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Effect of adrenergic and nitrergic blockade on experimental ileus in rats

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1 In a rat model of experimental ileus, the effect of blockade of adrenergic and nitrergic neurotransmission was studied on the intestinal transit of Evans blue.

2 Ether anaesthesia and skin incision had no influence on the transit. Laparotomy significantly inhibited the transit of Evans blue. This inhibition was even more pronounced when the small intestine was manipulated.

3 Reserpine (5 mg kg^{-1}), a drug that blocks adrenergic neurotransmission, completely reversed the inhibition of the transit induced by laparotomy but only partially reversed that induced by laparotomy with manipulation of the small intestine.

4 N^{ω}-nitro-L-arginine (L-NOARG, 5 mg kg^{-1}), a nitric oxide synthase inhibitor, completely reversed the reserpine-resistant inhibition induced by laparotomy with manipulation of the small intestine. The effect of L-NOARG was prevented by concomitant administration of L-arginine. L-Arginine itself slightly, but significantly enhanced the inhibition. S-methylisothiourea and aminoguanidine, selective inhibitors of the inducible NO synthase, had no effect on the transit after the three operations.

5 Treatment of the rats with reserpine plus L-NOARG had no additional effect on the transit after laparotomy as compared to reserpine alone. However, reserpine plus L-NNA completely reversed the inhibition of the transit induced by laparotomy with manipulation of the small intestine.

6 These findings support the involvement of adrenergic pathways in the pathogenesis of ileus and suggest that the additional inhibitory effect of mechanical stimulation results from an enhanced release of NO by the constitutive NO synthase.

Keywords: Intestinal transit; nitric oxide synthase; ileus; adrenergic pathways; NANC (non-adrenergic non-cholinergic)

Introduction

Postoperative ileus is a common complication after intraabdominal surgery leading to increased morbidity and higher hospitalization costs. However, the pathogenesis of postoperative ileus is still debated. It is suggested that hyperactivity of adrenergic pathways leads to the activation of α_2-adrenoceptors on the intrinsic cholinergic neurones and to a reduction of the release of acetylcholine, thereby inhibiting gastrointestinal motility (Furness & Costa, 1974; Dubois, 1988; Livingston & Passaro, 1990). Experimentally, postoperative ileus was markedly improved or prevented by chemical or pharmacological sympathectomy (Catchpole, 1969; Dubois *et al*., 1973). However, after abdominal surgery adrenergic blockade did not always completely restore gastrointestinal motility (Heimbach & Crout, 1971; Smith *et al*., 1977). Therefore, other mechanisms, such as a supplementary activation of inhibitory non-adrenergic non-cholinergic (NANC) nerves, which are believed to provide the main inhibitory supply to the gut (Burnstock & Costa, 1973), may also play a role (Abrahamsson *et al*., 1979; Glise & Abrahamsson, 1980). At present, nitric oxide (NO) is generally accepted as one of the main neurotransmitters of the inhibitory NANC nerves in different organ systems, including the gastrointestinal tract (Stark & Szurszewski, 1992; Rand & Li, 1995; Boeckxstaens & Pelckmans, 1996). Disturbances in NO biosynthesis have been implicated in numerous pathological conditions such as achalasia and Hirschsprung's disease, and in inflammatory conditions such as ileitis and sepsis (Stark & Szurszewski, 1992; Miller *et al*., 1993; Salzman, 1995; Seago *et al*., 1995; László *et al*., 1995; Goyal & Hirano, 1996). Since NO is an important inhibitory neurotransmitter in the gut, we hypothesized that in addition to adrenergic pathways, an inhibitory nitrergic NANC pathway is activated, contributing to the genesis of postoperative ileus. Therefore, in the present study we investigated whether an inhibitory non-adrenergic pathway is involved in postoperative ileus and whether this pathway involves the activation of nitrergic nerves.

