*บทความวิจัย*

# ฤทธิ์ของเคอคูมินที่ทำให้หลอดเลือดเอออร์ตาคลายตัว

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## บทคัดย่อ

เคอคูมินเป็นสารประกอบสีเหลืองซึ่งสกัดจากเหง้าของต้นขมิ้นชัน ในการแพทย์แผนโบราณมีการนำเคอคูมินมาใช้รักษาโรคหลายชนิด รวมทั้งภาวะความดันเลือดสูง อย่างไรก็ตามฤทธิ์ของเคอคูมินต่อการคลายตัวของหลอดเลือดยังไม่ทราบแน่ชัด การศึกษานี้มีจุดประสงค์เพื่อศึกษาฤทธิ์ของเคอคูมินต่อการตอบสนองของหลอดเลือดเอออร์ตาของหนูแรทต่อสารต่างๆที่มีผลต่อความตึงตัวของหลอดเลือด ผลการศึกษาพบว่าการหดตัวของหลอดเลือดโดยสาร methoxamine, phenylephrine, 5-hydroxytryptamine และ $CaCl_2$ ถูกยับยั้งโดยเคอคูมิน (10 และ 100 ไมโครโมลาร์) อย่างไรก็ตามเคอคูมิน (1 และ 10 ไมโครโมลาร์) ไม่มีผลต่อการคลายตัวของหลอดเลือดโดยสาร carbachol, histamine และ sodium nitroprusside ผลที่ได้จากการศึกษานี้แสดงให้เห็นว่าฤทธิ์ของเคอคูมินที่ทำให้หลอดเลือดเอออร์ตาของหนูแรทคลายตัวเกี่ยวข้องกับการยับยั้งการผ่านของแคลเซียมไอออนจากภายนอกเซลล์เข้าสู่เซลล์ และผลการศึกษานี้สนับสนุนการใช้เคอคูมินในการแพทย์แผนโบราณเพื่อเป็นยาขยายหลอดเลือด


**คำสำคัญ:** เคอคูมิน ขมิ้นชัน ช่องผ่านของแคลเซียมไอออน หลอดเลือดเอออร์ตาของหนูแรท

ภาควิชาสรีรวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยศรีนครินทรวิโรฒ

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# The Vasorelaxant Effects of Curcumin in the Rat Aorta

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## ABSTRACT

Curcumin is a yellow phenolic compound extracted from rhizomes of turmeric (*Curcuma longa* Linn). It has been widely used in Thai traditional medicine to treat several diseases, including hypertension. However, the vascular effects of curcumin are still unclear. The present study aimed to investigate the effects of curcumin on vascular responses to vasoactive agents in the rat aorta. It was found that contractions induced by methoxamine, phenylephrine, 5-hydroxytryptamine and $CaCl_2$ were inhibited after pre-incubation with curcumin (10 and 100 μM). However, pre-treatment with curcumin (1 and 10 μM) had no effects on vasorelaxations to carbachol, histamine, and sodium nitroprusside. The present findings in the rat aorta suggest that the vasorelaxant effects of curcumin involve the inhibition of extracellular $Ca^{2+}$ influx. Findings from this study will support the use of curcumin in Thai traditional medicine as a vasodilator.

**Keywords:** curcumin, turmeric, $Ca^{2+}$ channels, rat aorta

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## Introduction

Turmeric (dry rhizomes of *Curcuma longa* Linn.) has been generally used as a spices and coloring agent. The ethanolic extract of turmeric consists mainly of curcumin, demethoxycurcumin, bisdemethoxycurcumin, and ar-turmerone [1]. Curcumin (1,7-bis (4-hydroxy-3-methoxy phenyl)-1,6-heptadiene-3,5-dione) is a polyphenolic compound, and has a yellow pigment [1, 2]. Several pharmacological studies have demonstrated the beneficial effects of curcumin, including antidepressant [3], antioxidant [4-6], anti-inflammatory [7-9], antibacterial [10], and anti-cancer [11, 12] activities. In addition, previous studies in diabetes have shown that curcumin could reduce plasma glucose, very low-density lipoprotein (VLDL), low-density lipoprotein (LDL), cholesterol, triglyceride, free fatty acid, phospholipid levels [13-15]. Antispasmodic effects of curcumin have also been reported in guinea-pig ileum and rat uterus [16].

