Strategies to improve outcome after partial liver resection

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Chapter 9

Administration of alkaline phosphatase reduces hepatic and pulmonary injury in ischemia, partial resection and reperfusion of the rat liver

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Abstract

**Background.** Lipopolysaccharides mediate inflammation in liver ischemia-reperfusion (I/R) and partial liver resection (PHX). Bovine intestinal alkaline phosphatase (BIAP) detoxifies lipopolysaccharides by dephosphorylation and reduces inflammation in sepsis models. This study examines the protective effects of BIAP administration in models of partial (70%) liver I/R with or without PHX of all non-ischemic lobes during ischemia (30%).

**Methods.** Male Wistar rats (n=44) were divided into 6 groups: I/R+BIAP, I/R+saline, I/R+PHX+BIAP and I/R+PHX+saline; controls had PHX or sham laparotomy only. Single dose BIAP (0.5 IU/g) or vehicle (saline) was administered 5 min before reperfusion. Inflammatory response, hepatic and pulmonary injury were assessed during 24 hours reperfusion.

**Results.** I/R, with or without PHX, increased all inflammatory, hepatic and pulmonary damage parameters (p<0.05 vs. sham). I/R+PHX significantly increased AST/ALT release and hepatic neutrophil influx as compared to I/R only (p<0.05). BIAP treatment decreased hepatic wet/dry-ratios, neutrophil influx and histopathological damage after I/R (p<0.05), and also AST/ALT and IL-6 production after I/R+PHX (p<0.05). Pulmonary wet/dry-ratio and neutrophil influx decreased after I/R by BIAP treatment and pulmonary histopathological injury was reduced after I/R+PHX by BIAP treatment.

**Conclusions.** These data show that BIAP attenuates hepatic and concomitant pulmonary injury after partial liver I/R and partial liver resection.
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Introduction

In hepatic surgery, such as with partial liver resection (PHX), continuous or intermittent clamping of the hepatic artery and portal vein is frequently applied to reduce intra-operative blood loss (Pringle manoeuvre)\(^1\,^2\). The ensuing ischemia and reperfusion (I/R) potentially result in metabolic, immunologic and microvascular changes\(^3\). Bacterial translocation is one of the phenomena occurring during liver resection and hepatic I/R\(^4\,^6\). Intraluminal micro-organisms migrate across the intestinal mucosa to the systemic circulation mainly via the portal vein and directly through the peritoneum, and to a lesser extent via mesenteric lymph nodes, thoracic duct and other organs, leading to bacteraemia\(^5\,^7\,^9\).

Lipopolysaccharides (LPS) from Gram-negative bacteria play an important role in stimulating inflammatory responses, leading, among others, to remote injury in the lungs\(^5\,^10\). Therefore, liver I/R induces in addition to hepatic injury also systemic effects (e.g. release of cytokines) causing pulmonary injury\(^11\,^12\). Previous studies on liver I/R, using bactericidal/permeability-increasing protein (BPI) or antibodies against LPS, demonstrated reduced cytokine responses and decreased pulmonary damage both in animals and in humans\(^13\,^16\). Therefore, LPS seems to be an important mediator in hepatic I/R injury.

Previous studies in vitro and in vivo showed dephosphorylation of LPS through intravenous (i.v.) administration of exogenous alkaline phosphatase (AP)\(^17\,^18\). In studies of combined injection of alkaline phosphatase with LPS or living bacteria and in a model of peritonitis in which LPS/bacteria were not injected but derived from the animals own commensal flora, alkaline phosphatase reduced inflammatory responses in terms of reduced cytokine responses and neutrophil influx\(^19\,^22\). In peritonitis, a protective effect of AP administration on hepatic injury was demonstrated at the same time\(^22\). These findings suggest AP could be a promising therapeutic agent in hepatic I/R.

