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Dextromethorphan(DM) ‹ ` { Ş ⁄W40¥¸¥H⁄W“ ” « D ł ´ K˚¡⁄C«ƒy bfl¥ « e ™‹ ªDMł «Cł{ ⁄ Ć NMDA(N-methyl-D-aspartate)– ¤¯Ø”´ ⁄ l ł ₫D“fl¡C NMDA – ¤¯Ø⁄ voltage-gated ´ ł÷q „D¡ A • ¥ ƒ ⊕‹¡¡Ă˘fi _ † M‰¡⁄¥h•ë¶t˘ ⁄l⁄ ‘y¡ A › P †›M°¿.÷₩[¡ A ƒ † ›M⁄”¶lt ¿ @ « … ₩[•@¤¶B ‹ ¡ ˃†“”›M« › ¤ˆfl A ƒ⁄ o⁄@† ₴C“”¥ ˝ † z ' ¸ ffl†₱Cƒ˝ ƒ÷, DM ¤ ª ƒ ₭œS NMDA – ¤¯Ø⁄ Ø”, £ ₫,¥g ´ † z ¦fl˘Ť˜z⁄˘¡C„L¥h“”† Ş i ф{¡ADM ¥i¥ ₣bƒ ¤ „ « S¤⁄¥ ™« ‰Ł⁄ o' z“”S@¥¸¡Cƒ ƒ„¥ » „ Œ ¯ – ĐM ƒ bo¤|fi ·`™”¥fi„«, £⁄‹ OS_ƒ†ƒ P.¸™”S ' z S¥@¸¡CS › ¥H¥fi„« „ Œ °™«¡AŞQ¥¸kainic acid(KA) ¡Bpentylenetetrazol (PTZ)⁄ ¸γ-hydroxybutyric acid (GHB)»⁄ o ¯ w ' fo§S@A“ƒ†Ş°¥ĐM ¤ ⁄ F , ‹ O S _ ƒ§S“”fi ™G¡• C‰₦¥¡A‹ ¶ i ⁄ @ ¤ B ÷ Q«ø˜ „ L @fl℗ ” z ‹ O S _ • | … v ¯ T , £ † ¡ « P † ›M˘ƒ„˝T¡°AŞ”⁄ ‘› ƒ$“Q ₭{¸⁄ ˇ ´ ¿ »EƒX Q^ (Reverse transcription-polymerase chain reaction¡IRT-PCR)“”⁄ Ł ™ k»PŒZ „ ⁄j, f¥ ₴⁄e-fos¡B-jun¡B bcl-2 ⁄¸bax mRNA ™”™ †{⁄S.. v̄T¡A¤ ¥B⁄ F DM ‹ S_⁄ ₭ª ƒ ł ⁄ ƒ]' z⁄ _“”, ffl ‹gt › M”˃^ ¥\¥¸¡Cƒ ¥ Œ¯™G ƃt{¡C(1) DM ¥iS ¤ †˜14¡B30 ⁄¸60 ⁄ ⁄j“”ƒ „«¡A, gPTZ ' » ⁄ o“generalized clonic-tonic seizure¡Aƒ „ ¤ l“ ” zƒ ‹ ¤^ L ₫¯™”S ¤ S@¥¸¡C(2) DM ¥i¥ H·¥ › SCbcl-2/bax ratio ¤ S¤apoptosis “ ” ₤¥¡˝C ƒƒƒ„b ` { S“™V”¤Ť¥¸⁄W¡AŞ › „ w` DM ¥i‹ ⁄@ƒ ₩ ¡B' ⁄⁄→⁄ ¥B ˇS@¥¸ ⁄p“”S ' zˆ ™«¡A¥i¥¸ƒb„ß⁄j• ł … ¥fi⁄S generalized clonic-tonic seizure¡C

Abstract

Dextromethorphan (DM) is an effectively and widely used nonnarcotic antitussive agent for 40 years. Recent investigations have indicated that DM is an N-methyl-D-aspartate (NMDA) receptor antagonist. In particularly, DM could prevent or inhibit the NMDA receptor-mediated neuropathology including hypoxia-ischemia neurotoxicity and seizure activity. However, most of the studies were conducted on adult animals or adult patients. The anticonvulsant effect of DM on the seizure activity in the developing age is not yet well determined. We, therefore, determined whether DM could effectively attenuate the chemical-induces seizure and brain damage in developing rats. The chemical materials used to induced seizure are pentylenetetrazol (PTZ) and γ-hydroxybutyric acid (GHB), which induce absence-like seizure and generalized clonic-tonic seizure. We also used reverse transcription-polymerase chain reaction (RT-PCR) to determine the effect of DM on the gene expression associated with apoptosis, including c-jun, c-fos, bcl-2 and bax mRNA in the developing brain after PTZ and GHB-induced seizure. Our results showed that (1) DM could attenuate the PTZ induced- generalized clonic-tonic seizure on developing rats with age of 14, 30 or 60 rats, but could not affect the GHB-induced seizure; (2) DM could reverse the PTZ-induced decrease in the bcl-2/bax ratio in the cortex of rats with age of 7 days but not in other age. This result suggest that DM have anticonvulsant effect in treating generalized clonic-tonic seizure of PND 30 and 60 rats. And we can use DM to cure generalized clonic-tonic seizure in older children.

癎(Epilepsy)是一種腦部疾病，全球約有0.5%～1%(0.3%～0.7%)的人口罹患癎症，其中約有10～20%的癎症患者，雖然經過藥物治療，仍然無法控制發作。癎症發作(seizures)可分為局部發作(partial seizures)及全身發作(generalized seizures)。局部發作又可分為單純局部發作(simple partial seizures)，意識清楚的局部發作(partial with complex symptomatology)，局部發作續發全身發作(partial with secondary generalization)。全身發作包括失神發作(Absence seizures)、肌陣攣發作(Myoclonic seizures)、陣攣發作(Clonic seizures)、強直發作(Tonic seizures)、強直陣攣發作(Tonic-clonic seizures)、無張力發作(Atonic seizure)。癎症患者中約有75%的人口在18歲以前發病，其中以兒童發病率最高，而且男性多於女性。癎症發作的原因很多，包括腦部外傷、腦瘤、腦血管疾病、腦部感染、腦部先天畸形、代謝異常、藥物中毒、酒精戒斷、發燒、遺傳因素等。癎症發作的機轉是腦部神經細胞異常放電，導致腦部暫時性的功能障礙。癎症發作的臨床表現，視異常放電的腦區及擴散的範圍而定。

抗癎藥物(antiepileptic drug, AED)的作用機轉，主要是抑制腦部神經細胞異常放電的擴散。目前已知的機轉包括：增加抑制性神經傳導物質GABA的作用(Cherubini et al., 1991；Snead, 1995)，減少興奮性神經傳導物質glutamate的釋放(Ferkany et al., 1988；Kim et al., 1996；Meldrum et al., 1990)，抑制鈉離子通道(sodium channel)，抑制鈣離子通道(calcium channel)，增加GABA的合成，減少GABA的代謝，抑制carbonic anhydrase的活性，抑制GABA的再吸收，抑制GABA transaminase的活性，抑制succinic semialdehyde dehydrogenase的活性，抑制AED的代謝，增加AED的吸收，減少AED的排泄，抑制ethosuximide的代謝，減少AED的血中濃度，增加AED的血中濃度，減少AED的吸收，增加AED的排泄，抑制AED的吸收，減少AED的代謝，增加AED的代謝，抑制AED的排泄

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DM ⁄ w † Q ^„ N MDA (N-methyl-D-aspartate)– ¤ ¯Ø"⁄«D˜ v " S «« œ fS C NMDA – ¤ ¯Ø‹ O¿ †˜ ' ° ¢ i»˜ ¤ ¯Ø (glutamate receptor)"⁄ @ ¡A¥ «e⁄w" ˜ v " S «« œ fS¥ ‹ A pencyclidine (PCP)¡B 3-3 (2-carboxypiperazine-4-yl) propyl- 1- phosphonate (CPP)¡B MK-801¡B 2-amino-5-phosphonopentanoic scid (AP5)¡B .. ¥(Collingridge et al,1989¡B Lodge et al, 1990¡B Folbergrova, 1997¡B Greenamyre et al, 1994)¡C ¥ ' NMDA – ¤ ¯Ø‹ O⁄ @ voltage-gated "" ´ ⁄ ‡q¡„D ¥ƒ†Q‹ ¡⁄ˇfi ¡A† › M ‰ •⁄¥Ÿ¡A¥ ⁄ o¶t ´ ⁄ ‡"¸A› Þ ¿›M‡˜' °… W[¡Aƒ † › M ⁄ ¶t« ...⁄W¿¥ ¢⁄¶@¤ B¡⁄ˇ† ›M"› « › ¤^ƒA ⁄ o ⁄@† $C"¥˝†z' fl¸ƒ†z⁄ˇ ‡(Pumain et al, 1992)¡C b NMDA – ¤ ¯Ø"´ ⁄ ‡q„Bƒ†DM " "†ƒ X ƒ„¤A ƒ DM ‹ OS@¥ ¸ƒb† o ƒ ,m¤ "´N MDA "´ ⁄ ‡q¡„D ⁄ NMDA ´ ⁄ ‡q"¶ } – W†(Church et al., 1994; Takahama et al., 1997)¡C b "«„C¯ o† {¡A DM ¥i¥H¥¸¤ S ¤ NMDA – ¤ ¯Ø„L« ‹ ¡⁄ˇ' †£ ¥˝"", £ ‰,¥˝†z' fl¸ƒ†z¯ ⁄ˇ¡C‹ ƒ p¡(Feşkany et al., 1988)¡A ƒb, £† ¡ flƒi‰æ¸fl ƒ , £ ‰,ˆg ‚a"(Goldberg et al, 1987¡B Prince et al., 1988¡B Tortella et al., 1989, Choi et al., 1987¡B Haberecht et al.,1997)¡C ƒ]ƒ„¡A ƒ† ^ DM ¥¸¤ ‹ ` $ fle flƒ¤ ¥¸"", ¯ ⁄wƒ†‹ • ƒh"†‡ S flSSQ„ ' ¹z¸¯ ¤wŁ¡X¥ «e "«„C¯ ¯ª ¥ ¡A DM ¥i¥H S ¤ '¸· ‰wkainic acid ' ⁄ _ƒ¤ƒ~ "«"" z S@¥ ¸(Church et al ,1985¡B Feeser, 1988¡B Kim et al, 1996¡B Loscher et al, 1993)¡C ¥ ¥˜¡A⁄ ƒ†† \ƒh"^ $, ¯ ¤ ¥¸DM ¤ " v ‡ ƒ¥fi‹« ' zƒ ¤ †"G¤^ L⁄@›P' °¡C ƒ„‹ ª ¤ sp«„K‹ O• Q¶i⁄@¤B‰ Tw DM ‹ OS_¥i¥H· ‰w¥fiƒ~ "«ƒ]^˜"«' ⁄ o"" ' z¡A S ›–¥¸T" ⁄ £P""^˜"«¤ ⁄ o¥fiƒ~⁄ £P ƒ~˜ "" "«¤ †£¥˝' z S Y kian acid (KA), Pentylenetetrazol (PTZ) ⁄¸ gamma-hydroxybutyric acid (GHB)¡C KA ¥i¥H†£¥˝ complex partial seizure with secondary generalized seziutre¡C ƒ PTZ ¥H⁄¸ GHB ¥i¥H ƒb S C f¶ q U†£¥˝¥ ¢fl«' °¯ w' ¸ myoclonic seizures¡ A „ ⁄ "f¶ q fi ¡A¥i⁄ o generalized tonic-clonic seizure (Loscher et al, 1991)¡C

PTZ ‹ O GABA – ¤ ¯Ø"« S fl (antagonist)¡A¥ƒ¥D› n‹ OS@¥ ¸ƒb GABAA – ¤ ¯Ø (GABAA receptor) ⁄W¡C ƒ ' ‹ †«Æ M‰"⁄ GABA – ¤ ¯Ø• |»P–q fl ‹g‹ ˜†¥‰" ˜ 'æ¥X"⁄ GABA †ƒX¡A« h ´ ‡†q „ Þ |¥·¶}ƒ ›Þ ´ ⁄l""†q†z' °(conductance)... W[¡A' ‹ O† › M ‰•ƒ]⁄j¶q· ´ ‡¶¡Jƒ ‡Þ ‹g† ›M¿ †˜' °⁄U› ¡C⁄@¥„ PTZ S@¥ ¸ƒb GABA – ¤ ¯Ø⁄W¡A«h• |" ´_· ´ ⁄l""†q†z' °ƒ ¤ˇfl ‹g† ›M†S–'¿† ˜¡A ›P' z } o' °„q ƒ ⁄ b zƒ ‹ ""†£¥˝¡C¤ PTZ f¶q "S C' " †{¥X¤ ""ƒ ‹ ... ƒ¡¤ ^£‹ ƒP (Loscher et al, 1996, 1991¡B Ruethrich et al, 1996)¡C ƒb S C f¶q¥D› n |†£¥˝¥ ¤ › oS ¡B´ S ¡B«Æ"ˇ' ‹¡B

