Effects of Dopamine on the Contractility of the Circular Muscles in the Guinea-pig Gastric Antrum and Fundus*

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=Abstract= The effects of dopamine on gastric motility were investigated using circular muscle strips prepared from the antral and fundic regions of the guinea-pig stomachs. The spontaneous and phasic contractions induced by electrical stimulation were recorded with a force transducer. Dopamine potentiated the spontaneous contraction of the antral circular muscle, which was suppressed completely by α-blocker phentolamine and partially by α2-blocker yohimbine but was not blocked by TTX. Dopamine increased the basal tone of both the antral and the fundic circular muscles, which was suppressed by phentolamine but not affected by TTX. Dopamine increased the contraction evoked by direct electrical stimulation to the fundic circular muscle, which was suppressed by phentolamine but unaffected by TTX. Dopamine increased the basal tone and relaxation component of the phasic contraction evoked by transmural nerve stimulation in the fundic region, while it decreased the contraction component. Atropine decreased the contraction component in the fundic region, while it increased the relaxation component, which were suppressed by phentolamine.

In conclusion, dopamine increases the basal tone of both the antral and fundic circular muscles and the amplitude of spontaneous contraction of the antral circular muscle via α-adrenergic receptors, especially via the α1-receptor in the plasma membrane of circular muscle cells. Dopamine increases the relaxation component through the enhanced release of transmitters from non-adrenergic non-cholinergic nerve terminals, and suppresses contraction by inhibiting transmitter release from cholinergic nerves in the fundic region.

Key Words: Dopamine, Antral and fundic circular muscles, α-adrenergic receptor, Non-adrenergic non-cholinergic nerves

INTRODUCTION

The contractions of the gastrointestinal smooth muscles are initiated from smooth muscle cells themselves. In other words, gastrointestinal motility is under myogenic control. And the motility is thought to be modulated by intrinsic and extrinsic autonomic nervous systems as well as by some circulating hormones and drugs (Demol et al. 1989). Autonomic nervous systems are composed of not only sympathetic and parasympathetic nerves but also non-adrenergic non-cholinergic (NANC) nerves. It has been known that the neurotrans-
mitters released from the terminals of NANC nerves exert some influence on the contractility of the gastrointestinal smooth muscles directly or via the other nerves (Burnstock 1972, Komori and Suzuki 1986). It has been reported that dopamine is one of the neurotransmitters released from the NANC nerve terminals (Jorge and Valenzuela 1976).

Dopamine, one of the catecholamine substances, is well known to be an important neurotransmitter in the central nervous system. It has been found also in the peripheral autonomic nervous system of the cardiovascular system and the gastrointestinal tract of various species (Bech and Hovendal 1982) and is secreted from the mucosal endocrine cells of the gastrointestinal tract (Hakanson 1970; Ahonen and Penttila 1974).

From the fact that externally administered dopamine inhibited gastrointestinal motility in some experimental animals (Thorner 1975) and that dopamine was found in large amounts in human gastric juices (Bech and Hovendal 1982) it is suggested that endogenous dopamine might play some physiological role in the regulation of gastrointestinal motility. And clinically dopamine has been thought to be one of the etiologic factors eliciting gastroesophageal regurgitation and vomiting in newborn infants (Miolan et al. 1983).

The effects of dopamine on gastrointestinal motility are known to be varied depending upon animal species, regions of the gastrointestinal tract and muscle layers (Mukhopadhyay and Weisbrodt 1977; Cox and Ennis 1980a; Sahyoun et al. 1982a; Lefebvre et al. 1984).

There remains controversy concerning the action of dopamine on gastric motility. Some authors have reported that dopamine potentiated gastric contractility (Costall et al. 1983), while others have said that it induced gastric relaxation (Sahyoun et al. 1982b). Moreover, the sites and the mechanism of dopamine action are more indistinct. Some authors have reported that dopamine exerted its action through a specific dopaminergic receptor (Schuurkes and Van Nueten 1981, 1982, 1983), while others have reported that it displayed its effect through the \( \alpha \) - and \( \beta \)-adrenergic receptors (Komissarov and Reutskaya 1978; Cox and Ennis 1980b; Kamikawa et al. 1982; Costall et al. 1983).

The present experiments were undertaken to clarify the regional differences of dopamine action and its mode of action, especially its relation with the enteric nervous system in the guinea-pig stomach.

