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Bradykinin-induced iNOS expression and cytokines release in human airway epithelial cells: the interaction mechanisms and signal transduction pathways

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¥»› pe¥D›nƒb– ·Q bradykinin ¤°¿E⁄H ^ "˝– ƒ ⁄ W ¥ † A549¡¸^cyclooxygenase-2 (COX-2) " †{" "T„¶ · » „. ƒi┤ƒb† ˜⁄@ƒ~ ⁄ † ˜⁄Gƒ~"˝‹ ª§⁄ o†{¡AƒbA549 † ›M⁄¡A bradykinin ¥i,g¥ ‹⁄˘p44/42 MAPK ⁄¸ p38 MAPK " " ,fi┤ oNF-κB "˝‹ ⁄˘¡A† « Æ ›£COX-2 "˝" †{¡CƒbƒbT ƒ~"˝‹ ª§⁄ § › №§⁄¶‡B– ·Q bradykinin ›P COX-2 " †{" " ,fi┤⁄¡Ap44/42 MAPK ⁄¸ p38 MAPK »P NF-κB ⁄§¶ ¡ " " T §¶·» fi┤¡A¥H⁄¸¤ ¥L⁄ _ p44/42 MAPK ⁄¸ p38 MAPK ‹ ⁄˘" " T fi § ¶»¡CRa§i┤§ ¤ fl manumycin A (0.3, 1 'M3 μM) ⁄¸Raf § ¤ flGW 5074 (0.3, 1 'M3 nM) ¥H f¶ q ‹ ^"˝ ⁄ ¡§ ¤ bradykinin⁄ o⁄§COX-2 " †{¡C Manumycin A (3 μM) »PGW 5074 (3 μM) ⁄]¥i¥H§ ¤ bradykinin⁄ op44/42 MAPK "˝‹ ⁄˘¡Aƒ ª⁄£┤… v̄T p38 MAPK "˝‹ ¡ ⁄˘¡CBradykinin ¥Hfi ¶¡‹ ^ "˝⁄ ¡¤ ˝o IKKα/β ‹ ¡ ' ° … W ¥ [A•PD¥ 98059 (30 μM)¡BSB 203580 (1 μM)'Mmanumycin A (3 μM) «Æ¡A ф{ PD 98059 »Pmanumycin A ¥ i § „ ¥§ bradykinin⁄ o IKKα/β " ˝¡ ⁄˘¡A¸ƒSB 203580 ¥ u • ┤ † ⁄˘ ¡§KKα/β "˝ ‹ ¡ ⁄˘¡Bradykinin ¤ ¿E A549 † › M £F«Pof˜Ras/Raf/p44/42MAPK and p38 MAPK is upstream of bradykinin-induced IKKα/β activation. IκB-α"˝⁄ , ¶i¤ƒ˜p65 'Mp50 NF-κB ¶i⁄J † ›Mfi ⁄ § ¥ ~ ¡ A ⁄] ┼¥"Hfi ¶¡ƒ ⁄˘ o

IκB-α »P p65 ` ß˜⁄ ¡C" ƒX¥H⁄ W †"G – ϑ ¡AƒbA549 † ›M⁄¡Abradykinin , ¥ ‹ ¡ ⁄˘Ras/Raf/p44/42 MAPK ⁄¸ p38 MAPK "˝ , fi┤¡A¤ ⁄ oIKKα/β " " ‹⁄¡A¤˘IκB-α `C »˜⁄˘»P⁄ , ƒ ¶i@B‹ ⁄˘ NF-κB ¡C £F bradykinin⁄ oIκB-α ` ß˜⁄˘⁄ § ¥ ~ A┼H⁄y• ┤ ƒ¤p65 ` ß˜⁄ ¡C

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Abstract

The signal transduction pathway of bradykinin-induced COX-2 expression was studies in human pulmonary epithelial cell line (A549). The Ras inhibitor (manumycin A) and Raf inhibitor (GW 5074) concentration-dependently attenuated the bradykinin-induced COX-2 expression. The bradykinin-induced p44/42 MAPK but not p38 MAPK activation was inhibited by manumycin A and GW 5074. Bradykinin caused time-dependent increases in IKKα/β, IκB-α and p65 phosphorylation, IKKα/β activity in A549 cells. The IKKα/β activation was almost completely inhibited by manumycin A and PD 98059. However, SB 203580 partially inhibited IKKα/β activation. Taken together, these results suggest that bradykinin might activate IκB-α and p65 phosphorylation and IKKα/β activation in human airway epithelial cell line. The signal of Ras/Raf/p44/42MAPK and p38 MAPK is upstream of bradykinin-induced IKKα/β activation.

