在嬰兒點頭痙攣病人和紅藻胺酸誘發抽搐之幼鼠其親皮質素釋放激素及細胞激素的表現

The Expression of Corticotropin-Releasing Hormone(CRH) and Cytokines in Patients of Infantile Spasm and in Neonatal Rats with Kainate-Induced Seizure

中文摘要

嬰兒點頭痙攣(IS)是嬰兒時期特有的一種癲癇疾病。病嬰對一般抗痙攣藥物治療效應較差，然而對投與促腎上腺皮質素(ACTH)或類固醇的治療有明顯較佳的效果。ACTH 的分泌主要是受到下視丘的親皮質素釋放激素(CRH)的調控，且已證實 CRH 此神經荷爾蒙(neurohormone)在人類幼年癲癇或幼鼠痙攣的發生扮有相當重要的角色。因而有學者提出「CRH 的過量產生導致 IS 發生」之假說，此外在動物實驗方面，於幼鼠腦室注射 CRH 比起成鼠能更快速的引起痙攣。近年來許多研究發現細胞激素具有調節內分泌的功能，並參與許多中樞神經系統疾病的過程進展。基於以上原因，爲更深入了解 CRH 在癲癇所參與的病理機轉，我們測量 IS 病人其周邊血液 CRH 濃度的變化是否和 IS 有關？或在以紅藻胺酸(KA)引發癲癇的出生後 7 天、14 天、30 天老鼠其抽搐程度的加重是否能使 CRH 和細胞激素(IL-1(, IL-6, TNF-()在周邊或腦中表現增加？實驗結果指出，不論是 IS 病人血漿中 CRH 濃度(0.546(0.184 ng/ml, n=12, p<0.001)或是年齡相符的一般癲癇病人(0.294(0.032 ng/ml, n=13, p<0.01)都較控制組病人(0.135(0.022 ng/ml, n=12)爲高。在注射 KA 後 3 小時的出生 30 天老鼠(P30)其血中 CRH 濃度(0.368(0.06 ng/ml, n=4, p<0.05)明顯較控制組爲高；但在注射 KA 後 1 小時的 P14 天老鼠其血中 CRH 濃度(0.260(0.04 ng/ml, n=6)和控制組比起則無統計上的差異。此外以反轉錄聚合脢連鎖反應方法半定量測量到 CRH mRNA 在 P7、P14 天注射 KA 老鼠的大腦皮質部位之表現量分別較控制組增加了 7.84 倍及 1.55 倍；另外 IL-1(、IL-6、TNF-(mRNA 也在 P7 天注射 KA 老鼠的大腦皮質部位增加表現量。以上結果顯示支持 CRH 的過度產生和 IS 有極大的相關，並推測在腦部發育過程中 CRH 可能是一個致痙攣前驅物(pro-convulsant)，而因癲癇所導致 CRH 在大腦皮質的表現增加，進而活化細胞激素可能導致腦部不正常之過度興奮現象而對癲癇程度的進展極爲重要。

英文摘要

Infantile spasm (IS), is a form of epilepsy specifically occurring at infant s tage, is refractory to conventional anticonvulsant treatment but is exceptiona lly sensitive to adrenocorticotropic hormone (ACTH) treatment. Corticotropin-releasing hormone (CRH), a major regulatory factor of ACTH secretion in pituit

ary, has been implicated as an important neuro-hormone participating in seizure generation particularly in early life of both human and animals. In human, excessive production of CRH is speculated as one of the pathological mechanisms underlying the generation of IS. In animal, intracerebral injection of CRH potently produces seizure behavior since early life. Recently, cytokines also participated in communication between immunity and central nerve system diseases. To further understand the role of CRH in pathological mechanisms of seizure, we investigated whether increased plasma CRH level is associated with IS and whether seizure activity will increase the expression of CRH and cytokines (IL-1(, IL-6 and TNF-() in circulation and in brain of neonatal rats. Plasma CRH level in IS patients (0.546(0.184 ng/ml, n=12, P<0.001) or seizure patients (0.294(0.032 ng/ml, n=13, P<0.01) is significantly higher as compared to control (0.135(0.022 ng/ml, n=12). The plasma CRH level of postnatal 30-day (P30) rats at 3h after kainate (KA)-injection (0.368(0.06 ng/ml, n=4) is significantly higher (p<0.05) than that of control, whereas, plasma CRH level show no statistically difference in P14 rats at 1h after KA-injection (0.260(0.04 ng/ml, n=6) when compare to that of control. Furthermore, an 7.84 and 1.55 fold increased expression of CRH mRNA in cortex was observed in P7 and P14 rats with KA-induced seizure by RT-PCR analysis. In addition, IL-1(, IL-6 and TNF-(mRNA expression were increased in cortex of P7 rats with KA-induced seizure. These data support the hypothesis that over-production of CRH is likely associated with IS, and seizure activity induced by KA may also upregulate the CRH and cytokines expression in neonatal developing brain. Given that CRH is a pro-convulsant in developing brain, increase of CRH in cortex elicited by seizure may further potentiate the progression of the activity of seizure.