In most animal models of hepatic I/R, liver ischemia is induced in part of the liver (up to 90%) to assure adequate drainage of portal blood from the intestines, thus preventing (potentially) fatal splanchnic congestion. As a consequence, part of the liver is continuously perfused and blood is preferentially shunted through the non-ischemic lobes\(^23\). In the clinical situation however, vascular inflow occlusion may be applied by clamping the hepatic pedicle (Pringle manoeuvre), thus inducing total hepatic ischemia\(^1\). An animal model of partial (70%) liver ischemia combined with a resection of all non-ischemic liver lobes (30%) just before reperfusion prevents splanchnic congestion but exposes all remnant liver tissue in situ to post-ischemic reperfusion, thus reflecting the clinical situation\(^24\).

The aim of this study was to examine the effects of BIAP administration on hepatic injury as well as cytokine response and concomitant pulmonary injury in two settings, i.e. partial liver I/R and the combination of liver I/R with partial liver resection, respectively.
Methods

BIAP
Clinical grade BIAP from Biozyme (Blaenavon, UK) was kindly donated by AM-Pharma (Bunnik, the Netherlands). BIAP was diluted with saline (0.9% NaCl, Fresenius Kabi, 's-Hertogenbosch, the Netherlands) just before administration. BIAP or vehicle (saline) was injected in the penile vein 5 minutes prior to reperfusion as a single intravenous dose of 0.5 IU/gram body weight (approx. 50-100 times above blood levels). BIAP activity was measured by routine laboratory testing.

Experimental design
Male Wistar rats (285-310 g, Harlan, Horst, the Netherlands) were acclimatized for one week under standardized laboratory conditions in a temperature-controlled room with a 12h-light/dark cycle with standard chow and water ad libitum, and maintained under the same conditions after surgery. This study was approved by the Animal Ethics and Welfare Committee of the Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands. Rats were divided into 6 different groups. Two groups (n = 8 /group) had only partial I/R with BIAP or saline (I/R+BIAP and I/R+saline, respectively). Two groups (n = 8 /group) had partial I/R with PHX and received BIAP or saline treatment (I/R+PHX+BIAP and I/R+PHX+saline, respectively). Control rats (n = 6 /group), all receiving BIAP, had PHX only (PHX group) or only median laparotomy (sham group). Since we expected little variation and hardly any damage, the number of animals in the control groups was reduced after consulting a statistician.

I/R procedure
All rats were anesthetized by inhalation with a mixture of N₂O : O₂ (1:1 V/V, 2 l/min) and isoflurane 2.0-2.5% (Florene, Abbott laboratories, Queensborough, UK). After endotracheal intubation (14G Venflon’, Becton Dickinson, Franklin Lakes, NJ), rats were ventilated (Zoovent ventilator, Instruvet, Amerongen, the Netherlands); anaesthesia was maintained with the same mixture. Adequate ventilation was confirmed by continuous measurement of end-tidal CO₂, assuring physiological pH during the entire procedure. Rats were positioned on a heating pad and a rectal temperature probe (HP temperature module M 1029A, Agilent Technologies Netherlands B.V., Amstelveen, the Netherlands) was inserted up to two centimetres in the rectum. Rectal temperature was maintained at 37.0 °C (±0.1 °C). After disinfection with iodine, midline laparotomy was performed and the liver was mobilized. Partial (70%) liver ischemia was induced by clamping the vessels to the median and left lateral lobes with a microvascular clamp (Aesculap’ AG, Tuttingen, Germany) for 60 minutes after which blood supply was restored by releasing the clamp (reperfusion) 25. Control groups had similar manipulations of the liver hilus without clamping (no ischemia), and were kept under anaesthesia for an equal time period. The abdomen was closed in two layers using a 4/0 Vicryl suture (Ethicon’), and the animals were allowed to wake up. Adequate post-operative analgesia was achieved by administering buprenorphine (2.5-3.0 ml/kg subcutaneous,
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Temgesic®, Schering-Plough, Utrecht, the Netherlands). Twenty four hours after start of reperfusion, rats were sacrificed. Blood, liver and lungs were collected.

I/R+PHX procedure
Rats underwent partial ischemia as described above, except that the ischemic period was reduced to 30 minutes, during which 30% PHX was performed by resecting all non-ischemic liver lobes \(^{24}\). Briefly, the quadrate, caudate and right lateral lobes were identified, and sequentially ligated (Vicryl 3/0, Ethicon®, Johnson&Johnson Intl, St-Stevens-Woluwe, Belgium) and resected 5-10 minutes before reperfusion. Therefore, splanchnic congestion occurred only very shortly. Six rats underwent PHX as described above without I/R. In the I/R procedure, ischemic time was set at 60 minutes to assure sufficient hepatic damage, whereas in this combined I/R+PHX procedure, ischemic time had to be reduced to prevent hepatic failure \(^{26}\).

