

# THE EFFECT OF RETINOIC ACID ON HUMAN ADRENAL CORTICOSTEROID SECRETION *IN VITRO*

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## INTRODUCTION

**Retinoic acid**, a derivative of vitamin A, has recently yielded promising results in the treatment of **Cushing's disease** (Pecori Giraldi et al JCEM 2012). Its main site of action appears to be the **tumoral corticotrope** as retinoic acid **inhibits** *POMC* transcription and corticotrope proliferation (Paez-Pereda et al JCI 2001). Studies on **tumoral adrenal cell lines** have revealed an additional **inhibitory** effect on cell proliferation and stimulated corticosteroid secretion (Paez-Pereda et al JCI 2001).

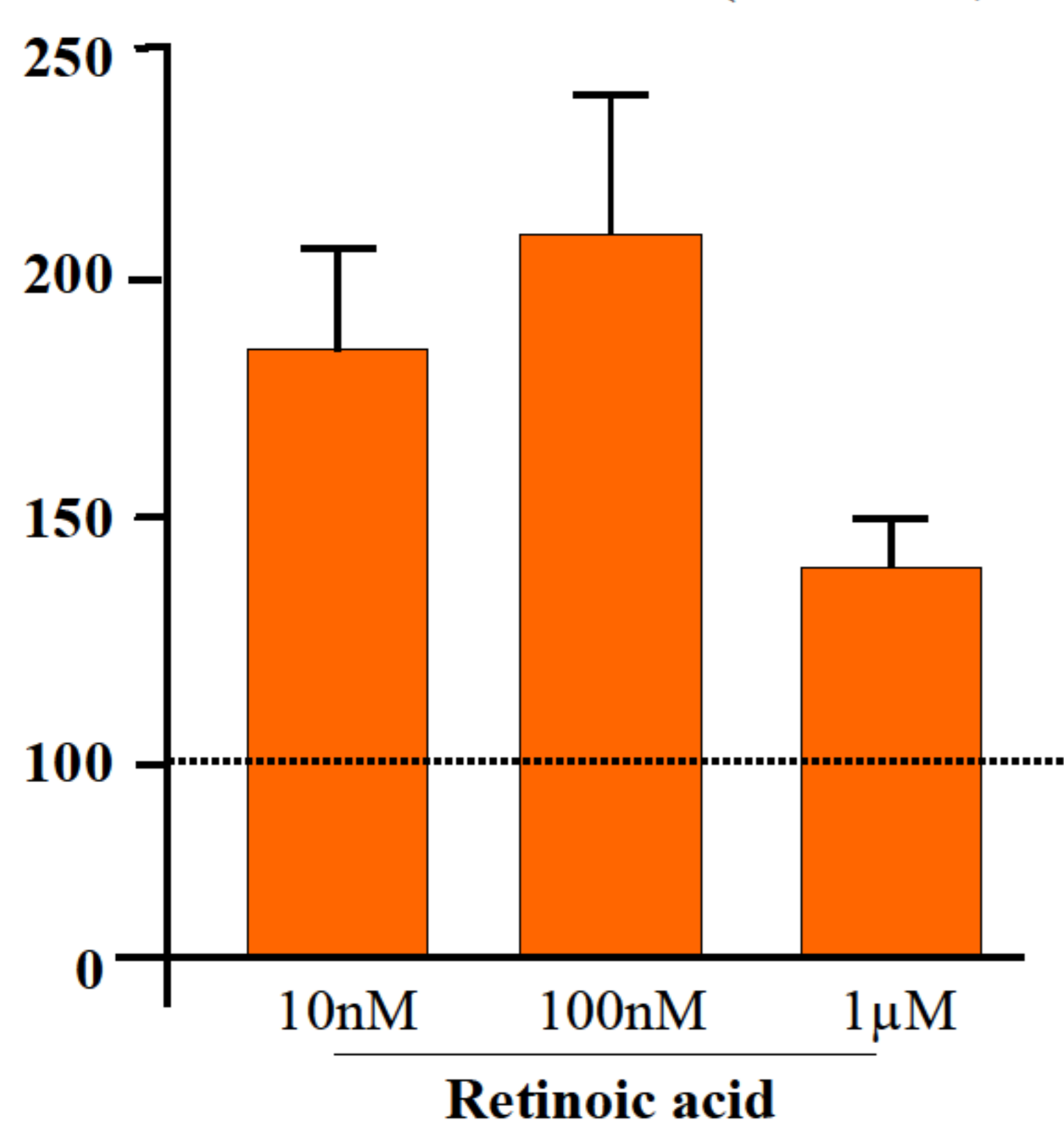
**Aim** of the current study was to evaluate whether **retinoic acid** modulates **corticosteroid secretion** and **genes** involved in **steroidogenesis pathway** by **normal adrenals *in vitro***.

