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Budesonide ameliorates early portal hypertension in the rat: possible antiexudative splanchnic action

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Abstract—Major portal pressure increase occurs on the second day post-stenosing–ligation of the portal vein in the rat and it is associated with pancreatic edema, intraperitoneal free exudate, hypoalbuminemia and hypoproteinemia. All this suggests the development of a regional exudative inflammatory response. In order to verify this hypothesis the steroid budesonide, whose antiinflammatory activity could prevent these alterations, was administered to rats with prehepatic portal hypertension. Wistar male rats were divided into the following groups: Control rats that were administered saline solution (CS; $n = 10$), Control rats that were administered budesonide (36 mg/kg per day; CB; $n = 10$), triple stenosing ligation of portal vein (TSLP) with saline solution ($n = 10$) and triple stenosing ligation of portal vein with budesonide (36 mg/kg per day; $n = 10$). In rats with prehepatic portal hypertension at 48 h of postoperative evolution, budesonide decreases the incidence of pancreatic edema, of peritoneal free exudate, of mesenteric adenopathies and prevents hypoproteinemia, hypoalbuminemia and hyper-β-globulinemia. Some of the macroscopic intra-abdominal alterations and some of the changes in the electrophoretic pattern found in portal hypertensive rats could have an inflammatory etiopathogeny because budesonide shows an effective prophylaxis.

Key words: Budesonide; inflammation; prehepatic portal hypertension; rat.

1. INTRODUCTION

Calibrated stenosis of the portal vein in the rat is an experimental model which is frequently used to study physiopathological mechanisms of prehepatic portal

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hypertension (Chojkier and Groszmann, 1981; Groszmann *et al.*, 1982; Lin *et al.*, 1991; Sikuler *et al.*, 1985).

Constriction of the portal vein is immediately followed by resistance-induced portal hypertension, characterized by increased portal resistance and portal pressure as well as decreased portal venous inflow (Sikuler *et al.*, 1985). The maximum increase of the portal pressure is produced between days 1 and 2. However, a progressive decrease in pressure associated with a gradual increase of portosystemic shunting is produced from day 2 until the day 8. In this phase the portal pressure reaches a plateau, coinciding with the total development of portosystemic shunting (Sikuler *et al.*, 1985).

In this initial phase of experimental prehepatic portal hypertension, the great portal pressure increase could make up a splanchnic venous mechanical injury factor because the action of acute mechanical energy can stimulate the endothelium (Davies and Hagen, 1993; Davies and Tripathi, 1993), which due to its strategic position, could play an important role in the induction of acute splanchnic inflammatory pathology.

In portal hypertensive rats with a stenosing ligation of the portal vein at 24 h postoperation there is an increase in the serum concentrations of tumor necrosis factor-α (TNF-α) and nitric oxide (NO), both proinflammatory mediators, associated to significant body weight decrease (Monterde *et al.*, 2000).

In this study, using a rat model of prehepatic portal hypertension, we have shown the efficacy of orally administered budesonide, a drug with antiinflammatory effects used in inflammatory bowel disease treatment (Gomollon *et al.*, 1999; Hanauer and Dassapoulos, 2001; Spencer and Tavish, 1995) to prevent some of the potentially inflammatory splanchnic alterations which are produced on the second day of induction. These alterations are mesenteric adenopathies and venous congestion, pancreatic edema, existence of intraperitoneal free fluid and liver atrophy. We have also studied the capacity of budesonide to avoid the alterations of the electrophoretic pattern of serum protein. Because it has been suggested that the initial intensity of the portal hypertension that immediately follows portal vein stenosis is involved in the posterior evolution of this experimental model (Lin *et al.*, 1991a, b, 1996), the administration of budesonide was started before the surgical intervention.

2. MATERIALS AND METHODS

Forty male Wistar rats, mean body weight was 234.52 ± 12.47 g, from the Vivarium of the Complutense University of Madrid (Spain) were used.

The experimental procedures employed in this study are in accordance with the principles and practices of the 1986 Guide for the Care and Use of Laboratory Animals, published in Spain in the Royal Decree 223/1988.