' CZ.. ¥ ° ℜƒ¡ ‹A ƒ b ƒ ‡ ‚ minimal seizure (» · • Lo)S@fb " fl ¶ q ¥ D › n ‹ Φ£¥ Ÿ¥¥"˘ L⁄O ƒ Ł ¡ B ¥ ¤ › ' ƒæ Ł$@... }¥¡¸A ƒ b ƒ ‡ ‚ major seizure (› « «'¥¸ † ¡ $@)¡Cfb⁄ S « e ™⁄ ˜m ¯ ¥ ¡A$C ¶lq"˝PTZ ' † ¥˝"˝minimal seizure • | ƒ ‡ ƒ absence "˝ƒ ‹ † ¥˝¡A¥ B g¥EEG ' · ŒX"˝ , £ „ q Ì¯‹Ø˘ƒ absence seizure¡Aƒ]ƒ„minimal seizure ' ¥ Ñ "˝‹Oabsence seizure "˝... ƒ¡¡Ł major seizure ƒ]‹ ¥]‹A⁄F generalized tonic-clonic seizure ⁄¸myoclonic seizure¡A' ¥Hƒ‡¥ fl ‹Ø˝ generalized motor seizure "˝... ƒ¡¡Ct z ‰⁄¡Œ‡ ø ˝ ⁄ £ ƒ ®‹˝˝Aseizure ¤ o¥˝"˝ ¤ ƒ‡« ⁄j"˝⁄ ŁP¡Ø j℘⁄Wa absence seizure ⁄ w{‹ ‹O o¥˝ƒb¥C„£ (thalamus) ⁄¸j„£¥ ‰Ł(cortex)⁄S¶¡¡Aƒ generalized seizure ⁄S o¥ ˝ Ø ›n ‹Oƒ ƒb⁄j„£¥ ‰Ł(Coulter et al, 1990¡EEbert et al, 1995¡EPrevett et al, 1995¡ERichards et al, 1995¡ESnead et al, 1995¡ESutor et al, 1995)¡ C ⁄ ß«e‡"˝$i¯ ¥ ¡APTZ "˝"' z¥ ¥H‡ Q @fl™˝S ' ˆ ž˜"˝«⁄¸NMDA – ¤ „"˝«œS flMK-801¡BCPP ' S ¤ (Fisher, 1989, Mares and Haugvicova, 1997, Velisek et al, 1992¡F Loscher et al, 1988, Velisek et al, 1991, Xie et al, 1991)¡Aƒ]ƒ„– ·œPTZ ¥ fl • |† ¥ƒ¤NMDA – ¤ ¯ ØL« ‹ ¡⁄˘(Chimirri et al, 1997¡EPumain et al, 1992¡EVelisek et al, 1997¡B1995)¡C¥ » Œ¯' ¥¸"˝¥t⁄@˝ ^˜"« GHB¥ D n‹GABA "˝¥N´ †£"«succinic semialdehyde,gdehydrogenation S@¥¸ƒ † ¥˝¡CGHB‹OGABAB – ¤ ¯Ø"˝›Pfi˜ fl (agonist) ¡A¥ƒ¥ ¥H$ ¤ GABA "˝˜ 'æ¡A¤^• |$@¥¸ƒbGABA – ¤ ¯Ø⁄W¡Aƒ ¤ ƒX⁄O « Ð ™˝fiz¡CGHB "˝$@¥¸¥ ¥H‡QGABA – ¤ ¯Ø"˝«œS fl (CGP35348) ' «œS (Banerjee et al, 1995a¡F Bernasconi et al, 1992)¡ C ß«ƒe‡⁄ ˜m« ¥X¡ Ab› Y ¤ fl°¥succinic semialdehyde dehydrogenase (¥i–N succinic semialdehyde fiæ˘ƒ¤succinic acid)"˝¥ fi £⁄¡A¤ GHB "˝¿@« • |... W[¤^• |† ¥˝⁄@¤`` $ ⁄W"˝ fl ϑ‹ (Cooper et al, 1996)¡C¤ ƒp¡A⁄ ·...' „B ° ƒ‹• |¿ ‰w (motor and mental retardation)¡Bƒ –i⁄O⁄£¤‹ (hypotonia)¡B„B °¥ ‰ (ataxia)... ¥¡C¥tƒ‡‹ ¤s« ¥X¡G¥ƒ$QY¸GHB ' ⁄ o⁄$' z¡A¥ D n‹Ø ' "xo ' °«D' z $@ (Generalized-nonconvulsion)"˝⁄@˝ ¯ w« ⁄A¡Fƒ b °"„Œ ot{GHB • |⁄ o" fi ¶¡ƒ¤ R⁄¸¥¢fl«"˝"˝‹"A¥H⁄¸¥ EEG ' · ŒX"˝, £ g"„¡˘^ ƒ ¥¢fl«' °¯ w (absence seizure) (Aizawa et al, 1997¡EBanerjee et al, 1992¡B1995b¡EMarescaux et al, 1992¡ESnead et al, 1993¡B1990¡EZhang et al,1991)¡F ƒ ƒb⁄H^ "˝" $ ‹ ¤s⁄ ot{¡A‡ơ ¤ «‹¥¢fl« $@` ⁄£• |"‰– † ¥ƒ¤¥˝' R M ¡IAƒ ƒ]¤ $@ W˜c¡A• |...v ¯ T ·‡fl ⁄O (Penry et al, 1975¡ESato et al, 1976)¡Aƒ]ƒ „b` $ ⁄Wƒ h˘¥¸ ˘$@¥¸⁄ ⁄Sethosuximide¡B valproate... ¥^ ˜"«¤ ∀ ¡C–q⁄W›zƒ ¤¥¡A$ › S˘SQ¥¸† ø ˝ ^˜"«¡ Ab⁄ ŁP ¶lq⁄U¡A¤ ⁄ o¥fiƒ~ ° "«† ¥˝absence-like seizure ⁄¸generalized seizure¡A¤ ‹ DM „ † ø ˝ ' z« ⁄Aƒ‡ƒ $@¥¸¡C

^ ' ' z $@• |„ ,ffl«,g† ›M† ¥˝¶ fi‘ƒ ›P† › M"(McDonald et al, 1993¡ESchmid et al, 1999¡EMoshe, 1998)¡C„I¥h»{‹ ‹Ofl°fiæfl°ƒ ' ›Pfl«,gˆaƒ"¡Aƒ ‹O† "æƒ‡⁄H o†{¡A¥ƒ‹O,g„L† ›M›p „"˝' °ƒ ⁄" (apoptosis) (Johnson, 1995)¡F¤ ƒp kainic acid " fig' ⁄ _"˝,£† › M"¡Aƒ†¯ª † ¡⁄ ‹O¥H

apoptosis " " ⁄ Ł ƒ¶i(Pollard et al, 1994)¡ C ‹ » apoptosis ? ƒ b fl Æ ¯ Ł "«† A´†⁄M′ƒ ″ ⁄ Ł¡ ¥ i † ⁄ ⁄ ‹ ¡¤ G″† M^(apoptosis)»P apoptosis (Duvall & Wyllie, 1986¡ EEllis *et al.*, 1991)¡ C ^ a ƒ‹ ⁄@ " † Q ° " ƒ″¡ A⁄Łƒ|¡ „ † › M † ¥ ¤¡Ra apoptosis fi h ©¥ƒ‰ , †{¶EA ‹ † ƒ›M o fi ¡L {⁄⁄ ¥ H ⁄ ¸ „ ¤°¿Ł⁄U¥$ • ·" ƒ ″ ⁄(McConkey *et al.*, 1990)¡ CApoptosis ƒ b ¥ ˝ " « · " ″‹» ›n'°‹ £ ƒ hl¡"B ƒ † fi "″¡† A›M ƒ p ƒ b F¡›Afifl·Æ · ¥ ˝ " »″¡fl«A, ¥g«Æ†«g⁄,† ›M»Pfl «c‰ƒ† ›M¡A ƒb ¤|"″„ L {⁄† ›M• | ƒ Mapoptosis¡Afl « , g ¤†S¸"¿″¡fl«KO†z„Lƒ „ ⁄ ©Ł¡ƒF ¥¥¡~Aapoptosis ⁄] ¥ i ‰ –¤SK‹ ¸"″cfii¡Bƒ ›'ƒ¿¤.. "″„ L{¥ H ⁄ ¸ , ‰F· ¶⁄¡ Ø⁄™″¥ ¿¯(Ferrer et al,1992,1994; Koike et al, 1994; Oppenheim et al, 1991)¡ CApoptosis ‹ C¥ ƒ]⁻¤ "″⁄ ˇ†¡ C¥ « e ₩™″‰ –ƒ ƒlƒ† †\fh¡ A ¤ƒ℗ S @ ƒ‹¶¡k℗proto-oncogene)' ¸ƒ ″ \«P¶if ƒl (oncogene) "″ Bcl-2 fi a (Bcl-2 family) ' ¸‹ Oimmediate early gene ⁄ ⁄S c-fos¡Bc-jun¡ A ¤ ¥ D › n " ¥\ transcription factor¡ ©b Bcl-2 fi a ⁄⁄¡A¥ i ¥ H « P ¶ ‡ "›Mƒƒ¤‹ ¡ ß ¥‹¡A Bcl-2¡Bbcl-xl¡Bbcl-w… ¥¡ ƒ « P ¶ ‡ ƒ›M′ ™″ƒ ¤ß«h¥] A⁄ƒG bax¡Bbad¡Bbak ⁄ ¸bik¡C⁄ W › z ƒ'™″"† ƒ{¥ †Qff¥ ¡A• | S¥Ç ″ (-COOH terminal) " ' † , ¢Ø‰W¡Bt ›Mi ‰⁄⁄W⁄ ¸ ″ ‰" (Newmeyer, 1994¡ EReed et al, 1994)¡ A• Bcl-2 family † ¤·† ¥ ›n ƒ ¤ ¥ƒfi ¡A• |¥ S ¸ƒ¤⁄ ©,¯Ø (homodimer ' ¸heterodimer)¡ Af A † o ¤ ⁄G¯Ø"″⁄ æ ¤ ƒh¤„Ł M w‹ O ›n» ⁄ ' ¸" ⁄ † ›M¤ « ƒ V p„™″ƒ°″ ‘¡C` ł ¤ »¡¡A• Bcl-2 (¥iS ¤ ƒ ″)"″† ¥ ⁄ ¶q" †{fi ¡ABcl-2/Bcl-2 ⁄ ©,¯Ø"″⁄ æ • |… ₩[¡A‹ „ "″• |«P¤ˇ† ›Mƒ ″™″⁄ ©,¯Ø (¤ ƒp¡ABad/Bad) ⁄ æ · ⁄ ¡C¥ ' †o ¤·† ¥ ⁄ æ "″¯ ⁄ˇ¡A• |¤ˇ–o apoptosis "″ ¤ †QS ¤ ƒ ¡C¥ ¥~¡Afos ⁄]‹ ƒ ″ \« ¶if]⁄l (oncogene) "″ ⁄ © ¡A¥ƒ¥ ¥H¤ †\fh¤ ° Ł™″‹ ¡⁄ˇƒ †yƒ¤ ƒ]⁄ ¶q" †{¡A¥] ‹ A ¥M′łƒ]⁄l¡Bƒ †M¡B¶ t ⁄l¿ @ "″ ¯ ⁄ˇ… ¥¡Fƒ ¤ ⁄ ¶q" †{"″ ƒ]«ofl‹ ƒ S "″S ¤ S@¥ ¿¤ˇ–o fos ¥H ‹ı¨"″⁄ Ł¡¥ ¥{fb† ›M⁄¡C, g fos ƒ]´ ˜¶¥ ¥ "″† ¥ ¡ A ″c⁄W¥]St†\fh"″ leucine zipper (Landschulz et al, 1988)¡ Af „ ˇ ¥i'M Jun "″ leucine zipper S ¸ƒ¤⁄ ©,¯Ø (heterodimer ' ¸homodimer) (Rauscher et al, 1988)¡ A¥ H R¶ transcription "″† ‡tv(Chiu et al, 1988)¡ C· ¿ ƒ † ‡S¥X¥A›Ł¥X¥˝` ƒb› ¤¯"″ƒ „«¡Af†⁄æ, ß j"″ fos " †{ (Wintrip et al, 1997)¡ ƒ £O (stress) ⁄]• |†yƒ¤ fos "′™ †{ (Senba et al, 1994¡ EUmemoto, 1994)¡ C¥ ¥~¡AKA ' »⁄ o "″' z¡Afbƒ¤ƒ ~°"«"″ hippocampus ⁄⁄• |⁄ _*bax* (apoptosis gene) " " " † ¶q..(Wiu[et al, 1999)¡ C ¤ † y ƒ] ¥ i fl ‹ O ƒ] ‹ fl « , g † ›M apoptosis gene ⁄ j¶ x P †"d¡"Af B †ƒ ‰M¡C fb„L¥h ƒ † ‰fi PTZ ⁄ ¸GHB ¤ ¥¯¡A o†{ c-fos¡Bc-jun • |… ₩[(Andre et al, 1998¡ EZhang et al, 1991)¡ Af ‹ O ¤Sƒ †H o†{†o¤ › ƒ]"′‹ ¡ ›'M apoptosis ƒ†^ ¡ C ¶ i ⁄ @ ¤ B – ·Q„k℗a˜fl P"′' z‹ OS_• |… v ¯ T£†¡ apoptosis gene " ƒ"… v̄T¡CS ›¥ PTZ ⁄ ¸GHB ' ƒ£¥"″S ¥ ¸¡Afl SO‹ C¥ ¸ " ¶q† ¥£˝« ø ¡B˜ ¥«"″ ' zƒ ‹ ¡A¤ ‹ ‹ OS_• |… v̄T⁄j, £¥ Ł⁄c-fos¡Bc-jun¡Bbcl-2 ⁄ ¸bax ƒ]" " "†¡{C¥H⁄ ¸DM ‹ OS_¥i¥H

… v ¯ T ƒ] ' z ⁄ _ " " , fl«¡¸©† ›Mƒ"⁄ ` " ¥ \ ¥ ¸

‹ ª ¤ s § fi ˘ P„Œ¯/Ł“k

⁄@¡ B „ Œ ¯ Š fi˘

(⁄@)¡ B Œ¯ ° " « ¿¤ •‰

ƒ Ł»„ Œ ' ¤ ˜ ¥ ¿ Š Sprague-Dawley „ « ‹ O ` ° ¶ Œ‹ " «• | ⁄ Š 200 ¤ 250 ⁄ ‰ Š J ñ ¥ ¥ ¥ ¶ A ¤ ¥ ˝ † £ « Æ i ƒ¡ AA• ƒ ł ¥ ˜ „ « fi „ Œ ⁄ ˜ ℘ „ ¡ A ⁄ † ¡ ¥ « h fl ⁄ Ú Š ¥ ¸ Š Œ t ”

