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2001. 11.

	1
I.	3
II.	5
1.	5
2.	5
3.	5
4.	8
III.	9
1. NE	9
2. KCl	9
3. NE	10
4. Ca ²⁺ NE 가	10
5. Ca ²⁺ caffeine 가	11
IV.	20
V.	23
	24
	28

1.	7
2. NE	12
3. KCl	13
4.	NE	14
5.	NE fluoxetine	15
6.	NE mirtazapine	16
7.	NE venlafaxine	17
8.	Ca ²⁺ NE 가	18
9.	Ca ²⁺ caffeine 가	19

가

(serotonin selective reuptake inhibitor, SSRI) , (Pacher , 1998) 가 3-6

가

(serotonin norepinephrine reuptake inhibitor, SNRI) venlafaxine (noradrenergic and specific serotonergic antidepressant, NaSSA) mirtazapine 가 .

NE, KCl, caffeine fluoxetine, mirtazapine venlafaxine . , NE fluoxetine mirtazapine venlafaxine 가 .

, KCl fluoxetine venlafaxine mirtazapine . , NE 가 .

, Ca²⁺ NE fluoxetine mirtazapine venlafaxine 가 . , Ca²⁺ caffeine venlafaxine 가 , fluoxetine mirtazapine .

, fluoxetine mirtazapine Ca²⁺
venlafaxine Ca²⁺

가 .

: , , , , fluoxetine,
mirtazapine, venlafaxine.

가

<

>

I.

(tricyclic antidepressant)

imipramine

가

(Kuhn, 1958).

(NE),

(5-HT)

(DA)

가

(Garver Davis,

1979).

(Marshall Forker, 1982; Glassman

Preud'homme, 1993).

(Vohra , 1975)

(Glassman , 1979)

(Glassman Shapiro, 1998)

, 1980

5-HT

(serotonin selective

reuptake inhibitor, SSRI) 가 , (Pacher , 1998) (Ferguson, 2001) 가 3-6 가 (Charney, 1998).

(serotonin norepinephrine reuptake inhibitor, SNRI) venlafaxine (noradrenergic and specific serotonergic antidepressant, NaSSA) mirtazapine 가 (Kent, 2000). Venlafaxine , , , mirtazapine 가 (Kent, 2000). 가 가

(Adrianus , 1999) 가 fluoxetine, mirtazapine, venlafaxine 100 nM NE 35 mM KCl NE Ca²⁺ Ca²⁺ NE caffeine

II.

1.

300gm (Sprague-Dawley rat)

2.