Concerning the cardiovascular effects of curcumin, it has been reported that curcumin has cardioprotective [17-18], vasodilator [19-20], and anti-angiogenic [12, 21] effects. For an example, curcumin could reduce myocardial infarction, and increase ventricular functions [17]. A previous study by Ramaswami *et al*. (2004) demonstrated that curcumin restored impairment of endothelium-dependent vasorelaxation, and increased eNOS levels in porcine coronary arteries with endothelial dysfunctions induced by homocysteine [19]. Recently, the direct vasorelaxant effects of curcumin have been reported in porcine coronary arteries [20]. However, there is no evidence for the vascular effects of curcumin in the rat aorta. The present study aimed to investigate the effects of curcumin on vascular responses to vasoactive agents in the rat aorta. Moreover, the involvement of extracellular $Ca^{2+}$ influx in the relaxant effects of curcumin was also investigated.

## Material and methods

### Preparation of the rat aorta

Experiments were performed using aorta obtained from male Wistar rats (300 - 350 g) bred and kept by the National Laboratory Animal Center, Mahidol University, Thailand. All experiments were reviewed and approved by the Animal Research Ethics Committee of the Faculty of Medicine, Srinakharinwirot University.

Male Wistar rats were anaesthetized with Zolitil (50 mg/kg, i.m.), and killed by cervical dislocation. Following a thoracotomy, the thoracic aorta was dissected from the rat. The aorta was cleaned of fat and connective tissue, and cut into 4-5 mm ring segments. Each ring was transferred to a jacketed organ bath filled with 20 ml of Krebs-Henseleit solution

(composition, mM; NaCl 118, KCl 4.7, $MgSO_4$ 1.2, $KH_2PO_4$ 1.2, $NaHCO_3$ 25, $CaCl_2$ 2, D-glucose 10) that was maintained at a temperature of 37 ˚C and bubbled with 95% $O_2$ and 5% $CO_2$ mixture. The solution in the organ bath was exchanged every 15 min for 1 h. The rings were mounted between two triangular stainless steel hooks that were passed through the lumen and stretched to an optimal passive tension of about 1 g, and maintained at this tension for 1 h. Tension was measured by a force transducer (MLT0210), and recorded on a MacLab 4e recording system (AD instruments).

**Experimental protocol**

To examine the effects of curcumin on contractile responses of aortic rings to vasoconstrictors, aortic rings were preincubated with curcumin (10 and 100 μM) for 30 minutes before concentration-response curves of methoxamine (0.1 - 300 μM), phenylephrine (0.1 - 100 μM), and 5-hydroxytryptamine (5-HT, 0.1 - 300 μM) were constructed. High concentrations of curcumin (10 and 100 μM) were used in this study as our preliminary studies found that lower concentrations of curcumin (0.1 and 1 μM) did not affect vascular responses to these vasoconstrictors.

Vasorelaxations induced by endothelium-dependent vasodilators, carbachol and histamine, as well as an endothelium-independent vasodilator, sodium nitroprusside were also investigated in the presence of curcumin (1 and 10 μM). For this investigation, aortic rings were contracted with methoxamine to increase tone by approximately 1 g. Once a stable contraction was achieved, carbachol (1 nM - 100 μM), histamine (0.1 - 300 μM) or sodium nitroprusside (0.1 nM - 10 μM) was added cumulatively. Low concentrations of curcumin (1 and 10 μM) were required for these investigations because methoxamine could not induce equivalent levels of tone in the presence of a high concentration of curcumin (100 μM).

In vehicle-control experiments, dimethyl sulphoxide (DMSO) alone was added in the same volume as those used in the experiments involving curcumin (1, 10, or 100 μM). The final concentration of DMSO in the organ bath was 0.1% (v/v) that did not affect the basal tone.

To examine the effect of curcumin on extracellular $Ca^{2+}$ influx, concentration-response curves to $CaCl_2$ (10 μM - 30 mM) were obtained in the presence and absence of curcumin (10 and 100 μM). Aortic rings were first allowed to equilibrate at 1 g tension in a $Ca^{2+}$-free Krebs solution, and then the rings were bathed with $Ca^{2+}$-free, high KCl (100 mM) Krebs solution. After the rings were incubated for 30 minutes with curcumin or DMSO, concentration-response curves to cumulative addition of $CaCl_2$ were constructed.