2.1. Experimental design

The animals were divided into four groups, two control (C) groups and two with prehepatic portal hypertension to which saline solution (S) (NaCl 0.9%) or budesonide (B) (36 mg/kg per day) were administered orally through an oroesophagic tube. Group I: C+S ($n = 10$); Group II: TSLP + S ($n = 10$); Group III: C + B ($n = 10$) and Group IV: TSLP + B ($n = 10$).

Budesonide (Aldo-Union Lab., Barcelona, Spain) was dissolved in carboxymethylcellulose (1%) by shaking at a temperature of 40°C for 2 h.

Saline solution and budesonide (9 mg) were administered as a bolus of 2 ml for three consecutive days. In the animals with TSLP, the first dose was administered 24 h prior to the operation and the two other doses during the first and the second days of the postoperative evolution. All the animals were killed by ether overdose on the third day of treatment and the body, liver (middle, left lateral, right lateral and caudate lobes), spleen and testes weights were determined.

2.2. Calibrated portal stenosis method

The rats were anesthetized with i.m. ketamine HCl (100 mg/kg) and diazepam (5 mg/kg). The surgical technique used to create portal hypertension consists of a triple stenosing ligation of the portal vein (Monterde *et al.*, 2000). First, the portal vein is dissected and then three stenosing ligations (silk 4/0) are placed in its superior, middle and inferior portion around a 20G needle. The laparotomy is closed on two layers, muscle and skin, with catgut and silk (3/0), respectively.

2.3. Abdominal cavity exploratory method

After induction of anaesthesia, a middle laparotomy with a bilateral subcostal extension was performed in all animals. Then, the dilation grade of the superior mesenteric vein branches, the macroscopic appearance and size of the mesenteric lymph complex, the existence of fluid in the peritoneal cavity, the pancreas appearance, and the existence of liver hilar adhesions were studied. Mesenteric venous vasculopathy is classified into three grades: Grade 0: normal macroscopic appearance of superior mesenteric vein branches. Grade I: dilation and tortuosity of these branches as a response to the Pringle handling and Grade II: spontaneous dilation and tortuosity of mesenteric vein branches.

2.4. Study of serum protein electrophoretic pattern

The serum concentration of total proteins was measured by refractometry (Clinical refractometer ERMA, Tokyo, Japan) and the serum proteins electrophoretic pattern by electrophoresis in cellulose acetate (Olympus Hite System 600, Olympus, Tokyo, Japan).

2.5. Statistical analysis

The results are expressed as the mean ± the standard deviation ($x \pm SD$). ANOVA and the Duncan test were used for the statistical comparison of the body, spleen and testes weights, as well as for the serum protein values. The results are considered statistically significant if $P < 0.05$.

3. RESULTS

One animal belonging to Group II was not included in the study because it had a neck abscess secondary to an esophageal perforation caused by the tube used to administer the drug.

The Group III animals (TPVS + S) show a body weight decrease in relation to Group I (C + S) animals ($P < 0.001$, Table 1). Budesonide caused a decrease in body weight ($P < 0.001$), in both the control animals (Group II), as well as in portal-hypertensive rats (Group IV) with regard to the animals to which saline solution was administered (Groups I and III) (Table 1). In addition, administration of budesonide produces a spleen weight decrease ($P < 0.001$) in control (Group II) and portal hypertensive rats (Group IV) in relation to the animals to which saline solution was administered (Groups I and III) (Table 1).

The animals belonging to Group III (TPVS + S) had reduced liver weights ($P < 0.001$) in relation to the Group I (C + S) animals. The decrease in liver weight in the Group III (TPVS + S) did not produce a significant change in weight percentage of the superior liver lobes (middle and left lateral) (66.3%) in relation to the inferior liver lobes (right lateral and caudate) (33.5%) (Table 2). Budesonide restored the alterations in liver weight in portal hypertensive rats (Group IV), while it causes a mild liver weight decrease in the control rats (Group II) (Table 2).

All the animals of Group III (TPVS + S) already showed Grade I ($n = 5$; 50%) of Grade II ($n = 5$; 50%) mesenteric venous vasculopathy. In Group IV (TPVS + B), the mesenteric venous vasculopathy percentage of Grade I (70%) is superior to that of Grade II (20%).

