International Scholars Journals

International Journal of Pharmacy and Pharmacology ISSN: 2326-7267 Vol. 9 (2), pp. 001-008, February, 2020. Available online at www.internationalscholarsjournals.org © International Scholars Journals

Full Length Research Paper

Biological activity of progesterone-dihydropyridimidine derivative on perfusion pressure and coronary resistance in isolated rat heart

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Accepted 15 October, 2019

Experimental studies suggest that progesterone can regulate blood pressure. Nevertheless, there is scarce information about the effects of progesterone and its derivatives at cardiovascular level. In addition, to date the cellular site and mechanism of action of progesterone at cardiovascular level is also unclear. In order, to clarify on those phenomena, we evaluated the effects of progesterone and progesterone-dihydropyridimidine derivative on perfusion pressure in isolated rat heart using Langendorff flow model. Our results demonstrated that progesterone- derivative at a concentration of 10^{-9} mM, significantly increase the perfusion pressure (p = 0.006) and coronary resistance (p = 0.005) in isolated heart. The activity exerted by progesterone-dihydropyridimidine derivative on perfusion pressure [10^{-9} to 10^{-4} mM] was blocked in presence of indomethacin [10^{-6} mM] and *PINANE* TXA_2 [10^{-6} mM]. These data suggest that activity induced by progesterone-derivative on perfusion pressure and coronary resistance involves the thromboxane A_2 (TXA_2) synthesis and secretion.

Key words: Progesterone-dihydropyridimidine derivative, Langendorff, perfusion pressure.

INTRODUCTION

Hypertension contributes substantially to cardiovascular disease incidence and premature mortality (Stary, 1989; Mahoney et al., 1996; Oparil et al., 2003). Studies using the technique of ambulatory blood pressure monitoring have shown that blood pressure is higher in men than in women of similar ages (Khoury et al., 1992; Wiinberg et al., 1995). The sex-associated differences in blood pressure regulation observed in humans have also been documented in various animal models (Ouchi et al., 1987; Ashton and Balment, 1991; Rowland and Fregly, 1992). For example, male spontaneously hypertensive rats (SHR) have higher blood pressures than do females of similar ages (Masubuchi et al., 1982; Cheng and Meng, 1991; Reckelhoff et al., 1998). Additionally, experimental and clinical studies (Khaw and Barret, 1988; Gray et al., 1991a; Gray and Feldman, 1991b) have demonstrated that steroids can be associated with changes in blood pressure. For example, there are evidences that progesterone can affect the blood pressure (Rylance et al., 1985). Some reports indicate that administration of progesterone increases the systolic blood pressure over time in gonadectomized rats (Crofton and Share, 1997). Nevertheless, there are studies which suggest that progesterone diminishes the blood pressure through mineralocorticoid antagonistic properties in male Sprague-Dawley rats (Wambach and Higgins, 1979).

On the other hand, there are reports which indicate that

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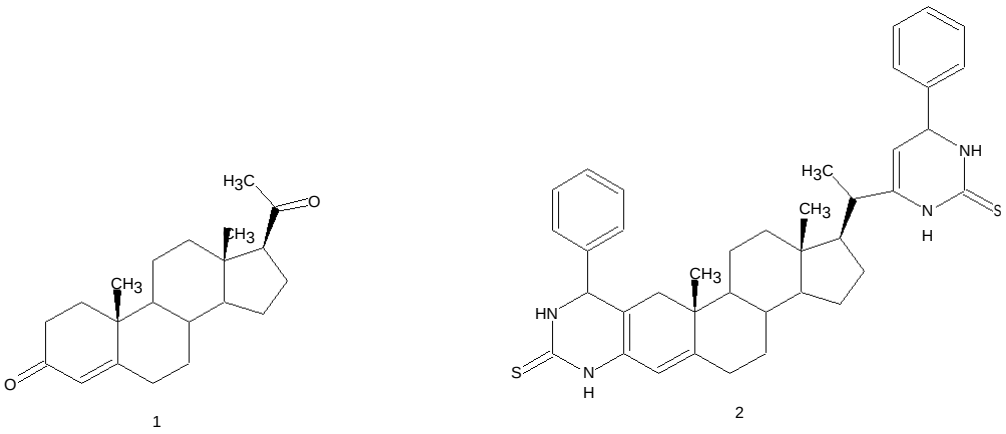