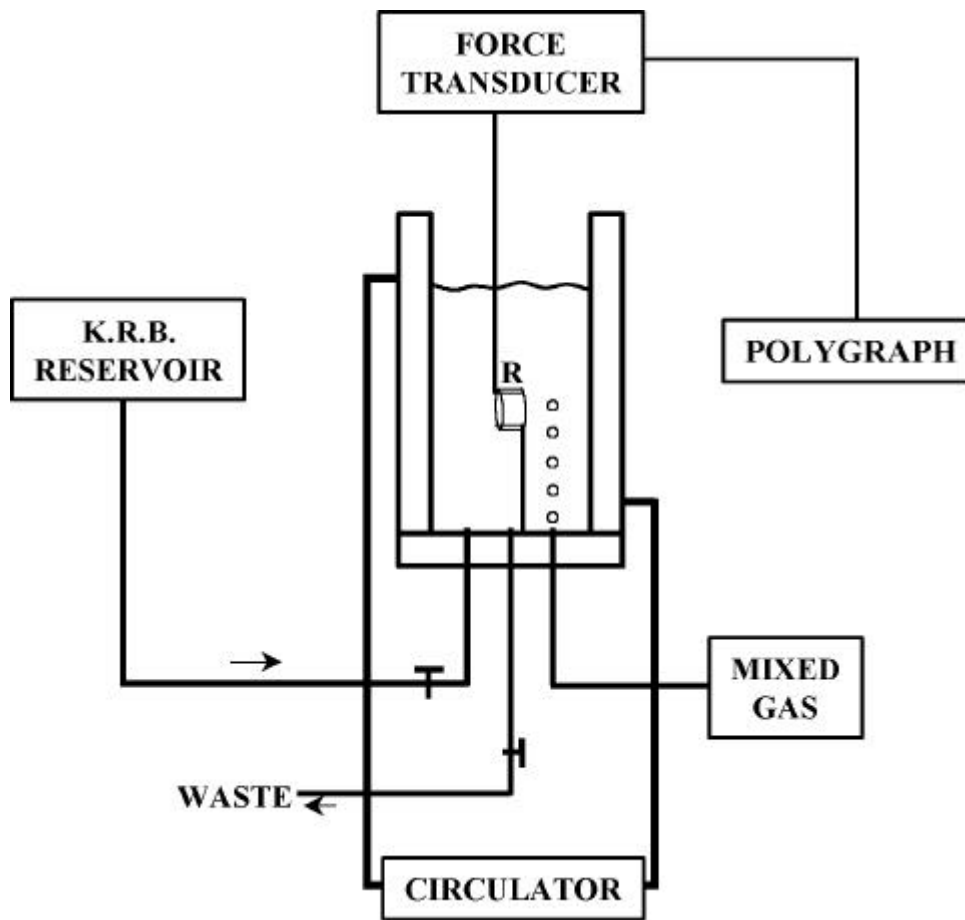
Kreb Ringer Bicarbonate(KRB),
(mM) NaCl 117, NaHCO₃ 24.8, KCl 4.7, MgSO₄ 1.44, CaCl₂ 1.91, KH₂PO₄
1.19, D-glucose 5.73, 95% O₂, 5% CO₂ pH 7.4
Ca²⁺ CaCl₂ calcium chelating agent
EGTA(1 mM) 가 SSRI fluoxetine,
SNRI venlafaxine NaSSA mirtazapine . Fluoxetine Lilly,
venlafaxine Wyeth-Ayerst mirtazapine Organon
. Mirtazapine methyl ether 100 mM
10 μM 1 mM 10 μ
M 10 mM, -20 °C
Acetylcholine(Ach), NE, caffeine KCl Sigma (Sigma Chemical Co.,
St. Louis. MO, USA)

3.

sodium thiopental(50 mg/ kg, i.p.)

heparin(500 IU/ kg)

3-4 mm KRB
 가 forcep
 KRB
 incubation bath L 가 stainless steel
 force transducer(Model FT03C, Grass Instruments, Quincy, MA, U.S.A.)
 polygraph(Model 7E, Grass Instruments)
 Incubation bath KRB 37 °C , 95% O₂, 5% CO₂
 500 mg 60
 KRB 3-4
 Furchgott Zawadzki(1980)
 100 nM NE 가 1 μM Ach
 80% 가 , 1 μM Ach
 가
 100 nM NE 35 mM KCl 3-4 가
 10
 100 nM NE 35 mM KCl
 100 nM
 NE
 Ca²⁺ 1 μM
 Ca²⁺ 100 nM NE 30 mM
 caffeine



1. . L 가 stainless steel bath , force transducer polygraph . Circulator organ bath 37 , KRB . R; ring, K.R.B; Kreb Ringer Bicarbonate .

4.

± , NE, KCl
(nonlinear regression analysis)
NE (two way
ANOVA) . 1 μM NE,
caffeine (one
way ANOVA) . p 0.05 가
Prism 3.0(GraphPad Software Inc., San Diego,
CA, USA)

III.

1. NE

100 nM NE, 1 μM Ach, 100 nM NE 3-4
가 . 가
20
NE .
3 incubation bath KRB
. Fluoxetine mirtazapine
. Fluoxetine log IC₅₀
-6.628 mirtazapine log IC₅₀ -6.430 . venlafaxine
가 (2).

2. KCl

Fluoxetine NE
log IC₅₀ -6.561 . Mirtazapine venlafaxine KCl
, venlafaxine NE
가가 (3).

3. NE

100 nM NE

1 μ M Ach

가

NE

가

(4).

가

가

(5, 6, 7).