(⁄G)¡ B Œ¯ ⁄ Łk

1. PTZ ⁄ ф „ «⁄ Š ' z ƒ ‹ … ⁄ ƒ ¸ ˜ ƒ

ƒ Ł»„ Œ „ ¥ ⁄ U " fi g PTZ « Æ " ” ƒ „ «⁄ Š ƒ ‹ … ƒ ¡ ⁄ fl „ ¡ A ¥ D n ‹ O ¤ Wolfgang L.(1996, 1991) ⁄ ¸ Hilmi U. (1996) ⁄ † „ ⁄ Š · y z ¡ Œ PTZ " fi g ƒ ¥ X ¥ ˝ ⁄ … ⁄ ƒ Ł P († ˜ 7 ¡ B 14 ¡ B 30 ¡ B 60 ⁄) ⁄ Š ƒ „ « ¥ « Æ • | Š e † { ⁄ U ƒ C fl g " ¸ A ¤ ¤ ˜ Y › « « ¤ ¥ ƒ – N ‹ … ⁄ ƒ ¸ 5 fl ¯ ¡ G

† ˜ „ s fl • L ¯ ⁄ (ňo pentylenetetrazol-induced phenomena)

† ˜ 1 fl • † Š – ' ƒ ‹ (" = automatisms)

¤ ƒ p ¡ G k ˜ p B ‹ ` ¸ y Š ¡ B ¥ ⁄ ¡ A ƒ b ƒ „ ¥ fl ‹ O ¥ H ˜ [„ Š

† ˜ 2 fl • « D ¤ « (atypical minimal seizures)

¤ ƒ p ¡ G … Š ¡ B « Æ " ' ¡ B ‹ C ˜ ¸ Z A ƒ b ƒ „ ¥ fl ¯ O ¥ H ˜ [„ ´ … Š

« Æ " ˘ ' ‹ ‹ •

† ˜ 3 fl • » · • L ¤ (minimal seizures)

¤ ƒ p ¡ G « e " ƒ (Ł † ¸ fl ¥)

† ˜ 4 fl • › « « ¤ (major seizures)

¤ ƒ p ¡ ¤ ˜ (¶ ¶]) ¡ B · " a (‹ 14d) ¡ B ƒ Ł (⁄ £ fl fl ,) ¥ B

¡ B fl ¥ Ł O (Š ƒ „ « Š _ ¤ , ‹ ƒ A ' k æ Š U ƒ G ¶ ¶ ¤ q

°)

† ˜ 5 fl • ¥ † ¡ ¤ (complete major seizures)

¤ ƒ p ¡ G ¥ ¤ › ' (¥ ¶ ˘ ' ‹) ƒ æ H } Š ¤ (⁄ £ fl fl ,) ¥

¥ ' ‹ I ¥ · " fl ¶ ¶ q | ⁄ z , ƒ x (¤ j fl P " " w ƒ ° « … ƒ ¡ – N ¥ „ ¥ ¶ ¤ ' † ˜ † ˜ ⁄ x ¸ fl Æ „

" ' ¥imajor seizure or motor seizure)¡ F ƒ S C fl¶'' ⁄ z„_ß'™M%(w¤ ƒ‹ … ƒ † ¥Ì'
„ F ¤ †⁄)ÏfiÁ ƒ„ '†G • | ƒ] ¥¥"™⁄⁄ ƒ£Pƒ ƒ † ¤ · Ð£fi‡ÞÁS‹ G ƒ b ¥ » Œ¯PŸŽ‹'Ì¥·fl¶•q|¤
⁄ …˘ƒ ƒ†' ‰ ª¡G

7 ⁄ ¡G " ¶lq‹ 90mg/kg

14 ⁄ ¡G " ¶lq‹ 90mg/kg¡AS C fl¶kq 40mg/kg

30 ⁄ ¡G " ¶lq‹ 90mg/kg¡AS C fl¶kq 60mg/kg

60 ⁄ ¡G " ¶lq‹ 90mg/kg¡AS C fl¶kq 60mg/kg

2 GHB ⁄ o ƒ „«'⁄S zƒ ‹ … ƒ¡⁄ ¸ Ì„

ƒ b ¥ »Œ„¯ ¥ Ù"™GfiflgB «Æ™"ƒ ⁄S‹ … ƒ¡˘ ƒ„ ⁄ fl¯¡A¥ D n‹«O Wolfgang L.(1996)⁄ †„
⁄S· y¤z¡ŒGHB " fl¤gƒ ¥ X ¥ ˝ ⁄ …˘(†£ƒÞ¡Bl4¡B30¡B60 ⁄)⁄S¥fi„«¥ «Æ• |S ¢{⁄Uƒ C fl¤"¡AS Y R⁄⁄£ °
(immobility)¡B‰ ⁄ (staring)¡B› †¡' z(facial myoclonus)⁄¸⁄£ –™"‹ ˜y¡B• k¤(vibrissal twitching) ¥ °
S@¡C¥ ' ‹ ¥·GHB ' »⁄ o™" °™«ƒ ‹ (SY™ ‡ fi ¶¡ƒ®R ⁄¸¥ fl«™"™‹"A)¥H⁄¸¥ EEG ' ·œ¥X™", £ ¤™i
„ ˘ ^ƒ¥ fl«' ° ¯ (wbsence seizure)(Marescaux et al, 1992¡BSnead et al, 1993¡B1990¡BZhang et al,1991)¡A
ƒ] ƒ „ ¥„Œ£ ⁄ F ¿ Ð£ŽZd »⁄ o' z™" °™«.. ƒ¡,' ⁄'™ " fl¶kq0100mg/kg(' ƒ†·œ, ⁄ …˘⁄S„«
S¡ƒP)¡C

3.S › ⁄ SO ⁄'¥ ¥˝«Æ†˜7¡Bl4¡B30 ⁄¸60 ⁄ ⁄S¥ ‡`ƒ „ « ¥ ⁄U¥"™fiq › „Q(normal saline)(––
¤ †)¡BDM 10mg/kg¡B30mg/kg¡B¸50mg/kg(„ Œ †)¡A30 ⁄ ˜`«Æ¡AƒA¥ ⁄U ⁄'KA ¡BPTZ '¸GHB (¤
⁄ …˘£¡ƒA¥ ¸" " fl¶kq£P¡F¥BƒP£,⁄ …˘⁄S¥fi„«⁄ SO‹ ¥· " ¶lq⁄¸S C fl¶p£‹ ø760 ƒ)¥H»⁄ ¯ wflg
"‹⁄S†£¥˝¡C‹ ¿ ˘ ⁄ 1 ⁄pfi ¡A¤ ^ † ¥£X†{ƒU" ' ƒz‹ ¥fi„«S ƒ…˘⁄ æ (ratio)¡B.. æ·(latency)⁄¸¥X
†{ƒ,…˘(frequency)¡C

¥~¡A⁄]¿ SQ¥¸GHB ¤ »⁄ o¥ fl«' ° oS@"™†£¥˝¤ ⁄F, DM‹ OS_¥i¥H· ‰w'¸S ¤ ƒ„" «‹"A
"™"' z¡C

(⁄T) °™«˜ ª„¡G

¥ » Œ¯' ¤˜¥¸⁄SSprague-Dawley „«' ‹ ¥·PTZ '¸GHB 2 ⁄pfi «Æ–N¤ ´ _Y˜ ª„¤œ,£¡AƒA¤
⁄ £P,£ ˘(cortex¡Bhippocampus…)⁄ " ,¸ƒbeppendorff⁄⁄¡A¶ ƒs' -70¢ J ‰pC

(⁄›) »·œƒU› ƒ ƒb7¡Bl4¡B30 ⁄¸60 ⁄ ƒ ⁄S¡,£¥ ‰Ł"™" †{¡G

‹ ' œ ` A ¤ ¥ ¿ PTZ(90mg/kg)／ ○ ƒ „ « £¥´¦A ∠ƒO S _ • | „ ／j bcl¥¿ bax¿B c-fos¡Bc-jun ¥ ƒ† ¥´… v̄T¡ F ¥／DM " " „／' O S•S| ¤ ¦· apoptosis "”† ¥´¡Cƒ]ƒ S › ¤ ¥ ¿／ Se " fl¶qPTZ／ _' z／S ° " « ' ˜"”„„„«£¡A¤ „ Œ ¯ †] › ¤£3H¥¡SYtime course †¡B2／fi sample †／¿24／fi sample †¡C¤ ‹ I ¥／¦Bƒ¡"«¤^／£‹ ƒP¡Cƒbtime course †／¡A¥ i／ƒ6 " †S¦AS¥• − − ¤† (¥ ... ¥ · ¥ ƒ¡Control¡F)¡F • • ‹ O／ S‹ normal saline (NS¡FN) 1／fi ¡B2／fi ／¿24／fi « Æ ˜ ° ‹„¤pe¥£¥•¡ A ‹ ¥·^ ˜ " « S／£¦AB2／fi ／¿24／fi sample † ¦¥i ƒ¤ ‹ ¥·• NS¡F• PTZ¡F• DM10 mg/kg¡F• DM 30 mg/kg¡F• DM 50 mg/kg¡ A ¤ ^ ／ S O2／†fi ／¿†˜24／fi ˜ ° ‹ ¤œ¡£C／S « Æ ' ¤ œ／¡£¥mRNA¡ »M¥S"¥¿ RT-PCR ¤／ "R¡A¥ H F, ‹ ¥·PTZ ' ／○S z ƒ‹¡A‹ O S _ • .|.v,¯fH¤¡"”fl ‹g† M／S ƒ ¦" ¡†C

1. RNA "” ¤œ
   a. −N' » tissue samples¡] ¤ fl ¶ q ' ˆ˜"«／£¦A¶P£ "‹ 50~100mg¡ ˆm' eppendorff／¡C
   b. ¥ {J1ml TRIzol¡C
   c. ¥Hk ª ¿ i · ¸ ª¿¡ifi¤ ‹tissue ‹ ／ ¡C
   d. ' æ ƒ k¤·(15~30¢J) R¸m5／ ˜`¡C
   e. ƒA¥ {J0.2ml chloroform¡C
   f. ¥¿／ »•m15 ‹ ¡C
   g. ' æ ƒ k¤·•／ R¸m2-3／ ˜`¡C
   h. ¥H12000rpm ´ ／ 15／ ˜`¡A4¢J¡C
   i. −N／ W † M¶GfI • s"” eppendorff／／¡C
   j. ¥ {J500λ¡]1λ=1μl¡ ^isopropyl alcohol¡C
   k. ' æ ƒ b « · ¯•／10 R¸m`¡C
   l. ¥H12000rpm ´ ／ 10／ ˜`¡A4¢J¡C
   m. † ¥ h W†¦M¶GÆ−¡¡^C
   n. ¥H75¢Malcohol 1ml wash
      ¡]TRIzol¡GAlc = 1¡Gl¡ ^
   o. ¥H¡ 7500rpm ´ ／ 10／ ˜`¡A4¢J¡C
   p. † ¥ h W†¦M¶GÆ−¡¡^A¥¿ Vacaum fl u " ¯fi¡Œ

q. −N20µl ⁄§TE ¥ [⁄ Jfi⁄§Esample ⁄⁄¡Apipeting¡C

r. ¤ œ @¤¡˙]1µl¡ ^œO.D. ›¨¡C

2. ·œO.D.

a. ¤œ1µl RNA ¥ ⁄J69µl TE ⁄⁄

(1µl RNA+ 69µl Q ⁄ ⇒70µl¡ i }˜70 › ¿j¡^

b. ¥HTE • § @ … •˙ ⁄DGD œ›¨¡C

2. RNA ⁄ ˇ ´¿§@¥ ¸

a. ƒb200 ml ""eppendorff ⁄ ⁄ ¥⁄J

RNA	2µg
oligo dT$^{12-18}$ primer¡]500µg/ml¡^	1µl
Milli-Q water ,	¤ƒ12µl

b. 'æ⁄JGeneAmp PCR system 9600 (Perkin Elmer)¡A70¢J¡C

c. ƒA¥ ⁄J5X First Strand buffer 4µl

0.1 M DTT	2µl
10 mM dNTP	1µl

d. † V ƒ X¡¡C

e. ƒA¥ ⁄J1µl Super Script II¡C

f. † V ƒ X¡¤ˆ ˆ § C ‡ ´¥H ⁄ £ ¥ h ƒA" ⁄W"•»†G¡C

g. 'æ⁄JPerkin Elmer GeneAmp PCR system(9600)⁄⁄

42¢J¡B50 ⁄ ˜` → ƒ XH70¢J¡B15 ⁄ ˜ ` ¥ h ƒ ˆ ƒC ‹ ¡'°

3. » E ƒ X Q $´Œ⁄ˇ ‡

a. ƒb200 ml ""eppendorff ⁄ ⁄ ¥⁄J

Reagent	**Stock conc.**	**Final conc.**
$MgCl_2$	50mM	2µg
PCR buffer	10X	1X
dNTP	25mM	0.25mM
primer (sence)	20µM	0.4µM
primer (anti-sence)	20µM	0.4µM
Taq polymerase	5U/µl	0.025U/µl
DNA		2µl

Milli-Q warter

Total 25µl

b. ¥HGeneAmp PCR System 2400¡]Perkin Elmer¡ ^ ¶ƒPCR¡C

4. ^ £ fl ƒ„q"a

a. ¤œ2g agarose ' æ ' ⁄ T ¤ ¡C~⁄⁄

b. ¥ ⁄J0.5X TBE 150ml(ƒ„gel conc.‹ 2%)¡C

c. • Li¥[... ¤ ˘ ¤ § „ ¥ ⁄,¡Cƒ¤‡z'œ"‹

d. ¥Hstir bar ¯ ' ¤ ¤ § N «ƒ50~60¢J¡C

e. ¥ ⁄JEtBr¡]10 mg/ml¡^15 µl¡C

f. › ¸ ⁄ J » s ‡ ˘ £fltrayƒ¡"A ¡⁄Womb¡A« ¤ fi'T¡C

g. § fi'T⁄§^ £ fl fi‰ƒJ„ q ª...⁄⁄¡Aƒ A[⁄Jbuffer¡C

h. −NDNA marker ⁄ ¸PCR product ⁄ §'loading dye § ¡ ⁄ †VƒX

¡AƒAload ƒ ƒ⁄§well ⁄⁄¡C

i. ¥ H ‹ _ „ F ... ˘ ƒ•−N ¤t"† G ¡CU¤

...˘ † ¿p/Ł"k

ƒ b ° " « „ Œ one-way ANOVA with Newman-Keuls test ¤ ⁄ æßPTZ 'MDM ƒ ¶ (PTZ vs. DM10¡BPTZ vs. DM30¡BPTZ vs. DM50) o ¥ ' "z. æ·(latency)‹ OS ƒ‡† ¸› p N,pF ¥¥¡A¤˘ ¥ ¸one-way ANOVA with Chi-square test ¥h⁄ æßPTZ 'MDM ƒ ¶ ƒ‡ o ¥ ' "z ƒ...˘⁄æ¤ (ratio) ‹ OS ƒ‡† ¸›p⁄W""• Nq¡C