**MATERIALS AND METHODS**

Guinea-pigs of either sex, weighing about 300 g, were stunned and bled. The whole stomach was excised and placed in a bath containing oxygenated phosphate-buffered Tyrode's solution (\( \text{NaCl} 147, \text{KCl} 4, \text{CaCl}_2 \cdot 2\text{H}_2\text{O} 2, \text{MgCl}_2 \cdot 6\text{H}_2\text{O} 1.05, \text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O} 0.42, \text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O} 1.81, \text{glucose} 5.5 \text{mM}, \text{pH} 7.35 \)) at room temperature. Then the antral and fundic regions were obtained and cut in a longitudinal direction along the lesser curvature. After the contents of the stomach were removed, patches of the muscle coat were obtained by removing the mucosal layer in Tyrode's solution. Circular muscle strips, 2 mm wide and 10 mm long, were made dissected along the direction of the circular muscle in both the antrum and fundus.

The mechanical contractions were recorded in a vertical chamber which had a capacity of 100 ml (Fig. 1). Before the main experiment the strip was recovered in oxygenated tris-buffered Tyrode's solution (\( \text{NaCl} 147, \text{KCl} 4, \text{CaCl}_2 \cdot 2\text{H}_2\text{O} 2, \text{MgCl}_2 \cdot 6\text{H}_2\text{O} 1.05, \text{tris} \cdot \text{HCl} 5, \text{glucose} 5.5 \text{mM}, \text{pH} 7.35 \)) for 1 hour at 35 \( ^\circ \text{C} \). The isometric contractions were recorded through a Grass FT-03 force transducer connected to a Device physiograph. The optimal length of the strip was determined by lengthtension curve of either spontaneous contractions, or contractions evoked by electrical field stimulation.

In fundic circular muscle strips, contractions were evoked by transmural electrical nerve stimulation or by direct electrical muscle stimulation. The former method evoked contraction by releasing neurotransmitters from the intrinsic nerve terminal, in which the electrical stimuli produced by a Grass S 88 stimulator were single square pulses with a duration of 50-100 \( \mu \text{s} \) and an intensity of 10-50 V. The latter method made the muscle contract by directly depolarizing the membrane of the smooth muscle, and its characteristic waves were trains of square pulses with a frequency of 30
the circular muscles in the guinea-pig gastric antrum

Dopamine increased the basal tone and the spontaneous contraction of the antral circular muscle in a dose-dependent manner from the concentration of $5 \times 10^{-6}$ M and exerted a maximal effect at the concentration of $5 \times 10^{-5}$ M (Fig. 2, upper trace).

The excitatory effect of dopamine ($10^{-5}$ M) was almost completely suppressed by a $\alpha$-receptor blocker, phentolamine (Regitine, $5 \times 10^{-6}$ M) (Fig. 2, lower trace).

Such excitatory action of dopamine on the spontaneous contraction of the antral circular muscle was not blocked by tetrodotoxin (TTX).

The spontaneous contraction potentiated by dopamine ($10^{-6}$ M) was not attenuated by treatment with TTX ($3 \times 10^{-7}$ M) (Fig. 3), but it was completely suppressed by regitine ($5 \times 10^{-6}$ M) (Fig. 3, upper trace) and partially by a $\alpha_2$-receptor blocker, yohimbine ($10^{-6}$ M) (Fig. 3, lower trace).

**RESULTS**

1. Effects of dopamine on the contractility of

Hz, a duration of 20 ms, an intensity of 70 V, a train duration of 5 sec and a train interval of 1 min.

In this experiment no statistics were used because the resulting analysis was a qualitative comparison between data groups, and the figures cited in this article were representative ones selected after confirmation of the same results.

Drugs used in this experiment were as follows; atropine sulfate (Sigma), dopamine (Sigma), guanethidine sulfate (Tokyo kasei), phentolamine (Regitine, CIBA), tetrodotoxin (TTX, Sankyo), and yohimbine (Nakarai).
2. Effects of dopamine on the contractility of the circular muscles in the guinea-pig gastric fundus

Dopamine increased the basal tone of the fundic circular muscle dose-dependently from the concentration of $10^{-6}$ M (Fig. 4).

Such enhancing action of dopamine ($5 \times 10^{-5}$ M) was almost completely suppressed by regitine ($10^{-6}$ M) (Fig. 4), but was never affected by TTX ($3 \times 10^{-7}$ M) (Fig. 4, lower trace) treatment.

Since most of the fundic strips did not show spontaneous contractions, they were electrically stimulated to evoke contractions.

The contractions evoked by the direct stimulation of the fundic circular muscle were increased by dopamine from the concentration of $5 \times 10^{-6}$ M in a dose-dependent manner. They were not affected by TTX ($3 \times 10^{-7}$ M) treatment, but were completely suppressed by regitine ($10^{-6}$ M) (Fig. 5).