4. Ca^{2+} NE

가

KRB

100 nM NE

가

KRB

CaCl₂

calcium chelating

agent EGTA 1 mM

가

100 nM NE

KRB

. 30

1 μ M

10

KRB

CaCl₂

calcium chelating agent EGTA

1 mM 가

100 nM NE

. NE

가

Ca^{2+}

, fluoxetine

mirtazapine

venlafaxine

가 (8).

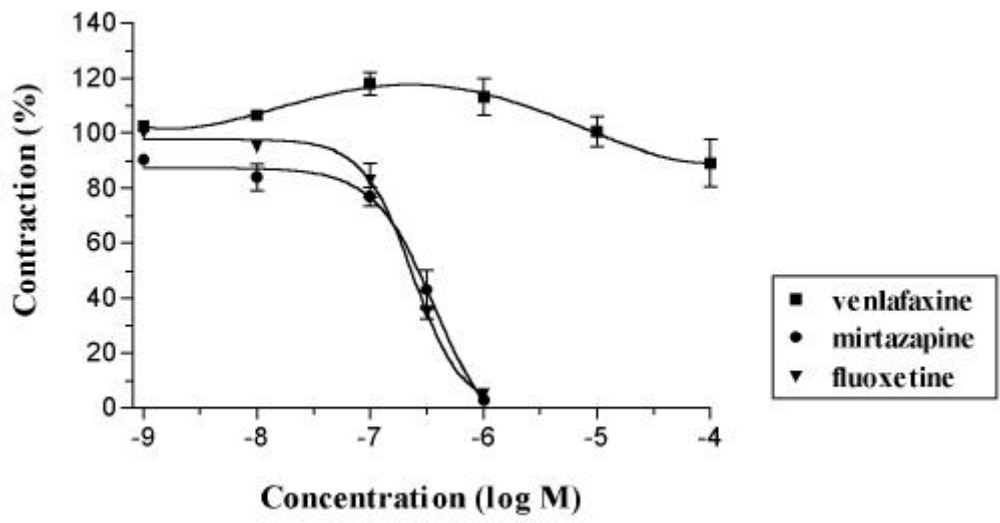
5. Ca^{2+} **caffeine**

가

.

KRB CaCl_2 calcium chelating agent EGTA 1 mM
가 가 caffeine 30 mM
가
Fluoxetine mirtazapine 가
venlafaxine 가

(9).



2. NE

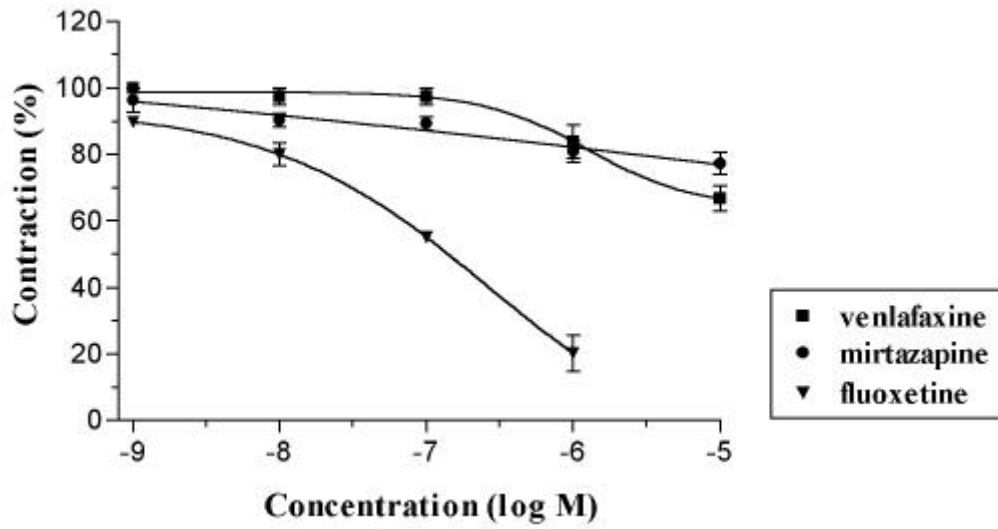
. 100 nM NE

, fluoxetine, mirtazapine, venlafaxine

10⁻⁹ M 10⁻⁴ M 10 NE(100
nM)

±

6 .