„ Œ¯ † G»P/ "R

⁄@¡B‹ ¥·PTZ ⁄§„ Œ ¯ °†"«

(1) ¥X¥"« Æ˜7 ⁄ ƒ„"«"ƒ ‹ ... ƒ¡˘[„

ƒbPTZ " fl¶(90mg/kg)⁄U¡A⁄ ‡¡⁄ ""ƒ „«• †£¥"¥ ¤ ›' ‹(¥ †˘' ‹)ƒ æ H }oS¸@(⁄£ fl fl¥)""− §¸¡Cƒb‡ " • |¥ ¥"§ ¡B´ § ""† ¶H¡F− ⁄ U « §·N|ƒ‡«Æ"˘' ‹""†£¥"⁄§«Æ• |¶} ' l ¥·""¥X†{¥ ¤ ›' ‹(¥ †˘' ‹)ƒ æ H }oS¸@(⁄ £ fl fl,)¥¸¥ †˘ƒ Æ ¡Aƒ „ † ¶H˜ Y «fi• |⁄@ " ‰ « ø ˜ ¤ ´_¡CY›Y¥‹¥„⁄U‹ ¥·DM 10mg/kg¡B30mg/kg¡B' ¸50mg/kg¡A ¥¤ 30 ⁄ ˜`«ÆƒA"` figPTZ ¤ » ⁄ ' zfl ¶‹⁄§†£¥"¡C ¸ ˘ „ 1 ⁄pfi ¡A o†{' z""− §¸¤ ¤Sƒ‡ − § ¡A‰·• |¥ ·

" " ¥ X † { ¥¤(¥'†˘'‹ ‹)ƒ æ H }¯(¿ ÐSŒfl,)¥¿¥ †˘ƒ Œ¡ A ƒ"†{¶ H ˜ Y › « fi ƒ•|«ø˜ ¤
´ _ Ÿ°ŗG„

(2) ¥X¥ ˝ Æ†14 ⁄ ƒ„Ÿ"ƒ ‹ … ƒ¡˘[„

ƒbPTZ Š C fl¶(40mg/kg)⁄U¡A⁄ j †⁄"ƒ „«•|¥ †£¥˝´ Š ¡A⁄Š«ÆƒbƒA¥ Ÿ{«Æ"˘' ‹ ¥†{¶H¡C
› Y ‹ O ¥ Ÿ¥DM¥10mg/kg¡B30mg/kg¡B'¸50mg/kg¡A ¥¤ 30 ⁄ ˜`«ÆƒA" figPTZ ¤ » ' z
fl ‹⁄ $£¥˝¡C @˘ ƒ 1 ⁄pfi ¡A¥ „Œ¯ †ðG{ z"–¡Š¸¤^¤Sƒ¡A¥oŠ¥‰†¸p †"G–o
"¡«Æ"˘' ‹"ƒ…˘ƒ'Œ…ª‰[(Table 12) (ratio ¥ 1/6 … ‰[ƒ 6/6)¡A¥ifl „ 14 ⁄ "ƒ „«ƒ ¤¥¡A
DM "" „'•|ƒ†‹ ±°""¶ ƒV¡R ¥·PTZ " ¶lq(90mg/kg)«Æ¡A⁄ j †⁄"ƒ „«• •|†£¥˝¥ ¤ › (¥‹|
"˘' ‹)ƒ æ H }¯(¿ ÐSŒfl,)¥"– $¸¿Cfb› Ł ¶'‹l¥·fi ¡ A|¥ o¥˝Š ¡B´ Š " ƒ{¶H¡F– ⁄U
¤ « Š·N|ƒ†«Æ"˘' ‹"ƒ£¥˝¡A⁄Š«Æ¶ } ' ¥ " " ¥ X † { ¥¤(¥'†˘'‹ ‹)ƒ æ H }¯(¿ ÐSŒ@
fl ¥)⁄¿¥ †˘ƒ Œ¡ A ƒ"†{¶ H ˜ Y «fi⁄ ‰Ð¾« ø ˜ ¤ ´ ¡ŸC›°¥„¥ ¥ ⁄UÐDM¥10mg/kg¡B
30mg/kg¡B'¸50mg/kg¡A ¥¤ 30 ⁄ ˜`«ÆƒA" figPTZ ¤ » ' z fl"‹ $£¥˝¡C @˘ ƒ 1 ⁄pfi ¡A
o†{DM ¥i' ‰w¥ ¤ › ƒ æ H }¯"¸"fi›¶‰(Table 25)

(3) ¥X¥ ˝ Æ†30 ⁄ ƒ„Ÿ"ƒ ‹ … ƒ¡˘[„

ƒb¤ ¥·PTZ Š C fl¶(60mg/kg)«Æ¡A⁄ j †⁄ƒ «ƒb¥·^˜ fl⁄£⁄[¡AŠY•|†£¥˝´ Š ¡B«Æ"˘' ‹
¥†{¶H¡C› Y ‹ O ¥ Ÿ¥« ‹ŒI¥flDM 10mg/kg¡B30mg/kg¡B'¸50mg/kg¡A ¥¤ 30 ⁄ ˜`«ÆƒA" fig
PTZ ¤ » ' z fl"‹ $£¥˝¡C @˘ ƒ 1 ⁄pfi ¡A¥ „Œ¯ †ðG{DM ¥i' ‰w´ Š Š@"˝fi ¶¡
(Table 7)¡F‹ ¥· " ¶lqPTZ (90mg/kg)«Æ¡A⁄ j †⁄"ƒ „«•|†£¥˝¥ ¤ › (¥‹†˘' ‹)ƒ æ H }¯¸
Š@(⁄ £ fl fl,)¥"– $¸¿Cfb¤ ¥·^˜"«⁄£⁄[¡ A|¥ ƒ†´ Š " ƒ{¶H¡F– ⁄U¤ « Š·N|ƒ†Š "ƒ†£¥˝¡A
⁄Š«Æ•|ƒ†´ _ ´ ˜ "˝ " ¥ ¤›'(¥ †˘' ‹)ƒ æ H }¯(¿ ÐSŒfl,)¥¿¥ †˘ƒ Œ¡ A ƒ"†{¶ H Y ›«
fi •|⁄ ‰%« ø ˜ ¤ ´ ¡ŸC›°¥„¥ ¥ ⁄UÐDM¥10mg/kg¡B30mg/kg¡B'¸50mg/kg¡A ¥¤ 30 ⁄ ˜`
«ÆƒA" figPTZ ¤ » ' z fl"‹ $£¥˝¡C @˘ ƒ 1 ⁄pfi ¡A o†{DM ¥i· ⁄ o¥˝ƒb Ł¡B¥ †˘ƒE
† ⁄¿¥ ¤ › (¥‹†˘' ‹)ƒ æ H }¯(¿ ÐSŒfl,)¥Š ƒ.˘(Table 18¡B22¡B26)¡Cƒ „ Š ¡B´ Š ⁄¸
«Æ"˘' ‹"˝ †{– ¡ Š ¸¤^¤Sƒ¡C¥ÐŠß⁄%ƒ „« Š@' z"ƒ‹ fl ⁄ ‰%« ø ˜ ¤ ¶i† ⁄ ¡C⁄æ
,ß¤ ¥·PTZ⁄¸DM † ƒ „«" Š@fl¯…˘(score)¡A o†{DM ¥i› ŠC " ¶lqƒ „«' z"†£¥˝¡C

(4) ¥X¥ ˝ Æ†60 ⁄ ƒ„Ÿ"ƒ ‹ … ƒ¡˘[„

ƒbPTZ§ C fl¶(60mg/kg)«Æ¡Cƒb† " < I ¥ ˆ˜¡"Æ⁄£⁄]Ł † ¡ ⁄ ƒ „ §Y¡• Ą†£¥§ Æ¶§ 'l
¥ X † { ¥ ¤ ›¡ Æ§– ⁄ U ¤ « § · N ƒ«Æ€˜ › Y «"Ø†¥{ ¶ŒÐM 10mg/kg¡B30mg/kg¡B'¸
50mg/kg¡A ¥ 30⁄ ˜`«Æƒ A "fiĢPTZ¤ » ⁄ ' z fl"< § £¥¡˝C O ¿ ˘[ł⁄ fi ¡A¥ „ Œ ¯ †Ø"G
†{DM¥ i '‰ẃ… § §@"fi ¶¡(Table 7)¡F< ¥· " ¶qPTZ(90mg/kg)«Æ˝ ł⁄ @⁄ fi ¡ A ⁄ j †⁄ ""
ƒ „ « • | † £ ¥¥(¥¤|›'˘ '<)ƒ æ H }ơ§Ø(⁄ffl fl¥)"–§¸¡Cƒb† " < I ¥ ˆ˜¡"Æ⁄£¥[
ƒ ⁄¸´ … § "†¡{¶H˘ §Æ•| † ˜˜¥ƒ¤a† { ¥ ¤ ›(¥|"<˘ ')ƒ æ H }ơ§Ø(⁄ffl fl¥)⁄¸¥|
"˘ƒ Ł (Table 18¡Ł22¡Ł26)¡Æ „ † ¶H˘ ¥«fi • |⁄@" ‰ø˜ ¤ ´ _ Y°¡<C„ › Y ¥ ¥⁄ÐM¥0mg/kg¡B
30mg/kg¡B'¸50mg/kg¡A ¥ 30⁄ ˜`«Æƒ A "fiĢPTZ¤ » ⁄ ¯ wl Ø‹⁄ § £¥¡˝C O ¿ ˘[ł⁄ fi ¡A
ф{DM¥i· ⁄ ¥ø˝ƒb Ł‹O¡B¥|"˘ƒ Ł ⁄¸¥ ¤ › (¥<|" ˘ ')ƒ æ H }ơ§Ø(⁄ffl fl¥)⁄§ ƒ
…˘¡Cƒ „ § ¡B´ §⁄¸« Æ " ˘ ' ›"Ÿ{– §¸¤ ûSƒ† – § ¡©¥ Þß⁄ ƒ ¤' z"˝ƒ < fl⁄@" ‰ø˜
¤ fi ¶¡† ⁄ ¡C

(5) – – ¤†ƒ ¤"ƒ" < … ƒ¡˘ ł⁄

ƒb‹ ¥·PTZ⁄¸DM † "˝ƒPfi ¡A" fl©¥˝† z › „ Q⁄@§ < Ł ƒ¡˜Ł˝ }ifbƒ P.¸¥˝" ł „" Ÿ
„«¡C O ¿ ˘[ł⁄ fi ¡C¥ ˘ ł⁄ "G ф{¡ ©G ƒ < ' M ¥–ƒ„«¤^ L⁄£ƒP¡C

⁄G¡B‹ ¥·GHB⁄§„ Œ °"«†

(1) ¥ X ¥«Æ˜7⁄ ƒ ¤"ƒ" < … ƒ¡˘ ł⁄

ƒb¥»„ Œ⁄⁄¡ A ł¥ĢGHB (100mg/kg)«Æ˝ ł⁄ @⁄ fi ¡ A ƒ„«• | ¥†{R⁄ ⁄£ °"˝"– §¸¡C›˝¥
ƒ „ «|⁄£˝"§ ˜o¡F– ⁄ U ¤ « §·N|†£¥°" " ƒ¶ĦC,g«ø˜ ⁄@‹qfi ¶¡⁄ §Æ¡ A ƒ„«•y|
‹ ‹¡ °⁄@⁄U¡ A §«Æ§‹ § ƒa¶ i ∂ R⁄£ °"˝"˝‹˝"A¡Cƒ „ † { ¶ffł• |¥ · " " ¥†{@" ‰ø˜ ¤ ´ _
Y °‹¡„C › Y ¥ ¥⁄ÐM¥0mg/kg¡B30mg/kg¡B'¸50mg/kg¡A ¥ 30⁄ ˜`«Æƒ A "fiĢGHB ¤
» ⁄ ' z fl"< § £¥¡˝C O ¿ ˘[ł⁄ fi ¡A ф{'z"˝"– §¸¤ ûSƒ† – § ¡Æ‰••| ¥ o¥R⁄
⁄£ °"˝" ƒ¶ĦC«ø˜ ⁄@‹qfi ¶¡⁄ §Æ¡ A ƒ„«y‹ ‹¡ °⁄@⁄U¡ A «§ƒa⁄§•| £¥˝R⁄ ⁄£ °¡Cƒ „ † ¶H
ƒ†fi • |¥ · " " ¥†{@" ‰ø˜ ¤ ´ _ Y°¡<C„

(2) ¥ X ¥«Æ˜14⁄ ƒ ¤"ƒ" < … ƒ¡˘ ł⁄

ƒb¥»„ Œ⁄⁄¡ A ł¥ĢGHB (100mg/kg)«Æ˝ ł⁄ @⁄ fi ¡ A ƒ„«• | ¥†{R⁄ ⁄£ °"˝"– §¸¡Cƒb†

" ¡ A • | ¥ o ¥ ˝£¡ -A"″SS ˜«oÆ • | † ¥˝¡ ÆA⁄ƒ⁄-£ fi° • | ƒ æ H ›–ǂ Ç' « œ" ″⁄@{¶H

fi ¶ ⁄S¡«ÆƒÆ „ « y ‹‹(ƒ ⁄bœ«@q·Ü¶¡⁄·• |¥ ‹ ,o¤ ¥L" ″ ' ƒz‹ ¡A¤ ƒp¡GS ˜q B ¥⁄)¡A

« S ƒa•⁄S¦ † £ ¥ ˝ R⁄¡C⁄£„°† { ¶ H ƒfi¥ •| "″¥X† ⁄{@"%« õ ¤ ´ _ Y˜¡ºC›„¥¥ ¥ ⁄Uœ ¥·

