นิพนธ์ต้นฉบับ

In vitro effects of allicin upon the contraction of pregnant rat uterine musculature.

Somsak Borvonsin*
Saifon Saridikhul** Ratree Sudsuang***

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Our experiments were designed to determine the effects of allicin on the contraction of Wistar rat uterine muscle. Single 1 cm. lengths of horns from 7, 14 and 21 day pregnant rats were used. The segments were mounted in 20 ml of van Dykes Hasting buffer at 37°C for 20 minutes. Three doses of allicin at 0.22, 0.44 and 0.88 mM were added to the solution for each treatment. The mechanism of allicin effects was determined by the application of prazosin for alpha-1 receptors; yohimbine for α-2 receptors, indomethacin for prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) receptors and calcium channel blockers, and nifedipine, verapamil and chlorpromazine for calcium channel. The results suggested that 0.44 and 0.88 mM doses of allicin significantly increased the force of contraction on 14 and 21 day pregnant rat muscle (P<0.01). The 21 day pregnant uterine muscle test results demonstrated that allicin exerts through α-1 adrenergic and $PGF_{2\alpha}$ receptors and calcium channel. The force of contraction was enhanced as the extracellular calcium concentration increased from 0.5-2.0 mM in a dose dependent fashion (P<0.01). Allicin also enhances the contraction induced by calcium. It was noted that allicin did not act via α-2 receptors in this study.

Key words : *Allicin, Rat uterus at preparturition, α adrenoceptors, $PGF_{2\alpha}$ receptor, Calcium channel.*

Reprint request : Borvonsin S, Department of Physiology, Pramongkutklao College of Medicine, Rajavithi Rd, Bangkok 10400, Thailand.

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*Department of Physiology, Pramongkutklao College of Medicine, Rajavithi Rd, Bangkok 10400, Thailand.
**Buddhachinarach Nursing College, Pitsanuloke Province.
***Department of Physiology, Faculty of Medicine, Chulalongkorn University.

สมศักดิ์ บวรสิน, สายฝน สฤษดิกุล, ราตรี สุดทรวง, ผลของอัลลิซินต่อการหดตัวของกล้ามเนื้อมดลูกหนูแรทตั้งท้องที่แยกออกมา. จุฬาลงกรณ์เวชสาร 2538 ธันวาคม; 39(12): 879-891

ใช้กล้ามเนื้อมดลูกหนูแรทยาว 1 ซม. จากหนูที่ตั้งท้อง 7, 14 และ 21 วัน แขวนลอยใน 20 มล. ของ Hasting buffer แล้วหยดอัลลิซิน 0.22, 0.44 และ 0.88 mM ลงไป และศึกษากลไกการออกฤทธิ์ของอัลลิซิน โดยใช้ prozosin, yohimbine, indomethacin, nefedipine, verapamil และ chlorpromazine

ผลการศึกษาพบว่าอัลลิซิน 0.44 และ 0.88 mM เพิ่มการหดตัวของกล้ามเนื้อมดลูกที่ตั้งท้องระยะ 14 กับ 21 วันได้ ($P<0.01$) ในมดลูกหนูแร็ทที่ตั้งท้อง 21 วัน อัลลิซินแสดงฤทธิ์ผ่านทาง α-1 adrenergic กับ $PGF_{2\alpha}$ receptors และผ่านทาง calcium channel, ($P<0.01$) แต่ไม่ผ่านทาง α-2 receptor การหดตัวเพิ่มขึ้นตามปริมาณของแคลเซียมนอกเซลล์ ($P<0.01$) อัลลิซินเพิ่มการหดตัวของกล้ามเนื้อมดลูกที่เหนี่ยวนำโดยแคลเซียมได้ ($P<0.01$)

A number of reports have demonstrated that garlic extract (Allium sativum, Linn) solution induces contraction of uterine muscle. 0.5 ml (3 mg) of commercial garlic fed to rats showed regulated rhythmicity, form and amplitude of contraction of uterine muscle. An in vitro study with garlic solution increased the rate of contraction during proestrus and diestrus.[1] 31-50 mg/ml of garlic extract contained an equivalent of 0.003 I.U. oxytocin for guinea pig uterus.[2] Many authors have claimed the estrogenic activity of garlic solution on uterine contraction in rats[3,4] and mice.[5] In humans, alcoholic extracts of garlic have been found to increase contractions of the non-pregnant uterus.[6,7] It is postulated that the garlic extract (allicin) induces the contraction of rat uterus muscle during the estrous phase by an opening of calcium channel.[8] It has also been found that the garlic extract exerts its action on uterine muscle at the proliferative phase of the menstrual cycle through the induction of increased intracellular free calcium.[9]

The objective of our study was:

1. to investigate the effects of allicin on 7,14 and 21 day pregnant rat uterine muscle.
2. to elucidate the mechanisms of allicin on pregnant rat uterus muscle at preparturition.