**Data and statistical analysis**

The concentration of vasorelaxant giving half-maximal relaxation ($EC_{50}$) was obtained from the concentration-response curve. Maximal responses were expressed as mean ± standard error of the mean (S.E.M.), and $pEC_{50}$ values (-ve log of $EC_{50}$ values) were expressed as means with 95% confidence intervals (CI). The number of animals in each group was represented by *n.* The data were compared, as appropriate, by the Student's unpaired *t*-test or analysis of variance (ANOVA) with statistically significant differences between groups being determined by Bonferroni's *post-hoc* test. The curve-fitting was carried out using the graphical package GraphPad Prism.

**Drugs and chemicals**

Curcumin was purchased from Cayman (U.S.A.). The remaining drugs and chemicals were purchased from Sigma Chemical Company. Curcumin was dissolved in DMSO, and diluted to various concentrations in distilled water.

## Results

**The effects of curcumin on contractions to methoxamine, phenylephrine and 5-hydroxytryptamine**

Pre-incubation with curcumin (10 and 100 μM) significantly ($p < 0.001$) inhibited maximal contractions to methoxamine ($R_{max}$: control = 0.75 ± 0.01 g, $n = 6$; 10 μM curcumin = 0.57 ± 0.01 g, $n = 6$; 100 μM curcumin = 0.45 ± 0.01 g, $n = 6$). In addition, the potency of methoxamine-induced contraction was significantly ($p < 0.01$) reduced by pre-incubation with curcumin at concentrations of 10 μM and 100 μM ($pEC_{50}$: control = 4.96(4.91-5.01), $n = 6$; 10 μM curcumin = 4.69(4.63-4.74), $n = 6$; 100 μM curcumin = 4.73(4.65-4.80), $n = 6$, Fig 1).

Similarly, the potency and maximal contractions to phenylephrine were significantly ($p < 0.001$) inhibited by pre-incubation with curcumin (10 and 100 μM) (control: $pEC_{50}$ = 5.94(5.85-6.04), with $R_{max}$ = 1.10 ± 0.02 g, $n = 6$; 10 μM curcumin: $pEC_{50}$ = 5.71(5.65-5.79), with $R_{max}$ = 0.89 ± 0.01 g, $n = 6$; 100 μM curcumin: $pEC_{50}$ = 5.62(5.51-5.74), with $R_{max}$ = 0.65 ± 0.02 g, $n = 6$, Fig 2).

Moreover, pre-incubation with curcumin (10 and 100 μM) significantly ($p < 0.001$) inhibited maximal contractile responses to 5-hydroxytryptamine ($R_{max}$: control = 1.01 ± 0.02 g, $n = 6$; 10 μM curcumin = 0.55 ± 0.01 g, $n = 6$; 100 μM curcumin = 0.39 ± 0.01 g, $n = 6$, Fig. 3). However, the potency of 5-hydroxytryptamine-induced contraction was not affected by pre-incubation with curcumin (10 and 100 μM) ($pEC_{50}$: control = 4.79(4.73-4.85), $n = 6$; 10 μM curcumin = 4.85(4.84-4.86), $n = 6$; 100 μM curcumin = 4.85(4.82-4.88), $n = 6$, Fig. 3).

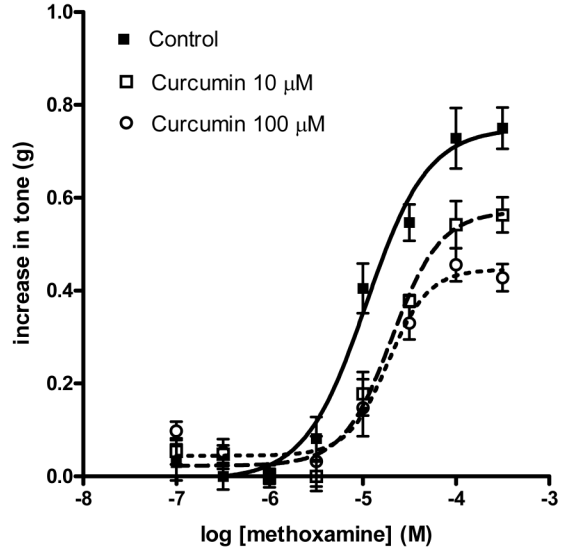


**Figure 1** The effect of pre-treatment with curcumin (10 and 100 μM) on methoxamine-induced contraction in rat aortic rings. Data are shown as mean ± S.E.M. $n$ = 6.