Figure 1. (1) Chemical structure of progesterone. (2) progesterone-dihydropyridimidine derivative.

progesterone derivatives (11-α and 11-β hydroxyprogesterone) increase the blood pressure and their activity depends on an intact adrenal and at least in part on the activation of mineralcoticoids receptors (Souness and Morris, 1996). Additionally, another studies made by Brown (1990) showed that progesterone-derivative (14 -aminopregnane) induce a positive inotropic and vasoconstrictor responses in isolated tissues from the guinea-pig and these phenomenon could induce indirect changes in blood pressure. Apart from the above experiments, which also do not show clearly the cellular site and actual molecular mechanisms of progesterone, data information are needed for characterizing the activity induced by this steroid at cardiovascular level. To provide this information, the present study was designed to investigate the effects of progesterone and progesterone-dihydropyridimidine derivative on perfusion pressure and vascular resistance in isolated rat hearts using Langendonff model (Figueroa et al., 2002).

In addition, the molecular mechanism involved in the activity induced by progesterone-derivative on perfusion pressure was evaluated using several substances such as *prazosin, WB-4101* [α_1 adrenoreceptor antagonists] (Graham et al., 1977; Butler and Jenkinson, 1978) metoprolol [selectiveβ_1 receptor blocker] (Bengtsson et al., 1975), indomethacin [inhibitor of prostaglandin synthesis] (Owen et al., 1975) and *PINANE* TXA_2 (antagonist of thromboxane A2) (Burke, 1983) were used as pharma-cological tools.

MATERIALS AND METHODS

General methods

All experimental procedures and protocols used in this investigation were reviewed and approved by the Animal Care and Use Committee of Universidad Autonoma de Campeche (UAC) and were in accordance with the Guide for the Care and Use of Laboratory Animals. Male rats (Wistar; weighing 200 - 250 g) were obtained from UAC.

Reagents

Progesterone-dihydropyrimidine derivative (11a,13a-dimethyl-phenyl-1-[1-(6-phenyl-2thioxo-1,2,3,6-tetrahydro-pyrimidin-4-yl)-ethyl]-ethyl-1,2,3,3a,3b,4,5,5a,7,9,10,10a,11,11a,11b,12,13,13a-octadeca-hydro-1*H*-7,9-diaza-indeno[5,4a]anthracene-8- thione) showed in Figure 1 was prepared according to a previously reported method by Figueroa and coworkers (2009[b]). Other reagents were obtained from Sigma-Aldrich Chemical Co. All drugs were dissolved in *methanol* and different dilutions were obtained using Krebs-Henseleit solution (≤ 0.01%, v/v).

Langendorff method

Briefly, the male rat (200 - 250 g) was anesthetized by injecting them with pentobarbital at a dose of 50 mg/Kg body weight. The chest was opened and a loose ligature passed through the ascending aorta. The heart was then rapidly removed and immersed in ice cold physiologic saline solution. The heart was trimmed of non-cardiac tissue and retrograde perfused via a non-circulating perfusion system at a constant flow rate. The perfusion medium was the Krebs- Henseleit solution (pH 7.4, 37°C) composed of (mM); 117.8 NaCl; 6 KCl; 1.75 $CaCl_2$; 1.2 NaH_2PO_4 ; 1.2 $MgSO_4$; 24.2 $NaHCO_3$; 5 glucose and 5 sodium pyruvate. The solution was actively bubbled with a mixture of O_2/CO_2 (95:5).

The coronary flow was adjusted with a variable-speed peristaltic pump. An initial perfusion rate of 15 ml/min for 5 min was followed by a 25 min equilibration period at a perfusion rate of 10 ml/min. All experimental measure-ments were done within the equilibration period.

Perfusion pressure

Evaluations of perfusion pressure changes induced by drugs in this study were assessed using a pressure transducer connected to the chamber where the hearts were mounted and the results entered into a computerized data capture system (Biopac).

Biological evaluation

Effect induced by progesterone and progesterone-dihydropyrimidine derivative on perfusion pressure

Time course changes in perfusion pressure of progesterone and

progesterone-dihydropyrimidine at a concentration of 10^{-9} mM were determined. The effects were obtained in isolated hearts perfused at a constant- flow rate of 10 mL/min (Ceballos et al., 1999; Figueroa et al., 2009a).