Materials and Methods

1. Animals

Thirty female Wistar rats, 2-3 months of age, were raised in a control room. The room was kept light for 12 hours and dark for 12 hours each day. The temperature was constant at 28°C. The animals were fed a standard commercial diet and given water ad lib. The animals that showed a proestrous phase were allowed to breed with male rats. Conception was confirmed the next day by vaginal smear.

2. Instruments

The instruments used in the experiment included an organ bath (double walled Harvard Bennett-type), a thermoregulating pump (Churchill type), dynograph (Beckman RM), isotonic force transducer (Statham UC3), blender, and a gas chromatograph.

3. Garlic and chemicals

3.1 Garlic: the allicin extracted by chloroform of which the technique was described by Poolsanong.[10]

3.2 The chemicals used were as follows: van Dykes Hasting solution, Norepinephrine HCl (Sigma), Prostaglandin F2 (Sigma), Calcium chloride (Merck), Prazosin HCl (Sigma), Yohimbine HCl (Sigma), Indomethacin(Sigma), Verapamil HCl (Isoptin, Knoll), Nifedipine (Bayer), Chlorpromazine HCl (Sigma) and EDTA (ABM Chemical). The standard allyl disulfide (Sigma) was also used to compare the purity of the allicin in the prepared solution.

4. Preparation of uterine muscle

One-centimeter of clear and clean uterine horn from the rats at 7, 14 and 21 days pregnancy were aerated with 95% oxygen and 5% carbon dioxide. The horn was then mounted in 20 ml. of van Dykes Hasting buffer in an organ bath. One end was ligated to the glass rod and the other to the isotonic force transducer. A weight of 1 gm was attached and allowed equilibrate for 15 minutes.

5. Preparation of allicin solutions

The concentration of allicin solutions were tested in the preliminary study. It was found that the concentration of 0.44 mM is the optimal dose for 21-day pregnant uterine contraction. Thus the lower concentration, 0.22 mM and the

higher one, 0.88 mM were applied in the study.

6. Experimental protocol

6.1 The experiments were recorded in terms of force, rate and form of contraction.

6.2 The following agonists and antagonists were used as pre-treatments. The opimal dose from each was applied to study the effects of the allicin on the uterine muscle. They were : norepinephrine as an agonist for α adrenergic receptors, prazosin for α-1 antagonist and yohimbine for α-2 receptors,[11,12] prostaglandin F2α as an agonist[13] and indomethacin as an antagonist[11]; verapamil and nifedipine as calcium antagonists[13,14], chlorpromazine as a calmodulin antagonist[15] and EDTA as a calcium chelator.

7. Statistical analysis

The results were presented as mean and standard deviations. The students paired t-test and analysis of variance of factorial design (4 x 3) were used to evaluate the levels of significant difference of the mean values. Probability values of less than 0.05 were accepted to be significant.

Result

1. Contractile responses of isolated uterine muscle with various doses of allicin versus different periods of pregnancy.

As shown in table 1 and figure 1 none of the all doses of allicin affected the contraction of uterine muscle at 7 day pregnancy. Also, allicin at 0.22 mM did not increase the force of contraction through the period of pregnancy. Allicin, 0.44 and 0.88 mM increased the contraction of uterine muscle on 14 and 21 days of pregnancy.($P<0.01$). There were also significant differences between the doses of allicin at each semester of pregnancy.

Table 1. Force of uterine contraction on various concentractions of allicin at each semester of preganacy.

