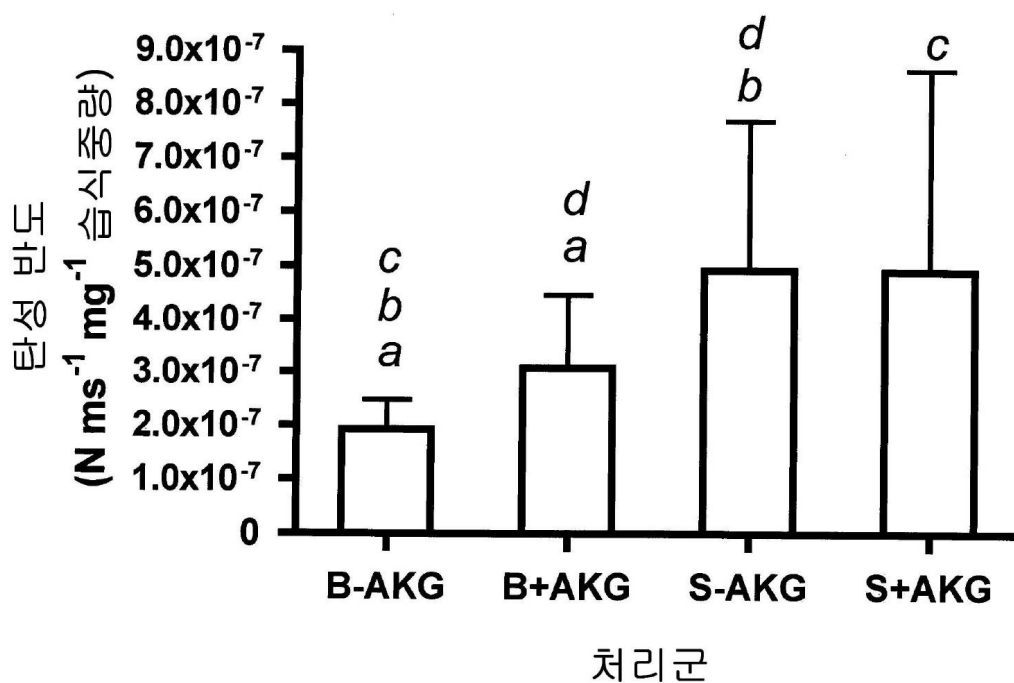
	(19) (12)	(KR) (A)	(11) (43)	10- 2010- 0039874 2010 04 16
(51)	Int. Cl.	(71)	17	- 111 57 14
	<i>A61K 31/194</i> (2006.01) <i>A61K 31/198</i> (2006.01)	(72)	- 211 14	21
	<i>A61P 9/14</i> (2006.01)	(74)		
(21)	10- 2010- 7002345			
(22)	( ) 2008 06 27			
(85)	2010 02 01			
(86)	PCT/SE2008/050797			
(87)	WO 2009/005464			
	2009 01 08			
(30)	0701602-5 2007 07 02 (SE)			
:	21			

(54)

(57)



1

, :

a) - (AKG);

b) - ;

c) , -  
;d) - ,  
.

2

1 , .

3

1 2 , , , ,  
/ .

4

1 3 , .

5

4 , , , .

6

1 5 , .

7

1 6 , .

8

1 7 , -  
.

9

8 , - - .

10

1 9 , , kg 1  
1000 ng .

11

1 10 , , kg  
10 400 ng .

12

1 11 , , kg  
10 100 ng .

13

- ;
- a. - (AKG) ;
- b. - ;
- c. , - ;
- d. - , .

14

13 , .

15

13 , , , , /  
.

16

13 , .

17

16 , , , .

18

13 , .

19

13 , .

20

13 19 , -  
.

21

20 , - - .

[0001]

- , , ,  
.