Evaluation of effects exerted by progesterone and progesterone-dihydropyrimidine derivative on coronary resistance

The coronary resistance in absence (control) or presence of progesterone and progesterone-dihydropyrimidine at a concentration of 10^{-9} mmol was evaluated. The effects were obtained in isolated hearts perfused at a constant flow rate of 10 ml/min.

The coronary resistance was determined by the relationship between coronary flow and perfusion pre-ssure (mm Hg/ml/min) (Figueroa et al., 2005; Figueroa et al., 2009a).

Effect exerted by progesterone-dihydropyrimidine derivative on perfusion pressure in the presence of α_1 adrenergic blocker

The boluses (50 µl) of progesterone-dihydropyrimidine [10^{-9} to 10^{-4} mM] were administered and the corresponding effect on the perfusion pressure was evaluated. It is important to mention that the bolus injection administered was done in the point of cannulation.

The dose-response curve (control) was repeated in the presence of prazosin or WB- 4101 at a concentration of 10^{-6} mM (duration of preincubation with prazosin or WB- 4101 was by a 10 min equilibration period). (Drew et al., 1979; Figueroa et al., 2009c).

Effects induced by progesterone-dihydropyrimidine derivative on perfusion pressure in the presence of β_1 adrenergic blocker

The boluses (50 µl) of *progesterone-dihydropyrimidine* [10^{-9} to 10^{-4} mM] were administered and the corres-ponding effect on the perfusion pressure was evaluated.

The dose-response curve (control) was repeated in the presence of *metoprolol* at concentration of 10^{-6} mmol (duration of preincubation with *metoprolol* was by a 10 min equilibration period) (Rajala et al., 1988).

Activities exerted by progesterone-dihydropyrimidine derivative on perfusion pressure in the presence of calcium-channel blocker

The boluses (50 µl) of progesterone-dihydropyrimidine [10^{-9} to 10^{-4} mmol] were administered and the corresponding effect on the perfusion pressure was evaluated. The dose-response curve (control) was repeated in the presence of nifedipine at a concentration of 10^{-6} mmol (duration of preincubation with nifedipine was by a 10 min equilibration period) (Figueroa et al., 2009c)

Effect exerted by progesterone-dihydropyrimidine derivative on perfusion pressure in presence of indometacin (inhibitor of prostaglandin synthesis) and PINANE TXA_2 (antagonist of TXA_2 receptor)

The boluses (50 µl) of progesterone-dihydropyrimidine [10^{-9} to 10^{-4} mM] were administered and the corresponding effect on the perfusion pressure was evaluated. The dose-response curve (control) was re-peated in the presence of indomethacin or PINANE TXA_2 at a concentration of 10^{-6} mM (duration of preincubation with indomethacin or PINANE TXA_2 was by a 10 min equilibration period) (Ceballos et al., 1999).

Statistical analysis

The obtained values are expressed as mean ± SE (standard error), using each heart as its own control. The comparation between means was made with a paired Student's t test. In the case multiple comparations was used an analysis of variance (ANOVA) using the Bonferroni correction factor (Hocht et al., 1999). The differences were considered significant when p was equal or smaller than 0.05.

RESULTS

In this work, the activity induced by progesterone and progesterone- dihydropyridimidine derivative on perfusion pressure and coronary resistance in isolated rat heart were evaluated. The results obtained from changes in perfusion pressure as a consequence of increases in the time (3 - 18 min) in absence (control) or in presence of progesterone and progesterone-dihydropyridimidine derivative (Figure 2), showed that progesterone - derivative [10^{-9} mM] significantly increase the perfusion pressure ($p = 0.006$) in comparison with the control conditions and progesterone [10^{-9} mM]. Additionally, another result showed that coronary resistance, calculated as the ratio of perfusion pressure at coronary flow assayed (10 mL/min) was higher in the presence of progesterone-dihydropyridimidine derivative than in control conditions and progesterone ($p = 0.005$) at a concentration of 10^{-9} mM (Figure 3). On the other hand, other experiments (Figure 4) showed that progesterone-dihydropyridimidine derivative increase the perfusion pressure in a dose dependent manner [10^{-9} to 10^{-4} mM] and this effect was not inhibited in presence of prazosin ($p = 0.005$), metoprolol ($p = 0.006$) or WB-4101 ($p = 0.005$) drugs at a concentration of 10^{-6} mmol.