Period of Pregnancy	Force of contraction (gm) (mean ± SD; n = 10)			
	Doses of allicin (mM)			
	Control	0.22	0.44	0.88
7 days	1.17 ± 0.47	1.18 ± 0.50^{NS}	1.34 ± 0.67^{NS}	1.55 ± 0.81^{**NS}
14 days	0.84 ± 0.23	1.23 ± 0.94^{NS}	2.25 ± 0.94**	2.16 ± 0.79**
		**		**
21 days	0.94 ± 0.18	1.02 ± 0.44^{NS}	1.63 ± 0.23**	2.23 ± 0.60**
		**		**
			**	**

**,$P<0.01$; NS, non-significant relative to control

**_____*, significant difference between doses

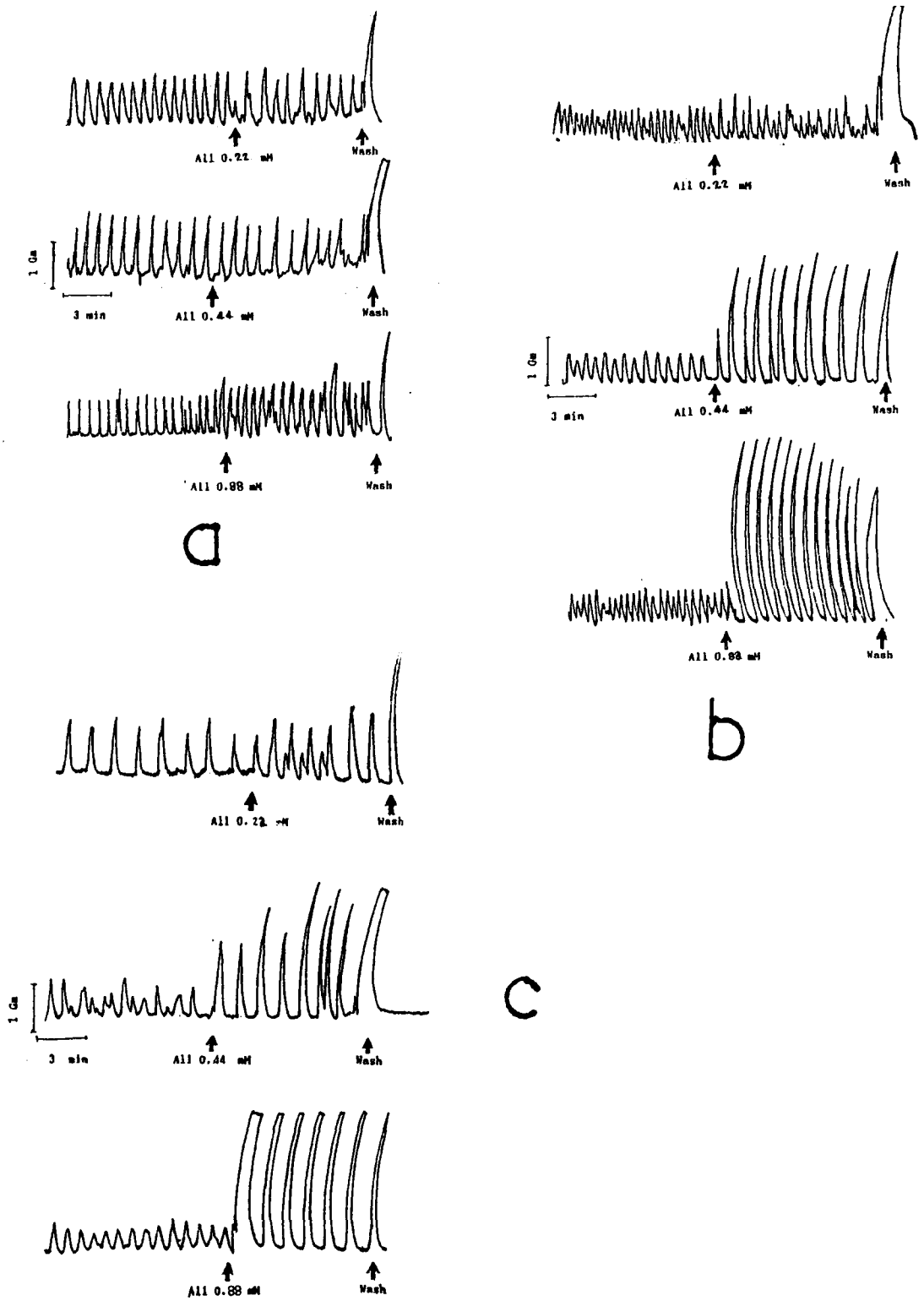

Figure 1. The contractile responses of pregnant uterine muscle of rats on 0.22, 0.44 and 0.88 mM through the periods of pregnancy.
(a), 7 days; (b), 14 days, (c) 21 days

None of the doses of allicin either enhanced the rate or affected the form of the contractions at any period of pregnancy.