Sampling
Just before sacrifice by exsanguination, the common bile duct was cannulated with a polyethylene catheter (Ø 0.4 mm) and bile was collected for exactly 15 minutes. The amount of bile was measured using a pipette. Total liver weight was measured using a scale. Bile production in mg/ml/h was calculated by the formula: bile in 15 minutes (µl) x 4 / 1000 / liver weight (g).

Blood samples were collected in heparin or EDTA containing microtainers (Becton Dickinson) from the caval vein and the tail vein, pre-ischemia, 30 minutes, 6 and 24 hours after reperfusion, respectively; blood was centrifuged (1200 x g, 10 minutes, 4 °C) and plasma was stored at -80 °C. AST, ALT and alkaline phosphatase plasma activities were tested by routine laboratory activity assay. Cytokines tumor necrosis factor-alpha (TNF-α), interleukin (IL) -1β, IL-6 and IL-10 were measured by Lincoplex assay (Linco, St Charles, MI) based upon the ELISA principle using a Luminex machine, according to the manufacturer’s instructions (detection limit 5 pg/ml).

Organ processing and histopathology
Livers and lungs were fixed in 4% buffered formaldehyde and routinely processed for haematoxylin and eosin (H&E) staining using 4 µm paraffin sections. Multiple sections were scored blindly by two independent observers. Both median (ischemic) and caudate (non-ischemic) liver lobes were scored on a semi-quantitative basis for the degree of steatosis, oedema, inflammation, necrosis and fibrin depositions (total score 17). Lungs were scored for pleuritis, thrombus formation, oedema, thickened septa and influx of inflammatory cells (mainly neutrophils)(total score 11) \(^{26,27}\).

Oedema was assessed by calculating the percentage of water in the tissue. Wet weights of the left lateral (ischemic) and right lateral (non-ischemic) liver lobes and left inferior lung lobe were measured using a scale. Tissues were subsequently kept in a stove at 60 °C, and dry weight was determined by the same scale when weight remained unchanged (approx. 14 days). Percentage of water was calculated by the formula: 1 - (dry weight / wet weight) x 100%.
Myeloperoxidase (MPO) assay
To assess neutrophil influx, MPO was measured as described elsewhere with some modifications. Briefly, lung and liver tissue from the median (ischemic) lobe were homogenized in 5 mM sodium phosphate buffer. Protein content was analyzed by a standard protein assay kit (Pierce, Rockford, IL) according to manufacturer's descriptions (detection limit 0.2 mg/ml). Remaining homogenate was centrifuged (10,000 x g, 10 min, 4 °C) and the pellet was resolved in buffered 0.5% hexadecyltrimethyl ammonium bromide with 10 mM EDTA. After freezing and thawing three times, samples were pottered and sonificated. Liver samples were then incubated for 2 hours at 60 °C to remove all heat unstable proteins (MPO is heat stable). Then, samples were centrifuged (8400 x g, 10 min, 4 °C). The supernatant was collected for MPO activity measurements. O-dianisidine dihydrochloride (Sigma Chemical Co., St Louis, MO) and 0.001% H$_2$O$_2$ (Merck, Darmstadt, Germany) were added. The change in absorbance was measured spectrophotometrically (Bio-Tek Instruments, Winooski, VM) at 450 nm during 10 min. The maximum slope of the linear part of the tracing was used for analysis. The absorbance of a blank was subtracted from the samples. One Unit is defined as the amount of enzyme necessary to produce a change in absorbance of 1.0 per minute. MPO activity is expressed as Units per mg protein.

Data analysis
Statistical Package for the Social Sciences (SPSS 12.0, SPSS Inc, Chicago, IL) for Windows was used for data analysis. Values represent mean ± SEM, unless indicated otherwise. For measurements over a time period (AST, ALT), ANOVA for repeated measurements was performed with LSD post-hoc testing. Kruskal-Wallis test was performed for comparisons at one time point for all groups together. If p<0.05, Mann-Whitney tests were performed afterwards between two groups. Significance was assumed when p<0.05. NS = not significant.