[0002]

[0003]

, 1992 NH  
5%  
(gastric bypass procedure)  
70% 10 ~ 14

[0004]

, Coate 25 (bone turnover)  
(hip trochanter)

[0005]

( > 160/90 mmHg) 67  
44 (66%)

[0006]

[0007]

(stiffness) (predictor)  
(Dernellis and Panaretou, Hypertension 2005; 45: 426- 431.).

[0008]

(PH) (exertion)  
(exercise tolerance)  
(VDI)  
(heart cause)

[0009]

) ( ) ( )

[0010]

/ / -

[0011]

[0012]

(bypass operation)  
:

[0013]

[0014]

a) - (AKG);



[0033]

[0034]

[0035]

[0036]

[0037]

[0038]

1000 ng 10 400 ng 10 100 ng kg 1

1 AKG (+AKG) (- AKG) (B) (sham operated  
 rat) (S) (elastic recoil) 1,000 /  
 A/D (force transducer)  
 $\pm$  SE : a & d = p < 0.05 b = p < 0.01,  
 c = p = 0.01. 4 : B- AKG n = 6, B+AKG n = 11, S- AKG n = 12  
 S+AKG n = 12

2 (stretch)  
 ( 13 ~ 14 kPa) 0.14% 1 /  
 2 3  
 ( (tension) 16%)  
 /

3

4 1 : (A) Na- AKG (B) Ca- AKG  
 1,000 / A/D  
 $\pm$  SE : a = P < 0.05  
 b = P < 0.01, c = P < 0.001. 3 n = 6

5 2 : (A) Na- AKG (B) Ca- AKG  
 1,000 / A/D  
 $\pm$  SE : a = P < 0.05  
 b = P < 0.01, c = P < 0.001. 3 n = 6

[0039]

[0040]

[0041]

[0042]

[0043]

[0044]

[0045]

[0046]

[0047]

[0048]

[0049]

[0050]

[0051]

[0052]

[0053]

[0054]

[0055]

[0056]

[0057]

[0058]

[0059]

[0060]

[0061]

[0062]

[0063]

[0064]

[0065]



(micelle), (erythrocyte ghost),

[0066]

[0067]

[0068]

pH 2 ~ 5, 2 ~ 4, pH 6  
~ 8

[0069]

[0070]

[0071]

0.05 M, 0.8%, 0.01 ~

[0072]

[0073]

[0074]

[0075]

[0076]

1:0.01 1:2 1:0.1 1:1.5 1:0.2 1:1.0

[0077]

100 ng/kg / 1 1000 ng/kg / 10 400 ng/kg / 10

[0078]

[0079]

[0080]

[0081]

[0082]

[0083]

[0084]

[0085]

[0086]

[0087]

[0088]

[0089]

[0090]

[0091]

[0092]

\_\_\_\_\_1

1) , 2)  
3)

AKC

(Lund University) (Department of Comparative Physiology)  
Sprague Dawley 12/12  
479 ± 5 g (Altronic no. 1314 Spezialfütterwerke, Lage, Germany)  
AKG  
(B-AKG) (n = 6), AKG (B+AKG) (n = 11), AKG (S-AKG)  
(n = 12), AKG (S+AKG) (n = 12)

95% CO<sub>2</sub>

(common iliac arteries)

3 ~ 4 mm 6 ~ 9 mm

(Harrison . Reprod Fertil Dev. 1997; 9(7): 731- 40, Harrison  
and Flatman Am J Physiol. 1999 Dec; 277(6 Pt 2): R1646- 53). 3.75 ±  
0.08 mm 8 ~ 25 ng ( 14.32 ng)

5.5 cm 3.2 cm NaCl 136.91 mM KCl 2.68 mM Na<sub>2</sub>HPO<sub>4</sub> 8.08  
mM NaH<sub>2</sub>PO<sub>4</sub> 1.66 mM (0.15 MPBS, pH 7.4) 44 ml

(37 °C) 8S PowerLab A/D (AD Instruments, Chalgrove, Oxfordshire,  
UK) (home-built bridge amplifier) FT03