2. Effect of allicin on α-1, and α-2 adrenergic receptors at preparturition.

In order to test whether the 21-day pregnant rat uterine contains α-1 receptor or not, norepinephrine, 10^{-11}, 10^{-12} and 10^{-13} M were used. It was found that at the concentration of 10^{-13} M significantly increases the force of contraction ($P<0.05$). Prazosin 10^{-5} M inhibited the increasing contraction caused by norepine-phrine, 10^{-13} M ($P<0.05$). The similar effect of prazosin, 10^{-5} M also inhibited the uterine contraction induced by allicin 0.44 mM ($P<0.01$). It is indicated that allicin acts on the uterine muscle through α-1 receptors. On the other hand, yohimbine, 10^{-5} M slightly inhibited the contraction caused by allicin. This presumes that the allicin may or may not exert its effect through α-2 receptors of the pregnant uterus muscle. (Fig.2)

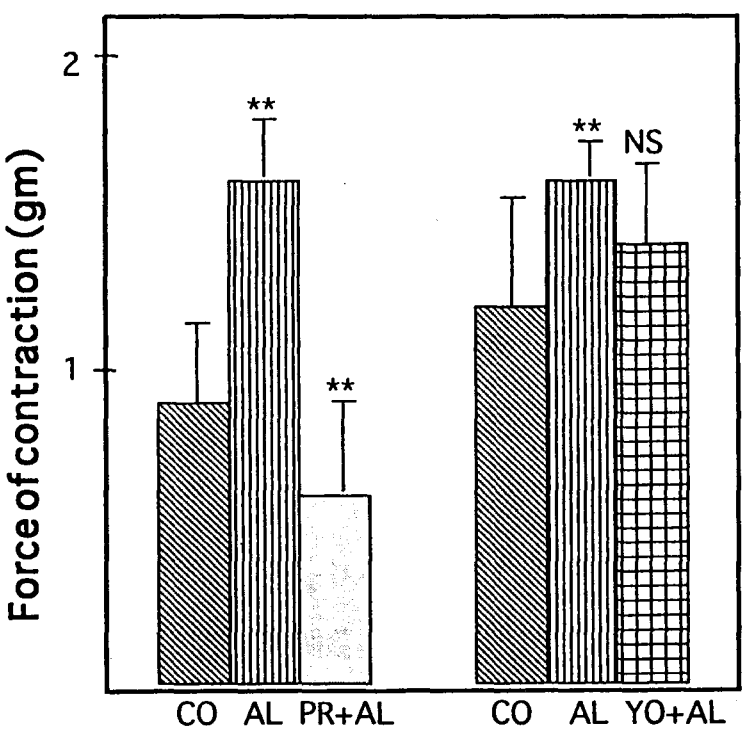

Figure 2. Effect of allicin (AL),0.44 mM followed the application of prazosin (PR),10^{-5} M and yohimbine (YO), 10^{-5} M on the contraction of pregnant uterus of rat at preparturition (21-day pregnancy).
CO,control;NS,non-significant;**,$P < 0.01$

3. Effect of allicin on $PGF_{2\alpha}$ receptor at preparturition

Figure 3 depicts the interaction of prostaglandin and allicin, and indomethacin and allicin. Prostaglandin increases the force of uterine contractions as well as allicin does whereas indomethacin decreases the contractions. In the presence of indomethacin, allicin and prostaglandin demonstrated a similar effect, i.e. they did not overcome the effect of indomethacin. It is postulated that allicin acts on pregnant uterus muscle at the preparturient period through prostaglandin F2α.

