and 50°C for 15 minutes is required for sustained cell death at 7-days post treatment. Sublethal hyperthermia, equivalent to that produced in the transitional zone during thermal ablation, produces a short-lived unsustained inhibition of steroidogenesis that recovers 7-days post treatment. Therefore, segmental adrenal sparing ablation is possible with recovery of transitional zone following ablation. This underlines the potential for precision technology development for bilateral adrenal ablation as definitive measure to treat PA caused by APA or Micronodular disease.

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