When phasic contractions were evoked by transmural nerve stimulation in the fundic strip, they were composed of three components. We called them the basal tone, the contraction component and the relaxation component, respectively (Fig. 6).

We observed the effect of dopamine on the contractions evoked by transmural nerve stimulation in the fundic muscle strip. The basal tone and the relaxation component increased, while the contraction component was decreased dose-dependently by dopamine from the concentration of $5 \times 10^{-6}$ M (Fig. 7). These effects of dopamine were reversible.

We studied the effect of dopamine on the contraction evoked by transmural nerve stimulation in the fundic muscle strip pretreated with guanethidine and atropine.

The contraction component was slightly decreased by guanethidine ($5 \times 10^{-6}$ M) and completely suppressed by atropine ($10^{-6}$ M), while
Fig. 5. Effect of dopamine on the contraction evoked by direct muscle stimulation in the fundic circular muscle. The stimulation waves produced by a Grass S 88 stimulator were trains of square pulses with a frequency of 30 Hz, a duration of 20 ms, an intensity of 70 V, a train duration of 5 sec and a train interval of 1 min. The contractions evoked by the direct stimulation of the fundic circular muscle were increased by dopamine in a dose-dependent manner. They were not affected by TTX but were suppressed by regitine.

Fig. 6. Three components of the contraction evoked by transmural nerve stimulation in the fundic circular muscle strip. The stimulation waves produced were single square pulses with a duration of 50-100 μs and an intensity of 10-50 V.

Fig. 7. Effect of dopamine on the contraction evoked by transmural nerve stimulation in the fundic circular muscle strip. The basal tone and relaxation component were increased, while the contraction component was decreased dose-dependently by dopamine. These effects of dopamine were reversible.

Fig. 8. Effect of dopamine on the contraction evoked by transmural nerve stimulation in the fundic circular strip treated with guanethidine and atropine. The contraction component was slightly decreased by guanethidine and completely suppressed by atropine, while the relaxation component was somewhat increased by atropine.
the relaxation component was somewhat increased by atropine treatment (Fig. 8).

In that condition dopamine increased the basal tone and the relaxation component in a dose-dependent manner. Such actions of dopamine were similar to those shown in Fig. 7 and were suppressed by regitine (10^{-6} M) treatment.

**DISCUSSION**

The effects of dopamine on gastrointestinal motility are known to be varied depending upon the animal species, regions of the gastrointestinal tract, the muscle layers and the externally administered dose (Cox and Ennis 1980a; Lefebvre et al. 1984).

It was reported that lower concentrations of dopamine suppressed contraction in the strips of the esophageal body of opossums, while dopamine in higher doses potentiated contraction (De Carle and Christensen 1976). And dopamine was known to relax the lower esophageal sphincter of dogs and men (Baumann et al. 1979; Itoh 1981). Recently Demol et al. (1989) reported that dopamine induced regurgitation of the duodenal contents to the stomach in man.

There have been many controversial reports on the action of dopamine upon gastric motility, too. Some authors have reported that dopamine induced contraction of the rat fundic region (Sonneville 1968), while others have reported that dopamine suppressed its contractility (Komissarov and Reutskaya 1978). And some authors have reported that dopamine evoked contraction of the rabbit antral region (Ercan 1981), while there were reports that dopamine suppressed contractility of rat antral circular muscles (Komissarov and Reutskaya 1978; Chey et al. 1983).

Cox and Ennis (1980a) reported that dopamine suppressed motility in guinea-pig stomachs. They presented the data that the intragastric pressure became lowered with the administration of dopamine in guinea-pigs. But there were reports that dopamine potentiated the contractility of guinea-pig stomachs (Sahyoun et al. 1982b; Costall et al. 1983).

As shown in the above brief review, there remains controversy concerning the actions of dopamine on gastric motility. And its sites and mode of action are even more indistinct.

In this experiment, dopamine increased the basal tone and the spontaneous contraction of the antral circular muscle in a dose-dependent manner (Fig. 2). And this excitatory effect of dopamine was suppressed completely by a α-receptor blocker, regitine (Figs. 2 & 3) or partially by a α2-blocker, yohimbine (Fig. 3) but was not blocked by TTX (Figs. 2 & 3).

These results suggest that dopamine directly potentiates the contractility of the antral circular muscle through activating α-adrenergic receptors in the muscle cell membrane, and not indirectly via nerves innervating the antral circular muscle.

Dopamine increased the basal tone of the fundic circular muscle, which was also suppressed by regitine but was never affected by TTX (Fig. 4). And the contractions evoked by direct stimulation to the fundic circular muscle were increased by dopamine. These were not affected by TTX but were completely suppressed by regitine (Fig. 5).

