GnRH agonist 與 GnRH antagonist在卵巢顆粒細胞內的不同作用機轉

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在試管嬰兒的誘導排卵過程中，GnRH agonist與GnRH antagonist已經被廣泛使用來防止 premature LH surge 。目前知道GnRH agonist是經由造成腦下垂體 desensitization 和 GnRH receptor down-regulation而達到抑制性腺刺激素(gonadotropin)分泌的目的。GnRH antagonist則是和體內的 GnRH 直接競爭位在gonadotropic cell membrance上的 receptor ，一旦 antagonist 佔據了 receptor ，血中性腺刺激素分泌濃度就明顯下降。近年來有愈來愈多的研究証明GnRH agonist與GnRH antagonist在不同的身體組織細胞也有不同的生理作用機轉。我們已經知道下視丘和腦下垂體是 GnRH 的主要來源及作用目標組織，然而許多研究指出下視丘外的 GnRH 及腦下垂體外的 GnRH receptor ，存在於生殖系統組織細胞，例如卵巢、子宮內膜組織、胎盤及子宮內膜癌細胞等。 Ortmann and Diedrich 在1999年時發現很多腦下垂體外有GnRH-1 receptor的表現；也有人在人類卵巢(Kakar et al., 1992; Minaretzis et al., 1995; Peng et al., 1994)、黃體組織(Bramley et al., 1987)、顆粒黃體細胞 (Brus et al., 1997) 、排卵前的卵泡顆粒細胞層上 (Choi et al., 2006) 找到 GnRH-1 receptor 的mRNA。也有証據顯示 GnRH 在卵巢內會表現自我調控 (autocrine) 及周邊調控 (paracrine) 的行為去調控卵泡的成長(follicle development)和荷爾蒙的生成 (steroidogenesis) (Andreu et al., 1998; Hsueh and Jones, 1981) 。Lin et al. 在1999年已提到GnRH agonist在卵巢內的desensitization作用是不同於GnRH antagonist。很多研究也發現接受GnRH antagonist治療的女性，其打hCG當天的血清中 estradiol 濃度 (Albano et al., 2000; Olivennes et al., 2000; Roulier et al.,2003) 和卵泡液中 estradiol 濃度 (Garcia-Velascoet al., 2001) 遠比接受 GnRH agonist治療者低許多 (Figure 1) 。所以這就說明了 GnRH agonist與GnRH antagonist在卵巢內存在不同的作用機轉。這也是為什麼用GnRH antagonist比較可以預防卵巢過度反應症候群的原因 (Hsieh et al., 2008; Lin et al., 2007)。

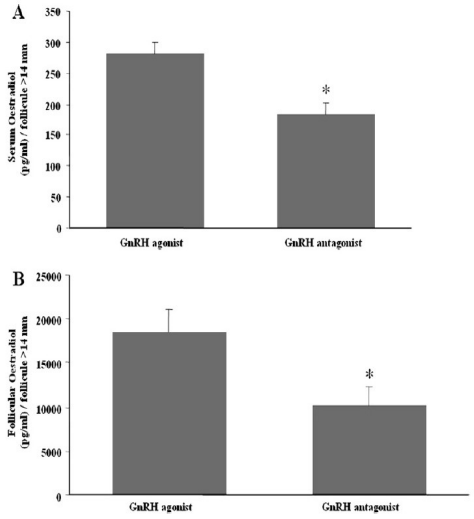


Figure 1 Concentrations of oestradiol in (**A**) serum and (**B**) follicular fluid (follicles >14 mm) in women undergoing gonadotrophin-releasing hormone (GnRH) agonist ($n = 28$) or antagonist ($n = 22$). Oestradiol was determined by radioimmunoassay. Values are mean ± SD. $^*P < 0.05$.

Annie 2010 年便探討了為何GnRH agonist與 GnRH antagonist protocol 的 estradiol 濃度有別的原因：首先卵巢顆粒細胞 (granulose cell) 內的 estradiol 合成是來自於aromatase enzyme expression和cAMP (30–50 adenosine monophosphate) pathway (Detail as figure below) 。而使用GnRH antagonist protocol 這一組病人的卵巢顆粒黃體細胞之 aromatase activity 和 aromatase(CYP19) gene expression 有顯著意義比較低 (Figure 2) 。Garcia-Velascoet 2001 年也提到GnRH antagonist組的卵泡液中之estradiol : testosterone ratio也是比較低。換言之使用GnRH antagonist這一組病人的 estradiol 濃度比較低是由於卵巢顆粒細胞內合成不足，不是鞘細胞 (theca cell) 提供的 androgenic precursors 不足。