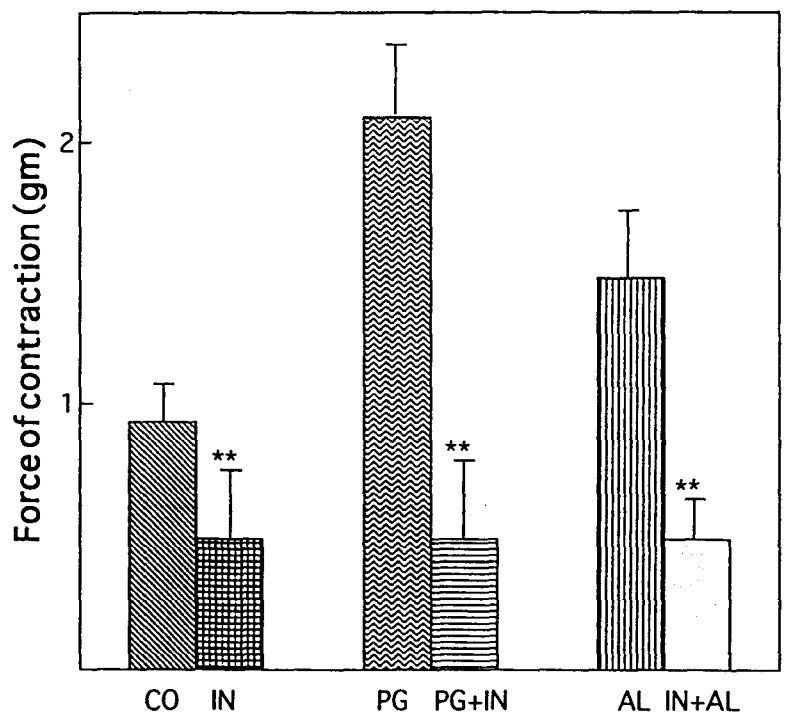

Figure 3. Effects of allicin (AL), 0.44 mM, indomethacin (IN), 10^{-5} M and prostaglandin $F_{2\alpha}$ (PG), 10^{-7} M on the contraction of pregnant uterus at preparturition.
CO,control; **,P < 0.01

4. Effect of allicin on calcium channel blocker.

Figure 4 demonstrates the interaction of allicin with calcium channel blockers, viz. nifedipine and verapamil, and a calmodulin blocker, chlorpromazine. It is noted that allicin acts on pregnant uterus muscle through calcium channel blocker and calmodulin blocker.

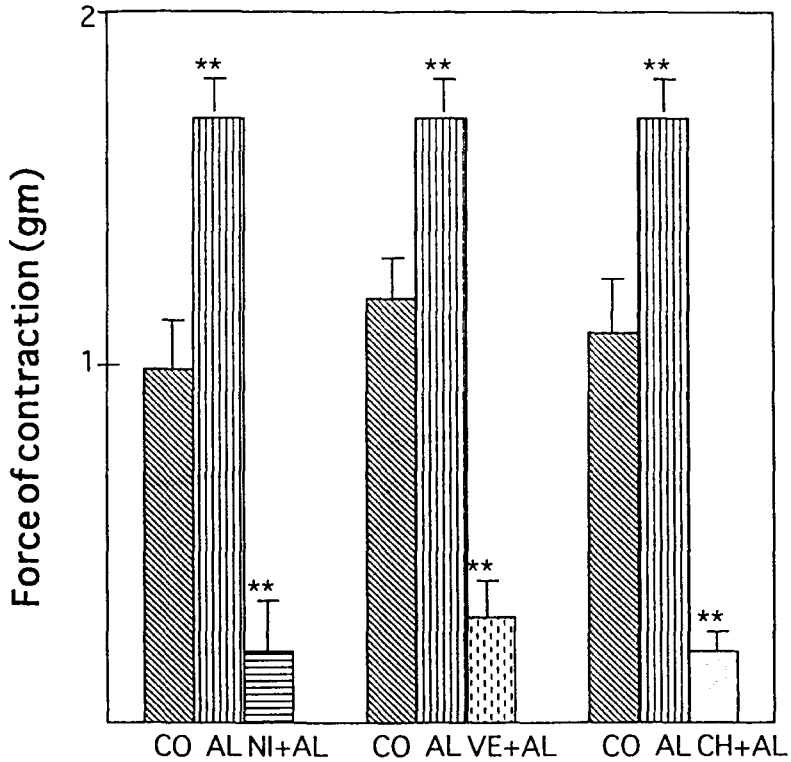

Figure 4. Interaction of allicin with calcium blockers and a calmodulin blocker on the contraction of uterine muscle at preparturient period.
**,P < 0.01;CO,control;AL,allicin, 0.44 mM;NI,nifedipine, 10^{-5} M;VE,verapamil,10^{-4} M;CH,chlorpromazine,10^{-2} M

5. Effect of allicin on the contraction of uterus at various concentration of $CaCl_2$ solution and in EDTA.

As shown in Table 2, the contraction of uterine muscle increased as the concentration of the calcium solution increased. Also, in the presence of allicin the contractions dramatically increased. On the contrary, in the presence of EDTA neither calcium nor allicin enhanced the force of uterine contraction.

Table 2. Force of contraction of rat uterus muscle caused by calcium, allicin and EDTA.