Methods

Operation protocol

Male Wistar rats (150–250 g) were fasted for 48 h with free access to water. The rats were divided in three groups in a randomized way and underwent an operation under ether anaesthesia. The first group underwent an abdominal skin incision (SI) after the abdomen had been shaved and disinfected. The second group underwent a laparotomy (L) consisting of the incision of the abdominal skin, abdominal muscle layers and peritoneum. The third group underwent a laparotomy followed by evisceration and manipulation (L + M) of the small intestine and the caecum. In these experiments, the caecum and small intestine were gently pulled out of the abdominal cavity, unfurled like a fan and exposed on two sterile gauzes covering the abdomen of the rat. Afterwards, the caecum and small intestine were gently touched by the fingers, starting from the caecum up to the duodenal end of the small intestine. This procedure was repeated three times during the five minutes exposure. Then the caecum and small intestine were replaced in the abdominal cavity and the suture was closed. After the operations the rats were allowed to recover

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for one hour. Then they received an intragastric injection of 0.1 ml Evans blue (50 mg in 1 ml 0.9% sodium chloride; Tanila *et al*., 1993) via a specially designed orogastric cannula introduced through the mouth. Twenty minutes later the rats were killed and the intestinal transit was measured from the pylorus to the most distal point of migration of Evans blue and expressed in cm.

Experimental protocol

In preliminary experiments the intestinal transit of Evans blue was measured in ether-anaesthetized and conscious rats.

In a first series of experiments the intestinal transit was measured in rats that underwent a skin incision (SI), in rats that underwent a laparotomy (L) and in rats that underwent a laparotomy followed by evisceration and manipulation of the small intestine and caecum (L + M).

In a second series of experiments the effect of reserpine, a drug that blocks adrenergic neurotransmission, was studied on the intestinal transit after the three operations (SI, L and L + M). Rats were divided randomly into three groups. The first served as control group and received an intraperitoneal (i.p.) injection of 0.57 M ascorbic acid, the solvent of reserpine, twenty four hours before the operations. The second group received an i.p. injection of reserpine (5 mg kg^{-1}), twenty four hours before the operations. The third group received an i.p. injection of reserpine twenty four hours before the operations plus an intravenous (i.v.) injection of the NO synthase inhibitor N^{ω}-nitro-L-arginine (L-NOARG, 5 mg kg^{-1}), one minute before the operation in the tail vein.

In a third series of experiments the role of nitric oxide was studied on intestinal transit. Rats were divided randomly into four groups. The first served as control group and received an i.v. injection of 0.9% sodium chloride (saline) in a tail vein. The second group received an i.v. injection of L-NOARG (5 mg kg^{-1}) in a tail vein. The third group was injected intravenously with the NO synthase substrate L-arginine (L-arg, 300 mg kg^{-1}) and the fourth group received an i.v. injection of L-NOARG plus L-arginine (5 mg kg^{-1} and 300 mg kg^{-1}, respectively). The rats received the i.v. injections one minute before the operation.

In a fourth series of experiments the rats were treated with selective inhibitors of the inducible isoform of NO synthase, S-methylisothiourea (SMT, 0.01 mg kg^{-1} or 1 mg kg^{-1}) or aminoguanidine (AG, 15 mg kg^{-1}) intravenously in a tail vein. Control rats received an i.v. bolus injection of saline.

Drugs used

The following drugs were used: diethyl ether, L-ascorbic acid (Merck, Darmstadt, Germany), aminoguanidine hemisulphate salt, Evans blue, L-arginine hydrochloride, N^{ω}-nitro-L-arginine, reserpine, S-methylisothiourea hemisulphate salt (Sigma, St. Louis, U.S.A.), sodium chloride 0.9% (Plurule, NV Baxter, Lessines, Belgium). Reserpine was dissolved in 0.57 M ascorbic acid. All other drugs were dissolved in 0.9% sodium chloride.

Presentation of results and statistical analysis

The total length of the small intestine was not statistically different between the groups. Therefore, results are expressed as cm migration of Evans blue, the measurements were from the pylorus to the most distal point of migration of Evans blue. Group differences were assessed by simple factorial analysis of variance (ANOVA), two-way analysis of variance or one way analysis of variance followed by the modified least significant difference (LSD) test (Bonferroni test). Values are shown as mean ± s.e.mean for the number of rats indicated. P values of less than 0.05 were considered to be significant. All data were analysed with the SPSS for Windows software (SPSS Inc., Chicago, IL, U.S.A.).