Results
BIAP recovery
BIAP activity was assessed by measuring AP plasma activity after administration. All animals receiving BIAP had elevated AP activity in plasma (> 5000 IU/l) shortly after the start of the reperfusion phase, whereas saline treated animals had normal AP activity levels (182 ± 11 IU/l; p<0.01). Administered BIAP was cleared rapidly from the circulation in all animals. Sham and PHX alone groups demonstrated a plasma half life of approximately 8 minutes after administration of BIAP. After 6 and 24 hours, AP plasma activities had returned back to pre-ischemic levels in the sham and PHX groups. After 6 and 24 hours after start of reperfusion, AP activity in the I/R groups was still slightly increased after BIAP treatment (231 ± 6 and 224 ± 9 IU/l, respectively; p<0.05 vs. pre-ischemia), but not after saline treatment (199 ± 12 and 199 ± 16 IU/l, respectively). In the I/R+PHX groups, AP plasma activity was significantly increased after 6 and 24 hours in BIAP treated animals (252 ± 24 and 234 ± 19 IU/l, respectively; p<0.05 vs. pre-ischemic levels). In saline treated I/R+PHX rats, AP plasma
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Bovine intestinal alkaline phosphatase (BIAP) reduces AST and ALT plasma activity after ischemia-reperfusion (I/R) with partial liver resection (PHX), but not after I/R alone. Rats were subjected to 70% ischemia-reperfusion of the liver with or without PHX of the remaining lobes during ischemia. BIAP was administered 0.5 IU/g intravenously 5 min pre-reperfusion.

activity was increased after 24 hours (211 ± 7 IU/l; p<0.05 vs. pre-ischemia), indicating that I/R+PHX per se, results in slight elevation of (endogenous) AP plasma activity.

Hepatocellular damage and liver function

Hepatocellular damage was quantified by measuring AST and ALT release in plasma (Figure 1A&B). AST and ALT activities rapidly increased in all I/R groups (with or without PHX) with elevated levels already after 30 minutes reperfusion when compared to pre-ischemic levels. AST and ALT activities were continuously elevated during the entire reperfusion phase compared to sham operated animals (p<0.05 and p<0.01, respectively), which showed no changes in AST and ALT activities. PHX did not significantly increase AST and ALT levels (p=NS vs. sham), whereas the combination of I/R+PHX significantly increased AST and ALT plasma activity as compared to I/R only (p<0.05 I/R+PHX vs. I/R). BIAP treatment reduced AST and ALT activities after I/R+PHX as compared to saline treatment (p<0.01), but not after I/R alone. All rats had an average bile production rate of 0.07 ± 0.02 ml/h/gram liver weight, except those in the I/R+PHX groups, which had significantly high bile production rates (0.11 ± 0.03 ml/h/g liver; p<0.05). BIAP treatment had no effect on bile production compared to saline treatment.

Cytokine responses

TNF-α and IL-1β plasma concentrations were below detection limit. Highest IL-6 plasma concentrations were observed after 6 hours reperfusion after I/R with or without PHX (p<0.05 vs. sham; Figure 2A). PHX alone had no effect on IL-6 plasma concentration (p=NS vs. saline).
Figure 2. Plasma interleukin(IL)-6 (A) and IL-10 (B) levels

Administration of BIAP reduced IL-6 response in the I/R+PHX group (p<0.05) but not after I/R alone, as compared to saline treated animals. IL-10 levels increased after I/R with or without PHX, although not significantly different from sham animals (Figure 2B). BIAP treatment showed a similar trend of reduction of IL-10 levels in the I/R+PHX groups (p=0.1 vs. I/R+PHX+saline).