## METHODS

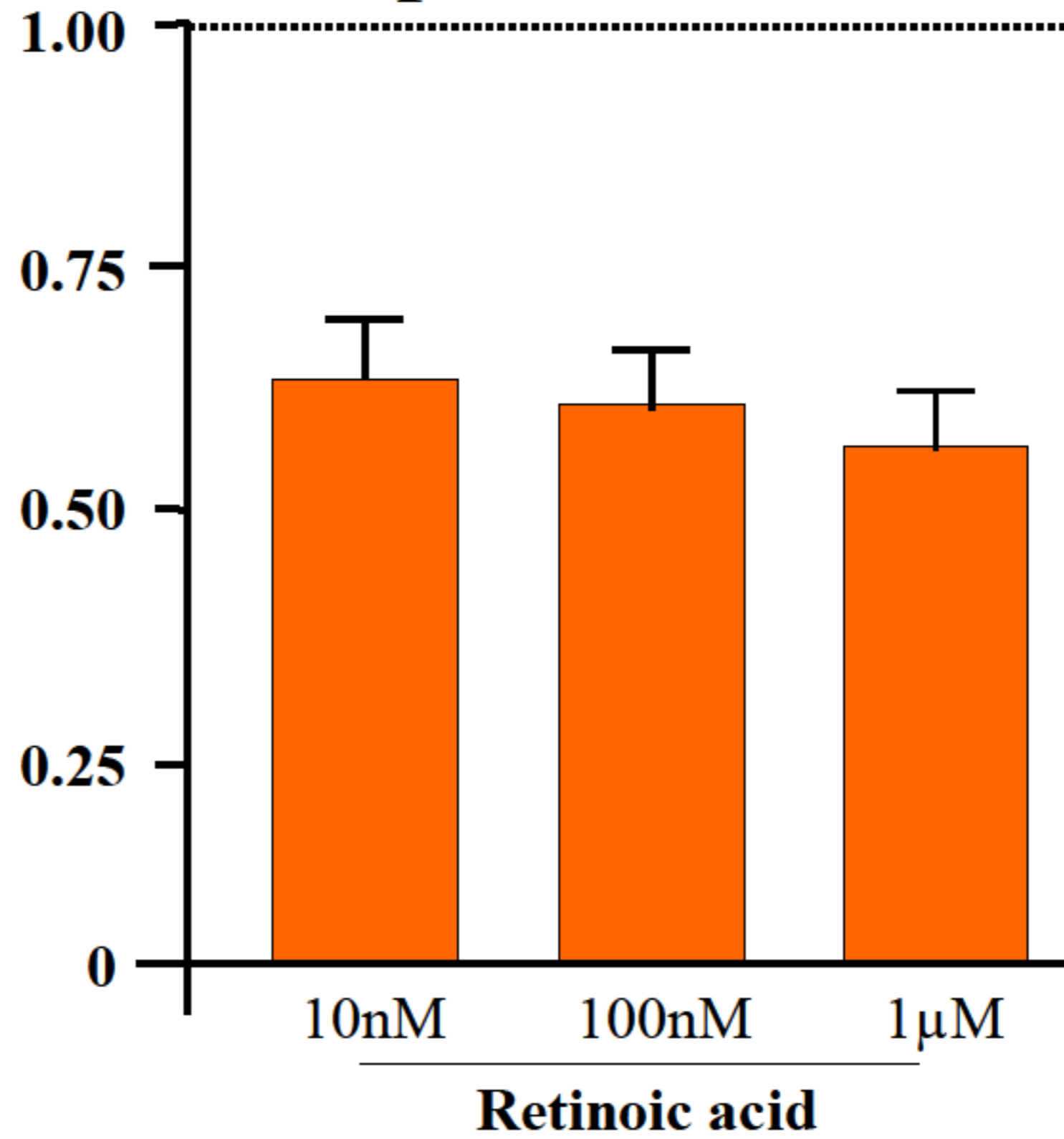
Primary cultures from 9 normal human adrenals were incubated with **10 nM**, **100 nM** and **1 μM retinoic acid** with and without **10 nM ACTH** for 24 hours. Control wells were incubated with plain medium. **Cortisol** levels in medium were measured by Coat-A-Count RIA (Siemens Healthcare Diagnostics, Erlangen, Germany); **CYP11A**, **STAR** and **MC2R** expression were analyzed by real-time PCR (7900 HT Sequence Detection System, Applied Biosystems, Foster City, USA) normalized to *RPLP0*.

