• 計畫中文名稱	中樞神經系統在肥胖型高血壓所扮演的角色: prolactin-releasing peptide 與 leptin		
• 計畫英文名稱	Neuronal mechanisms in obesity-related hypertension: Roles of prolactin-releasing peptide and		
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• 研究人員	黃玲玲		
• 中文關鍵字	高血壓；肥胖；自主神經系統；瘦素；；；；		
• 英文關鍵字	hypertension；obesity；autonomic nervous system；leptin；PrRP；；；		
• 中文摘要	高血壓及其相關的疾病是多年來臺灣地區重要的死亡主因，許多研究顯示肥胖者較易罹患高血壓，但是連結肥胖與高血壓之高相關性的病理機轉至今未明，近年來，在世界各國肥胖盛行率大幅上升，因此包括高血壓在內的各類肥胖相關疾病已成爲重要的公共健康議題，使得這個領域之研究日益重要，許多參與調控體內能量衡定系統之重要訊息分子陸續被發現，這些訊息分子多數是荷爾蒙或神經傳導物質，他們藉由調節神經系統功能達到其調控體內能量衡定之作用，本計畫主持人藉由自己及其他學者之研究結果，於上一份計畫書中提出一假說，能量衡定相關訊息分子藉由對自主神經系統之作用，參與心血管功能之調控，並因此連結肥胖與高血壓之共同病理機轉。該三年計畫獲國家衛生研究院補助，已進行兩年，其研究成果摘要如下。 第一，CART 是一類能量衡定相關訊息分子，我們發現它具有升高血壓的作用，並可能作用於腦幹之自主神經核區。第二，我們建立了高脂飲食引發肥胖(DIO)大鼠動物模式，並發現 leptin, CART 及 PrRP 三類能量衡定相關訊息分子在 DIO 大鼠之血漿及腦脊髓液中濃度上升，證實在能量衡定受擾時，能量衡定相關訊息分子之生物活性亦發生變化。第三，人類高血壓患者血漿中 PrRP 濃度較血壓正常者低，但 CART 濃度則無此變化。此發現進一步確認 PrRP 可能參與心血管功能之調控。第四，我們檢測 leptin 受器在腦幹的分佈情形，發現它分佈於數個與心血管功能相關之核區，例如 NTS, DNMV, RVLM 與 CVLM。第五，我們完成研究 leptin 對位於 DNMV 之副交感節前神經細胞之作用及機轉，發現 leptin 可直接作用於位於 DNMV 之副交感節前神經細胞，藉由調節其細胞膜對鉀離子的通透度而改變細胞興奮性。此外，我們也發現 DIO 小鼠之學習能力較正常小鼠差。這些研究結果引導計畫主持人確認數類能量衡定相關訊息分子參與心血管功能之調控，並將進一步探		

	討其機轉。 PrRP 是由下視丘分離出，爲人類 GPR10 受器或大鼠 UHR 受器之內生性活化劑，初步研究發現它具有促進 prolactin 分泌及抑制進食功能，進一步研究證實 PrRP 亦參與心血管功能之調控，例如，中樞投與 PrRP 造成血壓上升，基因分析研究發現人類 GPR10 受器之變異與血壓有密切相關性，另外，PrRP 神經細胞及受器之分佈亦反應其對心血管功能之調控之重要性。一電生理研究也證實 PrRP 調節 DNMV 內神經傳導活性。這些證據，因此計畫主持人合理地推論 PrRP 作用於腦幹自主神經核區，而調節能量衡定與心血管功能。 Leptin 是一荷爾蒙，由脂肪組織分泌，以負向回饋方式作用於下視丘而調節體內脂肪儲存量。許多證據顯示，人類高血壓患者交感神經活性上升，leptin 對此扮演重要角色。我們的研究亦證實 leptin 受器存在於分佈於腦幹數個與心血管功能相關之核區，因此提出 leptin 可能作用於 NTS, RVLM 或 CVLM，並藉以調節心血管功能。 本計畫的主要假說乃延續上一個計畫，認爲 PrRP 與 leptin 藉由對腦幹自主神經核區之作用，參與心血管功能之調控，並因此連結肥胖與高血壓之共同病理機轉。計畫主持人提出三個研究目標以測試此假說，第一，確認 PrRP 與 leptin 在腦幹自主神經核區之作用位置，第二，研究 PrRP 與 leptin 在腦幹自主神經核區之作用機轉，第三，檢測 PrRP 與 leptin 在原發性與次發性高血壓大鼠之生物活性變化，以了解其關聯性。本計畫的研究成果將有助於瞭解 PrRP 與 leptin 在中樞神經系統調節心血管功能中所扮演的角色及其作用機制，這些基礎研究之成果將有助於肥胖或高血壓之治療藥物的發展。
• 英文摘要	Hypertension and its related diseases have been the leading causes of death in Taiwan. Many people with hypertension are also overweight. The pathogenesis and mechanisms linking these two closely related disease status have not been fully understood. As the prevalence of obesity rises in many countries all over the world, obesity-related diseases, including hypertension, gradually become a major public health problem. Extensive researches have discovered numerous signaling molecules, including hormones and neurotransmitters, capable of regulating energy homeostasis by acting on the central nervous system (CNS). Our previous studies suggested the involvement of these molecules in regulating the cardiovascular homeostasis. The main hypothesis the PI proposed in the currently funded 3-yr project is that the neuronal signaling molecules of energy homeostasis (NSMEHs) link the pathogeneic mechanisms of obesity and hypertension through their actions on the autonomic nervous system. Major accomplishments during the first two years of the granting period are summarized. First, we had reported central cardiovascular pressor effects of cocain- and amphetamine-regulated transcript (CART) peptides, CART 61-102 and CART 55-102, by acting on the brainstem and thus affecting cardiovascular sympathetic activity. Second, the plasma and CSF levels of leptin, CART and prolactin-releasing peptide (PrRP) were altered when the energy homeostasis was altered in high-fat diet-induced obese (DIO) rats. Third, the plasma level of PrRP reduced in hypertensive human subjects, whereas the level of CART was not significantly altered. The