From these results we could conclude that dopamine directly potentiates the electrically-driven contraction of the fundic circular muscle through activating α-adrenergic receptors, and not indirectly via the nerves.

Some authors have suggested that dopamine exerted its action on gastrointestinal motility through activating specific dopaminergic receptors, such as those in the central nervous system. Schuurkes and Van Nueten (1981 & 1982) have supported this hypothesis by showing experimental results that a dopaminergic antagonist, domperidone blocked the effects of dopamine on gastrointestinal motility. But others have argued against this hypothesis. They have insisted that domperidone had a non-specific action on the peripheral nerve fibers and muscle cells (Kamikawa et al. 1982; Costall et al. 1983).

In this experiment we did not verify whether dopamine exerted its action via a specific dopaminergic receptor. But our results support the idea that dopamine may exert its action through activating α-adrenergic receptors, especially the α1-receptor. Contractions evoked by transmural nerve stimulation in the fundic muscle strip were composed
of the basal tone, the contraction component and the relaxation component (Fig. 6).

We observed the effect of dopamine on the contractions evoked by transmural nerve stimulation in the fundic muscle strip. The basal tone and the relaxation component were increased, while the contraction component was decreased by dopamine (Fig. 7).

We studied the effect of dopamine on the contractions evoked by transmural nerve stimulation in the fundic muscle strip pretreated with an adrenergic depletor, guanethidine and a cholinergic blocker, atropine.

The contraction component was slightly decreased by guanethidine and completely suppressed by atropine, while the relaxation component was somewhat increased by treatment with guanethidine and atropine. Under these conditions dopamine increased the basal tone and the relaxation component, which were suppressed by regitine (Fig. 8). This suggests that the contraction component is due to cholinergic activation and that the relaxation component originates from the activation of non-adrenergic non-cholinergic nerves (Martison and Muren 1963; Burnstock 1969), in which ATP (Burnstock 1972) and vasoactive intestinal polypeptide (Grider et al. 1985; Lefebvre 1986; Kamata et al. 1988) play an important role as neurotransmitters.

From the results shown in Figs. 7 and 8, it is suggested that dopamine increases relaxation through enhancing the release of transmitters from non-adrenergic non-cholinergic nerve terminals and suppresses contraction by inhibiting the transmitter release from cholinergic nerves in the fundic region.

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도파민이 기니피그 위 유문동과
위저부 윤상근의 수축성에 미치는 효과

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도파민이 위 운동성에 미치는 효과와 그 작용기전을 알아보기 위해 기니피그 유문동
및 위저부에서 윤상근 절편을 취해 실험을 하여 다음과 같은 결과를 얻었다.
1. 유문동 윤상근의 자발적 수축은 도파민에 의해 촉진되었다. 이러한 홍분성 반응은
아-차단제인 phenolamine에 의해 완전히, 그리고 α-차단제인 yohimbine에 의해 부
분적으로 억제되었지만 TTX의 영향은 받지 않았다.
2. 유문동 및 위저부 윤상근의 기초장력은 도파민에 의해 증가하였다. 이러한 반응은
α-차단제에 의해 억제되며 TTX의 영향은 받지 않았다.
3. 도파민은 위저부 윤상근을 직접 자극하였을 때 유발된 수축을 강화시켰다. 이러한
작용은 α-차단제에 의해 억제되며 TTX의 영향은 받지 않았다.
4. 위저부의 신경을 전기자극할 때 유발되는 수축은 기초장력, 수축성분, 그리고 이완
성분의 세 가지 구성 성분을 가졌다. 이 때 도파민을 투여하면 기초장력과 이완성분은
증가하였으며 수축성분은 감소하였다.
5. 아트로피온 신경자극으로 유발되는 위저부 윤상근 수축에 대해 수축성분은 감소시키고
이완성분은 증가시켰다. 이러한 상태에서 도파민을 투여하면 이완성분은 더욱 커졌
으며, 이러한 현상은 α-차단제에 의해 억제되었다.
저자들은 이상의 실험결과들을 토대로 하여 다음과 같은 결론을 얻었다.
첫째, 도파민은 윤상근 세포막의 α-수용체, 특히 α2-수용체를 통하여 유문동과 위저부
두 부위에서 윤상근의 기초장력을 증가시키며, 유문동 평활근의 자발적 수축을 촉진한다.
둘째, 도파민은 위저부에서 바이아드레날린 비콜린성(NANC) 신경섬유의 신경전달물질을
유리시킴으로써 이완을 촉진하며, 아세틸콜린의 유리함 감소시킴으로써 수축을 억제한다.