Keywords: Bradykinin, Cyclooxygenase-2, p44/42 MAPK, p38 MAPK, A549 cells.

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• † ·¤' ¶¸ƒ ┼ o"˝Ψ˝¤° ° ¿ E fi‹ •┤ ⁄ o ƒ … '¸kallikrein "˝‹ ¡ ⁄˘ A┼¶i⁄@

¤ B Æ–Nkininogen ⁄ , ƒ ¤ ¤ ª ƒ ¥˝ ”«d ¡¡'Â⁄¥ < ª A I $„Ð ”i⁄O¡ B † ›M ‴W¥˝¡ ¥ kinins[1] ¡C Bradykinin ‹ O @ » ¤ ƒ+⁄ E › i … ”˝˝ ¥X¡ B ´ ¥G”˝ e¸¥ •P»P ˜ ¥•fP« »˜⁄$kinin¡ A ¥ « e‹w ƒ¤« ƒh¥˝† z ¸flf , g”˝‹ ¦ °¡Cƒ L‰ƒpƒ ¡A†o¤ ·” ª¡' †£¥˝ † ²˝' °‰ Ł ¡ A ¥] ‹ A ⁄ _¥ ×•˜ƒY ”¥ƒ ”⁄S«eƒ Ç¢fl ¡ Æ ' $ Œt⁄S¥\fl ¥D›n‹O¤ ¿ ” ” ´ X – i ¡ B … W ¥ƒ' ”¡ B”˝+¥G²˝ ¢B ¥ ƒ ƒbS ‰ † ¡˜”˝¿ @ ”” $C¡B»P‹O$_ƒ † … W ¥ [” ⁄j †hista¥mine ”˝˜ 'æ¡B« ¶i ¤ fl $$”˝¤ ¯Øf ¥b¥H⁄ ¤ ' ‹ ¡⁄˜”˝ T„¶· neutrophil 'M eosinophil ” ‴W¥˝⁄» ⁄ fik h» … ,fi⁄S⁄ £P¡Aƒ]ƒ †£¥˝⁄ £P”˝¥\fl ¡C ”˝†£¥˝[1] ¡C Bradykinin ¥ ¥ i ¤ ° Ł«Ð˚k˜P † ”æ”„ Œ † $i¥ « ¥X bradykinin ¥i , g ¤†”¸˝¶ · ⁄ J ¤,⁄gƒ _ neuropeptide ”˝ ¤ ¿E eicosanoid ”˝ƒX¤⁄¸ cytokines ”˝†£ ˜ 'æ¡Aƒ]ƒ ⁄ ofl ¥g'° o” ¢ › ¡C• M„L ¥˝¡Cƒb⁄ ”„¥˝” ª¡† ´·¡Abradykinin ¥ ¤° – › ¤ ¿Efi † flf⁄ fi ¡A¥i o†{¤ ' I $„Ð$ ¿E IL-1β, IL-2, IL-6 ”˝” †{[9] ¡Fƒb⁄H^ ”˝– kinin ”˝¿ @ ƒ+– ª ” ” W¥ Ł B2 ¤ – ¥œ$ ”ß¥ † ›M bradykinin ¥ i ¤¿E IL-8 ”˝†£¥˝ fl¥if ¤fi ˜ $¤„ L –›' » ⁄o late phase ⁄$ [10] ¡Fƒb⁄H^ ”˝fi ” ¥ › • ƒ bradykinin ¥i o” ¢ › ²[2] ¡C¥ ¥~¡Abradykinin ‹ O @ ×« ›« ¤ ¿E COX-2 ”˝” †{'M PGE2 ”˝˜ 'æ[11] ¡C¥t ›n”˝» o”¢(pro-inflammatory)⁄¶‰ Ł Æ¤¥ ¡g¥ ¥~ƒb⁄H^ ”˝– ”ß¥ † M¡¥Æi o†{PGE2 ¥i…W … ¥[•Lƒ ”ƒ… ”˝” ¥X¡A¶if › Ł ”˝‹ –j IL-1β' ⁄ o⁄$ IL-6 'M IL-8 ”˝†£¥˝¡Cƒ fl Ł~¡Aƒ ⁄ o⁄ fi ” ”˝„L« ⁄ ˇ ª(bronchial bradykinin ¤ ª”‹O$_• |»⁄ ' I $„ÐW¥ † hyperreactivity)[1] ¡C ›M' ¸COX-2 ” †{¡ A ¸¤« O, g¥ ƒ ” Tfi$¶· ` C »^ƒA2 (phospholipase A2, PLA2) »...