(Grass Instrument, West Warwick, RI) 0 ~ 0.05 kg

0.004% 2 ng (reliable force) PowerLab 8S A/D

iBook G4 (running) Chart5 v. 5.4 (AD Instruments, Australia)

40,000 (40 KHz) 200

(differential)

3 (pre-amplifier unit)

(offset dial) 0

5 ( 0.09 N )

0.49 N (FT03 Grass )

2

1,000

[0093]

[0094]

LaPl ace

(T)

(r)

(p)

,  $T = p \times r$ 

LaPl ace

[0095]

[0096]

 $\pm$  SE

Gaussian Normal Distribution

student's paired t-  
(variance)

0.05

P

[0097]

[0098]

[0099]

, (wet weight) ng 0.034 N (0.49 N /14.32 ng  
) , LaPl ace 1.87 nm  
, 0.018 kPa  
(10 kPa) 0.18% , (13 ~ 14 kPa) 0.14%  
(Carroll . 2006; Duka . 2006).

[0100]

0.09 N ( $4.95 \times 10^{-3}$  Nng )

0.015 N (

16%

)

[0101]

[0102]

- (P = 0.007 ; B-AKG  
S-AKG  $1.9 \times 10^{-7} \pm 0.2 \times 10^{-7}$  N ns<sup>-1</sup> ng<sup>-1</sup> (vs)  $4.9 \times 10^{-7} \pm 0.8 \times 10^{-7}$  N  
ns<sup>-1</sup> ng<sup>-1</sup> ). AKG- (P = 0.44).

[0103]

[0104]

AKG- , -  
(P = 0.037 ; B+AKG S-AKG  $3.1 \times 10^{-7} \pm 0.4 \times 10^{-7}$  N ns<sup>-1</sup> ng<sup>-1</sup> (vs)  
 $4.9 \times 10^{-7} \pm 0.8 \times 10^{-7}$  N ns<sup>-1</sup> ng<sup>-1</sup> ). AKG- - ,  
- (B-AKG ; P = 0.047 ; B-AKG B+AKG  
 $1.9 \times 10^{-7} \pm 0.2 \times 10^{-7}$  N ns<sup>-1</sup> ng<sup>-1</sup> (vs)  $3.1 \times 10^{-7} \pm 0.4 \times 10^{-7}$  N ns<sup>-1</sup> ng<sup>-1</sup>  
( 1 ).

[0105]

[0106]

, ( , )  
( 2 ).

[0107]

[0108]

[0109]

[0110]

2

Roux-en-Y , Roux-en-Y ( ), , (bariatric) (Adrian 2003).

[0111]

(Coates 2004, Cowan and Buffington 1998, Fernstrom 2006),

[0112]

(phase)

[0113]

H<sub>2</sub>

[0114]

B12 B12 B12 70% (Lynch 2006, Shah 2006).

(Lynch 2006, Parkes 2006, Shah 2006).

pH (pumping syndrome)' (Lynch 2006).

[0116]

(Coates, Buffington 1998, Fernstrom 2006, Foley 1992).

[0117]

[0118]

[0119]

(2005)

?

?

Gokce

[0120]

[0121]

(turnover)

(bone turn-over)

%

[0122]

*(Stretch effect)*

[0123]

P Laplace  
 pn ,  $P = pn + T(1/r)$

r

T

 $P = T / r$ 

[0124]

AKG

[0125]

- AKG

AA

, AKG

AA

AKG

[0126]

[0127]

[0128]

AKG

[0129]

[0130]

2

[0131]

[0132]

1

[0133]

[0134]

(Lund University)

(the Ethical Review

Committee for Animal Experiments)

(M4-05),

(European Community regulations)

[0135]

[0136]