## RESULTS

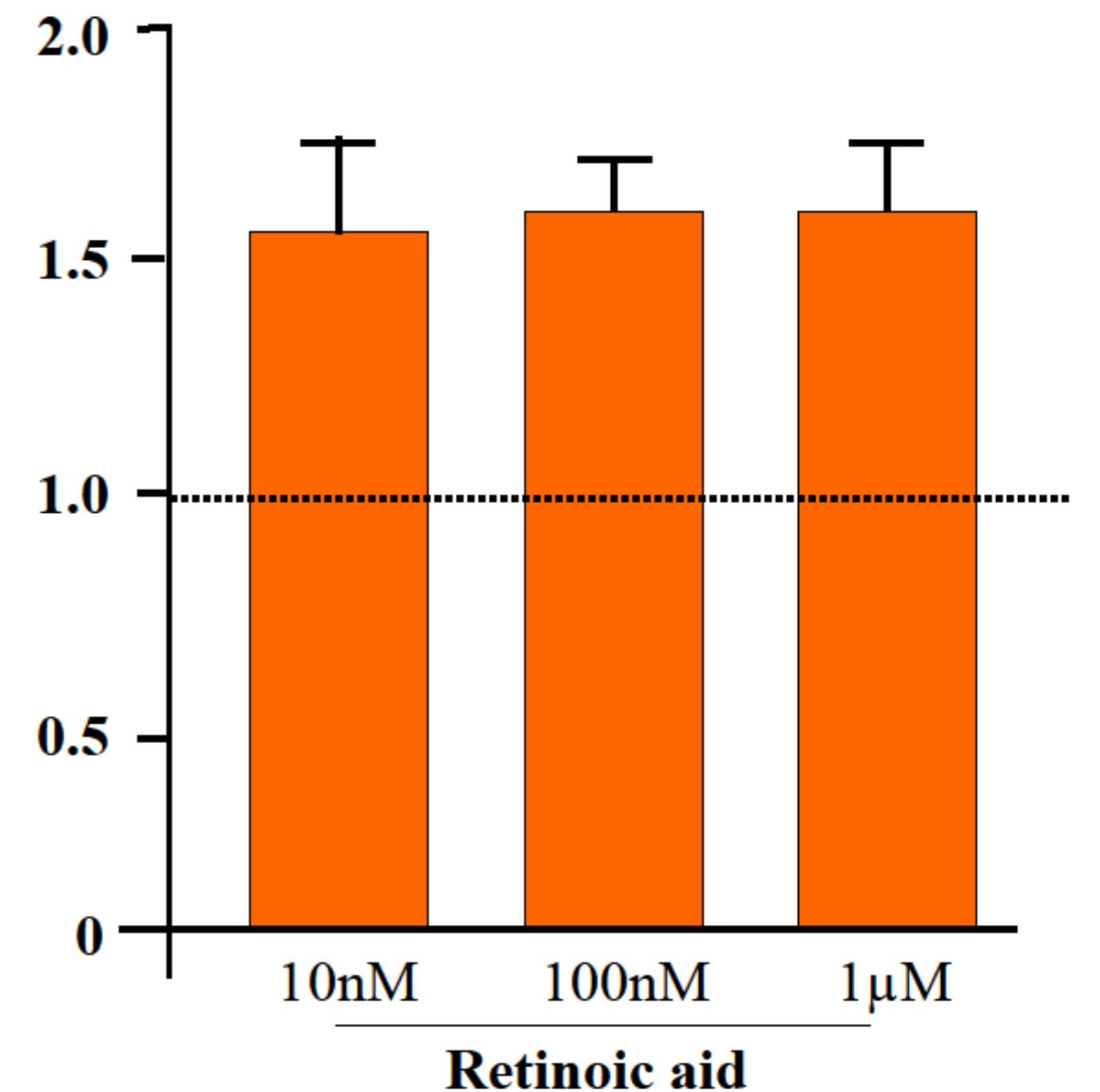
**Cortisol secretion** (% control)