3. KCl

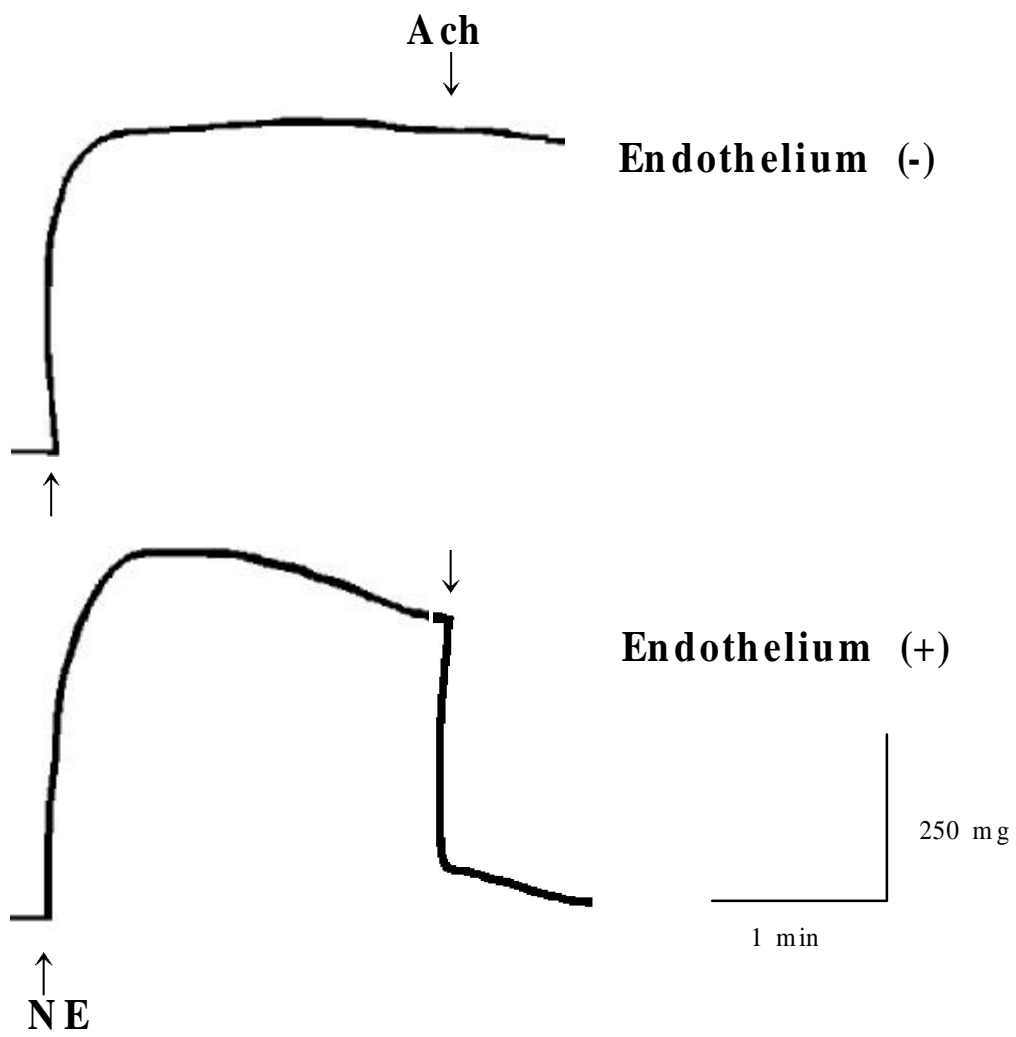
. 35 mM KCl

fluoxetine, mirtazapine, venlafaxine

10⁻⁹ M 10⁻⁵ M 10 KCl(35
mM)