findings in human subjects confirmed that the bioactivity of NSMEHs changes upon alterations in the energy and cardiovascular homeostasis and led to the identification of PrRP as a promising NSMEHs candidate for our future study. Fourth, immunoreactivity of leptin receptor, ObR, in the rat brainstem was detected in several nuclei relevant to autonomic cardiovascular regulation, such as the nucleus tractus solitarius (NTS), dorsal motor nucleus of the vagus (DNMV), rostral and caudal ventrolateral medulla (RVLM and CVLM), implying that these nuclei may be

	the target sites of leptin for exerting its cardiovascular effects. Fifth, we have demonstrated that leptin directly acted on the parasympathetic preganglionic neurons of DMNV by affecting membrane permeability to potassium ions. These findings confirmed our hypothesis had brought up the PI's attention on whether and how these NSMEHs play a role in the pathogenesis of hypertension. PrRP was isolated from the hypothalamus as the ligand of an orphan G protein-coupled receptor, GPR10 (human)/UHR (rat), and was functionally identified as prolactin-releasing factors and also involved in the regulation energy homeostasis. Further studies suggested that PrRP plays a role in cardiovascular homeostasis. PrRP administered centrally increased mean arterial pressure in conscious rats. More interestingly, a human genetic study showed an association between GPR10 polymorphisms and blood pressure. PrRP-containing neurons in the CNS of rat distributed exclusively in three areas, the dorsomedial hypothalamic nucleus, NTS and CVLM. These regions are well known to be involved in stress responses and in cardiovascular homeostasis. Further, PrRP receptors were found in the brainstem nuclei believed to be involved in the regulation of cardiovascular reflexes. An electrophysiological study had demonstrated that PrRP modulated synaptic transmission in the rat DMNV. Therefore, it is rational that PrRP may act on the brainstem autonomic nuclei and, thus, be able to regulate both energy and cardiovascular homeostasis. Leptin is a negative feedback signal of body adiposity regulation through its actions in the hypothalamus. Evidences support that leptin contributes to over-activation of the sympathetic nervous system in obese hypertensive subjects. Our previous results demonstrated that ObR-immunoreactivity distributed in several rat brainstem autonomic nuclei. Therefore, we hypothesized that NTS, RVLM and CVLM may be the potential targets in the brainstem for leptin to exhibit their cardiovascular impact. The hypothesis proposed here is that PrRP and leptin are involved in the regulation of both energy homeostasis and blood pressure and thus in relation to the disease status like obesity and hypertension, and autonomic neuronal circuitry in the brainstem involving in the regulation of cardiovascular homeostasis are target structures for PrRP and leptin to act on. Three specific aims are proposed to examine the hypothesis: (1) to locate target sites of PrRP and leptin in the brainstem autonomic nuclei; (2) to examine the cellular mechanisms of PrRP and leptin in neurons of the rat brainstem autonomic nuclei; and (3) to evaluate the bioactivities of PrRP in primary and secondary hypertension models of rats. The completion of these proposed studies will lead to a better understanding toward the medullary neuronal control pathways involved in the signaling relay of PrRP and leptin for energy homeostasis and their interactions with the central cardiovascular regulation.