大韓藥理學雜誌:第11卷 第1號 Korean J. of Pharmacology Volume II, Number 1, 1975

# A Comparison of the Responses of Lower Vertebrate Intestines to Prostaglandin E<sub>1</sub> and E<sub>2</sub>

# Ki Whan Hong, M.D.

Department of Pharmacology, College of Medicine, Busan National University, Busan, Korea

# SUMMARY

- The isolated strips of guinea-pig, fowl and reptiles (snake and tortoise) showed consistenly excitatory responses to PGE<sub>1</sub> and E<sub>2</sub>, which were dose-dependent.
- 2. Frog intestine revealed inhibitory responses to both PGE<sub>1</sub> and PGE<sub>2</sub> except a small of PGE<sub>2</sub> (1-10 ng/ml) caused slight contraction.
- 3. The intestines of pieces showed inconsistent responses to PGE<sub>1</sub> and E<sub>2</sub>. In fresh-water fish(carp), PGE<sub>1</sub> produced relaxation under the dose of 50 ng/ml, and contraction by the large doses, but PGE<sub>2</sub> consistently caused contraction in dose-dependent manner. However, the strips of sea-water fish revealed the different responses to PGE compound: PGE<sub>1</sub> caused relaxation and PGE<sub>2</sub> conversly contraction even though in small degree.
- 4. These results that there are genera differences in the responses of the longitudinal strips of intestine to PGE<sub>1</sub> and PGE<sub>2</sub> was assumed to be possibly correlated with evolutionally primitive function of gut.

# INTRODUCTION

Some of the naturally occurring prostaglandins (PGs) were reported to be biosynthesized

in many tissues (Flower, 1974), and these substances are also known to be found in all other gastrointestinal tissues including the stomach of man, rat and the small intestine of man, guinea-pig and rabbit, and the large intestine of swine (Bennett and Fleshler, 1970), and further, PGE and PGF types were found to be present in the rat stomach and released spontaneouly in vitro and acetylcholine or transmural electrical stimulation accelerated the PGs formation from precursors bound to membrane phospholipid, However, the responses of lower vertebrate intestine under the genus mammal to PGs were rarely reported, so that this paper is aimed to see the genera differences in the intestinal responses to PGE1 and PGE2.

#### METHODS

The experimental animals acquired near Busan city, Korea were as follows: 1. Mammal; guineapig, 2. Fowl; Gallus gallus domesticus, 3. Reptile; snake (Elaphe rupodorsata (Cantor)) and tortoise (Amyda japonica), 4. Amphibia; frog(Rana nigromaculata) 5. Pisces; freshwater fish, carp (Carassius carassius) and seawater fish, eel (Anguilla japonica) and Ditrema temminck: Bleeker.

This experiment was carried out from May to 30th September 1974.

The upper and middle portion of intestine were used and the lower portion discarded:

lower vertebrates. The segments of guinea-pig and fowl were mounted in organ baths containing 15ml Tyrode solution (37°C) and those of reptiles, amphibia and pisces were suspended in Frog-Ringer solution(at room temperature). All these were gassed with oxygen and muscle activity recorded with an isotonic lever (magnification 10:1). The preparations were pretreated with  $10^{-6}$ g/ml of atropine and guanethidine, respectively and bathed for  $30\sim$ 60 min until the tension being stabilized, and then washed out with working solutions.

# RESULTS

# 1. Excitatory responses of intestines

Isolated terminal ileum of guinea-pig and intestinal strips of fowl under gizzard contracted

to small amounts of PGE<sub>1</sub> and PGE<sub>2</sub> in dosedependent manner from 0.1 up to 100 ng/ml and the contraction height of fowl intestine even in large dose was less than those of guinea-pig.

The gut segments of snake and tortoise alsoshowed contraction but the strips of the latter exhibited high sensitive and dose-dependent response to both PGE<sub>1</sub> and PGE<sub>2</sub> at picogram level and snake intestine showed much slower response than do those of other lower vertebrates. (Table 1).