Intraperitoneal free fluid (in a volume >4 ml) was found in 70% ($n = 7$) of Group III (TPVS + S) animals and in 20% ($n = 2$) of Group IV (TPVS + B) animals. In addition, the pancreatic œdema was greater in Group III (TPVS + S) (40%; $n = 4$) in relation to Group IV (TPVS + B) (20%; $n = 2$). The mesenteric lymph node complex size was increased is more in Group III (TPVS + S) (90%; $n = 9$) than in Groups II (C + B) ($n = 3$; 33%) and IV (TPVS + B) ($n = 6$; 60%).

In Group III (TPVS + S) three animals (30%) showed adhesions between the duodenum-pancreas and the right lateral liver lobe and one animal (10%) between the left lateral liver lobe and the extraportal prosthesis. In Group IV (TPVS + B), two animals (20%) show adhesions between the duodenum-pancreas and the right lateral liver lobe.

Significant changes were observed in the serum proteins of the animals of Group III (TPVS + S) in relation to the animals of Group I (C + S). Total proteins,

Table 1.
Changes in body and organ weights in rats with triple portal vein stenosing–ligation and those given the steroid budenoside

Group	IBW (g)	FBW (g)	BWI (g)	SW (g)	TW (g)
1 (C + S) ($n = 10$)	236.46 ± 7.96	239.20 ± 10.42	2.74 ± 12.72	0.55 ± 0.10	3.04 ± 0.15
II (C + B) ($n = 9$)	237.04 ± 13.26	$210.89 \pm 14.09^{***}$	$-26.16 \pm 10.08^{***,\bullet\bullet}$	$0.28 \pm 0.06^{***,\bullet\bullet\bullet}$	2.89 ± 0.21
III (TPVS + S) ($n = 10$)	232.66 ± 14.06	$218.10 \pm 10.25^{***}$	$-14.56 \pm 7.78^{***}$	0.48 ± 0.10	2.92 ± 0.15
IV (TPVS + B) ($n = 10$)	231.92 ± 14.63	$204.24 \pm 15.47^{***,\bullet}$	$-27.68 \pm 4.23^{***,\bullet\bullet}$	$0.27 \pm 0.04^{***,\bullet\bullet\bullet}$	$2.78 \pm 0.23^{**}$

Initial body weight (IBW, g), final body weight (FBW, g), body weight increase (BWI, g), spleen weight (SW, g) and testes weight (TW, g) in control rats to whom saline serum was administered (C + S, Group I), in control rats who were given budesonide (C + B, Group II), in rats with triple portal vein stenosing–ligation to whom saline serum was administered (TPVS + S, Group III) and in rats with triple portal vein stenosing–ligation to whom budesonide was administered (TPVS + B, Group IV).

Statistically significant value in relation to Group I ($^{**}P < 0.01$ and $^{***}P < 0.001$, respectively). Statistically significant value in relation to Group III ($^{\bullet}P < 0.05$, $^{\bullet\bullet}P < 0.01$ and $^{\bullet\bullet\bullet}P < 0.001$, respectively).

Table 2.
Changes in liver weights of operated rats and those give budenoside

Group	LW	ML		LLL		AALL		RLL		CL		PPLL	
	(g)	(g)	%	(g)	%	(g)	%	(g)	%	(g)	%	(g)	%
I (C + S)	10.97	3.88	35.40	3.46	31.63	7.34	67.06	2.72	24.69	0.91	8.25	3.63	32.94
($n = 10$)	± 1.15	± 0.39	± 1.82	± 0.35	± 1.87	± 0.67	± 2.28	± 0.42	± 2.05	± 0.20	± 1.32	± 0.56	± 2.28
II (C + B)	$9.87^{\bullet\bullet\bullet}$	3.63	36.84	$2.97^{**,\bullet}$	30.37	$6.60^{**,\bullet}$	67.21	2.41	24.25	0.86	8.52	2.56^{*}	32.77
($n = 9$)	± 1.40	± 0.50	± 2.91	± 0.28	± 2.76	± 0.73	± 4.64	± 0.53	± 2.57	± 0.38	± 2.43	± 1.84	± 4.66
III (TPVS + S)	7.96^{***}	2.83^{***}	35.47	2.47^{***}	30.89	$5.30^{***,\bullet}$	66.37	1.97^{**}	24.84	0.69	8.71	2.66	33.55
($n = 10$)	± 0.71	± 0.34	± 2.12	± 0.38	± 2.64	± 0.69	± 3.89	± 0.29	± 3.85	± 0.13	± 1.49	± 0.29	± 3.89
IV (TPVS + B)	$9.81^{\bullet\bullet\bullet}$	3.34^{**}	34.27	$3.05^{*,\bullet\bullet\bullet}$	31.28	$6.39^{*,\bullet}$	65.55	$2.55^{\bullet}$	25.64	0.87	8.81	3.42	34.45
($n = 10$)	± 1.46	± 0.43	± 3.58	± 0.36	± 1.87	± 0.71	± 3.84	± 0.67	± 3.55	± 0.19	± 1.33	± 0.82	± 3.84

