Reçu le 11 mars 1983.

Effects of the administration of progesterone and adrenal medullectomy on the plasma fibrinogen levels in rats with surgical injury (laparotomy)

BY

J. A. PALMA, A. C. GAVOTTO and S. B. VILLAGRA

(Instituto de Fisiología, Facultad de Ciencias Médicas, Universidad Nacional de Córdoba, Argentina)

The probable rôle played by the adrenal medulla in the decrease of plasma fibrinogen due to the administration of progesterone (0.5 mg kg^{-1} day^{-1} during 72 h) in rats submitted to surgical injury (laparotomy) was studied. The results obtained lead to assume that the decrease of plasma fibrinogen observed in laparotomized rats injected with progesterone is indirectly produced through inhibition of the adrenal medulla. The action of progesterone on the plasma fibrinogen would be a pharmacological effect of the drug, since in doses of 0.10 mg kg^{-1} day^{-1} the decrease of the fibrinogen is not observed in laparotomized rats. The administration of progesterone in non injured rats does not modify the plasma fibrinogen as compared to the group of non injected rats.

Introduction

The fact that tissue injury and other suitable stimuli produce an increase of plasma fibrinogen in rats is well known (CHANUTIN *et al.*, 1938; REEVE *et al.*, 1966). However, the surgical signal that initiates the synthesis of fibrinogen through the liver has not been yet totally clarified. Through previous research work (PALMA *et al.*, 1981) it has been found out that the presence of the adrenal medulla and one of its products (epinephrine) are necessary to produce the rise of plasma fibrinogen in its total magnitude in rats submitted to surgical injury. Keeping in mind that the administration of progesterone decreases the secretion of plasma fibrinogen in rats submitted to surgical injury (PALMA *et al.*, 1980 & 1983), and that on the other hand, progesterone also decreases the induced secretion of catecholamines through the adrenal medulla (WIECHMAN & BOROWITZ, 1979), we have studied in this paper the rôle played by the adrenal medulla on the decrease of plasma fibrinogen produced through the administration of progesterone to rats submitted to surgical injury.

Materials and Methods

Suquía Strain rats were used, their weight ranging from 150 to 200 g. Surgical injury was made by posterior and central laparotomy. Through this incision, the adrenal medulla was removed.

The following groups were studied :

(1) *Laparotomized :* (*a*) without other treatment; (*b*) with injection of progesterone; (*c*) medullectomized; (*d*) medullectomized + progesterone; (*e*) medullectomized

+ progesterone + epinephrine; (*f*) with progesterone + epinephrine; (*g*) unilaterally medullectomized (LxMxu); (*h*) unilaterally medullectomized + progesterone (LxMxu + p).

(2) *Laparotomized :* (*a*) with injection of physostigmine; (*b*) medullectomized + physostigmine; (*c*) medullectomized + progesterone + physostigmine; (*d*) unilaterally medullectomized + progesterone + physostigmine (LxMxu + p + phy).

(3) *Uninjured rats :* (*a*) without injection; (*b*) with physostigmine.

All the drugs were administered s.c. during 72 h. Progesterone was administered in doses of 0.5 or 0.10 mg kg^{-1} day^{-1} dissolved in peanut oil. Epinephrine was injected in doses of 0.2 mg kg^{-1} day^{-1} and physostigmine (0.5 mg kg^{-1} day^{-1}) dissolved in saline.

72 h after the administration of the drugs and/or laparotomy blood was extracted. Plasma fibrinogen was dosed following RATNOFF & MENZIE method (1951). Anaesthesia was realized through ether inhalation. The statistical treatment was done applying Student's *t* test, *P* was considered significative when it was <0.05.

Results

The effects of administration of progesterone and/or epinephrine on the levels of plasma fibrinogen of laparotomized or laparotomized-medullectomized rats are presented in Table I.

In the group of intact rats the concentration of fibrinogen was 210 ± 14.0 mg/100 ml. Confirming what had been found out in previous research works, within the group of laparotomized animals, the fibrinogen had a significant increase in comparison to intact non injected rats ($P < 0.001$).

The administration of progesterone (0.5 mg) to laparotomized animals decreased significantly the plasma fibrinogen as compared to the group of laparotomized non injected rats. On the contrary, the administration of progesterone in doses of 0.10 mg

TABLE I. *Effects of adrenal medullectomy and administration of progesterone and epinephrine on plasma fibrinogen levels in laparotomized rats.*

	n	Fibrinogen (mg %)	*P*
Laparotomized	9	342.2 ± 19.9[a]	
Laparotomized + Progesterone (0.5 mg)	8	275.1 ± 16.2	<0.02
Laparotomized + Progesterone (0.10 mg)	9	336.9 ± 17.4	
Laparotomized + Medullectomized (u)	7	324.3 ± 9.7	
Laparotomized + Medullectomized (u) + Progesterone (0.5 mg)	8	268.6 ± 14.7	<0.01
Laparotomized + Medullectomized	9	261.4 ± 11.3	<0.01
Laparotomized + Medullectomized + Progesterone (0.5 mg)	8	253.2 ± 16.2	<0.01
Laparotomized + Medullectomized + Progesterone (0.5 mg) + Epinephrine	7	318.1 ± 14.3	
Laparotomized + Progesterone (0.5 mg) + Epinephrine	7	326.8 ± 12.4	
Intact rats	8	210.0 ± 14.0	

[a] Mean ± SE.

(u) : unilateral. *P* is indicated when the differences between each group and laparotomized animals were significant.