Results

Effect of ether anaesthesia and operative procedures on the intestinal transit

In untreated conscious rats, Evans blue migrated over a distance of 56.8 ± 4.1 cm of a total length of 98.2 ± 4.0 cm of the small intestine ($n = 6$) (Figure 1). Ether anaesthesia or skin incision (SI) had no effect on the intestinal transit (61.5 ± 5.4 cm of 111.2 ± 2.5 cm ($n = 5$) and 63.3 ± 2.3 cm of 109.4 ± 1.8 cm ($n = 6$), respectively) (Figure 1). After the laparotomy (L), the transit was significantly inhibited to 29.1 ± 5.0 cm of 103.2 ± 3.7 cm ($n = 7$) (Figure 1). The laparotomy with evisceration and manipulation (L + M) resulted in a transit of 11.7 ± 1.8 cm of 99.6 ± 2.2 cm ($n = 8$) which was significantly decreased as compared to the skin incision and the laparotomy without manipulation (Figure 1). The total length of the small intestine was not statistically different between the groups.

Effect of reserpine on the intestinal transit

Reserpine (5 mg kg^{-1}) significantly increased the transit after the skin incision (SI) from 62.2 ± 2.8 cm ($n = 9$) in control rats to 74.8 ± 4.1 cm ($n = 10$) in reserpine treated rats (Figure 2). Also transit after the laparotomy (L) was significantly increased from 44.3 ± 2.5 cm ($n = 9$) to 70.4 ± 5.3 cm ($n = 10$), abolishing the inhibitory effect on the transit induced by laparotomy alone (Figure 2). After the laparotomy with evisceration and manipulation (L + M), the transit was also significantly enhanced by reserpine but not completely reversed, from 20.3 ± 2.3 cm in control rats to 50.8 ± 5.0 cm in reserpine treated rats ($n = 10$, Figure 2). The total length of the small intestine was not significantly different between the groups.

Effect of L-NOARG and L-arginine on the intestinal transit

L-NOARG (5 mg kg^{-1}, i.v.), L-arginine (300 mg kg^{-1}, i.v.) and L-NOARG plus L-arginine had no effect on the transit

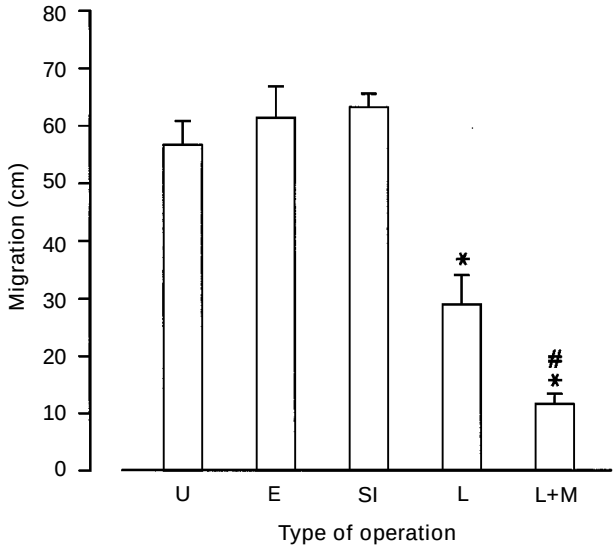

Figure 1 Intestinal transit of Evans blue in untreated rats (U), in rats that underwent ether anaesthesia (E) without operation and in rats that underwent a skin incision (SI), a laparotomy (L) or a laparotomy with evisceration and manipulation of the small intestine (L + M). Results are expressed as cm migration of Evans blue and shown as means ± s.e.mean for $n \geqslant 5$. *$P \leqslant 0.05$, significantly different from the transit after the skin incision (SI); #$P \leqslant 0.05$, significantly different from the transit after the laparotomy (L); one way analysis of variance followed by the Bonferroni test.