Alternative experimental indicate that effect induced by progesterone-dihydropyridimidine derivative on perfusion pressure (Figure 5) in presence of nifedipine at a concentration of 10^{-6} mM was not inhibited. Additionally, other results suggest that the activity exerted by progesterone-derivative [10^{-9} to 10^{-4} mM] on perfusion pressure (Figure 6) in presence of indomethacin or PINANE TXA_2 at a concentration of 10^{-6} Mm was significantly inhibited ($p = 0.005$). Finally, other dataindicate that under the different conditions experimental the coronary resistance (Figure 7) in presence of indomethacin or PINANE TXA_2 at a concentration of 10^{-6} Mm was low in comparison with the other inhibitors used in each a of experiments ($p = 0.005$).

DISCUSSION

In this work, the effect induced by progesterone and pro-gesterone-dihydropyridimidine derivative on the perfusion

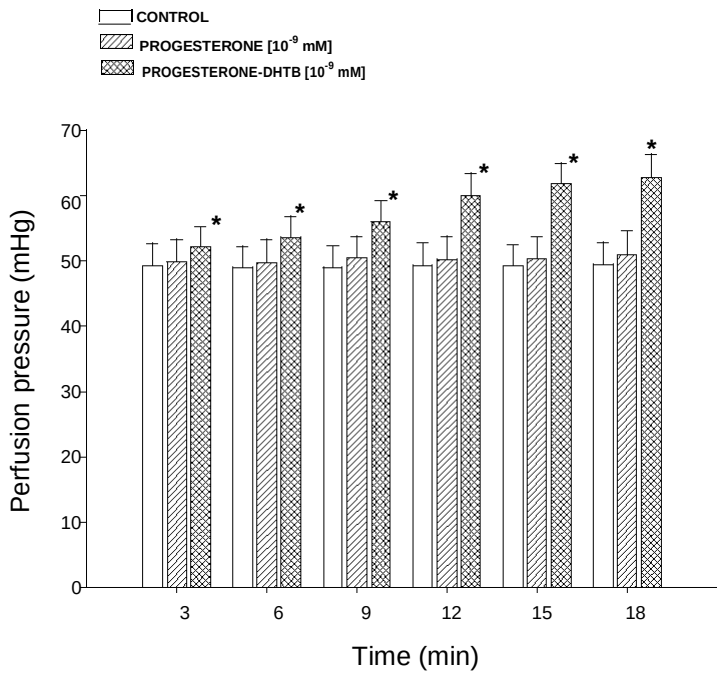

Figure 2. Effect induced by progesterone and progesterone-dihydropyridimidine derivative (progesterone-DHTB) on perfusion pressure. The results showed that progesterone-DHTB [10^{-9} mM] significantly increase the perfusion pressure ($p = 0.006$) through of time (3 - 18 min) in comparison with the control conditions and progesterone [10^{-9} mM]. The effect is expressed as the area under the curve and each bar represents the mean ± S.E. of 9 experiments.

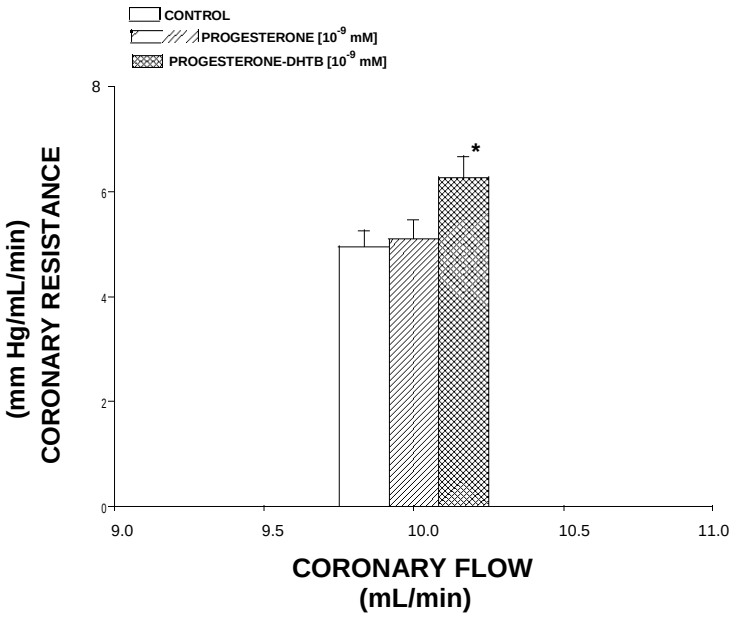

Figure 3. Activity induced by progesterone and progesterone-dihydropyridimidine derivative (progesterone-DHTB) on coronary resistance. The results showed that coronary resistance was higher ($p = 0.005$) in presence of progesterone-DHTB [10^{-9} mM] in comparison with the control conditions and progesterone [10^{-9} mM]. The effect it is expressed as the area under the curve and each bar represents the mean ± S.E. of 9 experiments.