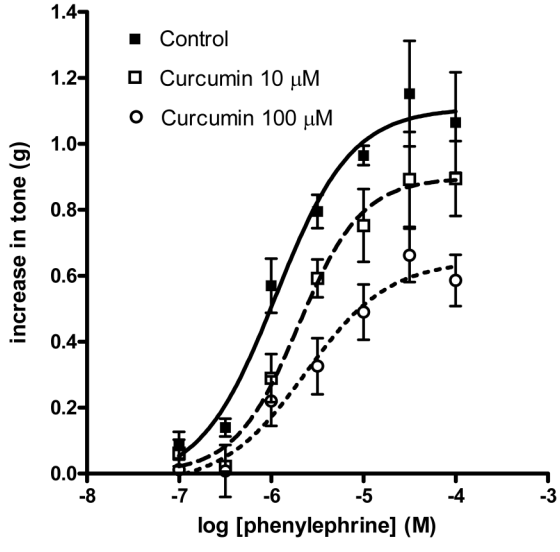


**Figure 2** The effect of pre-treatment with curcumin (10 and 100 μM) on contractile responses to phenylephrine in rat aortic rings. Data are shown as mean ± S.E.M. $n$ = 6.

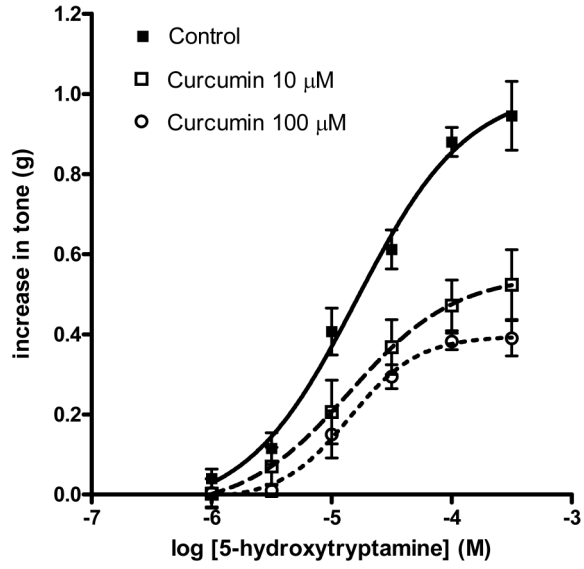


**Figure 3** The effect of pre-treatment with curcumin (10 and 100 μM) on contractions induced by 5-hydroxytryptamine in rat aortic rings. Data are shown as mean ± S.E.M. $n$ = 6.

**The effects of curcumin on $CaCl_2$-induced contractions**

$CaCl_2$ (10 μM - 30 mM) induced concentration-dependent contractions of rat aortic rings in calcium-free buffer depolarized by 100 mM KCl. Pre-incubation with 10 μM curcumin significantly ($p < 0.01$) inhibited contractions induced by $CaCl_2$, such that maximal contractions were 1.12 ± 0.02 g (control, $n$ = 7) and 1.03 ± 0.02 g (10 μM curcumin, $n$ = 7). In addition, pre-treatment with 100 μM curcumin largely inhibited $CaCl_2$-induced contractions ($R_{max}$ = 0.68 ± 0.01 g, $n$ = 7, $p < 0.001$, Fig. 4).

**The effects of curcumin on vasorelaxations to carbachol, sodium nitroprusside and histamine**

Pre-treatment with curcumin (1 and 10 μM) did not affect vasorelaxation to carbachol (1nM - 100 μM) (control: $pEC_{50}$ = 6.20(6.17-6.23), with $R_{max}$ = 111 ± 1%, $n$ = 9; 1 μM curcumin: $pEC_{50}$ = 6.14(6.12-6.17), with $R_{max}$ = 101 ± 1%, $n$ = 9; 10 μM curcumin: $pEC_{50}$ = 6.29(6.25-6.34), with $R_{max}$ = 113 ± 1%, $n$ = 9, Fig. 5).