Liver weight (LW, g) and middle lobe (ML, g), left lateral lobe (LLL, g), anterior lobes (AALL, g), right lateral lobe (RLL, g), caudate lobe (CL, g) and posterior lobes (PPLL, g) in control rats to whom saline serum was administered (C + S, Group I), in control rats to whom budesonide was administered (C + B, Group II), in rats with triple portal vein stenosing–ligation to whom saline serum was administered (TPVS + S, Group III) and in rats with triple portal vein stenosing–ligation to whom budesonide was administered (TPVS + B, Group IV).

$^{*}P < 0.5$, $^{**}P < 0.01$, $^{***}P < 0.001$: statistically significant value in relation to Group I; $^{\bullet}P < 0.05$, $^{\bullet\bullet}P < 0.01$, $^{\bullet\bullet\bullet}P < 0.001$: statistically significant value in relation to Group III.

Table 3.
Changes in serum proteins of operated rats and those given budenoside

Group	TP	Albumin		A/G	α_1-G		α_2-G		β-G		γ-G	
	(g)	(g)	%		(g)	%	(g)	%	(g)	%	(g)	%
I (C + S)	5.77$^{\bullet\bullet}$	2.95$^{\bullet\bullet}$	51.42	1.08	0.73	12.37	0.87	14.63	0.87	14.93$^{\bullet\bullet}$	0.40	6.63
($n = 6$)	±0.54	±0.31	±5.95	±0.23	±0.12	±1.03	±0.45	±6.50	±0.05	±1.96	±0.06	±0.71
II (C + B)	5.75$^{\bullet\bullet}$	3.25$^{\bullet\bullet}$	56.72$^{\bullet\bullet\bullet}$	1.31$^{\bullet\bullet\bullet}$	0.63	10.85	0.67	11.67	0.85	14.93$^{\bullet\bullet}$	0.33	5.83
($n = 6$)	±0.66	±0.35	±1.76	±0.09	±0.12	±0.91	±0.08	±1.23	±0.18	±1.44	±0.05	±0.57
III (TPVS + S)	4.78	2.30	47.88	0.92	0.62	12.98	0.67	14.33	0.95	19.58	0.23***	5.22**
($n = 6$)	±0.55	±0.30	±2.30	±0.08	±0.12	±1.72	±0.08	±2.22	±0.18	±1.67	±0.05	±0.97
IV (TPVS + B)	6.05$^{\bullet\bullet\bullet}$	3.30$^{\bullet\bullet\bullet}$	54.28$^{\bullet\bullet}$	1.19$^{\bullet\bullet}$	0.75	11.90	0.93	15.48	0.83	13.92$^{\bullet\bullet\bullet}$	0.28**	4.42***
($n = 6$)	±0.35	±0.18	±1.26	±0.06	±0.12	±1.33	±0.08	±1.00	±0.05	±0.92	±0.08	±0.54

Total proteins (TP, g), albumin (g), albumin/globulin ratio, α_1-globulin (α_1-G, g), α_2-globulin (α_2-G, g), β-globulin (β-G, g), γ-globulin (γ-G, g) in control rats to whom saline serum was administered (C + S; Group I), in control rats to whom budesonide was administered (C + B, Group II), in rats with triple portal vein stenosing–ligation to whom saline serum was administered (TPVS + S, Group III) and in rats with triple portal vein stenosing–ligation to whom budesonide was administered (TPVS + B, Group IV).