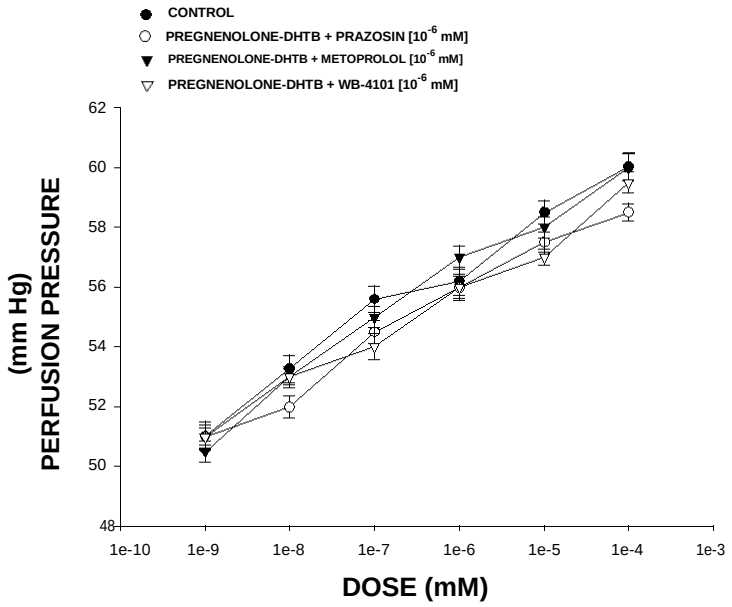

Figure 4. Effect exerted by progesterone-dihydropyridimidine derivative (progesterone-DHTB) on perfusion pressure through of adrenergic activity. Progesterone-DHTB [10^{-9} to 10^{-4} mM] was administered (boluses, 50 µl) and the corresponding effect on the perfusion pressure was evaluated in absence and presence of prazosin, WB-4101 or metoprolol [10^{-6} mM]. The results showed that activity induced by progesterone-DHTB on perfusion pressure was not inhibited in presence of prazosin, metoprolol or WB- 4101 compounds. The effect it is expressed as the area under the curve and each bar represents the mean ± S.E. of 9 experiments.

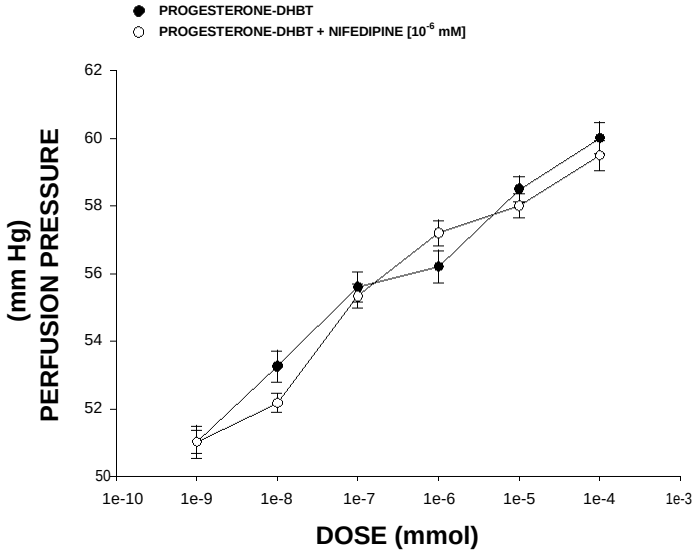

Figure 5. Effects induced by progesterone-dihydropyridimidine derivative (progesterone-DHTB) on perfusion pressure through L-type calcium channel. The boluses (50 µl) of progesterone-DHTB [10^{-9} to 10^{-4} mM] were administered in absence and presence of nifedipine [10^{-6} mM].The results showed that effect induced by progesterone-DHTB on perfusion pressure in presence of nifedipine was not inhibited. The effect it is expressed as the area under the curve and each bar represents the mean ± SE of 9 experiments.