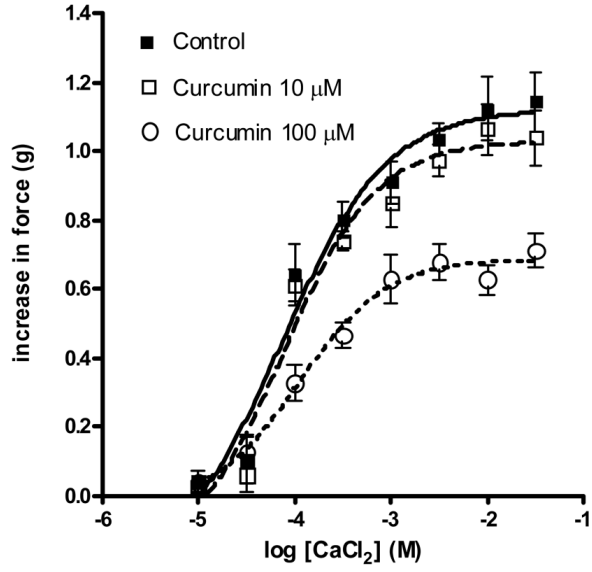


**Figure 4** The effect of curcumin (10 and 100 μM) on $CaCl_2$-induced contraction in rat aortic rings depolarized by 100 mM KCl. Data are shown as mean ± S.E.M. *n* = 7.

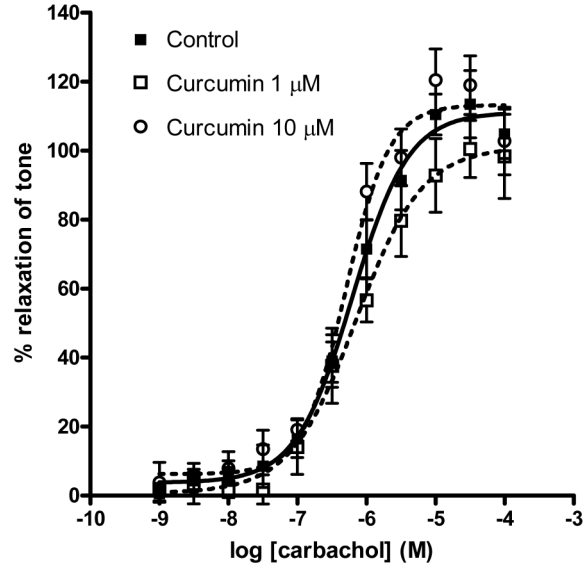


**Figure 5** The effect of pre-treatment with curcumin (1 and 10 μM) on vasorelaxation to carbachol in rat aortic rings. Data are shown as mean ± S.E.M. *n* = 9.

Similarly, pre-treatment with curcumin (1 and 10 μM) had no effects on relaxant responses to histamine (0.1 nM - 300 μM) (control: $pEC_{50}$ = 5.26(5.21-5.31), with $R_{max}$ = 81.1 ± 1.1%, *n* = 6; 1 μM curcumin: $pEC_{50}$ = 5.55(5.48-5.63), with $R_{max}$ = 74.1 ± 1.2%, *n* = 6; 10 μM curcumin: $pEC_{50}$ = 5.39(5.30-5.49), with $R_{max}$ = 80.4 ± 2%, *n* = 6, Fig. 6).