**Hepatic and pulmonary inflammatory responses**

Percentage of water in ischemic and non-ischemic liver lobes was increased after I/R with or without PHX compared to sham (p<0.01, Figure 3). PHX alone did not significantly increase water content of the remnant liver (p=NS vs. sham). After both I/R and I/R+PHX, BIAP treated rats showed significantly reduced water content compared to their saline controls (p<0.01). Also in the non-ischemic lobes after I/R, increased water content was observed (p<0.01 vs. sham), which was likewise reduced by BIAP treatment (p<0.05 vs. saline, Figure 3). In the I/R+PHX model, non-ischemic lobes were resected and thus, were not examined for water content. No differences in water content in the lungs were observed between all groups (78-79% in all groups, data not shown).

Neutrophil activity was assessed by MPO activity in liver and lung homogenates. Hepatic MPO activity increased after I/R with or without PHX compared to sham (p<0.01 and p<0.05, respectively; Figure 4A), as did PHX only (p<0.05). Note that the combination of I/R plus PHX increased the MPO activity much more than I/R alone or PHX alone (both p<0.05). BIAP treatment reduced hepatic MPO activity compared to their saline controls after I/R and I/R+PHX (both p<0.05). Pulmonary MPO activity increased significantly after
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Figure 3. Hepatic water content in ischemic and non-ischemic lobes

Hepatic I/R with or without PHX increased hepatic water content in previously ischemic lobes and non-ischemic lobes, which was reduced by bovine intestinal alkaline phosphatase (BIAP). * p<0.01 vs. sham, * p<0.05 and ** p<0.01 vs. saline equivalent, † p<0.05 vs. I/R+PHX+saline (Mann-Whitney).

Figure 4. Hepatic (A) and pulmonary (B) myeloperoxidase (MPO) activity

Hepatic MPO activity was reduced by BIAP treatment after I/R with or without PHX. Pulmonary MPO activity was reduced by BIAP treatment after I/R, but not after I/R+PHX. * p<0.05 or ** p<0.01 vs. sham, † p<0.05 or ** p<0.01 vs. saline equivalent, † p<0.05 vs. I/R+PHX (Mann-Whitney).
Figure 5. Hepatic and pulmonary histopathology scores

Hepatic and pulmonary histopathology

Histopathological damage in both ischemic and non-ischemic liver parenchyma as well as in lung parenchyma was assessed by semi-quantitative scoring. I/R with or without PHX, caused significant damage to liver parenchyma, as was shown by increased histopathology scores as compared to sham operated animals and PHX alone (all p<0.01; Figure 5). PHX itself induced no significant hepatic injury in the remnant liver (p=NS vs. sham). Significant damage was observed in the non-ischemic (right lateral) lobes of I/R groups compared to the same lobes of sham animals without ischemia (p<0.01), although histopathology scores were much lower in non-ischemic lobes as compared to ischemic lobes after reperfusion. BIAP treated rats showed less extensive injury in both ischemic and non-ischemic lobes after I/R, as compared to saline control rats (p<0.05). Also in the I/R+PHX groups, BIAP treatment

I/R (p<0.05 vs. sham), and was reduced by BIAP treatment (p<0.05; Figure 4B). Although MPO activity was increased after I/R+PHX, this was not significantly different compared to sham. There was no effect of PHX alone on pulmonary MPO activity.

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reduced histopathology scores (p<0.05) as compared to saline treatment. Pulmonary involvement was demonstrated by increased histopathology scores after PHX, I/R and the combination I/R+PHX when compared to sham (p<0.01). BIAP administration reduced histopathology scores in the lungs after I/R with or without PHX (p<0.05).

**Discussion**

Large liver resections are accompanied by injury of the remnant liver, the more so when the Pringle manoeuvre is applied to reduce blood loss, resulting in additional I/R injury. Hepatic I/R injury is known to cause remote pulmonary injury. Thirty percent liver resection in this study, did not result in substantial injury within the remnant liver or within the lungs as compared to sham operation, as was demonstrated by limited neutrophil influx (MPO) and histopathology scores of both liver and lungs. Partial I/R of the liver for 60 minutes resulted in substantial hepatic and pulmonary damage. From literature and from previous studies in our laboratory, it is known that 30 minutes of 70% ischemia will result in mild, reversible damage. The combination of 30% PHX with 60 minutes ischemia, however, invariably resulted in lethal hepatic injury (results not shown). Therefore, ischemic time was reduced from 60 to 30 minutes in the I/R+PHX groups. Despite the reduced ischemic time, the combination of I/R and PHX significantly aggravated hepatic and pulmonary injury in relation to I/R alone or PHX alone.