**MC2R expression** (fold change control)



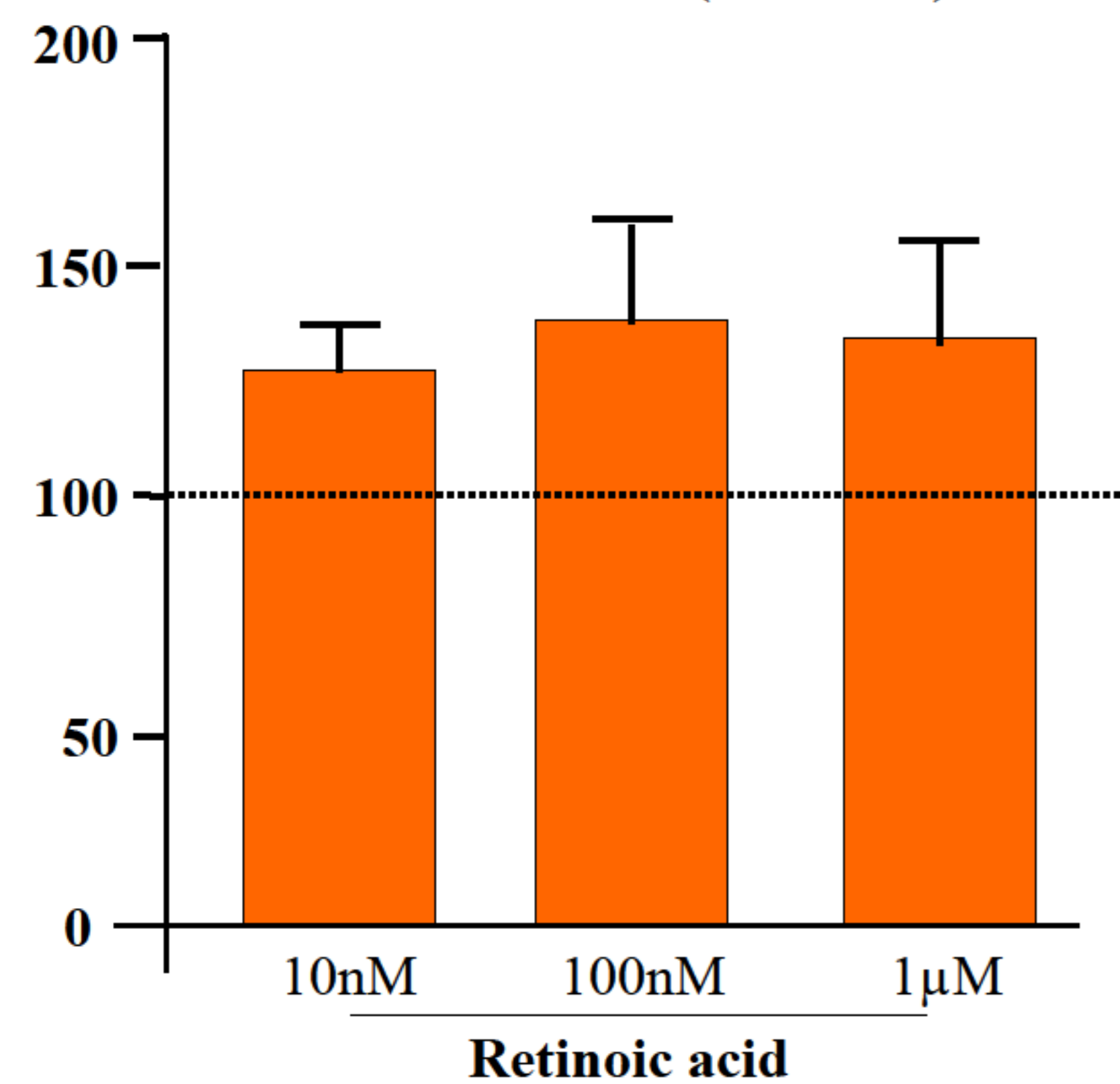
**STAR expression** (fold change control)