# 2. Inhibitory and inconsistent responses of intestine

The isolated upper intestine of frog consistenty revealed dose-dependent relaxation but PGE<sub>2</sub> showed the dual responses, that is, when

PGE	Mammal		Fowl		Reptiles		}	
Concent- ration	Guinea-pig		Gallus gallus domesticus		Snake Elaphe rupodorsata		Tortoise Amyda japonica	
g/ml	Contraction (mm), Mean±SD							
	PGE <sub>1</sub>	$PGE_2$	PGE <sub>1</sub>	$PGE_2$	PGE <sub>1</sub>	$PGE_{2}$	PGE <sub>1</sub>	$PGE_2$
$10^{-10}$	5.1±2.5(7)	2.4±1.3(7)	10.0±4.1(5)	6.3±2.2(6)		-		$8.8\pm3.5(12)$
$10^{-9}$	9.5±4.2(6)	15. 2±6. 1(6)	16.2±4.8(6)	) 21.5±6.7(6)	8.4±4.1(	7) 11.6±3.0(8)	50. 2±16.	3(11) 26. 5±6. 0(12)
10-8	57. 0±24. 1(6) 54	) 4, 2±13. 5(6)	48. 7±11. 0(6	5) 29. 4±10. 3(7)	13.5±4.4(	12) 25. 4±4. 8(8)	58.7±14.4	1(9) 53.8±9.1 <b>(9)</b>
10-7	90.6±18.3(6)	) ). 0±15. 5(5)	55. 4±12. 3(6	6) 41. 6±14. 1(6)	19.0±6.20	7) 40. 3±10. 2(7)	62. 8±13. 9	9(8) 57. 3±13. 5(8 <b>)</b>
$10^{-6}$			_		28. 5±11. 5		<b>—</b>	. <del></del>

Table 1. Excitatory responses of isolated intestine to PGE1 and PGE2

Numbers in brackets indicate numbers of observations

1 ng/ml PGE<sub>2</sub> applied, six out of 9 preparations caused no response and the remained three produce mild contraction and by 10 ng/ml PGE<sub>2</sub> ten out of 14 induced contraction, one had no response and 3 strips showed inhibitory response.

By 30 ng/ml PGE2 six out of 12 preparations

relaxed and others contracted in small height in amplitude and 50 ng/ml PGE<sub>2</sub> showed relaxation in 9 out of 12 and the remained 3 preparations contracted. PGE<sub>2</sub> 100 ng/ml consistently produced the inhibitory responses as shown in Fig. 1. The intestinal strips of frog responded inhibitory more sensitively to PGE.

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bia	a nigromaculata Fresh-water fish, Carassius carassius Eel, Anguilla 13200nica Ditrema temmincki Bleeker	-	PGF2a   PGE1	$+4.0\pm 2.2$ — $0(4)$ $0(5)$ — $0(6)$ $0(9)$ $0(5)$ $0(5)$ $0(5)$ $0(5)$	$+4.6\pm 2.1$   ##(7) $+10.2\pm 4.5 + 9.3\pm 3.8$   $-13.5\pm 2.1 + 7.1\pm 3.3$ (6) (6) (6)	$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$
Amphibia	Frog, Rana nigromaculata	Res		$-10.5\pm2.7 +4.0\pm2.2$ (9)#	$-18.7\pm5.4 + 13.6\pm5.1$ (16) (14)#	$-37.3\pm13.5$ $-42.0\pm18.6$ $+1$ (6)	+
PGs	Concent-	ration g/ml		10-9	10-8	10-7	10-6

Three preparations out of 7 showed slight inhibitory response. Nambers in brackets indicate numbers of observations. #, See the text.

Frog. Rana nigromaculata

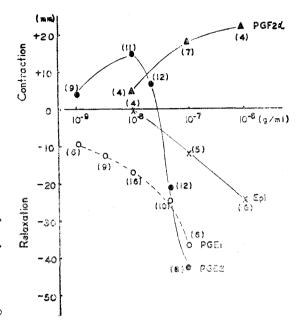


Fig. 1. Dose-response curves to  $PGE_1$ ,  $PGE_2$  and  $PGF_{2\alpha}$  as the mean response of intestinal strips from frog, which was compared with the action of epinephrine(Epi).