–N T„¥ † ›M‰⁄¶·ƒ † ›Mfi ¤ »⁄ †o¤· ‹O¤ ›¯Ø†£¥˝⁄@¤ fl ‰Ł^ o”¢⁄¶‰ Ł”⁄ @ ›« o”¢' °ª ¥ ‰ Ł”˝ †{¡A«hƒ ⁄ ' ¥¸..ƒª$ „ª ›n”˝» fl ¡ Æ ¥D›n”˝$ ¥ ¸O–N† ›M‰ ⁄W”˝ ”˝ª $i¡Cƒ ' I $„ÐW¥ † ›M‹O› «n”˝ o”¢ ` C ›‰Ł¥ Ñ´ƒ¤”Æ¥˝´¥ ┼m»˜¡Aƒ fiæ» fl † ›M ÆA»P' I $„Ð” o” ¢ › ª†› «n”˝^ (cyclo-oxygenase, COX)ƒA¶i⁄@¤ BÑ”Æ¥˝´¥| ª†s' °¡Cƒ]ƒ„¡A¥ »ª¤s› pe–N¤˜¥¸' I $„ÐW †m»˜ (arachidonic acid) ¥ Ñ´ƒ¤«eƒ Ç¢fl ¥ † M¡ºA–·¤s bradykinin ⁄ o COX-2 ” (prostaglandin) ¡ A ¥‹ A prostaglandin E2 †{”˝ T„¶· » … ,fi¡C (PGE2), prostacyclin (PGI2) 'M thromboxane A2 (TxA2)¡C¥ « e‹w”˝ C »^fl ⁄T¡B †”G»P Q‰ A2 ¤ ƒ+ƒh˝ £ƒP˝« ƒ¡¡A»P o” ¢ › ,ª3ƒ+ ƒbƒ ˜⁄@ƒ~⁄¸†˜⁄ Œ~”˝‹ ª¤s⁄⁄ o†{¡Afb ^ «Y”˝‹O⁄ ⁄ ¶q14 kDa ⁄$ secretory PLA2 A549 † ›M⁄¡ bradykinin ¥ ¡g¥ ‹ ¡⁄˜p44/42 (sPLA2) 'M 85 kDa ⁄$ cytosolic PLA2 MAPK ⁄¸ p38 MAPK ”˝, fi|⁄ o NF-κB (cPLA2)¡Cƒ fiæ» fl «hƒ+¤ ˝ £ƒP˝ƒP¥\ ”˝‹ ¡⁄˜¡A+ «Æ ›P COX-2 ”˝” †{¡C¢– » fl (isoforms) ⁄ $O‹O COX-1 ⁄¸ radykinin ¥ ¡g¥ ‹ ¡⁄˜B2 ¤ ¯Ø¤ ⁄ op44/42 COX-2[3] ¡C COX-1 ” ‹ ' Twƒ«sƒb MAPK ⁄¸ p38 MAPK ‹ ¡⁄˜¡Cƒb†˜⁄Tƒ~”˝‹ ª (constitutive form) ¤ ƒ $b« ƒh˝ ” ” † ›M¡A¤s⁄⁄$ › –N$ ¶i⁄@¤B–· Q bradykinin ›P ¥ ¡A⁄ ¥ † ›M¸ƒ P˝O¡A¥ ƒ ' †£¥ ˝$«e COX-2 ” ‹ »⁄ ««‹ (inducible form)¡A• ¤ ƒ Ç¢fl ¥D›n$ Œ ” ˝ß†«ø»M« 'w”˝¥\fl [3] ¡C ¤ ⁄@¤· o”¢' ª«‰Łƒp lipopolysaccharide (LPS) '¸ cytokines ƒp IL-1β, TNF-α ¥”˝ ¤ ¿E• |»⁄ ¤ ” † {[4,5] ¡C¶i⁄@¤B”˝„ Œ ¯⁄] ^ „ŒCOX-2 ¥D›n‹O› ¢d†£¥˝⁄@¤·, o”¢ƒ+ ^ ” «eƒ Ç¢fl [3] ¡Cƒ ¥B⁄£˝ ƒb¥ ¸ ”˝¥˝†z‹ ˝A' ¸ƒbfl f ²”˝ ‹ ª⁄µª” ª¡”˝† ´·$¡• |˜ 'æ¥X« ƒ ª˝ƒ«eÇ¢fl ¤ ‰,” I $„Ð˝¥\