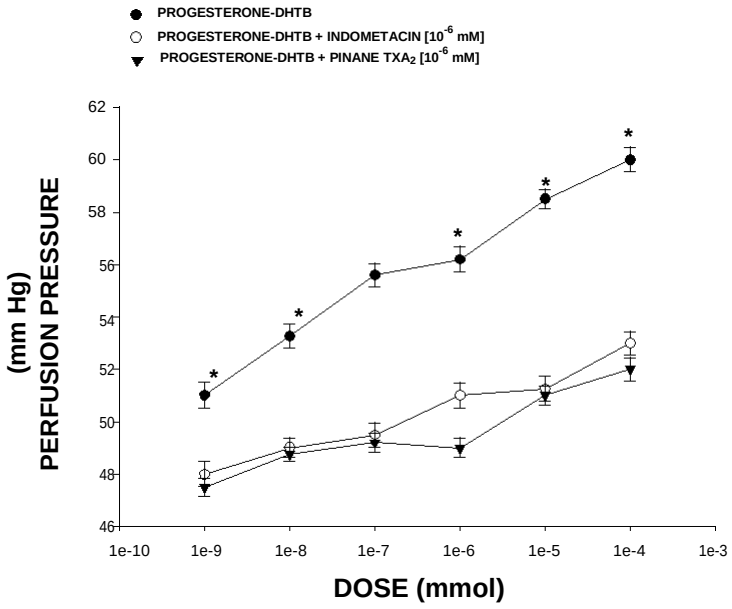

Figure 6. Activity exerted by progesterone-dihydropyridimidine derivative (progesterone-DHTB) on perfusion pressure through prostanglandins-via. The boluses (50 µl) of progesterone-DHTB [10^{-9} to 10^{-4} mM] were administered in absence and presence of indomethacin or PINANE TXA_2 [10^{-6} mM].The results showed that effect induced by progesterone-DHTB on perfusion pressure in presence of indomethacin or PINANE TXA_2 was inhibited significantly ($p = 0.005$) . The effect it is expressed as the area under the curve and each bar represents the mean ± SE of 9 experiments.