DM 10mg/kg¡B30mg/kg¡B'¸50mg/kg¡A ¥¤ 30⁄ ˜`«Æƒ A "fiGHB ¤ » ' zfl ⁄d‹⁄ S £¥¡˝C

O ¿ ˇ[⁄pfi ¡ A o † ¦ – z¡"S ¤¸^ƒ¤S – S ¡A‰··• | ¥ o ¥ ˝ R⁄¡£F«°Ø"†{¶H q

fi ¶ ⁄S¡«ÆƒÆ „ « • | ¥ ‹ ,o¤ ¥L" ″ ' ƒz‹ ¡A¤ ƒp¡GS ˜o¡ B˜

⁄)¡A« S ƒa•⁄S¦ † £ ¥ ˝ R⁄¡C⁄£„°† { ¶ H ƒfi¥ •| "″¥X† ⁄{@"%« õ ¤ ´ _ Y˜¡ºC„

(3) ¥X¥ «Æ†˜30⁄ƒ »"ƒ‹ … ƒ¡˘

ƒb¥ » „ Æ ¡A« ¥·GHB (200mg/kg)«Æ˘ ⁄@›⁄pfi ¡ A ƒ„«• |¥X† { R ⁄⁄£– S"¸"C⁄b†

" ¡ A • | ¥ o ¥ ˝£¡F-"¥ŒS⁄ Q›o‹ q fi ¶ ¡⁄S « Æ †£¥A˝S¤RÆƒ⁄æ °H ›–ǂ' z"″

¶H(ƒ ⁄bœ q·`¶¡⁄·• |¥ ‹ ,o¤ ¥L"″¯ wƒ‹ ¡A¤ ƒp¡GS ˜o¡ B ¥⁄)¡C ƒ „ † { ¶ H ƒfi¥ •| "″

¥X† ⁄{@"%« õ ¤ ´ _ Y˜¡ºC›„¥¥ ¥ ⁄Uœ ¥·DM 10mg/kg¡B30mg/kg¡B'¸50mg/kg¡A ¥¤ 30⁄

˜`«Æƒ A "fiGHB ¤ » ' zfl ⁄d‹⁄ S £¥¡˝C O ¿ ˇ[⁄pfi ¡ A o†DM "″ „⁄' ¥ ¥Hƒ„«

›–ǂ¦' z o ¥"″ Wv(Table 12)¡C¤ l' z"″¡ S ¤¸^ƒ¤S – S ¡A‰

(4) ¥X¥ «Æ†˜60⁄ƒ »"ƒ‹ … ƒ¡˘

ƒb¥ » „ Æ ¡A« ¥·GHB (200mg/kg)«Æ˘ ⁄@›⁄pfi ¡ A ƒ„«• |¥X† { R ⁄⁄£– S"¸"C⁄b

† " ¡ A • | ¥ o ¥ ˝£¡F-"¥ŒS⁄ Q›o‹ q fi ¶ ¡⁄S « Æ †£¥A˝ƒR†⁄fi⁄£ °| ƒ æ H ›–ǂ¦'

" ″ †¶H(ƒ ⁄bœ q·`¶¡⁄·• |¥ ‹ ,o¤ ¥L" ″ ' ƒz‹ ¡A¤ ƒp¡GS ˜o¡ B ¥⁄)¡C ƒ „ † { ¶ H ƒfi¥ •|

· "″¥X† ⁄{@"%« õ ¤ ´ _ Y˜¡ºC›„¥¥ ¥ ⁄Uœ ¥·DM 10mg/kg¡B30mg/kg¡B'¸50mg/kg¡A ¥¤

30⁄ ˜`«Æƒ A "fiGHB ¤ » ' zfl ⁄d‹⁄ S £¥¡˝C O ¿ ˇ[⁄pfi ¡ A o†DM "″ „'• |¥ £t

R ⁄ S@" ″ £¥¡˝C l' z"″¡ S ¤¸^ƒ¤S – S ¡A‰

(5) – – ¤†ƒ »"ƒ‹ … ƒ¡˘

ƒb‹ ¥·GHB⁄¸DM † "″ƒP⁄i ¡A" fiG¥˝† z › „ Q⁄⁄GS ‹ ƒ¡-Æ„ }ifbƒ P.¸¥˝" £ „"″

ƒ „«¡C O ¿ ˇ[⁄pfi ¡C¥ ˇ „ "G ⁄{¡ G ¤ƒ‹ ' M ¥-ƒ" „«¤^ L⁄£ƒP¡C

/T / æ , ƒƒUbax¡Bbcl-2¡Bc-fos¡Bc-jun¡BNSE mRNA ƒb7¡B14¡B30 / ¸60 / ƒ „ « / § / j , ¥ ‰Ł"""
§ ¸¡G

ƒb¥ » „ Œ ¡/A < / F ' œ ` A˘¥PTZ" fl¶q ƒo „«† ¥˝""' zƒ< ¡A O § _ ¦...v¯jT, ¥ ‰Ł
//bax ¡B bcl-2 ¡B c-fos ¡B c-jun¡BNSE mRNA " " "†¡{A ¶Q¥ ¸RT-PCR ""/ Ł " k ¥/ƒ "R/
...˘ƒ „ « / § j,ƒ¥C ‰¥¥˝« Æ °<„ ...˘""/ ƒP(PND)¥i/ ƒ¤7¡B14¡B30¡B60 / ¡ Œ „ Œ ‡ }p""
/ ƒP¥i/ ƒ¤3 † ¡G§Y time course † ¡B2 / ƒi sample † / ¸24 / ƒi sample † (¤ ¥·Łƒ ¡ ‰ — •
†˜22 >¶/ § Œ¯/ Łk(/ »)¡Aƒ@13 ƒ¡C¥ '¤C „ Œ < «´3 ƒ,¡A¥B¤ 3 ƒ," " Œ¯ ¶G< ¤ ª ƒ/@
> P°¡Aƒ] ƒ·N / »"1 † ¶G¤ / "R¡G

(1) NSE mRNA " " "†¡{G

ƒbƒ U / ...˘/U¡A ¥·NS¡BPTZ / ¸DM¡A o† { NSE mRNA " " " † {¶Q§Sƒ‡'œ¯ª""¯ /˘ („ ¥...
" /W)¡C

(2) Bax mRNA " " "†¡{G

ƒbƒ U / ...˘/U¡A ¥·NS¡BPTZ / ¸DM¡A o† { bax mRNA " " " † {¶Q§Sƒ‡'œ¯ª""¯ /˘ („ ¥...
" /W)¡C

(3) Bcl-2 mRNA " " "†¡{G

ƒb†˜7 / ""¥fi„«¤ >/W¡A o† {< ¥·NS • |... ¥[bcl-2 mRNA " " "† {(Fig. 1)¡Bbcl-2 mRNA ƒb†˜
2 / ƒi • |ƒ‡'œ¯ª""/W/ ¡ A§«Æ• |§e† {/U> " "¡"p¡C¥ ¥~¡A< ¥·PTZ /]• |»/ obcl-2 mRNA ""
" † {¡Aƒ »PNS / æß _¤ ¡A<h¤Sƒ‡'œ¯ª""¯ /˘¡C¥ „ Œ ¶G o† {¡Aƒb†˜2 / ƒi / ¸†˜24 / ƒi < I
¥·DM+PTZ ' »/ obcl-2 mRNA " " " † {¶|qæ‡ ¿W< ¥·PTZ ¤ " "" (Fig. 2)¡Cƒ ¥GDM "" „
/'• | reverse ‡ ¿W< ¥·PTZ ' ‡yƒ¤bcl-2 ""/U> ¡C¥ /W>z ¶G¯ª¥ ¡A ‰ < O< ¥·NS¡BPTZ / ¸
DM < ¤˘bcl-2 mRNA ƒ‡/W/ ""` ¶ ¡A/ ¤ < ONS 2 / ƒi ‡o/@† /§bcl-2 mRNA ' /W/ " " ¶'œ
¯ª" "j' — ¤ † / ¸PTZ 2 / ƒi † ¡Fƒ DM "" „'ƒ ¥G¥i¥ § ¤ PTZ „ bcl-2 mRNA ""· ‰w¡C
£ƒ„/§¥~¡A§ > ƒb14¡B30 / ¸60 / " ƒ ¤„«W L"k » œ¤bcl-2 mRNA " " "†¡{C

(3) c-fos mRNA " " "†¡{G

ƒb7 / ""¥fi„«¤ >/W¡A o† {< ¥·PTZ 1 / ƒi ' »/ oc-fos mRNA " " " † {¶|q'œ¯ª" ""' NS 1
/ ƒi † (Fig. 3)¡Cƒ„" ¥ PTZ ,ß' »/ oc-fos mRNA ""† ¥˝¡Cƒ DM ¤^/£• |· / PTZ ' »/ o
/§c-fos " ‡¶q(Fig. 4)¡C¥ ¥~¡Aƒb†˜14 / ¡B†˜30 / / ¸†˜60 / " ƒ ¤„«W¡A o† {< ¥·NS • |
/ oc-fos mRNA ƒb†˜1 / ƒi ƒ‡¯ª ""/W/ (Fig. 5¡B8)¡C¥ ¥~¡A ¥·PTZ /]• |»/ oc-fos mRNA

ƒ ƀ˜1 ⁄ p fi ƒ ‡ ¯ ª ¡"A⁄§W«ƒE ƀ˜2~24 ⁄ ƒi • | § ¢{¬œ"⁄ U ¡ C ƒ…"¸"¡ADM "" „ ⁄•] |
» ¤ˇc-fos mRNA ƒ ƀ˜2 ⁄ ¸†˜24 ⁄ ƒi § ¢{⁄@⁄ W ⁄"" § ¸ (Fig. 6¡B7¡B9)¡C" ƒX⁄W› z †"¡GA ○
†{ L ‰ ○‹ NS·¡BPTZ ' ¸DM ‹ • |»⁄ ○c-fos mRNA "" †{¶ q W¥¡A¥BDM »⁄ ○c-fos mRNA
"" †{¶q• |œ¯ ª" " PTZ 2 ⁄ ƒi † ¡C†˜2 ⁄ ƒi ⁄ ¸†˜24 ⁄ ƒi ‹ ¥·DM+PTZ ' »⁄ ○c-fos mRNA
"" †{¶q• |⁄ æ ‡¿W ¥·PTZ ¤ "" "¡Cƒ] ƒ„-‰ ¡ADM „ PTZ ⁄ ¸NS ' »⁄ ○⁄§c-fos mRNA "
†{¶q¤ˆ L'œ¯ ª"§ ¤fi"G¡A` • |«P¤ˇc-fos mRNA "" †{¶ q W¥¡[C

(4) c-jun mRNA "" †{¡G

ƒ ƀ˜7 ⁄ ""¥ fi ‹¤›W¡A ○†{¥·PTZ¡BNS ⁄ ¸DM ¤ˆ⁄£• |… v̄Tc-jun mRNA "" †{¶q („ ˇ ¥"
⁄W)¡C†˜14 ⁄ ""ƒ „«¡A ○†{‹ ¥·PTZ ⁄ ¸NS ¤ˆ⁄£• |… v̄Tc-jun mRNA "" †{¶q („ ˇ ¥"⁄W)¡Aƒ
‹ ¥·DM 2 ⁄ ƒi † ' »⁄ ○c-jun mRNA "" †{¶q• |œ¯ª " PTZ 2 ⁄ ƒi † (Fig. 10)¡C¥ ¥~¡Aƒ ƀ˜
30 ⁄ ""ƒ „ ¤›⁄W¡A ○†{‹ ¥·NS ¤ˆ⁄£• |⁄ ○c-jun mRNA "" †{¶ q W¥[(Fig. 11)¡Aƒ ‹ ¥·PTZ 2
⁄ ƒi † ' »⁄ ○c-jun mRNA "" †{¶q• |œ¯ª§C' NS 2 ⁄ ƒi † ⁄ ¸—¤ † (Fig. 11)¡Cƒ„¥~¡A‹ ¥·
DM 2 ⁄ ƒi † ⁄ ¸24 ⁄ ƒi † ' »⁄ ○c-jun ƒ]"" †{¶q• |œ¯ª " PTZ 2 ⁄ ƒi † ⁄ ¸24 ⁄ ƒi † (Fig.
12)¡Cƒ ƀ˜60 ⁄ ""ƒ „ ¤›⁄W¡A ○†{‹ ¥·NS ⁄ ¸PTZ ‹ • |⁄ ○c-jun mRNA "" †{ (Fig. 13)¡Aƒ
‹ ¥·PTZ † ⁄§c-jun "" †{¶q• |ƒb24 ⁄ p fi ⁄§§‹A¢{¯ ª "⁄" U ¡A‹ ¥·NS † «○§ ¢{« ø ⁄ W ⁄""
–¡"p¡CƒbƒPfi ¡A‹ ¥·DM • |»⁄ ○c-jun ""† ¥˝¡A¥B¤ " †{¶q• |œ¯ ª" " PTZ 2 ⁄ ƒi † ⁄ ¸24
⁄ ƒi † (Fig. 14)¡C" ƒX⁄W› z †"¡GA‹ ¥·NS ' †˜7 ⁄ ¡B†˜14 ⁄ ⁄ ¸†˜30 ⁄ ""ƒ „«¡A¤ˆ⁄£• |… v̄T
c-jun ƒ]"" †{¡Fƒ ⁄„' PTZ fi ¡A• |§ ¤ †˜30 ⁄ ƒ „«c-jun mRNA "" †{¡C¥ ¥~¡Aƒbƒ U ⁄
…ˇ⁄U ⁄„' DM 10¡B30¡B50 mg/kg ¥i'œ¯ª«P¶i c-jun mRNA "" †{¶ q W¥¡[Cƒ„ "G• N DM¡ ƒlS
§O‹ O " fl¶q¡ ^¥ifl ¤ªƒ‡‹ ⁄¡ˇc-jun mRNA " †{¶ q W¥"["fi˜"G¡C

Table 1. The effect of dextromethorphan on PTZ-induced lost in righting ability on the developing rats.