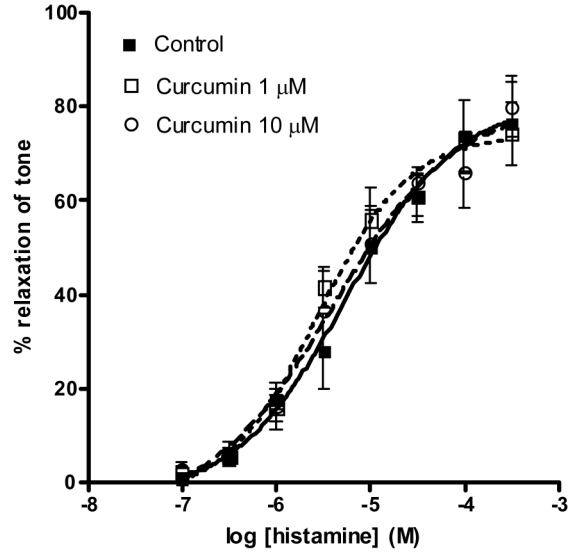


**Figure 6** The effect of pre-treatment with curcumin (1 and 10 μM) on vasorelaxation to histamine in rat aortic rings. Data are shown as mean ± S.E.M. *n* = 6.

In addition, vasorelaxations induced by sodium nitroprusside (0.1 nM - 10 μM) were not affected by pre-treatment with curcumin (1 and 10 μM) (control: $pEC_{50}$ = 7.74(7.71-7.77), with $R_{max}$ = 135 ± 1%, *n* = 6; 1 μM curcumin: $pEC_{50}$ = 7.97(7.91-8.02), with $R_{max}$ = 143 ± 1%, *n* = 6; 10 μM curcumin: $pEC_{50}$ = 7.57(7.54-7.60), with $R_{max}$ = 144 ± 1%, *n* = 6, Fig. 7).

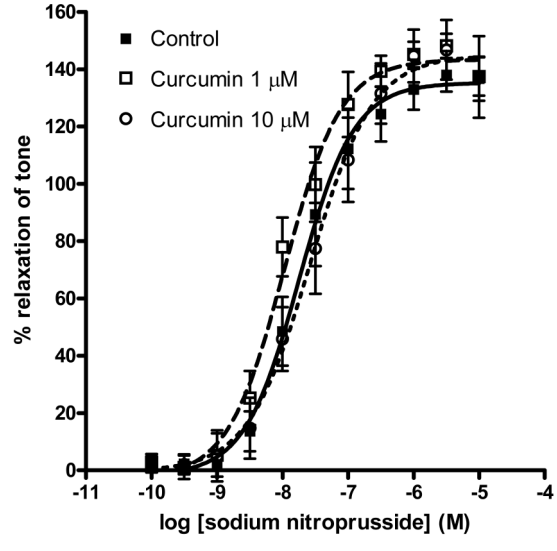


**Figure 7** The effect of pre-treatment with curcumin (1 and 10 μM) on vasorelaxation to sodium nitroprusside in rat aortic rings. Data are shown as mean ± S.E.M. *n* = 6.

## Discussion and conclusion

Findings from this study have clearly shown that curcumin reduces contractile responses of rat aortic rings to methoxamine, phenylephrine, and 5-HT. However, vasorelaxant responses to cabachol, histamine, and sodium nitroprusside are unchanged by curcumin. These results indicate that curcumin acts as a vasodilator in the rat aorta. Similar to our findings, curcumin also induces relaxation in porcine coronary arteries [20], guinea-pig ileum and rat uterus [16].

In the present study, we investigated the effects of curcumin on contractions induced by different types of vasoconstrictors. $\alpha_1$-Adrenoreceptor agonists, such as methoxamine and phenylephrine, caused vasoconstriction via activation of protein kinase C to increase extracellular $Ca^{2+}$ influx through receptor-operated $Ca^{2+}$ channels, and/or $Ca^{2+}$ release from intracellular store [22, 23]. Both methoxamine and phenylephrine act via different $\alpha_1$-adrenoreceptor subtypes. However, phenylephrine is more sensitive to $\alpha_1$-adrenoreceptor than methoxamine. Furthermore, phenylephrine is more potent than methoxamine in the aorta [24]. The present investigation found that contractile responses to methoxamine and phenylephrine were reduced by pre-treatment with curcumin. From these findings, it is suggested that curcumin induces vasorelaxation partly via inhibition of $Ca^{2+}$ influx from extracellular space through receptor-operated $Ca^{2+}$ channels, and/or via reduction of $Ca^{2+}$ release from intracellular stores. We also investigated the effect of curcumin on contractile responses of aortic rings to 5-HT, which caused contraction of vascular smooth muscle cells by binding to 5-HT receptors, resulting in increasing extracellular $Ca^{2+}$ influx through voltage-dependent $Ca^{2+}$ channels and protein kinase C [25]. It was found that pre-incubation of aortic rings with curcumin reduced contractions to 5-HT. These findings suggested that vasorelaxant effects of curcumin were partly mediated by inhibiting $Ca^{2+}$ influx from extracellular space through voltage-dependent $Ca^{2+}$ channels. Indeed, we found that curcumin inhibited contractile responses to $CaCl_2$ of the rat aorta depolarized by 100 mM KCl in $Ca^{2+}$-free medium. However, other possible mechanisms may be involved in the vasorelaxant effects of curcumin, such as inhibition of intracellular $Ca^{2+}$ release and/or reduction of contractile elements to $Ca^{2+}$.