50 NMR (Department of  
Cell & Organism Biology) 12/12  
(Altromin no. 1314 Spezialfutterwerke, Lage, Germany)  
1 3  
76 182 76  $28 \pm 7$  g 1  
+ (2% w/v)  $\text{Na}_2\text{AKG} \cdot 2 \text{H}_2\text{O}$  (n = 6) 2  
+ (2% w/v)  $\text{Ca-AKG} \cdot \text{H}_2\text{O}$  (n = 6) 3  
(n = 6). AKG  
2% 10 ~ 15%

[0137]

95%  $\text{CO}_2$   
1 mm 4.5 mm  
(Harrison  
Reprod Fertil Dev. 1997; 9(7): 731-40 Harrison and Flatman Am J Physiol. 1999 Dec; 277(6 Pt 2): R1646-53).  
0.01 ng  
2.75 ng

[0138]

5.5 cm 3.2 cm  $\text{NaCl}$  136.91 mM  $\text{KCl}$  2.68 mM  $\text{Na}_2\text{HPO}_4$  8.08 mM  
mM  $\text{NaH}_2\text{PO}_4$  1.66 mM (0.15 MPBS, pH 7.4) 44 m  
(37 ) 8S PowerLab A/D (AD Instruments, Chalgrove, Oxfordshire, UK)  
(home-built bridge amplifier) FT03  
(Grass Instrument, West Warwick, RI) 0 ~ 0.05 kg  
0.004% 2 ng (reliable force) PowerLab 8S A/D  
iBook G4 (running) Chart5 v.5.4 (AD Instruments, Australia)  
40,000 (40 KHz) 200  
(differential)

[0139]

[0140]

2 (pre-amplifier unit)  
(offset dial) 0  
5 (0.09 N )  
0.49 N (FT03 Grass)  
2

[0141]

Chart v.5.4 (AD Instruments, Australia)  
(Average Slope calculation)  
(Average Slope) ( $\text{ms}^{-1}$ ) (trace selection)  
(best fit) (least-square line)

[0142]

[0143]

LaPlace (T) (r)  
(p)  $T = p \times r$   
LaPlace

[0144]

( $\text{ms}^{-1}$ ) ( $\text{N ms}^{-1}$ )

,  $\text{N ms}^{-1} \text{ ng}^{-1}$

[0145]

[0146]

$\pm$  SE Gaussian Normal Distribution  
 - (one-way) ANOVA  
 (variance) 0.05 P

[0147]

[0148]

[0149]

, (wet weight)  $\text{ng}$  0.178 N (0.49 N /2.75  $\text{ng}$   
 ) , Laplace 1.0 mm  
 , 0.178 kPa

[0150]

0.09 N ( $4.95 \times 10^{-3} \text{ N ng}$ )  
 0.015 N (16%)

[0151]

[0152]

1 2  $3.3 \times 10^{-5} \pm 7.8 \times 10^{-7} \text{ N ms}^{-1} \text{ ng}^{-1}$   
 $3.4 \times 10^{-6} \pm 9.4 \times 10^{-7} \text{ N ms}^{-1} \text{ ng}^{-1}$   
 90% ; 2 (vs) 1 (5).

[0153]

Na- AKG (A)

[0154]

Na- AKG , 1 2  $4.3 \times 10^{-5} \pm 1.6 \times 10^{-6}$   
 $\text{N ms}^{-1} \text{ ng}^{-1}$   $3.7 \times 10^{-6} \pm 1.1 \times 10^{-6} \text{ N ms}^{-1} \text{ ng}^{-1}$  Na- AKG  
 (4).  
 91% ; 2 (vs) 1 (5).

[0155]

Ca- AKG (B)

[0156]

Ca- AKG , 1 2  $6.4 \times 10^{-5} \pm 2.7 \times$   
 $10^{-6} \text{ N ms}^{-1} \text{ ng}^{-1}$   $3.8 \times 10^{-6} \pm 1.2 \times 10^{-6} \text{ N ms}^{-1} \text{ ng}^{-1}$  , Ca- AKG  
 (4).  
 94% ; 2 (vs) 1 (5).