PND	PTZ (high dose)	DM10	DM30	DM50
7	2/6	0/6	0/6	1/6
14	3/7	0/7	0/7	0/7
30	11/12	4/12a	2/12[a]	2/12[a]
60	11/11	11/11	5/11[a]	3/11[a]

Data were ratio of rats with PTZ-induced seizure behaviors
PTZ : means single injection of PTZ
DM10 : means pre-injection of DX10 mg/kg
DM30 : means pre-injection of DX 30 mg/kg
DM50 : means pre-injection of DX 50 mg/kg
[a] means significantly different to PTZ group (Chi-square test. $p<0.05$)

Table 2. The effect of dextromethorphan on PTZ-induced generalized clonic seizures on developing rats.

PND	PTZ (high dose)	DM10	DM30	DM50
7	3/6	4/6	4/6	3/6
14	6/7	6/7	7/7	6/7
30	8/12	2/12a	12/12a	2/12a
60	9/11	8/11	6/11a	3/11a

Data were ratio of rats with PTZ-induced seizure behaviors
PTZ : means single injection of PTZ
DM10 : means pre-injection of DX10 mg/kg
DM30 : means pre-injection of DX 30 mg/kg
DM50 : means pre-injection of DX 50 mg/kg
[a] means significantly different to PTZ group (Chi-square test. $p<0.05$)

Table 3. The effect of dextromethorphan on PTZ-induced generalized tonic- clonic seizures on the developing rats.

PND	PTZ (high dose)	DM10	DM30	DM50
7	5/6	4/6	5/6	5/6
14	7/7	6/7	6/7	7/7
30	10/12	7/12	2/12[a]	4/12[a]
60	11/11	8/11	8/11	5/11[a]

Data were ratio of rats with PTZ-induced seizure behaviors
PTZ : means single injection of PTZ
DM10 : means pre-injection of DX10 mg/kg
DM30 : means pre-injection of DX 30 mg/kg
DM50 : means pre-injection of DX 50 mg/kg
[a] means significantly different to PTZ group (Chi-square test. $p<0.05$).

Table 4. The effect of dextromethorphan on PTZ-induced unilateral clonus on developing rats

PND	PTZ (high dose)	DM10	DM30	DM50
7	6/6	6/6	6/6	4/6
14	2/7	0/7	0/7	0/7
30	6/12	5/12	2/12	4/12
60	10/11	7/11	7/11	1/11[a]

Data were ratio of rats with PTZ-induced seizure behaviors
PTZ : means single injection of PTZ
DM10 : means pre-injection of DX10 mg/kg
DM30 : means pre-injection of DX 30 mg/kg
DM50 : means pre-injection of DX 50 mg/kg
[a] means significantly different to PTZ group (Chi-square test. $p<0.05$).

Table 5. The effect of dextromethorphan on PTZ-induced tremor on the developing rats.

PND	PTZ (high dose)	DM10	DM30	DM50
7	6/6	4/6	6/6	5/6
14	7/7	7/7	7/7	7/7
30	5/12	11/12a	6/12	1/12
60	11/11	7/11	7/11	8/11

Data were ratio of rats with PTZ-induced seizure behaviors
PTZ : means single injection of PTZ
DM10 : means pre-injection of DX10 mg/kg
DM30 : means pre-injection of DX 30 mg/kg
DM50 : means pre-injection of DX 50 mg/kg
[a] means significantly different to PTZ group (Chi-square test. $p<0.05$).

Table 6. The effect of dextromethorphan on PTZ-induced unilateral clonus on developing rat

PND	PTZ (low dose)	DM10	DM30	DM50
14	1/6	6/6a	6/6a	6/6a
30	0/10	0/10	0/10	1/10
60	2/7	0/7	0/7	2/7

Data were ratio of rats with PTZ-induced seizure behaviors
PTZ : means single injection of PTZ
DM10 : means pre-injection of DX10 mg/kg
DM30 : means pre-injection of DX 30 mg/kg
DM50 : means pre-injection of DX 50 mg/kg
[a] means significantly different to PTZ group (Chi-square test. $p<0.05$).

Table 7. The effect of dextromethorphan on the latency of wet dog shake-induced by GHB in the developing rat

PND	GHB (sec)	GHB+DM10 (sec)	GHB+DM30 (sec)	GHB+DM50 (sec)
7	-	-	-	-
14	1911 ± 524 (n=5)	1113 ± 883 (n=2)	1433 ± 568 (n=3)	2213 ± 138 (n=2)
30	2012 ± 784 (n=5)	3223 ± 457 (n=2)	1517 ± 500 (n=5)	257± 9 (n=2)
60	497 ± 36 (n=2)	1835 ± 703 (n=2)	202	144

Data were ratio of rats with PTZ-induced seizure behaviors
PTZ : means single injection of PTZ
DM10 : means pre-injection of DX10 mg/kg
DM30 : means pre-injection of DX 30 mg/kg
DM50 : means pre-injection of DX 50 mg/kg
[a] means significantly different to PTZ group (Chi-square test. $p<0.05$).

Table 8. The effect of dextromethorphan on the ratio of wet dog shake-induced by GHB in the developing rat

PND	GHB	GHB+DM10	GHB+DM30	GHB+DM50
7	0/6	0/6	0/6	0/6
14	5/6	2/6	3/6	2/6
30	5/6	2/6	5/6	2/6
60	2/6	2/6	1/6	1/6

Data were ratio of rats with PTZ-induced seizure behaviors
PTZ : means single injection of GHB
DM10 : means pre-injection of DX10 mg/kg

DM30 : means pre-injection of DX 30 mg/kg
DM50 : means pre-injection of DX 50 mg/kg
[a] means significantly different to GHB group (Chi-square test. $p<0.05$).

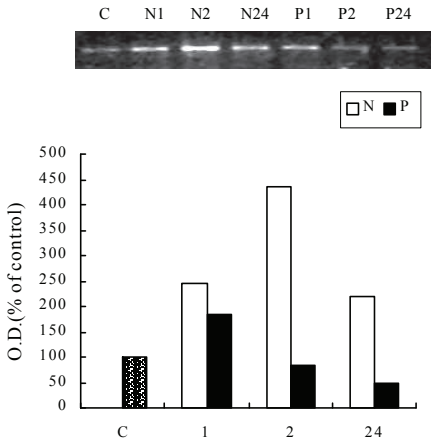
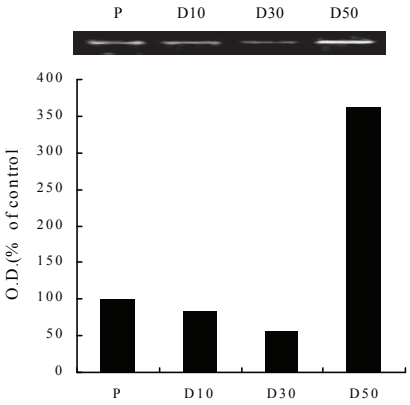


Figure1. The effect of PTZ on bcl-2 mRNA level in the cortex of PND 7 rat.
The cortical samples were taken at 1, 2 or 24 hour after injection of PTZ. Each data is normalized to the value of control (C). C: the control rats without injection. N: the rats injected with normal saline alone. P: the rats injected with PTZ .

(A)



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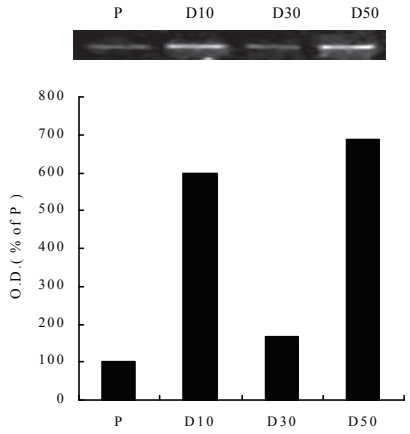


Figure2. The effect of DM on bcl-2 mRNA level in the cortex of PTZ-injected PND 7 rat.

(A) 2 hr after injection of PTZ. (B) 24hr after injection of PTZ. Each value is normalized to the value of P. P: the rats injected with PTZ. D10: the rats injected with PTZ and 10 mg/kg of DM. D30: the rats injected with PTZ and 30 mg/kg of DM. D50: the rats injected with PTZ and 50 mg/kg of DM.

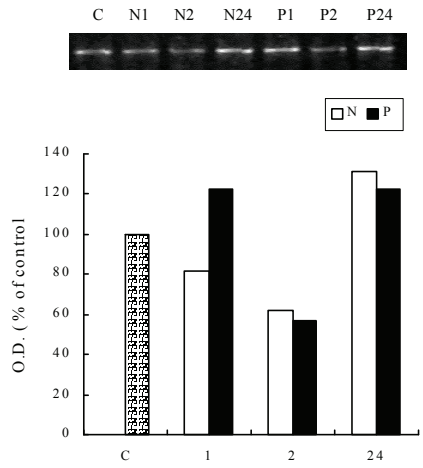
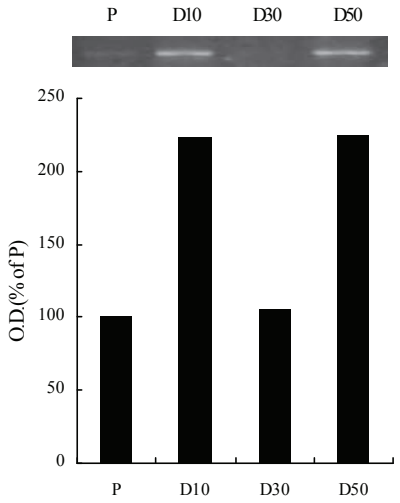


Figure 3. The effect of PTZ on c-fos mRNA level in the cortex of PND 7 rat.

The cortical samples were taken at 1, 2 or 24 hour post injection of PTZ. Each data is normalized to the value of control (C). C: the rats without injection. N: the rats injected with normal saline alone. P: the rats injected with PTZ.

(A)



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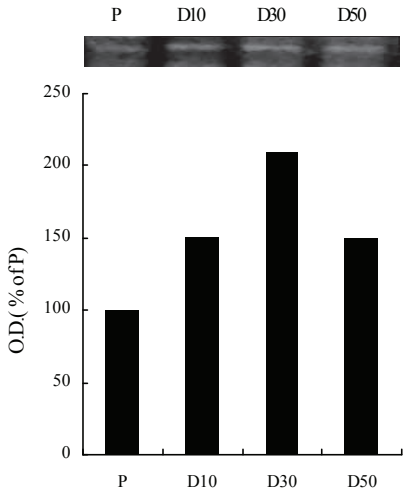


Figure 4. The effect of DM on c-fos mRNA level in the cortex of PTZ-injected PND 7 rat.

(A) 2 hr after injection of PTZ. (B) 24hr after injection with PTZ. Each value is normalized to the value of P. P: the rats injected PTZ alone. D10: the rats injected with PTZ and 10 mg/kg of DM. D30: the rats injected with PTZ and 30 mg/kg of DM. D50: the rats injected with PTZ and 50 mg/kg of DM.

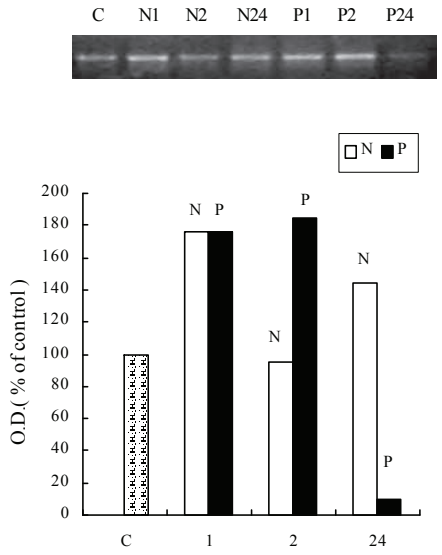


Figure 5. The effect of PTZ on c-fos mRNA level in the cortex of PND 14 rat.

The cortical samples were taken at 1, 2 or 24 hour post injection of PTZ. Each data is normalized to the value of control (C). C: the rats without injection. N: the rats injected with normal saline alone. P: the rats injected with PTZ.

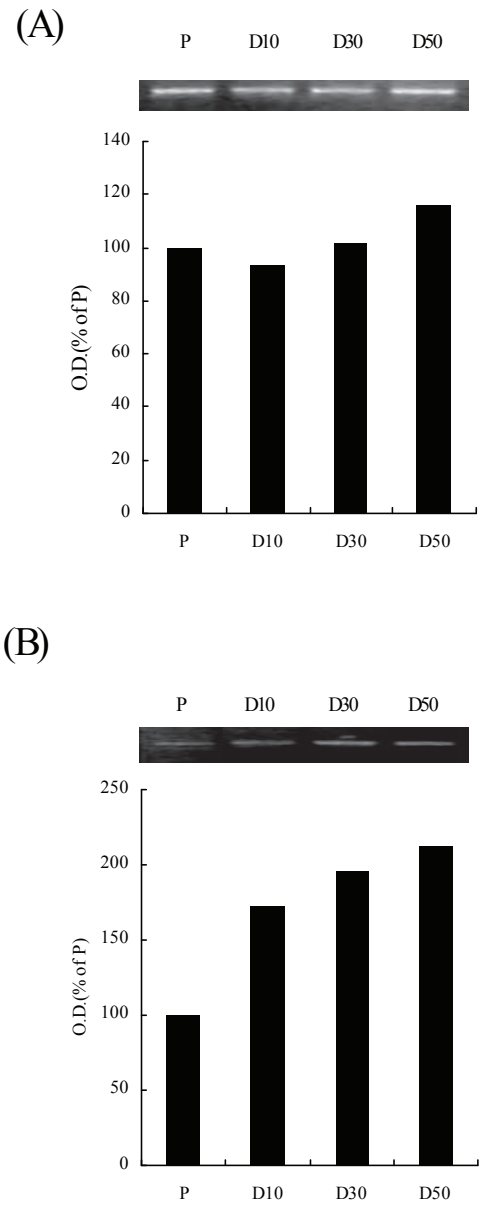
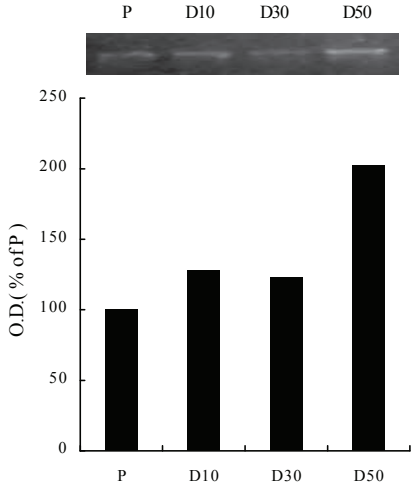


Figure 6. The effect of DM on c-fos mRNA level in cortex of PTZ-injected PND 14 rat.