The observed increased injury of I/R + PHX is likely the result of two factors. Firstly, the impact of LPS on hepatic injury is more substantial in I/R+PHX than in partial I/R alone, because in the latter, there still is “healthy” non-ischemic liver parenchyma in situ for detoxification. Secondly, after partial I/R, preferential shunting to the non-ischemic lobes occurs bypassing the damaged liver parenchyma, whereas in I/R + PHX, increased blood flow through the remnant liver compromises the already disturbed microcirculatory state of the post-ischemic parenchyma, augmenting hepatocellular injury. Remarkably, despite the increased injury in the I/R + PHX group, metabolic activity of the liver remnant was increased as shown by significantly increased bile production per gram liver. This phenomenon was also noted in previous animal liver resection models.

After partial hepatic I/R, BIAP treatment reduced hepatic inflammatory responses as was demonstrated by reduced tissue oedema and neutrophil influx. Concomitantly, pulmonary injury and neutrophil influx were reduced by BIAP treatment. However, no significant effects of BIAP treatment on AST and ALT release and cytokine production were observed after I/R. The extent of injury after partial hepatic I/R probably is too low to benefit from BIAP treatment. Also, LPS can be eliminated by the non-ischemic lobes as blood is preferentially shunted to these lobes following reperfusion.

After I/R with PHX, BIAP treatment reduced AST and ALT release, hepatic oedema and MPO, indicating that LPS plays a role by inducing parenchymal hepatic injury in this combined model of hepatic I/R and PHX. Also IL-6 production and, to a lesser extent, pulmonary injury, which are both known to be caused by LPS were decreased after BIAP treatment.
There are several reasons why BIAP treatment is more effective in I/R+PHX than in I/R alone. Due to PHX, all blood and thus all LPS was exposed to the damaged liver during the reperfusion phase. Since the liver is involved in LPS clearance, this also might be impaired after PHX, especially in combination with I/R. Therefore, LPS challenge had more impact after I/R+PHX than after I/R alone. Another factor is that BIAP is mainly cleared by the liver with a plasma half life of 5-10 minutes. Impaired clearance due to PHX, will result in more prolonged elevated AP plasma activity after BIAP treatment. Therefore, the combination of greater hepatic injury, more profound LPS challenge and persisting high alkaline phosphatase activity levels, render BIAP treatment more successful in I/R+PHX than I/R alone.

Whether dephosphorylation of LPS is the mechanism behind this effect, could not be proven explicitly in this study, because the Limulus assay, the golden standard to measure LPS, does not discriminate between LPS and dephosphorylated LPS. Alternatively, phosphate release can be assessed as measure of dephosphorylation, but, this assay can not be performed in vivo. Also, the endocarp test can not be applied in this situation. The specific dephosphorylating action of BIAP on LPS has, however, been clearly proven in previous in vitro studies. Also, the proof of principle of simultaneous LPS and BIAP administration has been performed in two different in vivo studies. Furthermore, injection of living bacteria combined with BIAP has demonstrated the same principle. The effectiveness of BIAP has ultimately been demonstrated in a model of fecal peritonitis, in which the LPS/bacteria were not injected but derived from the animal's own commensal intestinal flora. Therefore, the efficacy of BIAP administration has been well demonstrated before.

Although inhibition of endogenous alkaline phosphatase synthesis has been shown to increase hepatic injury after LPS challenge, endogenous alkaline phosphatase probably plays only a minor role in this study. Plasma AP activity did not increase significantly after I/R throughout the entire reperfusion phase. In the I/R-PHX rats, AP plasma activity increased for approximately 10-20% after 24 hours reperfusion when compared to pre-ischemic levels. Administration of exogenous AP (BIAP) increased plasma AP activity more than 3000%.

In conclusion, these results demonstrate that administration of bovine intestinal alkaline phosphatase appears a promising therapeutic tool to attenuate both hepatic and pulmonary injury after liver ischemia-reperfusion and partial liver resection.

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Reference list