[0157]

(arterial robustness)

[0158]

, ( , )  
 (5).

1

[0159]

, 0.49 N (3 1 )			
	1	2	(%)
	6 4	6 4	66.7
Na- AKG (A)	6 4	6 5	75.0
Ca- AKG (B)	6 4	6 5	75.0

[0160]

[0161]

[0162]

[0163]

[0164]

[0165]

6 119 mmHg ( 150 mmHg 92 mmHg) (Durant, 1927).

[0166]

120 mmHg (16 kPa) 1.8% (13 ~ 14 kPa) 1.4% (Carroll . 2006; Dika . 2006). (aortic media) (tangentially) (sheet) ; (tone) (McEnery . 2007).

[0167]

Laplace

Laplace

[0168]

Laplace ,  $P$   $r$   $T$   $p_n$   $P = p_n + T(1/r)$

$$P = T / r$$

Laplace

[0169]

[0170]

(Calabresi . 2007). (media) (Marin & Rodriguez-Martinez, 1999; Dao . 2005), (arterial tree) (Hjdu . 1990; Moreau . 1998; Laurant . 2004). (Jacob, 2003; Dao . 2005). (Cliff, 1970; Glandi . 1993), I III (Jacob, 2003; Dao . 2005; Marin, 1995).

[0171]

1 2 0.178 kPa 2 60 20 ( x ) (McEnery . 2007),



90% ( $\text{N ns}^{-1} \text{ ng}^{-1}$ ) , AKG 2

[0172]

AKG

[0173]

[0174]

(Krebs)

(MEni ery . 2007).

(Hammarqvist ., 1991).

, AKG

4-

-4

(pool)

(Son

[0175]

Na- AKG

Ca- AKG

Ca- AKG

AKG

Ca-

AKG

Ca- AKG

100 ml

2 g

, Na- AKG

50

, AKG

Na- AKG

AKG

10 /ml

Na- AKG

, AKG

10 /ml

Ca- AKG

AKG Ca- AKG

, AKG

[0176]

, AKG

(CPR99)

(He ., 2004).

G

G

AKG TCA

/

[0177]

[0178]

, AKG

( 1)

[0179]

[ ]

[0180]

[ ]

[0181]

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[0182]

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[0183]