Concentration of calcium (mM) and EDTA	Force of contraction by calcium (gm) (mean ± S.D.); n=6	Force of contraction by calcium after allicin was applied (gm) (mean ± S.D.); n=6
0	0.48 ± 0.29	0.48 ± 041^{NS,NST}
0.1	0.80 ± 0.15**	1.07 ± 0.45**,^{a}
0.5	0.95 ± 0.46^{NS}	1.24 ± 0.54^{NS,a}
1.0	1.28 ± 0.79**	1.67 ± 0.37**,^{b}
2.0	1.61 ± 0.54**	2.00 ± 0.48**,^{b}
EDTA	0.34 ± 0.14	0.19 ± 0.19^{NS,NST}

NS, non-significant within treatment; NST, nonsignificant between treatments;
**,P<0.01 within treatment; a, P<0.05 between treatments; b, P<0.01 between treatments

Discussion

Our study indicates that the three doses of allicin did not affect the contraction of the uterine segments of 7-day pregnant rat muscle. The doses neither changed the rate nor the form of the contractions. However the contractions of uterine muscle at 14 and 21 days of pregnancy were enhanced by 0.44 and 0.88 mM of allicin (Fig.1 and Table 1). Contraction of the preparturient (21-day) uterine muscle increased in a dose-dependent manner. Similar effects in rats during proestrus, diestrus[1,16] and estrus[8] have been described. On the other hand, the effect of allicin on human myometrium during the proliferative phase of menstrual cycle both increase and decrease the force of contraction.[9] This may be due to species difference or the concentration of applied allicin. It has been postulated that allicin contains oxytocic and estrogenic activities.[2-4] In many species, including human, the oxytocin receptors rise toward the end of the pregnancy.[17,18] Estrogen concentration increases from the mid-term of pregnancy. Estrogen is found to increase the number of oxytocin receptors which in turn enhance the force of uterine contractions during the second semester towards preparturition.[19]

Allicin causes the maximal contractions of uterus muscle in the second period of pregnancy (Table 1), and declines toward the preterm of pregnancy. This phenomenon is originated by a rising of progesterone while estrogens decline. It has been proposed that the uterine concentration of norepinephrine is reduced during the last trimester of pregnancy in rats.[20] It is suggested that the decrease in norepinephrine in the preparturient period interacts with α-adrenoceptors located post-synaptically to improve overall excitability of the myometrium.[21,22] The decline in norepinephrine may also lead to the lower activity of the uterus during the final trimester of pregnancy.

Norepinephrine increases the force of uterine muscle contraction.[22] The α1-receptors mediating smooth muscle contraction and α2-receptors, including mainly presynaptic receptors mediating feedback inhibition of norepinephrine, release from adrenergic nerve ending.[23] The population of α-adrenoceptors in rat myometrium were noted and the α1-receptors represent 45% and the α2-receptors 55% of the entire α receptors. The application of prazosin indicates that α2-receptors were left intact while all of the α1-receptors were blocked.[24] A previous study demonstrated that there is an increase in α1-adrenoceptors to 70% during the last 6 hours of pregnancy.[25] The pretreatment of this experiment found the inhibition of contractions caused by prazosin. Norepinephrine increased the force of uterine contraction. The result obtained in the present experiment is in accordant with those reported by the former investigators.[12,22] Prazosin also inhibited the contractions induced by norepinephrine. As shown in Fig.2, prazosin reduced the uterine contractions induced by the allicin. It is postulated that the allicin exerts its effects through the α1-adrenoceptors in the pregnant uterus at preparturition.

Figure 2 depicts that yohimbine slightly decreased the uterine contractions induced by the allicin. In our pretreatment, yohimbine did not decrease the contraction of uterus muscle in the control group. However, it significantly decreased the contractions in an induced-epinephrine uterus ($P<0.01$). This presumes that α-2 adrenoceptors enhance α-1 adrenoceptor mediated contractions by norepinephrine.[26] Some authors have reported that α-2 adrenoceptors plays no role in contractile function in pregnant uterus muscle.[26,27] During preparturition the estrogens markedly increase. Yohimbine is claimed to be used to label α-2 adrenoceptors in rabbit myometrium; but for rat myometrium rauwolscine is possibly a more potent α-2 adrenoceptor antagonist than yohimbine.[24] By these postulations, and by our current experimental results, it appears that allicin may or may not exert its action through α-2 receptor in preparturition rats.