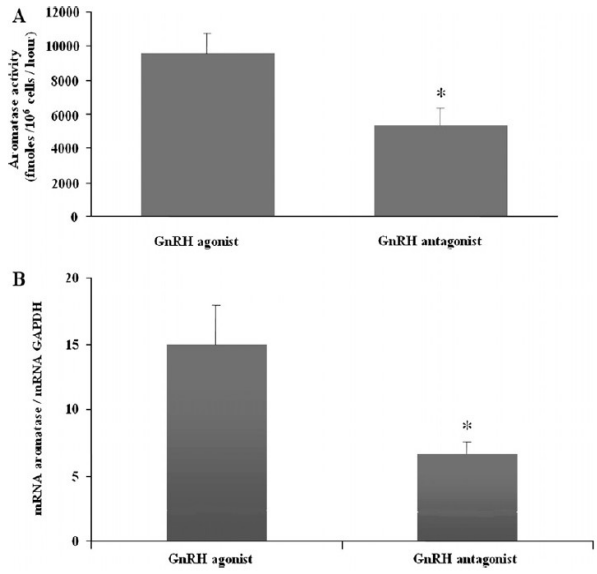
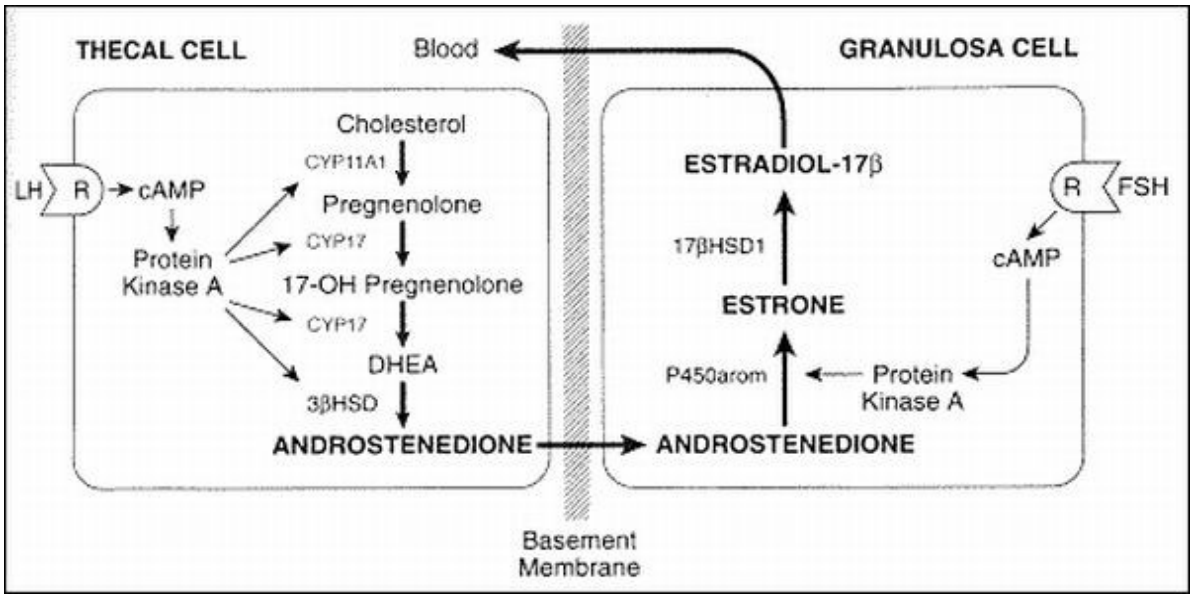
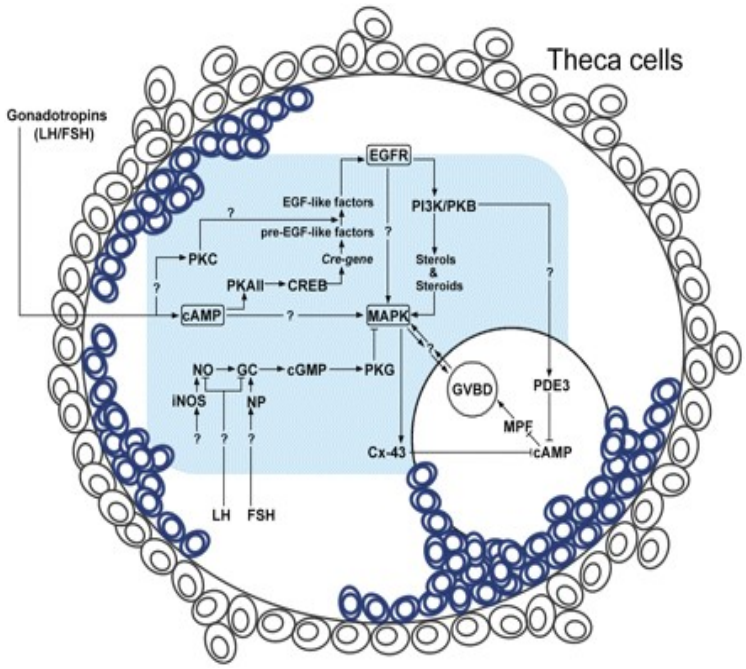
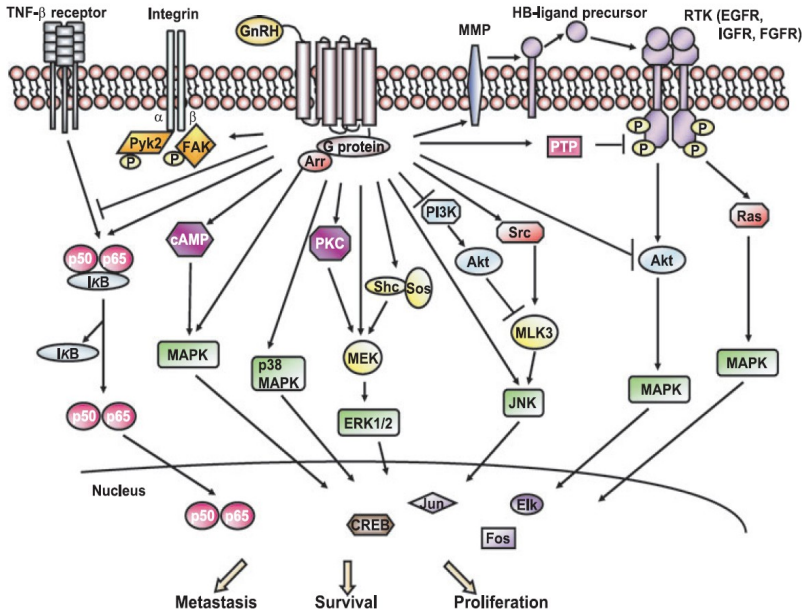