1. Ras ⁄¸ Raf ¥]$tƒb bradykinin ¤°¿E COX-2 ” †{”˝ T, „¶· »..., fi|

• „ ¥ ¥Ł$ ¤ fmanunycin A (0.3, 1 'M 3 μM) ⁄¸ Raf $ ¤ fGW 5074 (0.3, 1 'M 3 μM) « e ª†z30 ⁄ ˜ ` « Æ ªƒA¥[⁄J

bradykinin (10^{-8} M) § ¥ ¸ 4 ⁄ p fi A o†{ manunycin A ⁄ ¸ GW 5074 ‹ ¥ H fl ¶‹ ˆ ˝ ⁄ Ł ƒ § COX-2 ˝ †{¡ C ¥ ‡ o ¤ ˙ †˝G¥ Ras ⁄ ¸ Raf ˝˝‹ ¡ ⁄ ˘ ‹ ¥] bradykinin ⁄ o COX-2 ˝ †{˝˝ T fi § ¶ ›…¡C fi|

2. Ras ⁄ ¸ Raf ¥]§tƒb bradykinin ¤°¿E p44/42 MAPK ‹ ¡⁄˘˝˝ T, „¶˙›…, fi|

¶ i ⁄ @ ¤ B § ›Ras ⁄ Raf ‹ O § _ »P‰ −−p44/42 'Mp38 MAPK ˝ ˝ ‹ ¡ ⁄ ˘ ¡ ● „w¥ manunycin A (3 μM) ⁄ ¸ GW 5074 (3 μM) « e B†20 ⁄ ˜ ` « Æ A ƒ bradykinin (10^{-8} M) § ¥ ¸ 5 ⁄ ˜ ¡A] ¥ io manunycin A ⁄ ¸ GW 5074 ¥i¥H§ ¤ bradykinin ⁄ o⁄§ p44/42 MAPK ˝ ˝ ‹ ¡ A ⁄ £vp38MAPK ˝ ‹ ¡' ° ¡C¥ ¥H⁄ W †˝¥i¥H− ¤ ¡A bradykinin ¥i¥H, g¥ , g¥ Ras ⁄ ¸ Raf ˝˝ T , „ ¶ ›…, ¤ ‰ −−p44/42 MAPK ˝ ˝ ‹ ¡˘ ¡C

3. Bradykinin ⁄ o A549 † ›M IκB-α ⁄ ¸ p65 ` C»˜⁄˘

§ › §Q¥ ¸ anti-phospho-IκBα 'M anti-phospho-p65 ⁄ § § ¯ ø ¶Western blot ¡ A ¥ H œIκBα 'Mp65 ` C » ˜ ⁄ ˘ ˝ {« ¡C • ¥H bradykinin ($10^{-8}$ M) ¤ ¿EA549 † ›M 5, 10, 20, 30 'M60 ⁄ ˜ «Æ A ¢{ IκBα ˝ ˝ C»˜ ⁄ ˘ƒb20 ⁄ ˜ `fi „ F ¤ ‡ ¡A30¶q ˜ «§E ¥v ˝ ¥ ·⁄¡Aƒ p65 ˝ ˝ ` ¤˜¡A ƒA10 ⁄ ˜ `fi „ F ¤ ‡ ¡C¥ ƒ ¥i¡Aƒb A549 † ›M⁄⁄¡A bradykinin ¥i¥H⁄ oIκBα ⁄ ¸ p65 ` C » ˜⁄˘ ¡C