In the present study, the effects of curcumin on endothelium-dependent vasodilators, carbachol, a muscarinic receptor agonist [26], and histamine, a histamine receptor agonist [27] were studied. In addition, endothelium-independent relaxation to sodium nitroprusside, a NO donor [26] was investigated in the presence and in the absence of curcumin. It was found that pre-treatment with curcumin had no effects on relaxant responses to carbachol, histamine, and sodium nitroprusside. These results suggest that curcumin does not participate in mechanisms

contributing to vasorelaxations induced by these vasodilators. However, a previous study in porcine coronary arteries has demonstrated that vasorelaxation to curcumin is mediated via a NO-dependent pathway as curcumin-induced response is reduced by *N*-nitro-L-arginine [20]. In addition, Ramaswami *et al.* (2004) have shown that curcumin increases eNOS protein in porcine coronary arteries with endothelial dysfunction induced by homocysteine [19]. These differences may result from tissue and species specific, as well as the extraction method of curcumin used in each study.

In conclusion, the present findings in the rat aorta have shown that the vasorelaxant effects of curcumin largely involve inhibition of extracellular $Ca^{2+}$ influx (Fig. 8). However, other possible mechanisms involved in the vasorelaxant effects of curcumin are required for further investigations.

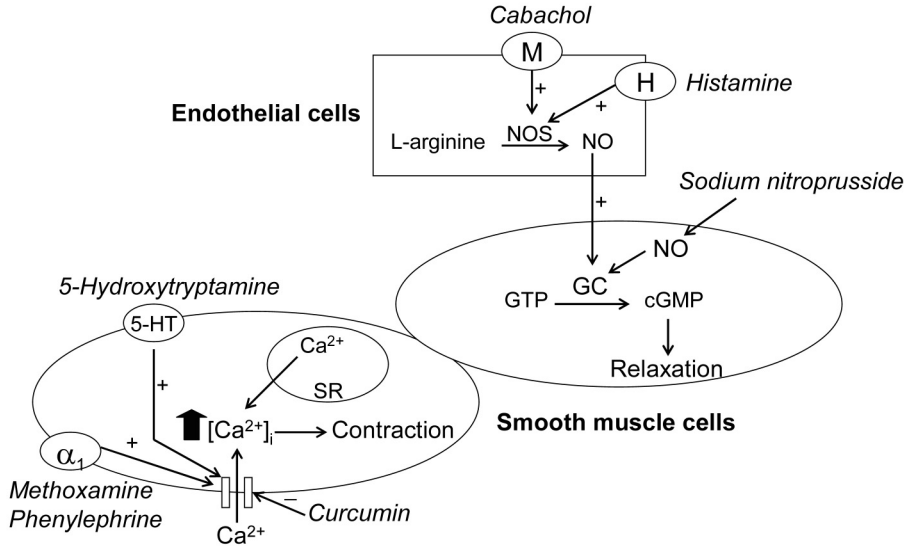


**Figure 8** Mechanisms of vasorelaxant effects of curcumin in the rat aorta. +, stimulate; -, inhibit. Abbreviations: M, muscarinic receptor; H, histamine receptor; 5-HT, 5-hydroxytryptamine receptor, $\alpha_1$, $\alpha_1$-adrenoreceptor; NO, nitric oxide; NOS, nitric oxide synthase; GTP, guanosine triphosphate; GC, guanylyl cyclase; cGMP, cyclic guanosine monophosphate; SR, sarcoplasmic reticulum

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## เอกสารอ้างอิง

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