TABLE II. *Effects of adrenal medullectomy and administration of physostigmine on plasma fibrinogen levels in laparotomized rats.*

	n	Fibrinogen (mg %)	*P*
Laparotomized	9	342.2 ± 19.9[a]	
Laparotomized + Medullectomized	9	261.4 ± 11.3	<0.01
Laparotomized + Medullectomized + Physostigmine	8	253.0 ± 11.4	<0.01
Laparotomized + Medullectomized + Progesterone (0.5 mg) + Physostigmine	7	264.1 ± 12.4	<0.01
Laparotomized + Medullectomized (u) + Progesterone (0.5 mg) + Physostigmine	7	315.5 ± 11.7	
Laparotomized + Physostigmine	7	308.8 ± 8.8	
Physostigmine	8	241.6 ± 16.6	<0.01

[a] Mean ± SE.
(u) : unilateral. *P* is indicated when the differences between each group and laparotomized animals were significant.

kg^{-1} day^{-1} to laparotomized rats did not modify the fibrinogen as compared to the group of laparotomized non injected animals. On the other hand, no significant differences were observed when comparing the group of laparotomized + progesterone rats with the group of laparotomized-medullectomized or laparotomized + medullectomized + progesterone rats. The administration of progesterone + epinephrine to laparatomized + medullectomized rats increased the plasma fibrinogen to similar levels to those observed in the group of only laparotomized rats.

In unilaterally laparotomized-medullectomized rats, plasma fibrinogen was not significantly modified as compared to the group of laparotomized rats. But the administration of progesterone to the group of unilaterally laparotomized rats decreased the figures of fibrinogen to similar levels to those observed in the group of laparotomized-medullectomized animals.

With the purpose of studying the behaviour of plasma fibrinogen in rats submitted to stimulation induced from the secretion of adrenal catecholamines, a group of laparotomized rats injected with physostigmine was studied. This drug increases secretion of catecholamines after the physiological stimulation of the sympathetic nervous system (FELDBERG *et al.*, 1934; HERMANN, 1937) when it is administered in adequate doses. The results are presented in Table II.

Physostigmine did not modify the plasma fibrinogen when it was administered to normal intact rats. On the other hand, the administration of physostigmine to laparotomized-medullectomized or laparotomized-medullectomized + progesterone rats did not modify the plasma fibrinogen as compared to the group of non injected laparotomized-medullectomized rats. Conversely, in the group LxMxu + p + phy the fibrinogen increased significantly as compared to the LxMxu + p group (Table I), and no significant differences were observed comparing the LxMxu + p + phy group with the group of only laparotomized rats.

Discussion

The results obtained show that the administration of progesterone to laparotomized rats produces a significant decrease in plasma fibrinogen. Keeping in mind that progesterone decreases the induced secretion of catecholamines through the adrenal

medulla (WIECHMAN & BOROWITZ, 1979), that epinephrine participates on the rise of plasma fibrinogen in laparotomized rats (PALMA *et al.*, 1981), and that there is a relationship between blood levels of steroids, hormone levels of catecholamines in urine and enzymes involved in catecholamine's metabolism and synthesis (ZUSPAN & ZUSPAN, 1973; PARVEZ *et al.*, 1976; DOMÍNGUEZ *et al.*, 1975), it is reasonable to deem that the effect of progesterone on the decrease of plasma fibrinogen in laparotomized rats may be due to the depressing action of progesterone on epinephrine. The following facts would back this hypothesis : (1) The decrease of fibrinogen in laparotomized + progesterone animals is similar to that observed in laparotomized-medullectomized animals. (2) In LxMxu + p rats the fibrinogen decreases significantly as compared to the LxMxu group. (3) In the group of LxMxu + p + phy rats (in which physostigmine would participate increasing the secretion of epinephrine through the adrenal medulla), the fibrinogen was increased to figures similar to those observed in the laparotomized group. (4) In the group of laparotomized + progesterone + epinephrine animals, fibrinogen was increased significantly as compared to the group of laparotomized rats injected with progesterone.

There are other plasma proteins (in addition to fibrinogen) which rise because of surgical injury or stress and require the presence of epinephrine to manifest this increase (*i.e.* α-globulin) (PALMA, 1966). A hypothetic nervous pathway has been suggested for α-globulin : centres or nucleus of the nervous system-spinal cord-adrenal medulla (LOYBER *et al.*, 1972). One cannot rule out the existence of similar pathway to explain the increase of fibrinogen observed after surgical injury.

Neither norepinephrine nor corticosterone (the main corticoid of the adrenal cortex) modifies the plasma fibrinogen levels in normal (ATENCIO *et al.*, 1969; CARLSON *et al.*, 1977) or injured animals (unpublished data). The fact that corticosterone does not participate on the rise of fibrinogen, discards the idea that a metabolic transformation of progesterone into corticosterone hormone may be responsible for the variation observed in the fibrinogen after injection of progesterone.

According to our results, the effects of the administration of progesterone on the plasma fibrinogen is a pharmacological effect of the drug, since it is observed only when greater doses are used (0.5 mg kg^{-1} day^{-1}) and it is not observed with doses of 0.10 mg kg^{-1} day^{-1} (which however produces hormone concentration in blood even above the physiological concentrations in rats). The fact that progesterone does not modify the plasma fibrinogen in non injured animals suggests that the effect of the hormone is produced only when there is surgical injury and also, perhaps, when there is an increase of epinephrine secretion through the adrenal medulla. On the other hand, ether (PALMA *et al.*, 1979), saline (PALMA *et al.*, 1981) or progesterone solvent (PALMA *et al.*, 1983) do not modify the levels of plasma fibrinogen in rats.

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J. A. PALMA
Instituto de Fisiología, Cátedra de Física Biomédica, Facultad de Ciencias Médicas, Universidad Nacional de Córdóba
Santa Rosa 1085, 5000 Cordoba, Republica Argentina.