Opiate-like inhibitory effect of trimebutine on the twitch response of the isolated guinea pig ileum.

Teruhiro Yamasato*    Miyako Takaki†
Sosogu Nakayama‡
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Abstract

Trimebutine at low concentrations (6 X 10(-9)-1.4 X 10(-8) M) slightly enhanced the twitch response of isolated guinea pig ileum induced by transmural stimulation. At high concentrations (2 X 10(-8)-2 X 10(-7) M), however, it inhibited the twitch response in a dose dependent manner. This inhibitory effect of trimebutine was reversed by naloxone (8.1 X 10(-9) M). These results suggest that trimebutine has an opiate-like action on the myenteric plexus.

KEYWORDS: naloxone, trimebutine, twitch response

*PMID: 3565073 [PubMed - indexed for MEDLINE]
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Opiate-like Inhibitory Effect of Trimebutine on the Twitch Response of the Isolated Guinea pig Ileum

Teruhiro Yamasato, Miyako Takaki and Sosogu Nakayama

Department of Physiology, Okayama University Medical School, Okayama 700, Japan

Trimebutine at low concentrations ($6 \times 10^{-8}$–$1.4 \times 10^{-8}$ M) slightly enhanced the twitch response of isolated guinea pig ileum induced by transmural stimulation. At high concentrations ($2 \times 10^{-8}$–$2 \times 10^{-7}$ M), however, it inhibited the twitch response in a dose dependent manner. This inhibitory effect of trimebutine was reversed by naloxone ($8.1 \times 10^{-9}$ M). These results suggest that trimebutine has an opiate-like action on the myenteric plexus.

Key words: naloxone, trimebutine, twitch response

Trimebutine maleate (2-dimethylamino-2-phenylbutyl-3,4,5-trimethoxybenzoate hydrogen maleate; trimebutine) has been used in the treatment of various gastrointestinal disorders.

Trimebutine is known to induce an excitatory effect on the low tone colon, to cause a relaxation of the high tone colon (1) and to regularize irregular contractions of the intestine (2) in the guinea pigs. Fioramanti et al. (3) have reported that trimebutine excites the motility of the small intestine in conscious dogs, and that this action of trimebutine is antagonized by naloxone, suggesting that trimebutine has a stimulatory action on the opiate receptors in the intestine. However, such an opiate-like action of trimebutine has not been recognized in isolated preparations of the small intestine of guinea pigs. Therefore, in the present experiment, the effects of trimebutine were studied in relation to its opiate-like action on the twitch response of the guinea pig ileum.

Materials and Methods

Guinea pigs of either sex (250–500 g) were stunned by a blow to the head and bled. Segments, 2.5–3 cm long, were removed from the ileum 15–20 cm oral to the ileocecal junction. The luminal contents were washed out with Tyrode solution, and each segment was placed in an organ bath containing 15 ml of Tyrode solution ($34.0 \pm 0.5 ^\circ$C) which was aerated with 95% O$_2$ and 5% CO$_2$. The longitudinal contractions of the segments were recorded with an isotonic transducer and pen oscillograph. After a 1.5 h control period, the effects of the drug on the preparation were examined. The preparation was washed with Tyrode solution 4 times after the drug treatment, and 5 min later the additional wash was carried out 3 times. In order to investigate the potentiation and inhibition of the twitch response induced by trimebutine, 50–70% of the maximal twitch response to transmural stimulation (0.5–msec pulse of 40–100 mV at 6–10 sec intervals) was used as a control. The preparations which showed almost the same twitch response in amplitude during a control period were used. The contractile height of the twitch responses were measured 2 min after trimebutine application. The drugs
used were trimebutine maleate (supplied by Tanabe Seiyaku Co., Tokyo), naloxone hydrochloride (Endo Lab.), atropine sulfate (Merck) and tetrodotoxin (Sankyo).

Results and Discussion

Trimebutine at low concentrations, $6 \times 10^{-9} - 1.4 \times 10^{-8} \text{ M}$, produced a slight enhancement of the twitch response induced by transmural stimulation (no significant difference from the control value), and high concentrations, $2 \times 10^{-8} - 2 \times 10^{-7} \text{ M}$, trimebutine caused an inhibition of the twitch response in a dose-dependent manner. Trimebutine at concentrations of $2 \times 10^{-8} - 10^{-7} \text{ M}$ reduced the twitch response by 7-60%, and at $2 \times 10^{-7} \text{ M}$ reduced the twitch response by over 90% 2 min after the drug administration, but 3-4 min later the twitch response recovered to about 13% of the control response. The dose-response curve of trimebutine is shown in Fig. 1.

The inhibition of the contraction by high concentrations of trimebutine was reversed by naloxone $(8.1 \times 10^{-9} - 1.4 \times 10^{-8} \text{ M})$. The inhibitory effect induced by higher concentrations of trimebutine $(2 \times 10^{-8} \text{ M})$ was not reversed to the control level by low concentrations of naloxone $(8.1 \times 10^{-9} - 1.4 \times 10^{-8} \text{ M})$, but was reversed to about 60% of the control level by a high concentration of naloxone $(2.7 \times 10^{-7} \text{ M})$.

Atropine $(1.4 \times 10^{-8} \text{ M})$ and tetrodotoxin $(10^{-7} \text{ g/ml})$ completely abolished the twitch response induced by transmural stimulation.

Trimebutine at $6 \times 10^{-9} - 1.4 \times 10^{-8} \text{ M}$ produced a slight enhancement of spontaneous motility, and at $2 \times 10^{-8} - 2 \times 10^{-7} \text{ M}$ trimebutine produced an inhibition of the spontaneous motility similar to the inhibition of the twitch response. The excitatory and inhibitory effects of trimebutine on the spontaneous motility were abolished by atropine $(1.4 \times 10^{-6} \text{ M})$ and tetrodotoxin $(10^{-7} \text{ g/ml})$. The inhibitory response was antagonized by naloxone, but the effect of naloxone on the excitatory response was not examined.

Paton (4) reported that transmural electrical stimulation induced increased release of acetylcholine from cholinergic nerve terminals of the myenteric plexus. This increase was blocked by morphine. Fioramanti et al. (3) reported that the excitatory effects of trimebutine on the dog duodenum were antagonized by naloxone in vivo. Opioids induced the excitatory response via opiate receptors in the myenteric neurons and intestinal muscle in the canine small intestine (6, 7). In the present experiment, trimebutine reduced the submaximal twitch response in a dose-dependent manner $(2 \times 10^{-8} - 2 \times 10^{-7} \text{ M})$, and this effect of trimebutine was reversed by naloxone, a pure antagonist of narcotic substances (5). The inhibitory effect of trimebutine on spontaneous motility was abolished by.

![Fig. 1 Inhibitory effect of trimebutine on submaximal twitch response of isolated guinea pig ileum induced by transmural electrical stimulation.](http://escholarship.lib.okayama-u.ac.jp/amo/vol41/iss1/5)
atropine and tetrodotoxin. These results suggest that trimebutine acts on cholinergic neurons in the myenteric plexus. Therefore, trimebutine appears to have characteristics similar to opiates and opioids in inhibiting acetylcholine release from the cholinergic nerves in the myenteric plexus of the guinea pig ileum.

References


Received: May 13, 1986
Accepted: November 13, 1986

Correspondence to:
Teruhiro Yamasato
Department of Physiology
Okayama University Medical School
2-5-1 Shikata-cho
Okayama 700, Japan