$^{**}P < 0.01$; $^{***}P < 0.001$: statistically significant value in relation to Group I; $^{\bullet\bullet}P < 0.01$; $^{\bullet\bullet\bullet}P < 0.001$: statistically significant value in relation to Group III.

albumin and γ-globulin levels ($P < 0.001$) decreased, and β-globulin levels increased (Table 3). Treatment of the control animals with budesonide (Group II) did not produce significant alterations in the serum proteins electrophoretic pattern. However, budesonide restored the alterations in the total proteins, albumin and β-globulin concentrations in the rats with portal hypertension (Group IV) but it did not modify the alterations of the γ-globulin concentration (Table 3).

4. DISCUSSION

The results of this study show that portal triple stenosing–ligation in the rat causes a weight increase in the mesenteric lymph node complex and mesenteric venous congestion, liver atrophy and hypoproteinemia with serum concentration decrease of albumin and β-globulin increase at the second day of the postoperative evolution (Tables 2 and 3). This inflammatory nature can be hypothesized, since the oral administration of budesonide prevents these early alterations after portal vein constriction. Budesonide is a patent steroid with high affinity to the glucocorticoid receptor and low systemic bioavailability due to its high first-pass metabolism in the liver. Thus, its oral administration in inflammatory bowel disease enhances its mucosal anti-inflammatory effect with less systemic activity than that of conventional steroids (Hamedani *et al.*, 1997; Hanauer and Dassapoulos, 2001). These properties of budesonide suggest that the prevention of the alterations found in the early evolutive period of prehepatic portal hypertension in the rat could be attributed to its antiinflammatory action on the intestinal mucosa.

On the first day, partial ligation of the portal vein in the rat is followed by an increase in portal venous resistance and portal pressure; on the second day there is a further increase in portal resistance and pressure that has been attributed to partial thrombosis of the portal vein or to edema around the constricted portal vein which could lead to a further obstruction to the blood flow (Sikuler *et al.*, 1985). If so, the triple stenosing ligation of the portal vein technique used in this study could cause a higher grade of portal hypertension on the second day of evolution because the increase in the length of the stenosed tract would also increase the extent of partial thrombosis or the œdema around the portal vein and, consequently, the portal venous resistance. The increase in portal pressure found in this early development phase of the experimental prehepatic portal hypertension produces splanchnic venous congestion and the postcapillary splanchnic venules are exposed to the influence of high hydrostatic pressure. This is a fluid mechanical force that can cause biomechanical activation of the vascular endothelium (Davies and Tripathi, 1993; García-Cardeña *et al.*, 2001), which induces an inflammatory phenotype expression and, therefore, the pathological releasing of vasoactive substances, cytokines, growth factors and hormones (Aller *et al.*, 2001; Cines *et al.*, 1998; Davies and Hagen, 1993; Davies and Tripathi, 1993; Inagami *et al.*, 1995). Particularly, the acute inflammatory endothelial response can cause exudation secondary to an endothelial permeability increase which is the cause of swelling (Lum and Malik, 1994).

The alterations found by gross macroscopic study of the abdominal cavity in portal hypertensive rats, the pancreatic edema and the accumulation of fluid in the peritoneal cavity suggest that there is a splanchnic regional exudative response. If so, the increase in endothelial permeability would explain the existence of hypoalbuminemia and hypoproteinemia secondary to the plasmatic protein extravascular escape in these animals. Since the rats with portal hypertension to which budesonide is administered do not show hypoproteinemia or hypoalbuminemia and the incidence of pancreatic edema and peritoneal effusion decreases, it could be considered that the endothelial permeability increase, which is the cause of these alterations, has an inflammatory etiopathogeny. In this experimental model of portal hypertension, the early plasmatic increase of TNF-α and NO, both of which are important proinflammatory mediators (Monterde *et al.*, 2000), occurs before a hyperdynamic splanchnic circulatory state or porto-systemic shunting has developed (Sikuler *et al.*, 1985; Vorobioff *et al.*, 1983). This may represent an argument that would support the inflammatory hypothesis mentioned in order to explain the alterations which are associated to the resistance-induced portal hypertension.