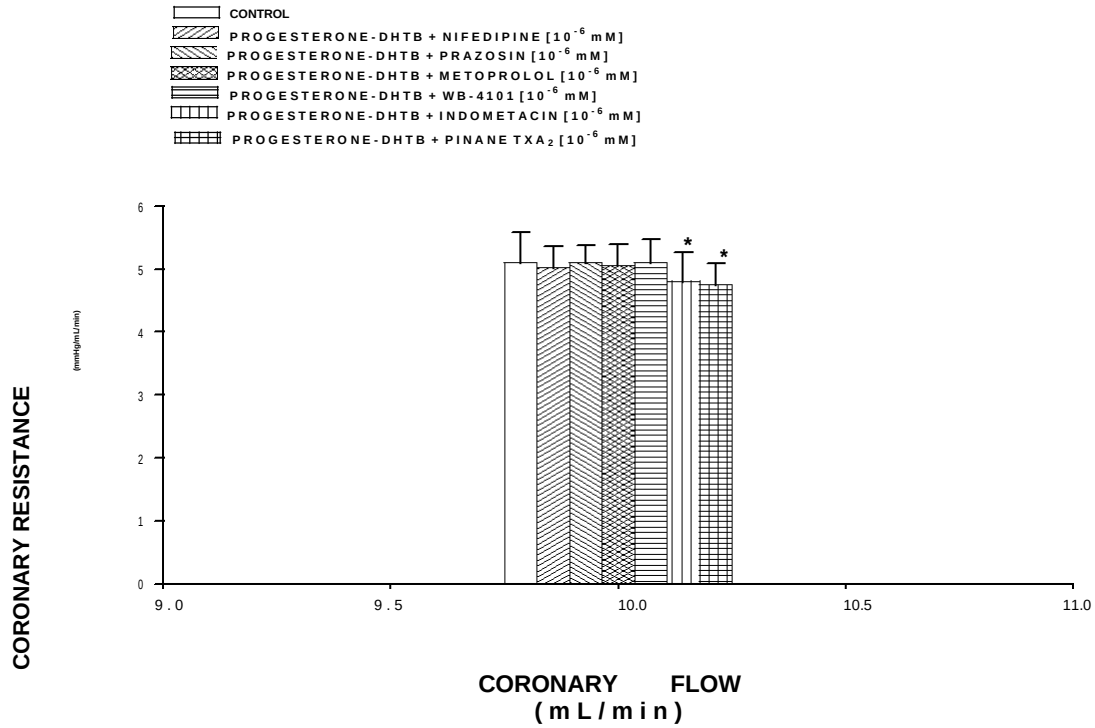

Figure 7. Effect induced by progesterone-dihydropyridimidine derivative (progesterone-DHTB) on coronary resistance under the different conditions experimental. The results showed that activity induced by progesterone- DHTB [10^{-9} mM] in presence of indometacin or PINANE TXA_2 on coronary resistance was low ($p = 0.005$) in comparison with the presence of different inhibitors. The effect it is expressed as the area under the curve and each bar represents the mean ± S.E. of 9 experiments.

pressure and coronary resistance in isolated rat heart (Langendorff model) was evaluated. The results obtained showed that progesterone-derivative significantly increased the perfusion pressure in comparison with the control conditions and progesterone. Those experimental data indicate that progesterone-dihydropyridimidine derivative exerts effects on perfusion pressure, which could consequently bring modifications in coronary resistance. In order to verify this hypothesis, the effects induced by progesterone and progesterone-derivative on coronary resistance were evaluated. The results indicate that coronary resistance in presence of progesterone-dihydropyridimidine derivative was higher in comparison with progesterone and control conditions. In order to characterize the molecular mechanism of this phenomenon and analyzing the reports of Tollana and coworkers (1993), who suggests that progesterone exert an indirect tonic effect on adrenal catecholamines concentration, which has an important role in the development or maintenance of elevated blood pressure (Lilley et al., 1976). In order, to evaluate this hypothesis in this study, the effect exerted by progesterone-dihydropyridimidine derivative on perfusion pressure was evaluated in absence or presence of prazosin or WB-4101 (α_1 adrenoreceptor antagonists) and metoprolol (selective β_1 receptor blocker). The results showed that effect induced by progesterone-derivative was not inhibited in presence of these compounds. These data indicate that molecular mechanism involved in the effects of this steroid-derivative on perfusion pressure is not through adrenergic activity.

Therefore, analyzing these results and other reports which suggest that activity induced by other type of steroid derivatives on blood pressure involved a molecular mechanism via calcium -channels (Figueroa et al., 2009c) in this work the activity induced by progesterone-dihydropyridimidine derivative on perfusion pressure was evaluated in absence or presence of nifedipine. The results showed that effect exerted by progesterone-derivative was not inhibited in presence of nifedipine. On the other hand, analyzing experimental data obtained, we also considered validating the effect induced by some steroids on perfusion pressure via-prostanglandins (Sheillan et al., 1983) and to evaluate the possibility that the activities exerted by progesterone-dihydropyridimidine derivative involve stimulation and secretion of prostaglandins. In this sense, in this study we evaluated the effect exerted by progesterone-derivative in absence or presence of indomethacin. The results showed that activity of progesterone-dihydropyridimidine derivative in presence of indomethacin was blocked significantly. These results indicate that activity exerted by steroid-derivate on perfusion pressure involve the prostanoids synthesis and secretion. In this direction, analyzing the possibility of that progesterone-derivative could induce its activity on perfusion pressure through syntheses of thromboxane A_2 (TXA_2) as it happens in another type of steroids (Schork et al., 1994, Figueroa et al., 2005), in this study the effect of progesterone-dihydropyridimidine derivative in absence and presence of PINANE TXA_2 (antagonist of TXA_2 receptor) on perfusion pressure was evaluated. The experimental data showed that effect of progesterone-derivative on perfusion pressure in presence of PINANE TXA_2 was inhibited significantly. Nevertheless, it is important to mention that the activity induced by progesterone-dihydropyridimidine derivative to different doses in presence of PINANE TXA_2 was not totally blocked.

Analyzing these data and the results obtained in each experiment, in this work the coronary resistance under the different conditions experimental was evaluated. It is important to mention that the same concentration [10^{-9} mM] in initial conditions was used. The results indicate that the activity induced by progesterone-derivative in presence of PINANE TXA_2 or indometacin was low in comparison with nifedipine, prazosin, metoprolol or WB-4101. These results suggest that activity of progesterone-derivative induced by progesterone-dihydropyridimidine derivative involve stimulation and secretion of prostangladins (TXA_2).

ACKNOWLEDGEMENT

Dr. Figueroa Valverde L. is grateful to Angelica Leon García for his technical assistance.

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