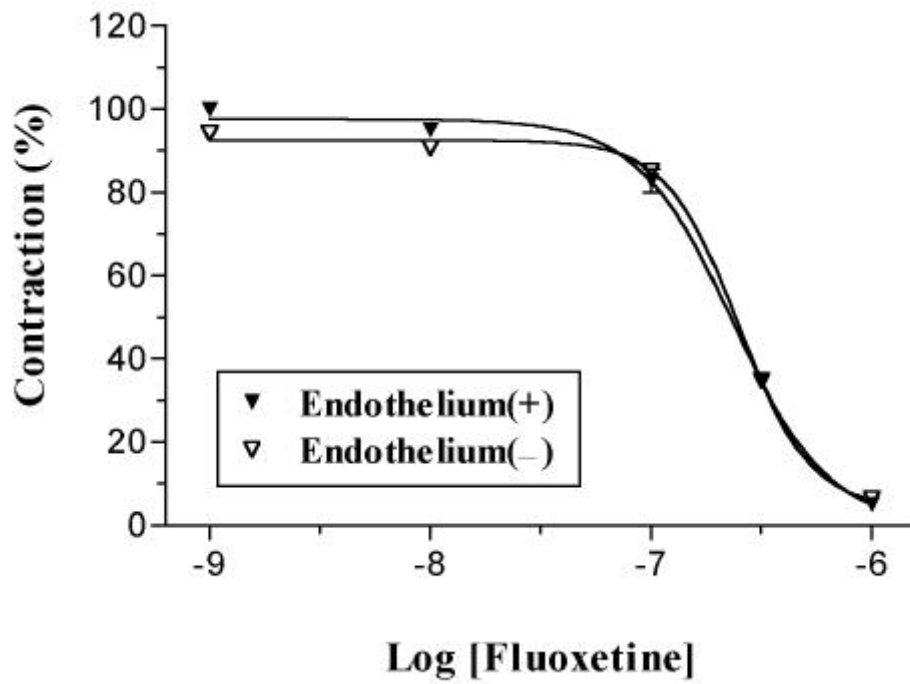
±

5 .



4.

NE (100 nM) , Ach (1 μ M) 가 , 가



5.

NE

fluoxetine

. 100 nM NE

, Ach(1 μ M)

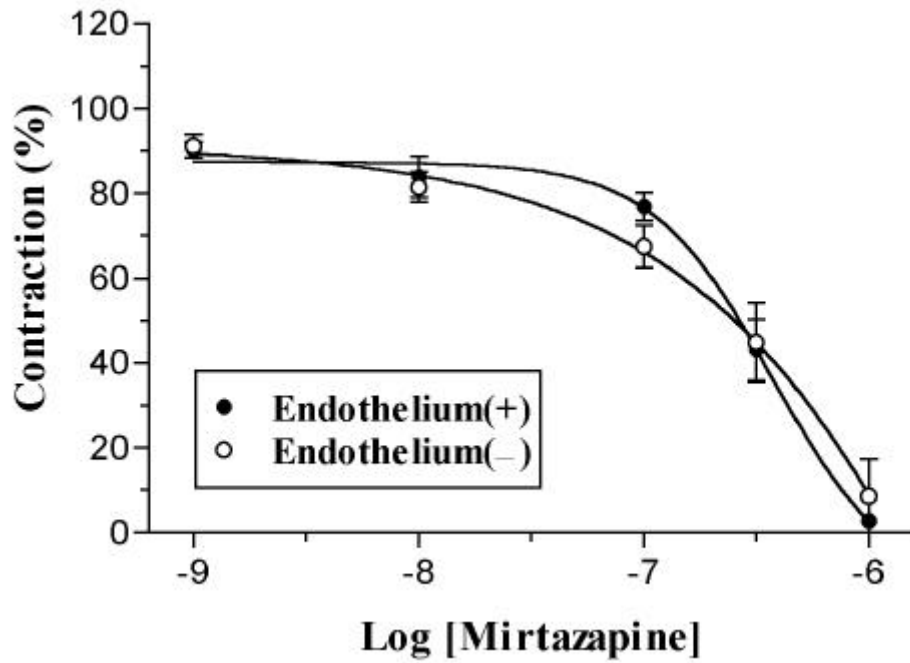
. Fluoxetine 10^{-9} M 10^{-6} M

10

NE(100 nM)

\pm

5 .



6.