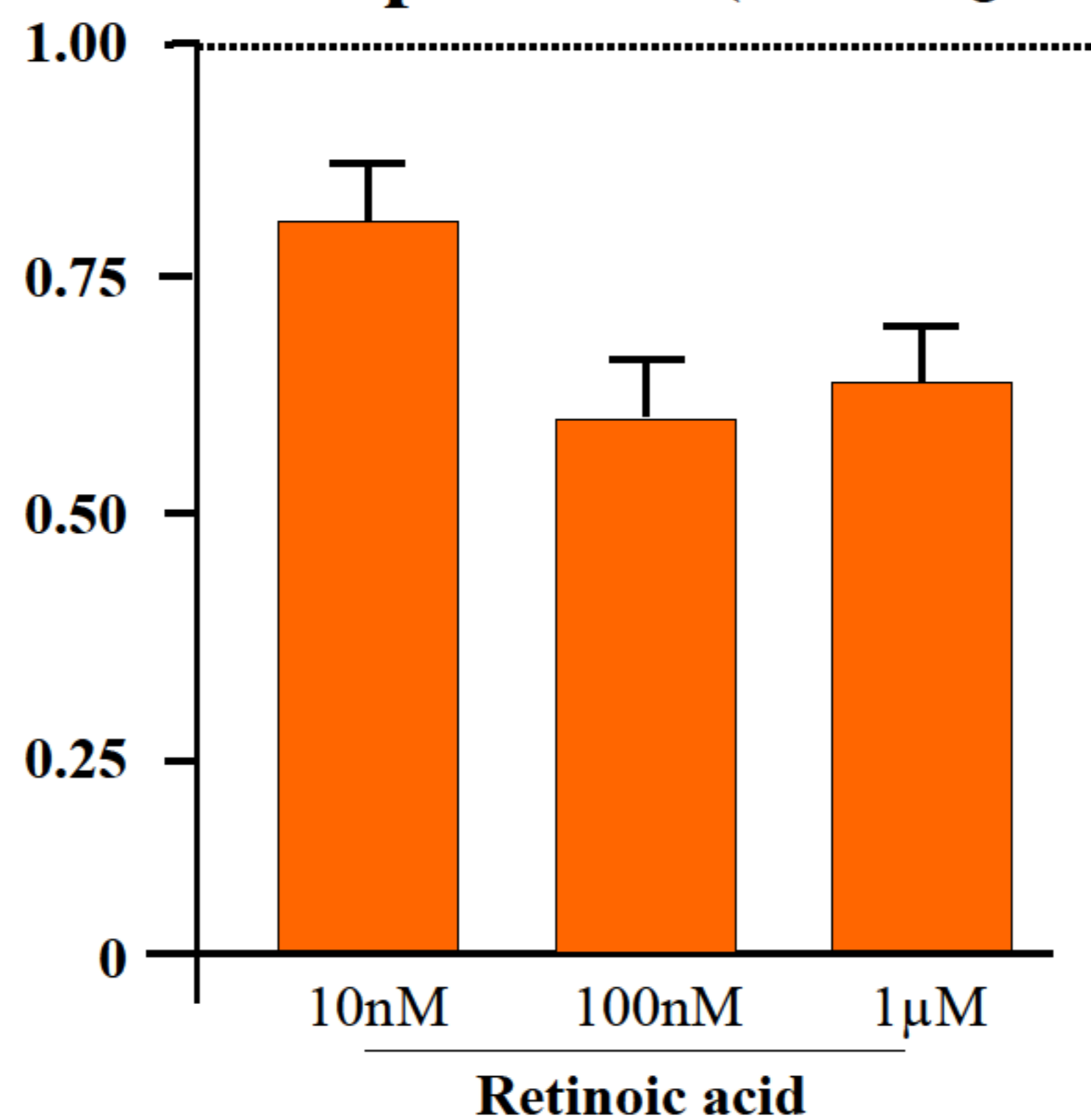
A clear-cut **increase** in spontaneous **cortisol secretion** was observed in **5 adrenal specimens**.

Gene expression analysis revealed a **marked decrease** in **MC2R** expression and an **increase** in **STAR** in wells treated with retinoic acid. **CYP11A** expression was **unchanged** by retinoic acid.

**Cortisol secretion** (% ACTH)



**MC2R expression** (fold change ACTH)



**Retinoic acid** and **ACTH** co-incubation resulted in a **slightly greater cortisol release** and **MC2R inhibition** than ACTH alone

## CONCLUSIONS

Retinoic acid exerts a **stimulatory effect** on adrenal **corticosteroid secretion *in vitro***, **activates STAR** expression and **blunts MC2R transcription**. These findings pave the way to novel avenues of research in patients with **Cushing's syndrome**.