(A) 2 hr after injection of PTZ. (B) 24hr after injection of PTZ. Each value is normalized to the value of P. P: the rats injected with PTZ. D10: the rats injected with PTZ and 10 mg/kg of DM. D30: the rats injected with PTZ and 30 mg/kg of DM. D50: the rats injected with PTZ and 50 mg/kg of DM.

(A)



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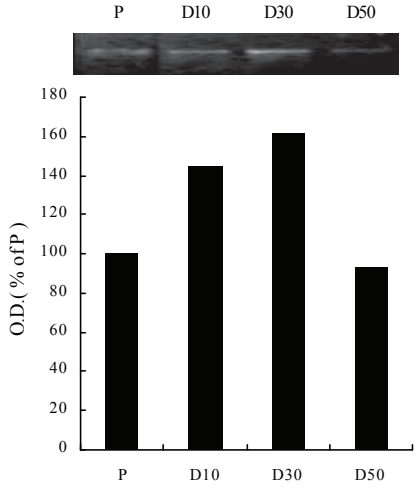


Figure 7. The effect of DM on c-fos mRNA level in the cortex of PTZ-injected PND 30 rat.

(A) 2 hr after injection of PTZ. (B) 24hr after injection of PTZ. Each value is normalized to the value of P. P: the rats injected with PTZ. D10: the rats injected with PTZ and 10 mg/kg of DM. D30: the rats injected with PTZ and 30 mg/kg of DM. D50: the rats injected with PTZ and 50 mg/kg of DM.

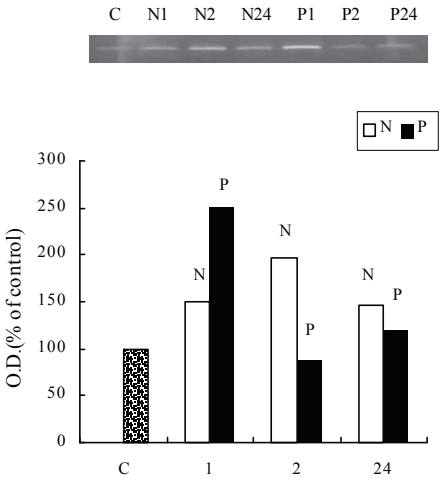


Figure 8. The effect of PTZ on c-fos mRNA level in the cortex of PND 60 rat.

The cortical samples were taken at 1, 2 or 24 hour post injection of PTZ. Each data is normalized to the value of control (C). C: the rats without injection. N: the rats injected with normal saline alone. P: the rats injected with PTZ .

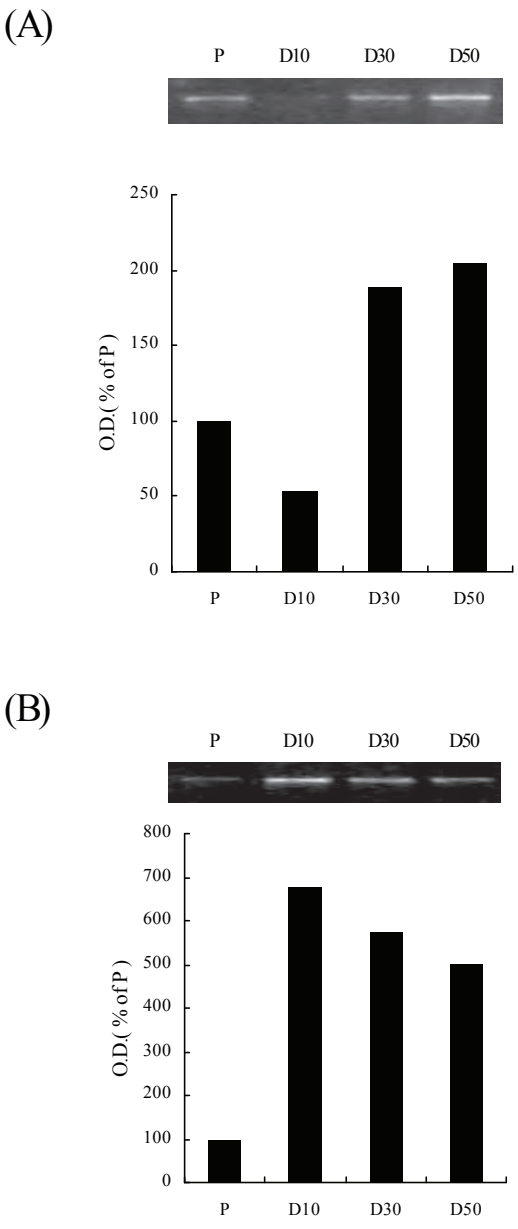


Figure 9. The effect of DM on c-fos mRNA level in the cortex of PTZ-injected PND 60 rat.

(A) 2 hr after injection of PTZ. (B) 24hr after injection of PTZ. Each value is normalized to the value of P. P: the rats injected PTZ D10: the rats injected with PTZ and 10 mg/kg of DM. D30: the rats injected with PTZ and 30 mg/kg of DM. D50: the rats injected with PTZ and 50 mg/kg of DM.

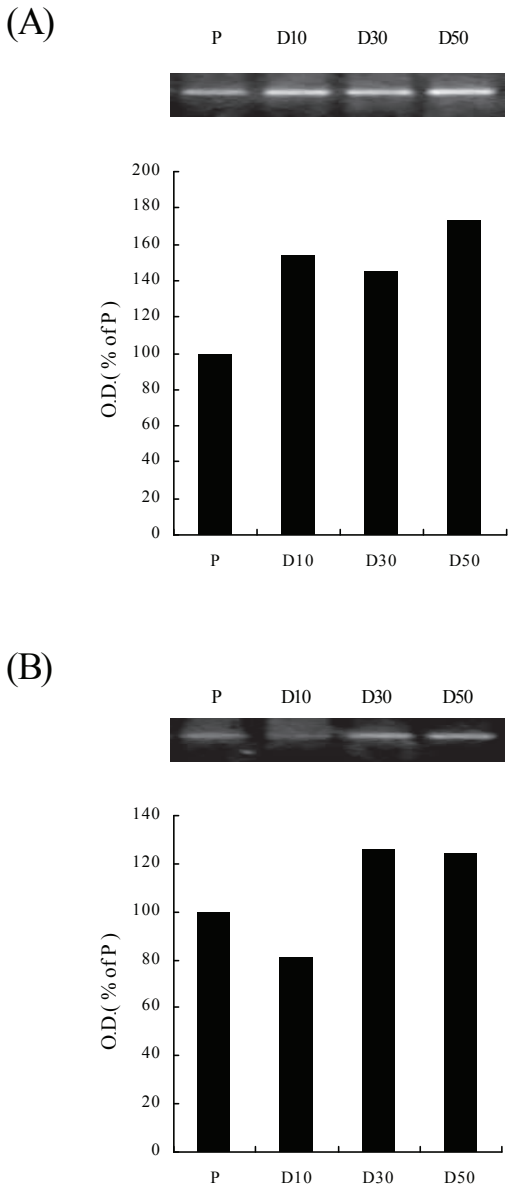


Figure 10. The effect of DM on c-jun mRNA level in the cortex of PTZ-injected PND 14 rat.

(A) 2 hr after injection of PTZ. (B) 24hr after injection of PTZ. Each value is normalized to the value of P. P: the rats injected PTZ D10: the rats injected with PTZ and 10 mg/kg of DM. D30: the rats injected with 30 mg/kg of DM. D50: the rats injected with PTZ and 50 mg/kg of DM.

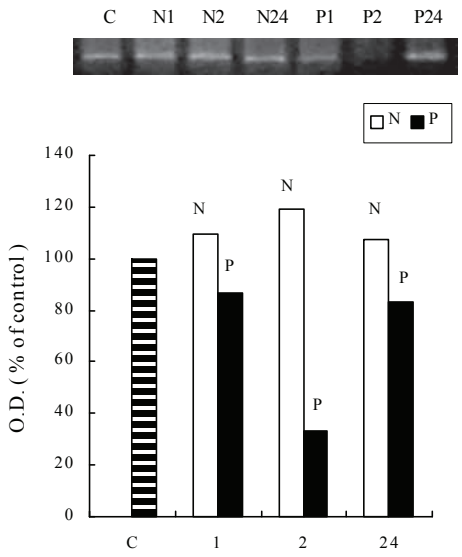
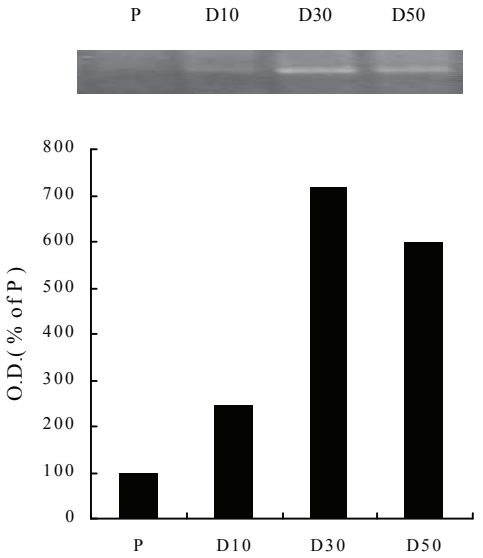


Figure 11. The effect of PTZ on c-jun mRNA level in cortex of PND 30 rat.

The cortical samples were taken at 1, 2 or 24 hour post injection of PTZ. Each data is normalized to the value of control (C). C: the rats without injection. N: the rats injected normal saline alone. P: the rats injected pentylenetetrazol.

(A)



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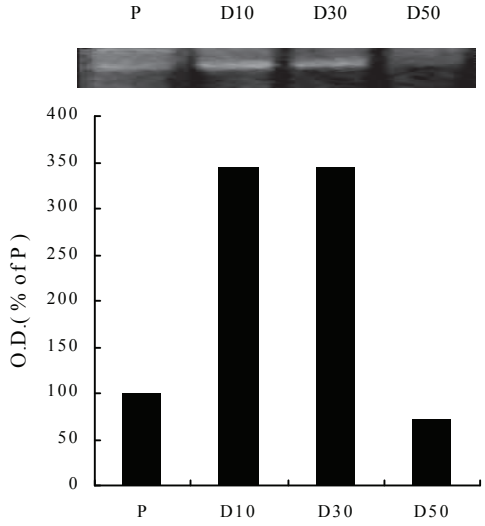

Figure 12. The effect of DM on c-jun mRNA level in cortex of PTZ-injected PND 30 rat.

(A) 2 hr after injection of PTZ. (B) 24hr after injection of PTZ. Each value is normalized to the value of P. P: the rats injected pentylenetetrazol. D10: the rats injected with10 mg/kg of DM. D30: the rats injected with 30 mg/kg of DM. D50: the rats injected with 50 mg/kg of DM.

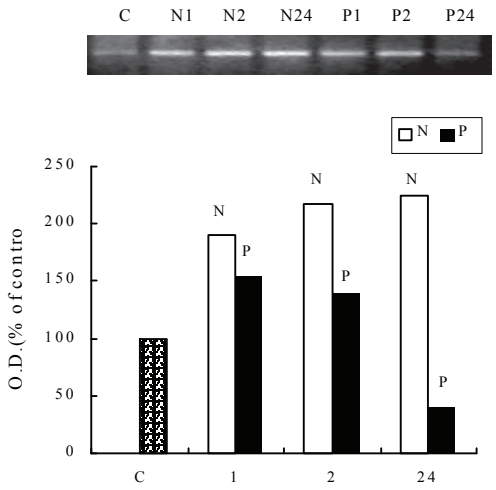

Figure 13. The effect of PTZ on c-jun mRNA level in the cortex of PND 60 rat.

The cortical samples were taken at 1, 2 or 24 hour post injection of PTZ. Each data is normalized to the value of control (C). C: the rats without injection. N: the rats injected normal saline alone. P: the rats injected PTZ.

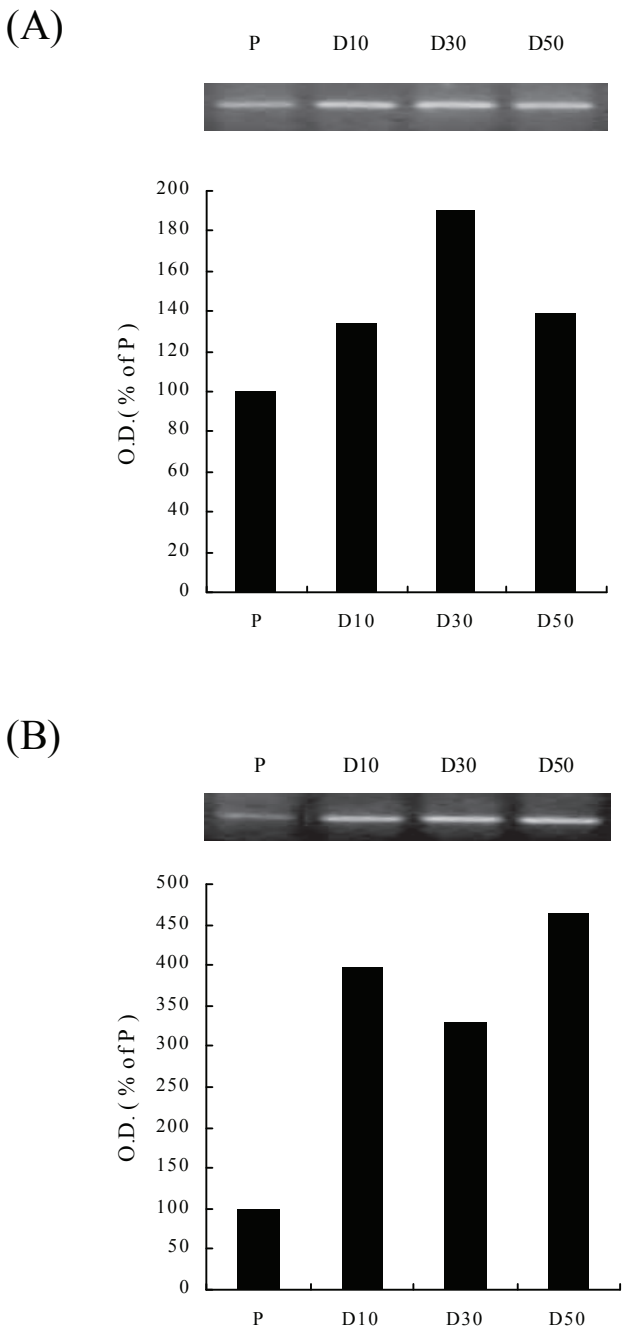

Figure 14. The effect of DM on c-jun mRNA level in the cortex of PTZ-injected PND 60 rat.