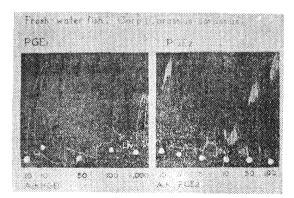


Fig. 2. Effects of PGE<sub>1</sub> and PGE<sub>2</sub> on the intestinal strips of carp, Carassius carassius.

compounds than epinephrine.

The middle portion of intestinal strip (freshwater fish) was initially applied with 10<sup>-8</sup>g/ml acetylcholine to see the responsiveness to the stimulant and thereafter, by applying 50 ng/ml PGE<sub>1</sub> they slowly and slightly relaxed, but

PGE<sub>1</sub> from 100 to 1,000 ng/ml consistently contracted the segment. In contrast to PGE<sub>1</sub>, PGE<sub>2</sub> strongly caused contraction even by the dose of 5 ng/ml in dose-dependent up to 100 ng/ml. PGF<sub>2</sub><sup>α</sup> also induced contraction but less potent than PGE<sub>2</sub> (Fig. 2).

As a sea-water fish the intestine of eel, which is oviparous fish, was relaxed by PGE<sub>1</sub> but conversly contracted by PGE<sub>2</sub>. And the intestinal strips of Ditrema temmincki Bleeker, which is characteristically viviparous fish, revealed the similar responses as shown in those of eel (Table 2).

#### DISCUSSION

Recent works have shown that relatively large amounts of PGs may be released after nerve stimulation (Horton and Main, 1967; Ramwell et al., 1965; Davies et al., 1967; Gilmore et al., 1968; Shaw, 1966), so that in this experiment atropine and guanethidine were previously treated in the bath to exclude the actions of adrenergic and cholinergic fibers.

In each instance the longitudinal muscle strips were used and the effects of PGE1 and  $E_2$ , sometimes with  $PGF_{2\alpha}$  have been compared on the five genera, of which were mamml, fowl, reptile, amphibia and pisces. Not only the intestines of domestic fowl but those of reptiles (snake and tortoise) were consistently responded with contraction by the small amounts of PGE compound like as shown in guinea-pig ileum and other mammals (Bennet and Fleshler, 1970). However, the isolated intestine of frog revealed inhibitory responses to both PGE<sub>1</sub> and E<sub>2</sub> except the small dose of PGE<sub>2</sub> (10 ng/ml) showed inconsistency. There can be seen much more inconsistent responses of the intestines of pisces to PGE, that is, the intestine of carp was contracted by PGE1 and E2, in this case the small amount of PGE1

caused trivial contraction, irregularly. The intestinal strips of sea-water fish showed inhibitory responses to PGE<sub>1</sub>, and excitatory to-PGE<sub>2</sub>, but both of responses were insensitive.

A clear role for PGs in gut motility has not yet been established, but recently interest has been focused on the role of PGs in the action of neurotransmitters of autonomic nervous system and on the maintenance of smooth muscletone in the rabbit jejunum and guinea-pigileum (Hedqvist and Wennmalm, 1971; Samuelsson and Wennmalm, 1971; Wennmalm, 1971; Ferreira et al., 1972; Kadlec et al., 1974, and Botting and Salzmann, 1974).

It is interesting to observe that the longitudinal strips of intestine obtained from lower vertebrates under amphibia phylogenetically in contrast to the animals above reptile have shown a variety of responses to PGE<sub>1</sub> and E<sub>2</sub> as inhibitory or excitatory, and these are seemed to be possibly correlated with evolutionally primitive function of gut.

It is harder to rationalize the effects of PGs but these genera differences in the action of PGE compounds may presumably be the same case as the fact indicated by Campbell and Burnstock (1968), concerning the vagal supply to the gut of lower vertebrates as interpreting that the vagal outflow is primitively inhibitory, but that these fibers are accompanied by excitatory fibers.

#### Acknowledgments

We wish to thank Dr. J. Pike(The Upjohn Co. Kalamazoo, Mich., U.S.A.) for the generous supply of prostaglandins.

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