Figure 3 demonstrates the effect of prostaglandins and its antagonist and that of allicin on the contractions of rat uterus muscle during the preparturient period. It has been established that prostaglandins is an eicosanoid and indomethacin blocks its biosynthesis by inhibiting cyclooxygenase activity. Prostaglandin $F_{2\alpha}$ uniformly induces the contractions of pregnant and nonpregnant human uterus. Uterine responsiveness to prostaglandin increases as pregnancy progresses. Prostag-landins associates with stimulation of adenylcyclase (enhancing cAMP) and stimulation of phospholipase C (enhancing IP_3 by which leading to an increase in cytosolic Ca^{2+}).[28] Some physiological factors increase biosynthesis of prostaglandins i.e. estrogens, oxytocin and calcium.[17] Since indomethacin antagonizes the activity of both prostaglandins and allicin, we elucidate that allicin may act on pregnant uterus muscle in a similar mechanism as that of prostaglandins.

It is postulated that allicin may induce and opening of calcium channel and/or activate cytosolic calcium mobilization in rats during estrous phase.[8] In nonpregnant myometrium during the proliferative phase of the menstrual

cycle suggests that the garlic extract (allicin) exerts its action through an induction of increased intracellular free calcium.[9] It has been shown that nifedipine reduced the contractions of pregnant and nonpregnant human myometrium caused by potassium, prostaglandin F2α, oxytocin and vasopressin.[29] The effects of verapamil[8] and verapamil and nifedipine on the contractions of uterine muscle which had been induced by allicin[9] are in agreement with our study. The specific channel for calcium-entry blocker remains controversial for allicin activity. It is suggested that these two calcium blockers possibly have a direct and/or indirect effect action through calcium channel.[9] Our study found that the effect of allicin demonstrates a similar reduction of contractions in the presence of nifedipine and verapamil. Allicin may enter the cell through an ion channel with an action potential as described for calcium.[17] However by which specific calcium channel that allicin exerts its mechanism of action remains to be determined.

A report on in vitro effects of calcium entry blockers suggests that the order of potency is as follows : nifedipine > verapamil > chlorpromazine.[15] It is suggested that calmodulin involves a spontaneous contraction of pregnant uterus muscle. Degrees of inhibition on muscle contractions caused by nifedipine, verapamil and chlorpromazine were similar in our experiments. The indifferent degree of inhibition appears to be the tissue studied and the species. However, these findings are in agreement with our study. It is postulated that allicin may open calcium channel and then elevates cytosolic calcium.

Table 2 shows that the higher the concentration of calcium and allicin, except 0.1 mM, the stronger the force of uterine muscle contraction. This result indicates the significant role of extracellular calcium on uterine contraction. Allicin exhances the contractions induced by calcium in a dose-dependent manner, particularly at higher doses. Thus it may be concluded that allicin exerts its action through a calcium-channel, and enhances the activity of calcium on the contraction of pregnant rat uterus muscle at preparturition or at term. In the presence of EDTA, the effect of allicin is inhibited as well as that of calcium. Thus there are no contractions of the pregnant rat uterus muscle.

Conclusion

The garlic extract, allicin increases the contraction of rat uterus muscle in the preparturient period in vitro. The mechanisms of action of allicin is that it operates through α-1 adrenoceptors, prostaglandin $F_{2\alpha}$ receptors and calcium channel. It may open calcium-channel and lead to an increase in cytosolic calcium. It also enhances the activity of calcium on the contraction of uterine muscle during the preparturient period.