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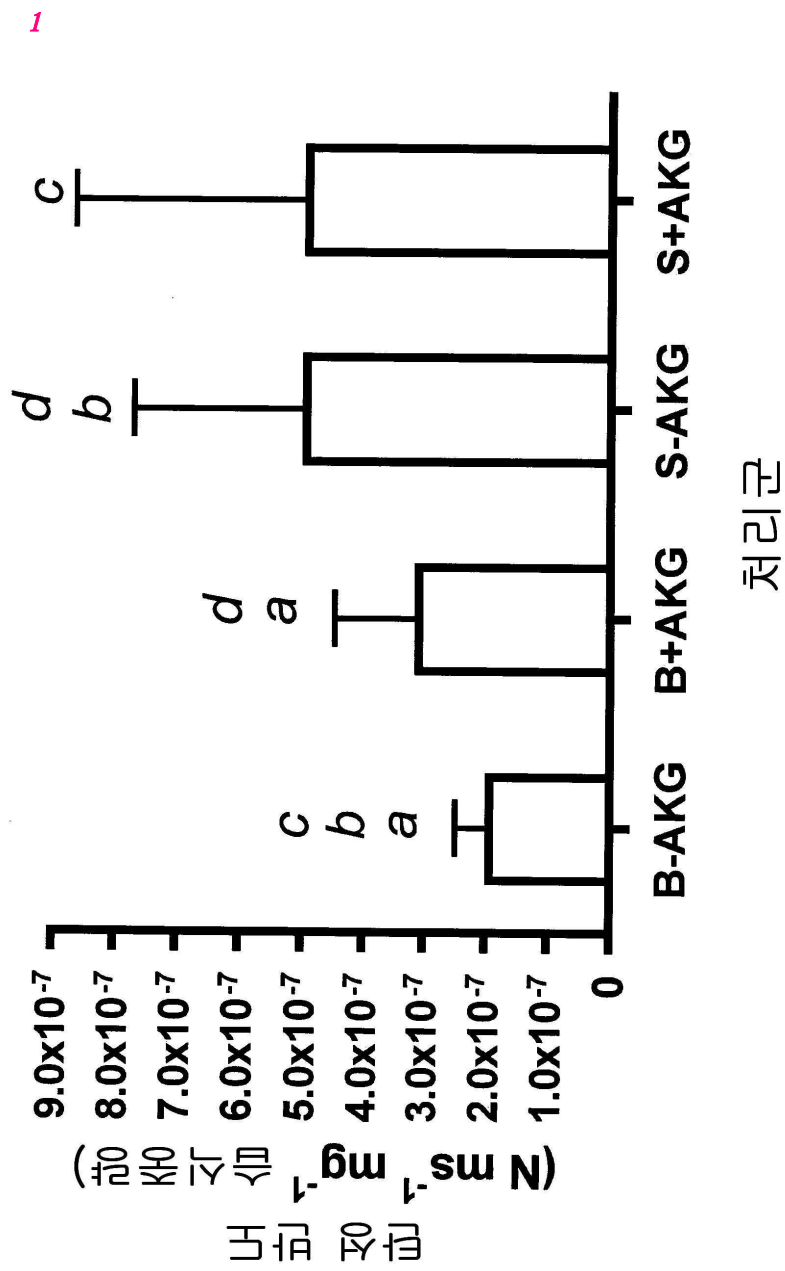
[0184]

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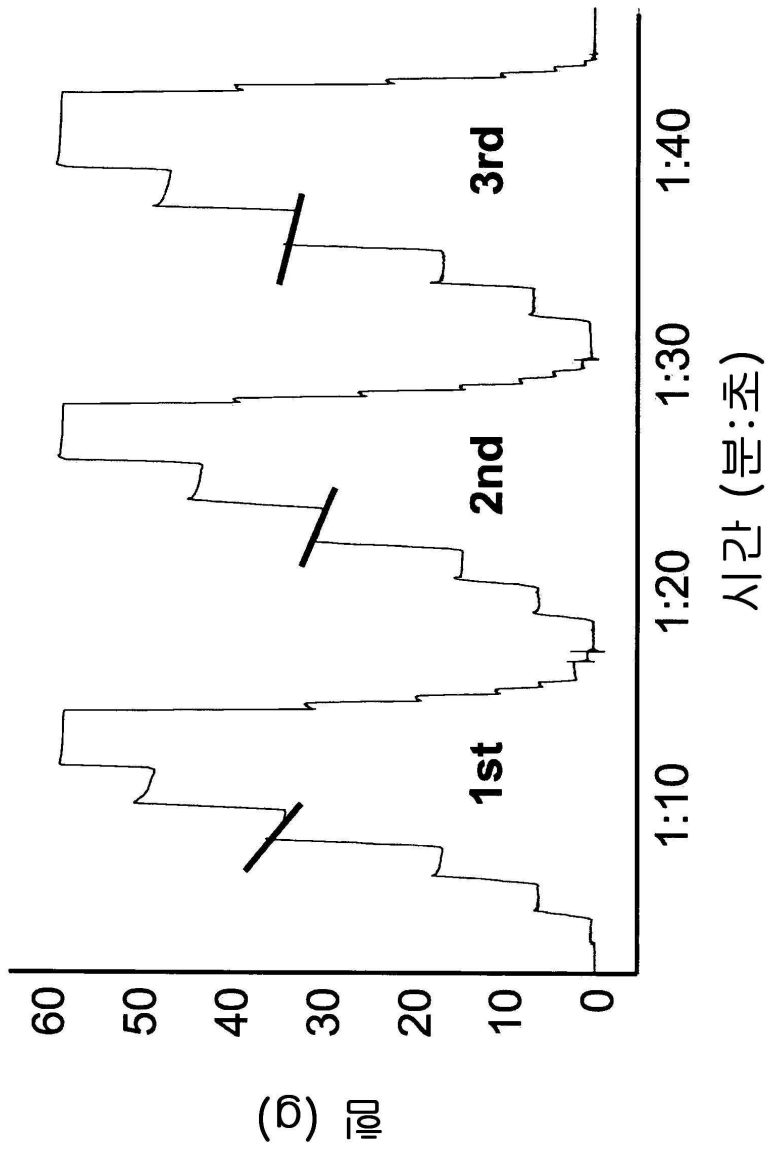
[0185]