NE

mirtazapine . 100 nM NE

, Ach(1 μ M)

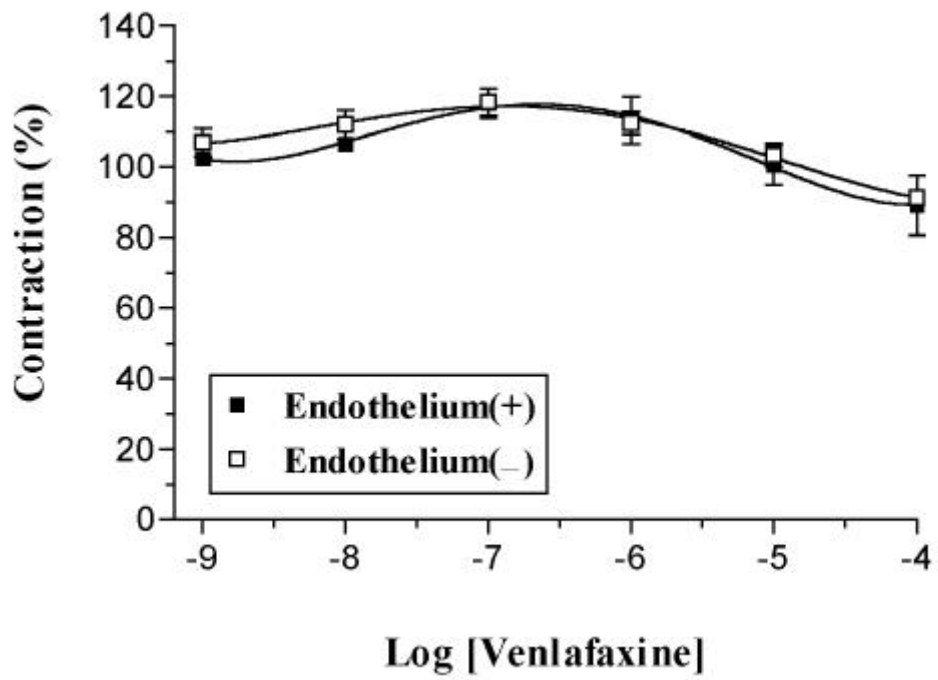
. Mirtazapine 10^{-9} M 10^{-6} M

10

NE(100 nM)

\pm

5 .



7. NE

venlafaxine . 100 nM NE

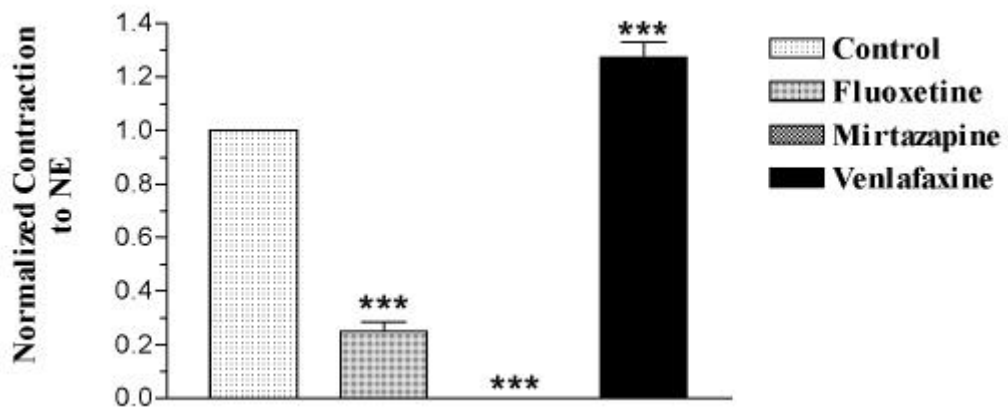
, Ach(1 μ M)

. Venlafaxine 10^{-9} M 10^{-4} M

10 NE(100nM)

\pm

5 .



8. Ca^{2+} NE

가

. 100 nM NE

,

10^{-6} M

Ca^{2+}

NE(100 nM)

.

±

.

5

. ***

P<0.001

IV.