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References

1. Borvonsin S, Chumpolbunchorn K. The effect of garlic (Allium sativum) on uterine motility. Royal Thai Army Med J 1988 Jan; 41(1) : 3-10
2. Saha JC, Kasinathan S. Ecbolic properties of Indian medicinal plants II. Indian J Med Res 1961 Nov; 49(11) : 1094-8
3. Lorenzo VB, Sanchez B, Murias F, Dominguez MC. Garlic extracts as an oxytocic substance (II.) Arch Inst Pharmacol 1958; 10(1): 10-14
4. Bickoff EM. Estrogen-Like Substances in plants, Physiology of reproduction. Iowa : Oregon State University Press, 1963.
5. Tewari PV, Mapa HC, Chaturvedi C. Experimental study on estrogenic activity of certain indigenous drugs. J Res Indian Med Yoga Homeopathy 1976; 11(1) : 7-12
6. Tiano M, Terren RC. Actions of Allium sativum (garlic) and combination on uterine motility (I and II). Arch Inst Pharmacol Exptl 1955; 8 : 127
7. Ayensu ES. Medicinal plants of the West Indies Washington D.C. Office of Biol Conservat Smithsonian Institute, 1978 (unpublished manuscript).
8. Borvonsin S, Permpintong A, Sudsuang R. The effect of allicin on rat uterine contraction. Chula Med J 1995 Apr; 39(5) : 257-69
9. Somboonwong J, Borvonsin S, Sudsuang R. Effects of garlic extract on the contraction of isolated human uterine muscle. Chula Med J 1993 Apr; 37(4) : 227-36
10. Poolsanong N. Pharmaceutical production of sugar-coated tablets and capsules of garlic. Production Division, Armed-Force Pharmaceutical Factory,1984 (unpublished)
11. Bass VA, Phillippe M, Valles L. Effect of prazosin and indomethacin on the α-adrenergic stimulation of rabbit myometrium. Gynecol Obstet Invest 1988; 25(1) : 42-6
12. Legrand C, Vivat V, Rigolot C, Maltier JP. Selective distribution of α-1 and ß adrenoceptors in pregnant rat uterus visualized by autoradiography. J Pharmacol Exp Ther 1990 Feb; 256(2):46 : 767-72
13. Forman A, Gandrup P, Andersson KE, Ulmsten U. Effects of nifedipine on oxytocin and prostaglandin $F_{2\alpha}$- induced activity in the postpartum uterus. Am J Obstet Gynecol 1982 Nov 15;144(6): 665-70
14. Maigaard S, Forman A, Andersson KE, Ulmsten U. Comparison of the effects of nicardipine and nifedipine on isolated human myometrium. Gynecol Obstet Invest 1983; 16(6): 354-66
15. Ballejo G, Calixto JB, Medeiros YS. In vitro effects of calcium entry blockers, chlorpromazine and fenoterol upon human pregnancy myometrium contractility. Br J Pharmac 1986 Nov; 89(3):515-23
16. Borvonsin S, Thawal R, Chumpolbunchorn K. Effect of dose, dosage form and manufacturing date of garlic on uterine motility. Royal Thai Army Med. J 1989 Apr; 42(2) : 54

17. Carsten ME, Miller JD. A new look at uterine muscle contraction. Am J Obstet Gynecol 1987 Nov;157(5): 1303-15

18. Fuchs AR, Fuchs F, Husslein P. Soloff MS. Oxytocin receptors in the human uterus during pregnancy and parturition. Am J Obstet Gynecol 1984 Nov 15; 150(6) : 734-41

19. Csapo AI, Puri CP, Tarro S, Henzl MR. Decaptivation of the uterus during normal and premature labor by the calcium antagonist nicardipine. Am J Obstet Gynecol 1982 Mar 1; 142(5) : 483-91

20. Arkinstall SJ, Jones CT. Regional changes in catecholamine content of pregnant uterus. J Reprod Fertil 1985 Mar; 73(2) : 547-57

21. Legrand C, Maltier JP. Evidence for noradrenergic transmission in the control parturition in the rat. J Reprod Fertil 1986 Jan; 76(1): 415-24

22. Permpintong A. Effect of allicin on rat uterine contraction. A thesis submitted for M.Sc. (Physiology), Graduate School, Chulalongkorn University, 1991

23. Hoffman BB, Lefkowit RJ. α-adrenergic receptor subtypes. N Engl J Med 1980 Jun 19; 302(25):1980-6

24. Maltier JP, Legrand C. Characterization of α-adrenoceptors in myometrium of preparturient rats. Eur J Pharmacol 1985 Oct 29; 117 (1): 1-13

25. Maltier JP, Legrand C, Corazza S. α-adrenergic receptors in the myometrium of the preparturient rat. Pathol Biol 1984 Oct; 32(8) : 878-83

26. Kyozuka M, Crankshaw DJ, Crankshaw J, Berezin I, Kwan CY, Daniel EE. α-2 adrenoceptors on nerves and muscles of rat uterus. J Pharmacol Exp Ther 1988 Mar; 244(3) : 1128-38

27. Jacobs MM, Hayashida D, Roberts JM, Human myometrial adrenergic receptors during pregnancy : identification of the α-adrenergic receptor by [3H] - dihydroergocryptine binding. Am J Obster Gynecol 1985 Jul 15; 152(6 pt 1) : 680-94

28. Campbell WB. Lipid-derived autacoids eicosanoids and platelet-activating factor. In : Goodman and Gilmans the Pharmacological Basis of Therapeutics.Vol 1. 8th ed. Tokyo. Mc. Graw-Hill Inc. 1992; 600-17

29. Maigaard A, Forman K, Andersson KE, Ulmsten U. Comparison of the effects of nicardipine and nifedipine on isolated human myometrium. Gynecol Obstet Invest 1983; 16(6): 354-66