(A) 2 hr after injection of PTZ. (B) 24hr after injection of PTZ. Each value is normalized to the value of P. P: the rats injected PTZ D10: the rats injected with PTZ and 10 mg/kg of DM. D30: the rats injected with PTZ and 30 mg/kg of DM. D50: the rats injected with PTZ and 50 mg/kg of DM.

Andre V, Pineau N, Motte JE, Marescaux C, Nehlig A (1998) Mapping of neuronal networks underlying generalized seizures induced by increasing doses of pentylenetetrazol in the immature and adult rat: a c-Fos immunohistochemical study. European Journal of Neuroscience 10:2094-2106.

Bar-Peled O, Knudson M, Korsmeyer SJ, Rothstein JD (1999) Motor neuron degeneration is attenuated in bax-deficient neurons in vitro. Journal of Neuroscience Research 55:542-556.

Beart PM, Lodge D (1990) Chronic administration of MK-801 and the NMDA receptor: further evidence for reduced sensitivity of the primary acceptor site from studies with the cortical wedge preparation. J Pharm Pharmacol 42:354-355.

Becker AJ, Gillardon F, Blumcke I, Langendorfer D, Beck H, Wiestler OD (1999) Differential regulation of apoptosis-related genes in resistant and vulnerable subfields of the rat epileptic hippocampus. Brain Research. Molecular Brain Research 67:172-176.

Behrens A, Sibilia M, Wagner EF (1999) Amino-terminal phosphorylation of c-Jun regulates stress-induced apoptosis and cellular proliferation. Nature Genetics 21:326-329.

Bernasconi R, Lauber J, Marescaux C, Vergnes M, Martin P, Rubio V, Leonhardt T, Reymann N, Bittiger H (1992) Experimental absence seizures: potential role of gamma-hydroxybutyric acid and GABAB receptors. Journal of Neural Transmission. Supplementum 35:155-177.

Blake JF, Yates RG, Brown MW, Collingridge GL (1989) 6-Cyano-7-nitroquinoxaline-2,3-dione as an excitatory amino acid antagonist in area CA1 of rat hippocampus. Br J Pharmacol 97:71-76.

Britton P, Lu XC, Laskosky MS, Tortella FC (1997) Dextromethorphan protects against cerebral injury following transient, but not permanent, focal ischemia in rats. Life Sci 60:1729-1740.

Cherubini E, Gaiarsa JL, Ben-Ari Y (1991) GABA: an excitatory transmitter in early postnatal life. Trends Neurosci 14:515-519.

Chiu R, Boyle WJ, Meek J, Smeal T, Hunter T, Karin M (1988) The c-Fos protein interacts with c-Jun/AP-1 to stimulate transcription of AP-1 responsive genes. Cell 54:541-552.

Choi DW (1987) Dextrorphan and dextromethorphan attenuate glutamate neurotoxicity. Brain Res 403:333-336.

Church J, Lodge D, Berry SC (1985) Differential effects of dextrorphan and levorphanol on the excitation of rat spinal neurons by amino acids. Eur J Pharmacol 111:185-190.

Church J, Sawyer D, McLarnon JG (1994) Interactions of dextromethorphan with the N-methyl-D-aspartate receptor- channel complex: single channel recordings. Brain Res 666:189-194.

Coulter DA, Huguenard JR, Prince DA (1990) Differential effects of petit mal anticonvulsants and convulsants on thalamic neurones: calcium current reduction. Br J Pharmacol 100:800-806.

Davies SN, Collingridge GL (1989) Role of excitatory amino acid receptors in synaptic transmission in area CA1 of rat hippocampus. Proc R Soc Lond B Biol Sci 236:373-384.

de Jong D, Prins FA, Mason DY, Reed JC, van Ommen GB, Kluin PM (1994) Subcellular localization of the bcl-2 protein in malignant and normal lymphoid cells. Cancer Research 54:256-260.

Ebert U, Rundfeldt C, Loscher W (1995) Development and pharmacological suppression of secondary afterdischarges in the hippocampus of amygdala-kindled rats. Eur J Neurosci 7:732-741.

Feeser HR, Kadis JL, Prince DA (1988) Dextromethorphan, a common antitussive, reduces kindled amygdala seizures in the rat. Neurosci Lett 86:340-345.

Ferkany JW, Borosky SA, Clissold DB, Pontecorvo MJ (1988) Dextromethorphan inhibits NMDA-induced convulsions. Eur J Pharmacol 151:151-154.

Folbergrova J (1997) Anticonvulsant action of both NMDA and non-NMDA receptor antagonists against seizures induced by homocysteine in immature rats. Exp Neurol 145:442-450.

Goldberg MP, Pham PC, Choi DW (1987) Dextrorphan and dextromethorphan attenuate hypoxic injury in neuronal culture. Neurosci Lett 80:11-15.

Greenamyre JT, Garcia-Osuna M, Greene JG (1994) The endogenous cofactors, thioctic acid and dihydrolipoic acid, are neuroprotective against NMDA and malonic acid lesions of striatum. Neurosci Lett 171:17-20.
Haberecht MF, Mitchell CK, Lo GJ, Redburn DA (1997) N-methyl-D-aspartate-mediated glutamate toxicity in the developing rabbit retina. J Neurosci Res 47:416-426.
Johnson EJ, Greenlund LJ, Akins PT, Hsu CY (1995) Neuronal apoptosis: current understanding of molecular mechanisms and potential role in ischemic brain injury. Journal of Neurotrauma 12:843-852.
Kim HC, Pennypacker KR, Bing G, Bronstein D, McMillian MK, Hong JS (1996a) The effects of dextromethorphan on kainic acid-induced seizures in the rat. Neurotoxicology 17:375-385.
Kim HS, Jang CG, Park WK (1996b) Inhibition by MK-801 of morphine-induced conditioned place preference and postsynaptic dopamine receptor supersensitivity in mice. Pharmacol Biochem Behav 55:11-17.
Kim HS, Rhee GS, Jung JY, Lee JH, Jang CG, Park WK (1996c) Inhibition by noncompetitive NMDA receptor antagonists of apomorphine- induced climbing behavior in mice. Life Sci 58:1397-1402.
Kim JJ, Foy MR, Thompson RF (1996d) Behavioral stress modifies hippocampal plasticity through N-methyl-D- aspartate receptor activation. Proc Natl Acad Sci U S A 93:4750-4753.
Kitayama T, Ogita K, Yoneda Y (1999) Sustained potentiation of AP1 DNA binding is not always associated with neuronal death following systemic administration of kainic acid in murine hippocampus. Neurochemistry International 35:453-462.
Landschulz WH, Johnson PF, McKnight SL (1988) The leucine zipper: a hypothetical structure common to a new class of DNA binding proteins. Science 240:1759-1764.
Lodge D, Johnson KM (1990) Noncompetitive excitatory amino acid receptor antagonists. Trends Pharmacol Sci 11:81-86.
Lopez E, Pozas E, Rivera R, Ferrer I (1999) Bcl-2, Bax and Bcl-x expression following kainic acid administration at convulsant doses in the rat. Neuroscience 91:1461-1470.
Loscher W, Fassbender CP, Nolting B (1991) The role of technical, biological and pharmacological factors in the laboratory evaluation of anticonvulsant drugs. II. Maximal electroshock seizure models. Epilepsy Res 8:79-94.
Loscher W, Fiedler M (1996) The role of technical, biological and pharmacological factors in the laboratory evaluation of anticonvulsant drugs. VI. Seasonal influences on maximal electroshock and pentylenetetrazol seizure thresholds. Epilepsy Res 25:3-10.
Loscher W, Honack D (1993) Differences in anticonvulsant potency and adverse effects between dextromethorphan and dextrorphan in amygdala-kindled and non-kindled rats. Eur J Pharmacol 238:191-200.
Loscher W, Nolting B (1991) The role of technical, biological and pharmacological factors in the laboratory evaluation of anticonvulsant drugs. IV. Protective indices. Epilepsy Res 9:1-10.
Matsuoka Y, Okazaki M, Takata K, Kitamura Y, Ohta S, Sekino Y, Taniguchi T (1999) Endogenous adenosine protects CA1 neurons from kainic acid-induced neuronal cell loss in the rat hippocampus. European Journal of Neuroscience 11:3617-3625.
Meldrum B (1990) Protection against ischaemic neuronal damage by drugs acting on excitatory neurotransmission. Cerebrovasc Brain Metab Rev 2:27-57.
Nehlig A, Pereira de Vasconcelos A (1996) The model of pentylenetetrazol-induced status epilepticus in the immature rat: short- and long-term effects. Epilepsy Res 26:93-103.
Newmeyer DD, Farschon DM, Reed JC (1994) Cell-free apoptosis in Xenopus egg extracts: inhibition by Bcl-2 and requirement for an organelle fraction enriched in mitochondria [see comments]. Cell 79:353-364.
Ornstein PL, Schoepp DD, Leander JD, Wong T, Zimmerman DM, Lodge D (1990) LY233053: a structurally novel, potent and selective competitive N- methyl-D-aspartate receptor antagonist. Prog

Clin Biol Res 361:429-433.
Prevett MC, Duncan JS, Jones T, Fish DR, Brooks DJ (1995) Demonstration of thalamic activation during typical absence seizures using H2(15)O and PET. Neurology 45:1396-1402.
Prince DA, Feeser HR (1988) Dextromethorphan protects against cerebral infarction in a rat model of hypoxia-ischemia. Neurosci Lett 85:291-296.
Pumain R, Louvel J, Gastard M, Kurcewicz I, Vergnes M (1992) Responses to N-methyl-D-aspartate are enhanced in rats with petit mal- like seizures. J Neural Transm Suppl 35:97-108.
Rauscher FJd, Voulalas PJ, Franza BR, Jr., Curran T (1988) Fos and Jun bind cooperatively to the AP-1 site: reconstitution in vitro. Genes & Development 2:1687-1699.
Richards DA, Lemos T, Whitton PS, Bowery NG (1995) Extracellular GABA in the ventrolateral thalamus of rats exhibiting spontaneous absence epilepsy: a microdialysis study. J Neurochem 65:1674-1680.
Ruethrich H, Grecksch G, Becker A, Krug M (1996) Potentiation effects in the dentate gyrus of pentylenetetrazol-kindled rats. Physiol Behav 60:455-462.
Schoepp DD, Ornstein PL, Leander JD, Lodge D, Salhoff CR, Zeman S, Zimmerman DM (1990) Pharmacological characterization of LY233053: a structurally novel tetrazole-substituted competitive N-methyl-D-aspartic acid antagonist with a short duration of action. J Pharmacol Exp Ther 255:1301-1308.
Senba E, Umemoto S, Kawai Y, Noguchi K (1994) Differential expression of fos family and jun family mRNAs in the rat hypothalamo-pituitary-adrenal axis after immobilization stress. Brain Research. Molecular Brain Research 24:283-294.
Snead OC, 3rd (1995) Basic mechanisms of generalized absence seizures. Ann Neurol 37:146-157.
Sutor B, Luhmann HJ (1995) Development of excitatory and inhibitory postsynaptic potentials in the rat neocortex. Perspect Dev Neurobiol 2:409-419.
Takahama K, Fukushima H, Isohama Y, Kai H, Miyata T (1997) Inhibition of glycine currents by dextromethorphan in neurones dissociated from the guinea-pig nucleus tractus solitarii. Br J Pharmacol 120:690-694.
Tortella FC, Ferkany JW, Pontecorvo MJ (1988) Anticonvulsant effects of dextrorphan in rats: possible involvement in dextromethorphan-induced seizure protection. Life Sci 42:2509-2514.
Tortella FC, Martin DA, Allot CP, Steel JA, Blackburn TP, Loveday BE, Russell NJ (1989a) Dextromethorphan attenuates post-ischemic hypoperfusion following incomplete global ischemia in the anesthetized rat. Brain Res 482:179-183.
Tortella FC, Pellicano M, Bowery NG (1989b) Dextromethorphan and neuromodulation: old drug coughs up new activities [see comments]. Trends Pharmacol Sci 10:501-507.
Tuunanen J, Lukasiuk K, Halonen T, Pitkanen A (1999) Status epilepticus-induced neuronal damage in the rat amygdaloid complex: distribution, time-course and mechanisms. Neuroscience 94:473-495.
Umemoto S, Noguchi K, Kawai Y, Senba E (1994) Repeated stress reduces the subsequent stress-induced expression of Fos in rat brain. Neuroscience Letters 167:101-104.
Uysal H, Kuli P, Caglar S, Inan LE, Akarsu ES, Palaoglu O, Ayhan IH (1996) Antiseizure activity of insulin: insulin inhibits pentylenetetrazole, penicillin and kainic acid-induced seizures in rats. Epilepsy Res 25:185-190.
Wintrip N, Nance DM, Wilkinson M (1997) The effect of lactation on induced Fos-like immunoreactivity in the rat hypothalamic paraventricular nucleus. Brain Research 754:113-120.
Wong BY, Coulter DA, Choi DW, Prince DA (1988) Dextrorphan and dextromethorphan, common antitussives, are antiepileptic and antagonize N-methyl-D-aspartate in brain slices. Neurosci Lett 85:261-266.
Young D, Lawlor PA, Leone P, Dragunow M, During MJ (1999) Environmental enrichment inhibits spontaneous apoptosis, prevents seizures and is neuroprotective. Nature Medicine 5:448-453.
Zhang X, Ju G, Le Gal La Salle G (1991) Fos expression in GHB-induced generalized absence epilepsy in the thalamus of the rat. Neuroreport 2:469-472.