• 計畫中文名稱	芳香烴受體在 NMDA 受體調控神經存活與死亡中所扮演的角色		
• 計畫英文名稱	Roles of the aryl hydrocarbon receptor in the NMDA receptor-mediated neuronal survival and death		
• 系統編號	PG9901-0670	• 研究性質	基礎研究
• 計畫編號	NHRI-EX99-9940NI	• 研究方式	補助(研究/辦理)
• 主管機關	行政院衛生署	• 研究期間	9901 ~ 9912
• 執行機構	台北醫學大學醫學系		
• 年度	99 年	• 研究經費	1500 千元
• 研究領域	基礎醫學類		
• 研究人員	李怡萱,謝奉勳		
• 中文關鍵字	戴奧辛；芳香烴受體；NMDA 受體；憂鬱症；神經死亡；神經退化性疾病；；		
• 英文關鍵字	dioxin；aryl hydrocarbon receptor；NMDA receptor；depression；neuronal death；neurodegenerative disease；；		
• 中文摘要	在精神疾患中，憂鬱症及阿茲海默症在近數十年來的罹患率在全世界都呈現增加的趨勢，病人的年齡層遍及青壯年及老年人，對病人及其家人的生活造成了沉重的負擔；在台灣，自殺在近年來躍居國人十大死因中的第九位，而憂鬱症正是造成自殺的主因。諸多證據指出，神經傳導物質的恆定與神經滋養因子的作用在發生精神疾患病變的腦部中有被擾亂的情況，近來在發展治療憂鬱症及阿茲海默症的神經性藥物策略上，都共同朝向發展可調節興奮性胺基酸傳導物質受體 NMDA (N-methyl-D-aspartic acid) receptor 的活性，及增加腦神經滋養因子(BDNF)基因表現來緩解症狀及延緩疾病的惡化。NMDA 受體爲麩胺酸受體（glutamate receptors）的亞型之一，能透過啓動細胞內訊息傳遞而影響神經細胞的生死存亡，進而廣泛參與在各種腦部功能的維持。NMDA 受體在神經細胞的存活上同時扮演了作用兩個相反的角色，目前主要被認爲與 NMDA 受體所存在的位置有關，位在突觸(synaptic)與外突觸(extrasynaptic)的 NMDA 受體，相對於細胞的存活上分別扮演了有利與不利的角色。然而，NMDA 受體的次單元或是 BDNF 的基因變化，與這些精神疾病發生的原因，至今尚未被釐清。在我們先前的研究中，已發現環境污染物戴奧辛（2,3,7,8-TCDD），其爲對細胞內芳香烴受體 (aryl hydrocarbon receptor, 簡稱 AhR)具高親和力的促效劑(agonist)，當戴奧辛活化 AhR，會藉由 NMDA 受體，進而引發 calcium/calmodulin-dependent protein kinase IV(CaMK-IV)/ CBP signaling 誘使初代培養的大腦皮質神經細胞死亡(Lin et al., 2008)。AhR 又被稱爲戴奧辛受體 (dioxin receptor)，是一在演化上高度被保留的轉錄因子(transcription factor)，會透過提高體內負責代謝外來物質酵素的活性，進行解毒的功用，但對於 AhR 在腦部所扮演的生理功能角色研究，卻一直十分		

	欠缺。AhR 的催動劑 (ligand) 已知有存在於體內和外在的環境中，而最明確的就是常被發現在環境有機污染物中的戴奧辛、多芳香環碳氫化合物 (PAHs)及多氯聯苯 (PCBs)，近年的研究中發現，胚胎時期曝露於存在 AhR 催動劑的環境中，會造成實驗動物的腦部發育遲緩；此外，流行病學上顯示環境中的 AhR 催動劑在人類會引起認知功能缺陷。我們目前正在進行中的研究進一步發現，AhR 的催動劑會增加大腦皮質神經細胞及微膠細胞（microglia）中 NMDA 受體的表現，並提高 NMDA 所造成的興奮性毒性；在我們的持續研究中也發現, 以小干擾 RNA (siRNA) 減少 AhR 於神經細胞中的表現，會降低 NMDA 所誘發的興奮性神經毒性,，且提高 NMDA 所誘發的 cAMP response element binding protein (CREB) 活化而增加下游基因 BDNF 的表現。根據這些結果顯示，AhR 在 NMDA 受體的表達及生理功能上扮演相當重要的角色，這可能成爲環境毒物造成神經系統疾病的重要病理機制。目前所知，我們的研究是首先提出 AhR 能參與 NMDA 受體活性的調節，因此，本計畫的目標旨在於瞭解 AhR 在精神醫學上所扮演的角色，並特別著重於 AhR 所參與調控的 NMDA 受體表現、突觸分佈位置，及 NMDA 影響微膠細胞與神經細胞間相互作用所造成的神經元存亡。本研究的中心假說爲，AhR 是參與 NMDA 受體次單元，例如 NR2A 基因表現的關鍵轉錄因子，並調節 CREB 的轉錄因子活性，進而調節 NMDA 受體所誘導的 BDNF 的神經滋養作用、促進微膠細胞活化及神經細胞死亡。在第一年，我們將研究 AhR 如何調控 NMDA 受體次單元基因表現的分子機轉，並觀測 AhR 基因剔除鼠(AhR KO mice)腦中 NMDA 受體表現的情形；第二年，我們將進一步研究 AhR 如何參與在 NMDA 受體所影響的 BDNF 基因表現，特別是觀察 AhR-CREB-CBP 的相互作用上，並探究 CREB/BDNF signaling 下游的神經化學特性，並觀測 AhR-KO mice 之與 BDNF 有關之正向行爲表現；在第三年中，我們將研究 AhR 在 NMDA 受體活化所引起之細胞死亡中的角色，將特別針對 AhR 對於 NMDA 誘發微膠細胞引起發炎作用而影響神經元存活進行研究。本研究之最終目標乃在於闡明芳香烴受體 AhR 在調控 NMDA 受體活性中所擔任的新角色，所得的結果將不僅能爲 AhR 在腦部所扮演的生理功能開啓一道新視窗，對於有能力活化 AhR 的環境毒物在引起憂鬱症與阿茲海默症的原因上，也提供了重要的線索，並提供環境醫學與精神醫學結合以治療精神疾病的新策略。
• 英文摘要	Mental illness, especially depression and Alzheimer's disease (AD), has affected the quality of life in patients at broad spectrum of age, and in their family members. The incidence rate of these depression and AD has been increasing over the past decade worldwide. Depression is the major cause of suicide, which has become one of the leading causes of death in Taiwan. Ample evidence indicates that neurotransmitter homeostasis as well as neurotrophic support are disrupted in the diseased brains. Recent advances regarding the drug development for depression and AD therapies have converged upon a common strategy, i.e. regulation of the excitatory NMDA (Nmethyl- D-aspartic acid) receptor activity and elevation of brain-derived neurotrophic factor (BDNF) levels. NMDA receptors, a glutamate receptor subfamily that broadly involve in brain function, mediate intracellular signaling for both neuronal survival and death. The mechanisms regarding the paradoxal role of NMDA receptors are attributed to their synaptic and extrasynaptic localization which give rise to beneficial and detrimental effects on the neuronal viability, respectively. However, lack of association between the genetic variation of NMDA receptor subunits or BDNF genes and these diseases makes the etiological mechanism remains unknown. In our previous study, we have demonstrated that

