• 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		
• 計畫英文名稱	Neuronal Mechanisms in Obesity-Related Hypertension		
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• 研究人員	黃玲玲		
• 中文關鍵字	肥胖；高血壓；能量恆定；瘦素；中樞神經系統；自主神經系統		
• 英文關鍵字	obesity；hypertension；energy homeostasis；leptin；central nervous system；autonomic nervous system		
• 中文摘要	肥胖是導致心血管疾病(包括高血壓)的一個重要危險因子，近年來肥胖人口比例不斷成長，使肥胖逐漸成爲一個全球性的健康問題，類似的趨勢也在臺灣出現。因此，研究肥胖相關之生物內生性分子與這些分子所扮演的生理角色及其作用機制已吸引了相當多研究者的興趣與投入，一系列的相關分子因而被發現並引起研究肥胖機制的熱潮。其中，leptin 是由脂肪組織所分泌的一種荷爾蒙，其分泌量與脂肪組織的脂肪儲存量成正比，並且被認爲藉由作用於中樞能量衡定中心下視丘，以負向回饋方式調節脂肪組織的脂肪儲存量。較高的交感神經活性是肥胖型高血壓常見的特徵，而 leptin 被認爲與交感神經活性的昇高有關。許多研究證據也顯示多種參與能量衡定的神經訊息傳遞分子也具備調節心血管或自主神經功能的特性，這些分子包括 orexins, neuropeptide Y, galanin, a-melanocyte-stimulating hormone, corticotropin-releasing hormone, cholecystokinin, glucagon-like peptide-1 以及 prolactin-releasing peptide。本計畫主持人與研究夥伴就對一類促進食慾的分子 orexins 所得的研究發現提出一個假說: 認爲 orexins 與肥胖及高血壓之間有某種關連。神經系統調節機制的高度複雜性與可塑性暗喻著更多與肥胖及高血壓狀態相關之共同內生性分子仍待發掘。 至於那些中樞神經結構參與這些能量衡定之神經訊息分子(在此計畫中簡稱爲 NSMEHs)對心血管功能的調節作用，仍需進一步的研究與探討。根據本計畫主持人與其他學者的研究發現，除了下視丘以外，腦幹與脊髓也可能是 NSMEHs 在中樞神經系統的作用位置，而腦幹與脊髓中的許多核區已知是對調控心血管與自主神經功能扮演重要角色。因此本計畫的主要假說是：NSMEHs 同時參與能量衡定與血壓之調節，因此連繫肥胖與高血壓的疾病狀態，另外，位於腦幹與脊髓的自主神經相關神經核區爲 NSMEHs 影響心血管功能之重要作用位置。爲了提供科學證據		

	以支持此假說，在本計畫中四項研究目標將被執行，包括：(1)探討 NSMEHs 對心血管與自主神經功能的影響，(2)尋找 NSMEHs 在腦幹與脊髓的作用位置，特別是與調控心血管與自主神經功能相關的神經核區，(3)研究 NSMEHs 對腦幹與脊髓的作用位置之神經細胞的作用機制，(4)在飲食引起肥胖(DIO)之動物模式測試此假說。選用此種動物模式是根據研究發現 DIO 動物具血壓升高且其中樞神經系統對 leptin 的敏感度下降，因此 DIO 動物模式爲研究肥胖型高血壓之適當動物模式。 本計畫主持人的初步結果顯示 leptin 作用於位於腦幹之 nucleus of the solitary tracts 核區的神經細胞，引發興奮性膜電位去極化反應，另一項發現是，由中樞投與一類抑制食慾的 neuropeptides，稱爲 peptides of cocaine- and amphetamine-regulated transcript (CART peptides)，有升高血壓與心跳速率的效果，這兩種 NSMEHs，leptin 與 CART peptides，將會在本計劃中深入研究其中樞作用位置與作用機制，其它 NSMEHs 亦將於本計劃中研究。本計畫的研究成果將有助於瞭解 NSMEHs 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	Obesity is one of the leading risk factors of cardiovascular diseases, including hypertension. Obesity is also now one of the major public health problems in the world and an emerging health problem in Taiwan. Extensive research efforts have been focused on discovery of obesity-related endogenous molecules and exploration on their physiological roles and underlying mechanisms of action. A panel of the relevant molecules has been discovered. Among these molecules, leptin is a hormone secreted from adipose tissues. The plasma level of leptin is in proportion to the adiposity and serves as a negative feedback signal of body adiposity by acting on the hypothalamus, a major integrating center for energy homeostasis. Elevated sympathetic activity appears pivotal to obesity-related hypertension and leptin is believed to contribute to the activation of sympathetic nervous system and to the elevated blood pressure. Evidences also shown that many neuronal signaling molecules involving in energy homeostasis are capable of regulating cardiovascular and/or autonomic functions. These molecules include orexins, neuropeptide Y, galanin, a-melanocyte-stimulating hormone, corticotropin-releasing hormone, cholecystokinin, glucagon-like peptide-1 and prolactin-releasing peptide. The principal investigator and former colleagues have hypothesized that obesity-related hypertension may be associated with a pathological status of the feeding-related physiological factors, which also affect the autonomic nervous system (Chen et al, 2000 & Hwang et al, 2001). The well-known complexity and plasticity of neuronal regulations warrant further explorations of the hypothesis on other relevant endogenous molecules. The central neuronal circuitries mediating cardiovascular effects of neuronal signaling molecules of energy homeostasis (NSMEHs) remain to be verified. In addition to the hypothalamus, brain stem and spinal cord seem to be important target sites of NSMEHs based on our and other??s observations. It is well known that several areas in the brain stem and spinal cord are important central structures in the regulation of cardiovascular and autonomic homeostasis. The main hypothesis of this proposal is that the NSMEHs are involved in the regulation of both energy homeostasis and blood pressure and thus autonomic neuronal circuitry in the brainstem and spinal cord involving in the regulation of cardiovascular homeostasis are target structures for the NSMEHs to act on. To provide scientific evidences supporting the hypothesis, studies of the four specific aims proposed in the present proposal will be carried out. The specific aims include 1) to examine effects of the NSMEHs on cardiovascular and autonomic functions; 2) to

	locate target sites of action of the NSMEHs in the brainstem and spinal cord, especially the neuronal circuits involving in the autonomic control of cardiovascular functions; 3) to probe cellular mechanisms of the NSMEHs in the targeting neurons using electrophysiological approaches; and 4) to test the hypothesis in a diet-induced obesity (DIO) animal model. DIO rats was found hypertensive and a reduced central sensitivity to leptin in DIO SD rats was reported. Therefore, the high-fat DIO model mimics the occurrence of clinical obesity in humans and, thus, is adopted in the present proposal. PI??s preliminary observations showed that leptin evoked neuronal depolarization of the neurons in nucleus of the solitary tracts and peptides of cocaine- and amphetamine-regulated transcript (CART peptides), novel anorectic neuropeptides, intracisternally administered caused increases in the arterial pressure and heart rate in rats. These two promising NSMEHs, leptin and CART peptides, will be further studied for their targeting CNS neurons and underlyi