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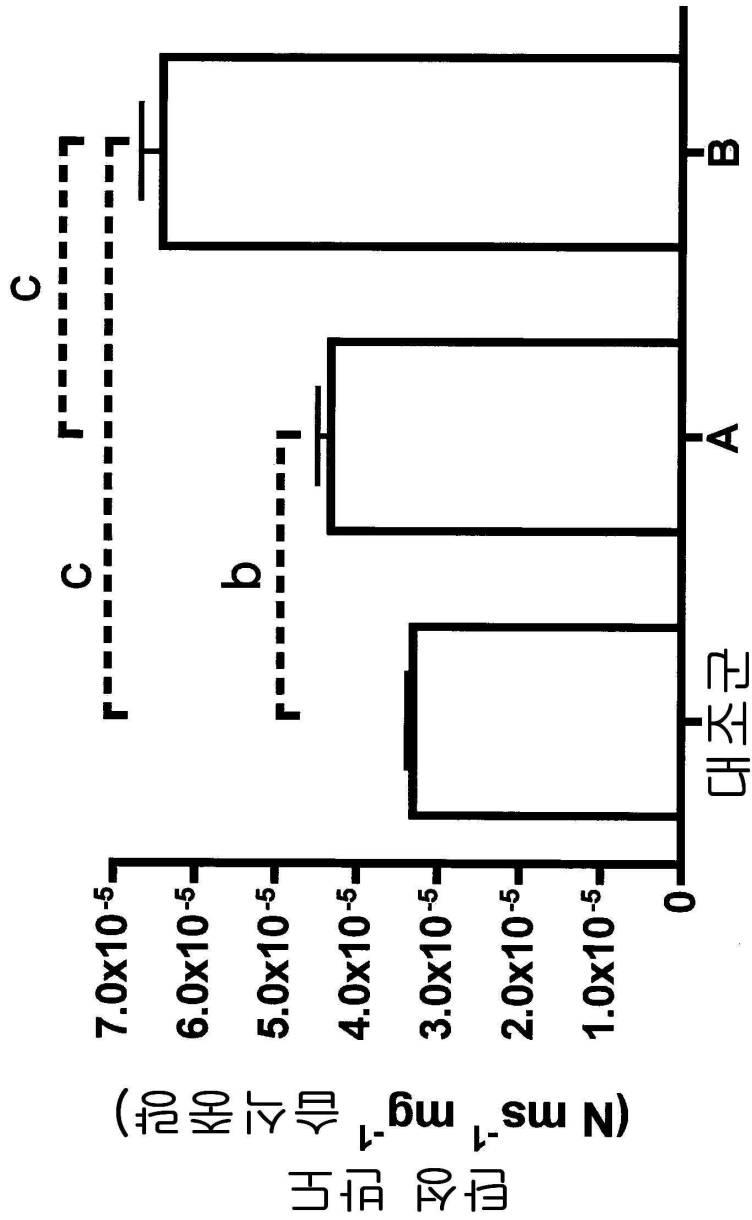
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4



5