	2,3,7,8-TCDD, the most potent aryl hydrocarbon receptor (AhR) agonist derived from environmental pollutant, induced neuronal death in primary cultured cortical neurons in a NMDA receptor- dependent manner via calcium/calmodulindependent protein kinase IV(CaMK-IV)/CBP signaling (Lin et al., 2008). The AhR, also known as the dioxin receptor, is an evolutionarily conserved ligand-activated transcription factor that mediates xenobiotic enzyme expression for detoxification. However, the physiological role of AhR in mammalian brain function remains unclear. AhR ligands are present in both human body and external environment, and the well-characterized ones are mostly found in the environmental organic pollutants such as dioxins, polyaromatic hydrocarbons (PAHs), and polychlorinated biphenyls (PCBs). Recent studies revealed that prenatal exposure to the environmental AhR ligands is associated with delayed neural development in animal models and cognitive deficits in humans. Our current study further found that AhR ligand upregulates NMDA receptor expression in both cortical neurons and microglia and enhances NMDA excitotoxicity. Moreover, knockdown of AhR expression with siRNA diminishes the NMDA-induced excitotoxicity, and enhances NMDA-induced activation of cAMP response element binding protein (CREB) and downstream BDNF gene expression. To our knowledge, this is the first time that AhR has been linked to the regulation of NMDA receptor activities. Therefore, the aim of this project is to decipher the role of AhR in mental health with special focus on its involvement of NMDA receptor expression, synaptic localization, and NMDA-dependent microglial-neuron interaction for neuronal survival and death, neurochemical features, and psychomotor behavior. Our central hypothesis is that AhR is a key transcription factor for the expression of NMDA receptor subunits, at least NR2A, and a key regulator for CREB activity, thereby differentially regulates the NMDA receptor-mediated excitotoxicity, microglial activation, and BDNF neurotrophism. In the first year, we will examine the genomic mechanism and regional distribution of AhR-mediated NMDA receptor subunit gene expressions in vitro and in vivo. In the second year, we will examine the role of AhR in the NMDA receptor-mediated BDNF gene expression, with special focus on the AhR-CREB-CBP cross talk. The CREB/BDNF-related psychomotor behavior that is often reduced in depression will also be examined. In the third year, we will examine the role of AhR in the NMDA receptor-mediated neuronal death with special focus on the microglia-neuron interaction. The ultimate goal of this project is to delineate the new role of AhR as a key mediator of NMDA receptor activity. The obtained information will not only shed new light on our understanding of the AhR function in the brain, but also provide important clues for the etiology and therapeutic strategies of depression and AD considering AhR-related environmental toxins as potential risk factors for mental diseases.