Figure 2 (**A**) Aromatase activity and (**B**) aromatase gene expression in human granulosa lutein cells treated with gonadotrophin-releasing hormone (GnRH) agonist or antagonist. Aromatase activity was quantified by ^3H_2O method. mRNA aromatase were quantified by real-time reverse-transcription PCR and values were normalized to mRNA GAPDH. Values are means ± SD. $^*P < 0.05$.



人類卵巢的GnRH-1 receptor比腦下垂體少 200 倍 (Minaretzis et al., 1995) 。 GnRH-1 receptor 經由活化 Gq/G11 heterotrimeric 蛋白而激活一系列的 mitogen-activated protein kinase 活動 (Figure 3) 。





卵巢上的GnRH-1 receptor並沒有因為使用GnRH agonist或GnRH antagonist後減少。GnRH antagonist像在腦下垂體般透過直接競爭GnRH-1 receptor而達到減少 estradiol 合成；而GnRH agonist則是經由抑制 PKC (protein kinase C) activity(Figure 4) 使得 estradiol 濃度比較高，因為活化PKC會抑制 gonadotrophin-induced steroidogenesis。

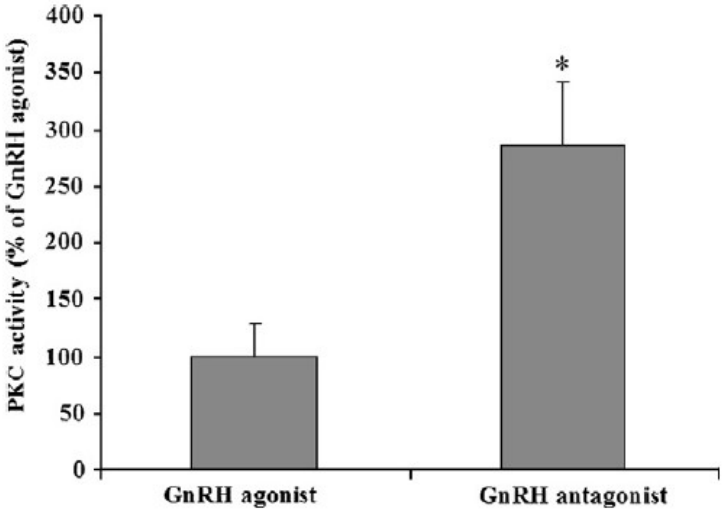


Figure 4 PKC activity in granulosa lutein cells treated with gonadotrophin-releasing hormone (GnRH) agonist or antagonist.

所以從目前有限的文獻資料中已經知道GnRH agonist與GnRH antagonist在卵巢顆粒細胞內有著不同的生理作用機轉，而這也還需要更多的研究去探討証實GnRH的生理、分子及細胞功能機轉。由於GnRH agonist與GnRH antagonist已廣泛的應用於臨床治療，如果我們能更清楚的了解GnRH的整個系統全貌，相信對於未來GnRH的臨床應用，會帶來更適合且更有效的治療。

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