SSRI SNRI NaSSA

fluoxetine 가 가 NE KCl

Ca²⁺ KRB NE caffeine

. Fluoxetine NE, KCl

(Park , 1999). Mirtazapine

가 가 NE KCl

Ca²⁺ KRB NE caffeine

. Venlafaxine NE

가 KCl 가 10⁻⁷

M Ca²⁺ KRB NE

caffeine 가

NE

phospholipase C Ca²⁺

inositol 1,4,5-triphosphate (Villalobos-monila , 1982) Ca²⁺

Ca²⁺ 가 phospholipase C activator

diacylglycerol (Shearman , 1989). K⁺

Ca²⁺ 가

(Van , 1970). Ca²⁺ Ca²⁺

. fluoxetine

Ca²⁺

. Mirtazapine K⁺

Ca²⁺

가

Venlafaxine 가

K^+
 Venlafaxine caffeine 가
 sarcoplasmic reticulum (SR) Ca^{2+} inositol
 1,4,5-triphosphate Ca^{2+} 가
 ryanodine (RyR)가 (Sanders, 2001) caffeine ATP
 (Duke Steele, 1998) RyR
 (Hymel, 1988). Venlafaxine 가
 RyR inositol 1,4,5-triphosphate 가 SR
 Ca^{2+} Ca^{2+}
 inositol 1,4,5-triphosphate 가
 (Iino, 1999). inositol 1,4,5-triphosphate
 가 , heparin inositol
 1,4,5-triphosphate (Kume, 1997)
 inositol 1,4,5-triphosphate
 xestospongine C RyR 가 (Gafni
 , 1997). caffeine venlafaxine
 fluoxetine, mirtazapine, venlafaxine
 NE
 (Yu, 1996). 가
 NE 가
 가 NE nitric oxide(NO) 가
 (Ishibashi, 1997). NO cyclic
 guanosine-3',5'-monophosphate(cGMP) 가
 , cGMP protein kinase G dihydrophyridine sensitive Ca^{2+}
 Ca^{2+} (Clapp Gurney,

1991) myosin light chain kinase(MLCK) MLCK

.

, fluoxetine

. Mirtazapine fluoxetine

(Mongomery, 1995)

fluoxetine Ca²⁺

가 . Venlafaxine

O-desmethylvenlafaxine , venlafaxine 75 mg

375 mg 15 O-desmethylvenlafaxine 341 nM

1715 nM (Harvey , 2000). venlafaxine

, venlafaxine NE

가

(Abdelmawla , 1999) venlafaxine

90mmHg

(Kent, 2000). venlafaxine

.

가

,

.

가

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Abstract

Effects of antidepressants on contractions of rat inferior vena cava

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The therapeutic action of antidepressants may be accompanied by unwanted effects on the cardiovascular system. This study was undertaken to investigate the effects of antidepressants (fluoxetine, mirtazapine and venlafaxine) on contractions induced by NE, high K^+ (35 mM) and caffeine on rat inferior vena cava.

Inferior vena cava was isolated from Sprague-Dawley rat, and vascular tone was measured under isometric condition.

The main results were as follows;

1. Fluoxetine and mirtazapine significantly reduced the maximal contractile response to NE. But, venlafaxine increased contractile response to NE.
2. Fluoxetine dose-dependently inhibited the high K^+ induced contraction. In contrast, mirtazapine and venlafaxine did not affect the high K^+ induced contraction.

3. Effects of antidepressants on contraction were independent of the presence endothelium.

4. Fluoxetine and mirtazapine concentration-dependently inhibited NE-induced contraction in calcium-free solution. Venlafaxine increased contractile response to NE.

5. Venlafaxine increased caffeine-induced contraction in calcium-free solution. Fluoxetine and mirtazapine were without effect.

These results showed that fluoxetine, mirtazapine and venlafaxine affect on rat inferior vena cava through different mechanisms. Fluoxetine could act as both adrenoceptor antagonists and inhibitors of voltage dependent calcium channels. Mirtazapine, a structurally distinct from fluoxetine, might principally exert its action at adrenoceptors on rat inferior vena cava. Venlafaxine can potentiate vasoconstrictor response to NE and caffeine. In conclusion, effects of antidepressants on vasoconstrictions are related to Ca^{2+} , and these effects may contribute to their side effects such as orthostatic hypotension and hypertension.

Key Words: antidepressant, orthostatic hypotension, inferior vena cava, Ca^{2+} fluoxetine, mirtazapine, venlafaxine.