4. Bradykinin ⁄ oIKKα/β ‹ ¡⁄˘

− ⁄ U ¡A § › ƒ§Q¥ ¸ anti-phospho-IKKα/β ⁄ § § ¯ ø ¶iƒ Western blot ¡ A ¥ H œIKKα/β ` C » ˜ ⁄˘˝˝ { « ¡ AH⁄ ¸ §¥ immunopreciptation ˝˝⁄ Łk¡A − N ¤ ¤ ‹ ¡˝˝ IKKα/β ¤ I ⁄U ¡Aƒ A „⁄' § @ ¤ ‰Ł¤ ¶ƒ⁄ ˘ ‡ A ˆ§ ¥ ¸ anti-phospho-IκBα ⁄ § § ¯ ø ¶Western blot ¡ A ¥ H œ'w IKKα/β˝˝‹ ¡' ° ¢ •¥H bradykinin ($10^{-8}$ M) ¤ ° ¿E A549 † ›M 3, 5, 10, 20, 30 'M60 ⁄ ˜ ` «Æ¡A ¢{˝˝ IKKα/β ` C ›˜⁄»P‹ ¡' ° … ¥[⁄ § ƒb5 'M10 ⁄ ˜ `fi „F¤ ‡ ⁄ j¡A⁄§«Æ H fi ¶¡… ¥[ƒ ‡ v ¥ ·¡C¥ ƒ„¥H⁄W † ˝ Go¡˝A bradykinin ¥ ¿ oIKKα/β ‹ ¡' ° … ¥[¡C

5. Ras ¡B p44/42 'M p38 MAPK ¥]§tƒb bradykinin ⁄ o IKKα/β ‹ ¡⁄˘˝˝ T, „ ¶˙›…, fi|

• „ ¥ ¥H manunycin A (3 μM)¡B (30 μM) ⁄ ¸ SB 203580 (1μM) « e B†20 ⁄ ˜ ` Æ¡AƒA ¥ ƒJ bradykinin ($10^{-8}$ M) ¤ ¿E3 'M5 ⁄ ˜ ` « ÆA ¢{ manunycin A ⁄ ¸ PD 98059 · X ¥¥i ¥ H§ „ ¥ ˝˝§IKKα/β ` C » ˜ ⁄ ›P¡A§ SB° 203580 « h ¥ ƒ‡ ‡ § ¤ ¡ ¥ ¥H⁄W˝˝ † G−o ˝ bradykinin ⁄ o IKKα/β ˝˝‹ ¡˘¥ifl , g ¥ Ras ⁄ ¸ p44/42 MAPK ˝˝ T fi § ¶ ›…¡A fi| ƒ p38 MAPK ¥ifl ¥ ¡ ⁄ »P‰ −−¡C ˝ ƒX¥H⁄W˝˝ † ˝ Go¡˝Aƒb A549 † ›M ⁄⁄¡A bradykinin , g¥ ‹ ¡˘ Ras/Raf/p44/42 MAPK ⁄ ¸ p38 MAPK ˝˝, fi|¡A¤ ⁄ o IKKα/β ˝˝‹ ¡˘¡A¤˘ IκB-α ` C » ˜⁄˘»P, ƒ ¶ i @¤B ¡˘ NF-κB¡C £F bradykinin ⁄ oIκB-α ` C ›˜⁄˘ §˜¡A⁄] • ‡ yp65 ` ¤˜ ⁄˘¡C

¥|¡B›p eƒ¤˝Gƒ ß

⁄@¡Bƒ„›p e− ·Q Bradykinin ⁄ o⁄ H ˆ 'I§l „D⁄W¥ † ›M COX-2 ˝ †{˝˝ T fi ¶˙›… , fi|¡C‡ o ¤ ˙ ‹ ¤s bradykinin ⁄ o ˝ ¢ fl g ˘ ¤ ·⁄@› ¥ifl ˝˝› P fl f ›ƒ]¡F ¥B‹ § o˝¢ˆ ˝«˝˝¶} o· ¤ ⁄@› •s˝˝ ⁄ ƒV¡C

⁄G¡B¥›‹ ¤s›p e· ¤ ⁄@ƒ ˝ ⁄ ƒZ§„ƒ¥˝ ¤ ˝ h‰¡C ¤ ‹ p44/42 'M p38 MAPK ¥ §tƒb bradykinin ⁄ o⁄ H ˆ'I § „D⁄W¥ † ›M COX-2 ˝ †{˝˝ T §¶˙ » … , fi¡C

⁄›¡B ƒ ⁄ ˜m

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