• 計畫中文名稱	高濃度 FSH 引發停經婦女骨質疏鬆之機轉研究與其拮抗劑之探討(I)		
• 計畫英文名稱	Study on the Mechanism of Elevated Fsh-Induced Postmanoposal Osteoporosis and Its Possible Antagonists		
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• 計畫編號	NSC97-3112-B038-003	• 研究方式	學術補助
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• 研究領域	基礎醫學類		
• 研究人員	蔡郁惠,周志銘,楊良友		
• 中文關鍵字	促濾泡激素; 更年期; G-蛋白質 ; 骨母細胞; 蝕骨母細胞; 骨質疏鬆; 骨生成; 骨質流失		
• 英文關鍵字	FSH, G-protein, Gi, Gs, Gαh, osteoblast, osteoclast, osteoporosis postmenopausal, bone formation, bone resorption, bone loss.		
• 中文摘要	促濾泡激素(FSH)是 ，由腦下腺前葉細胞所合成，經由血液促使促濾泡激素釋放激素/促性腺激素釋放素的分 ，進而促使腦下垂體分泌 FSH 及腺的發育和成熟是不可或缺的，分別對女性卵子和男性精子的形成扮演十分重要的角色！FSH 作用在標 ，特別是和生殖相關的細胞上，在與其受體結合後，活化 Gs/c-AMP/ ，而產生後續一連串的細胞內反應。最近我們發現一條新的 FSH 訊息 徑，在大鼠的史托利細胞中，高劑量的 FSH αδ-1/IP3 這條傳遞路徑引發立即性 。這種 FSH 引起的鈣入現象，與細胞內鈣離子的釋放無關。在接近停經期、停經期或是停經後的婦女，以及卵巢不夠成熟或是功能有障礙之女性，或只有極低量的男性賀爾蒙的男性體內，都可發現其體內有高量的 FS 。這些體內有高量 FS ，通常也會有骨骼密度較低甚或骨質疏鬆的現象。根據最近的研究報導，對於促進蝕骨細胞生成，和造成停經後骨質疏鬆的主因，是體內高量的直接作用所造成，而不是雌激素降低所引起。這個現象只發現於較年長的婦女，而不在年長的男性。高量的 FSH 可以活化蝕骨細 Gi 而 Gs，而對於骨母則是沒有任何作用。骨質疏鬆症爲一常見的老年期退化性疾病，亦爲老年期其他骨骼相關疾病之重要危險因子。爲了進一步探討對停經後婦女，血液中高濃度 FSH 對其骨骼系統之影 可能防治之療法，本研究計劃將探討: 獨自在細胞層面上即可直接造成蝕骨細胞之分化，成熟及活化，另外將以 GnRHleuplin 或覆液給予已去除卵巢之 OVX-SAMP8 小母 是否可有效地減緩或抑制骨質疏鬆的發生; (2) 成蝕骨細胞之分化，成熟及活化，其分子機轉又如何? 我們將研究 牽涉到的訊息傳導路徑; (3 雌激素受體功能以及投與異黃酮素如 geni 維他命 C/K，抗氧化物及微量元素等有利於升之物質後，高濃度 FSH 是否還對蝕骨細胞以及骨母細胞之分化，成熟以及活化有影響; c-DNA Arra ，進一步對高 FSH 濃時投與上述實驗所得最好的藥物組合後，對蝕骨細胞和骨母細胞在基因表現上以及蛋白表現之變化; (5) 利 OV (會快速產 骨質疏鬆現象)，探 其對阻斷骨質疏鬆和對骨質密度之影響以及機轉。本計畫將探討 FSH 上升所引發婦女停經後骨質疏鬆的分子機制及找尋預防或治療藥物。本計劃將在高 FSH 濃度下觀察雌激素受體 、異黃酮素(例 geniC 等有利於保持骨質或骨質生成物質之最佳組合 ，是否可預防或干擾蝕骨細胞之生成、成熟和活化，以及骨質疏鬆的發生，期待能進一步找出預防或延緩停經後婦女產生骨質疏鬆症之可行方法。		

• 英文摘要	Follicular stimulating hormone (FSH) is glycolpeptide, synthesized in anteria pituitary cells and released into blood stream in response to the stimulation of FSH releasing hormone (FSHRH)/ Gonadotropine releasing hormone (GnRH). FSH is essential for gonad development and maturation. It plays a crucial role in oogenesis in females and spermatogenesis in males. Its working mechanism is known to activate Gs/c-AMP/PKA signal pathway upon its binding to cell surface receptor of the target cells, mainly the reproduction-related cell types, and leads to the subsequent cellular responses. Recently, we identify a novel FSH signal pathway. Higher doses of FSH induce an immediate calcium-influx in rat Sertoli cells mediated by Gαh/ PLCδ-1/ IP3 pathway. This FSH-induced calcium influx is independent of cellular instore calcium release. Physiologically, the high circulating FSH level is found to be associated with peri-menopausal, menopausal and post-menopausal woman, in addition to premature ovarian failure females as well as males with extremely low androgen levels. Those who with high FSH levels are often associated with low bone density and osteoporosis. Recently, the direct action of elevated circulating FSH level, rather than the decreased estradiol level, was reported to promote osteoclastogenesis and is the main cause of the post-menopausal osteoporosis. This phenomenon is only observed in the elder woman but not in the elder man. Such high FSH level was reported to activate Gi not Gs in the osteoclast but exerts no effect on the osteoblast. Osteoporosis is one of the major physical disorders during aging and a high risk factor for the mortality of bone-related complications in the elderly. To further understand the impact of high FSH level and the prevention of its negative effects on the health of post-menopausal women from occurring, we intend to study: (1) whether elevated FSH level alone is enough to induce the differentiation, maturation and activated function of the osteoclast; If GnRH antagonist leuplin and the fruit extract of Rubus Chingii are effective agents in preventing or delaying osteoporosis from occurring; (2) the molecular mechanism and signaling pathway mediates the FSH-induced osteoclastogenesis and bone mass loss; (3) the effects of estradiol/ estrodiol receptor modulator, or isoflavone genistein, with/without ascorbic acid, Zn and/or other vitamins, in the presence/absence of FSH on the differentiation, maturation and functions of osteoclasts (for bone resorption) as well as osteoblasts (for bone formation); (4) the alterations in gene expression caused by the most effective combination of agents in combating bone loss using microarray and proteomic analysis; (5) The intervention /prevention of osteoporosis with the selected combination of agents using the osteoporosis animal model ovariectomied (OVX-SAMP8) female mice. The data obtained from these elaborated studies will advance our knowledge about the physiological role of elevated FSH level in aging-related bone disorder and help to identify agents capable of reversing the negative effects of high FSH level in the non-reproductive tissues of the elderly. The information may, in turn, provide strategy to combat the aging-related bone lose and allow us to grow old gracefully.