Acute portal hypertension could also cause intestinal venous congestion with microvascular leakage induced by inflammatory mediators, edema and ischemia, all of these being factors that favor bacterial translocation from the gut (Garcia-Tsao *et al.*, 1993). If so, toxins and bacterial intestinal translocation to the regional lymph nodes would explain the high incidence of mesenteric adenopathies found in rats with prehepatic portal hypertension at 48 h of postoperative evolution. However, budesonide may have an inhibitory action on intestinal microvascular leakage by a direct action on postcapillary venular epithelial cells (Barnes, 2001). This action produces an exudation, edema, ischaemia and intestinal mucosa barrier permeability decrease, which, in turn, limits the intestinal bacterial translocation which would, therefore, decrease the mesenteric adenopathies incidence in the early experimental portal hypertension.

In rats with prehepatic portal hypertension, the liver weight decrease already occurred at 24 h of evolution (Monterde *et al.*, 2000). This could be secondary to the total liver blood flow decrease because the hepatic arterial blood flow increase does not compensate the blood flow decrease produced by the portal hypertension (Sikuler *et al.*, 1985; Vorobioff *et al.*, 1983). However, as this study shows, budesonide prevents early post-stenosis portal liver atrophy, which thus allows to consider the inflammatory mechanisms involved in its production. Although cytokines initiate signals that are involved in liver regeneration (Diehl *et al.*, 1996) they also cause liver injury under certain circumstances, for example, following transient hepatic ischemia and reperfusion or when hepatocytes have been pre-exposed to toxins like lipopolysaccharide (LPS) (Diehl, 2000). Both are present in the experimental model of portal hypertension used. In the first place, transient ischaemia-reperfusion is necessary when the triple portal stenosing–ligation is performed (Monterde *et al.*, 2000). The hepatic injury can also be induced by cytokines when the liver is previously sensitized by LPS secondary to bacterial

intestinal translocation (Lum and Malik, 1994; Sorell *et al.*, 1993). Therefore, it can be hypothesized that budesonide has a beneficial hepatic effect in early portal hypertension by a cytoprotector direct action when ischaemia–reperfusion injury occurs and by an intestinal indirect action if it decreases or inhibits the inflammatory exudative response. Both these actions are characteristic of this corticosteroid (Barnes, 2001; Gustafsson *et al.*, 2001; Hanauer and Dassapoulos, 2001).

In portal hypertensive rats, the β-globulin serum level increase could be a component of the acute phase reaction in which the liver increases the synthesis of lipoproteins which are mediated by proinflammatory cytokines in the stress response (Jamieson and Ashton, 1973; O'Connor *et al.*, 2000; Barnes, 2001; Carra *et al.*, 2001). The inhibition of its excessive synthesis by budesonide would indicate the efficacy of this steroid in the prophylaxis of the early acute phase response in this experimental model. It could be speculated that budesonide produces a down-regulation of the proinflammatory cytokines due, at least partially, to an inhibitory effect on the transcription factors that regulates the inflammatory genes induction, including activator protein-1 (AP-1) and nuclear factor-κB (NF-κB) (Barnes, 2001; Carra *et al.*, 2001). However, budesonide does not prevent the hypogammaglobulinemia in this early phase of the experimental portal hypertension. The serum γ-globulin decrease is an unexpected finding because the hepatic insufficiency generally causes an increase in its synthesis by plasmatic cells and by the liver itself (Feizi, 1968; Sherlock, 1989) associated with a β-globulin increase. These alterations make up a beta-gamma linking in the electrophoretic pattern because the dip between both types of globulin disappears (Sherlock, 1989) and this is associated with an inversion of the albumin/globulin ratio. Since an excessive hypothalamic-pituitary-adrenal axis response with a serum concentration increase of corticosterone (Monterde *et al.*, 2000) has been described in this early phase of the prehepatic portal hypertension in the rat it is possible to consider that the antiinflammatory and immunosuppressant actions mediated by the endogenous corticosteroids could negatively influence the γ-globulin synthesis, this effect being strengthened by budesonide in these animals.

In conclusion, some of the abdominal macroscopic alterations as well as the plasmatic electrophoretic pattern changes which are found in an early evolutive period in rats with prehepatic portal hypertension suggest the existence of a splanchnic inflammatory exudative response. Prophylaxis with budesonide of these alterations reinforces the above mentioned hypothesis because its antiinflammatory effects, in terms of antiexudative capacity, has been also demonstrated in an allergen-challenged rat model.

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