after the skin incision (SI) and the laparotomy (L). The transit values were comparable to those obtained in control rats: 63.0 ± 3.7 cm after the skin incision (SI) and 32.4 ± 3.0 cm after the laparotomy (L) ($n \geqslant 9$) (Figure 3). However, L-NOARG significantly enhanced the transit in rats that underwent the laparotomy with evisceration and manipulation (L + M), from 18.9 ± 1.7 cm ($n = 9$) in control rats to 34.1 ± 3.4 cm ($n = 9$) in L-NOARG-treated rats ($P = 0.001$, Figure 3). This effect of L-NOARG was prevented by concomitant administration of L-arginine (Figure 3). L-arginine alone (300 mg kg^{-1}, i.v.) caused a small, but significant decrease in the transit after the laparotomy with evisceration and manipulation (L + M) from 18.9 ± 1.7 cm in control rats to 15.6 ± 1.4 cm in L-arginine-treated rats ($n = 9$) ($P = 0.0001$, Figure 3). After treatment with L-NOARG, the transit after the laparotomy with evisceration and manipulation was no longer significantly different from the transit after the laparotomy alone. The total length of the small intestine was not significantly different between the groups.

Effect of reserpine plus L-NOARG on intestinal transit

Treatment with reserpine plus L-NOARG had no additional effect on the transit after the skin incision (SI) and the laparotomy (L) as compared to reserpine alone (Figure 2). However, reserpine plus L-NOARG completely reversed the inhibition induced by the laparotomy with evisceration and manipulation (L + M) from 20.3 ± 2.3 cm in control rats to 73.1 ± 3.8 cm in rats treated with reserpine plus L-NOARG ($n = 10$, Figure 2). In the rats treated with reserpine alone, the transit after the laparotomy with evisceration and manipulation (L + M) was significantly different from the transit after the skin incision (SI) and the laparotomy alone (L). However, in the rats treated with reserpine plus L-NOARG there was no difference between the transit after the three operations.

Effect of SMT and AG on the intestinal transit

Treatment with the inhibitor of the inducible isoform of NO synthase, S-methylisothiourea (SMT, 0.01 and 1 mg kg^{-1}) had no effect on the transit after the skin incision (SI), the laparotomy (L) and the laparotomy with evisceration and manipulation (L + M) ($n \geqslant 9$, Figure 4a) as compared to control rats. Also treatment with aminoguanidine (AG), another inhibitor of the inducible NO synthase, had no effect on the intestinal transit after the three operations, SI, L and L + M ($n = 10$, Figure 4b) as compared with control rats. The differences in transit between the three operations remained significant after SMT and AG treatment. The total length of the small intestine was not significantly different between the groups.

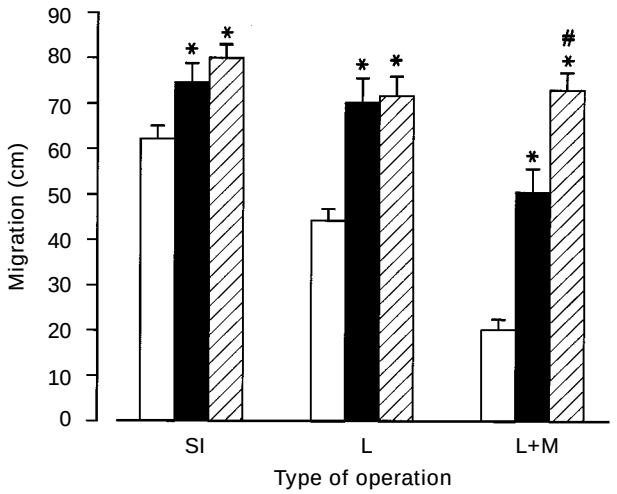

Figure 2 Effect of skin incision (SI), laparotomy (L) or laparotomy with evisceration and manipulation of the small intestine (L + M) on intestinal transit in control rats (open columns, $n \geqslant 9$) and in rats treated with reserpine 5 mg kg^{-1} (solid columns, $n = 10$) or with reserpine 5 mg kg^{-1} plus L-NOARG 5 mg kg^{-1} (hatched columns, $n = 10$). Results are expressed as cm migration of Evans blue and shown as mean ± s.e.mean. $*P \leqslant 0.05$, significantly different from the transit of the control rats with the same operation, $\#P \leqslant 0.05$, significantly different from the transit of the reserpine treated rats that underwent the laparotomy with evisceration and manipulation (L + M); one way analysis of variance followed by the Bonferroni test.

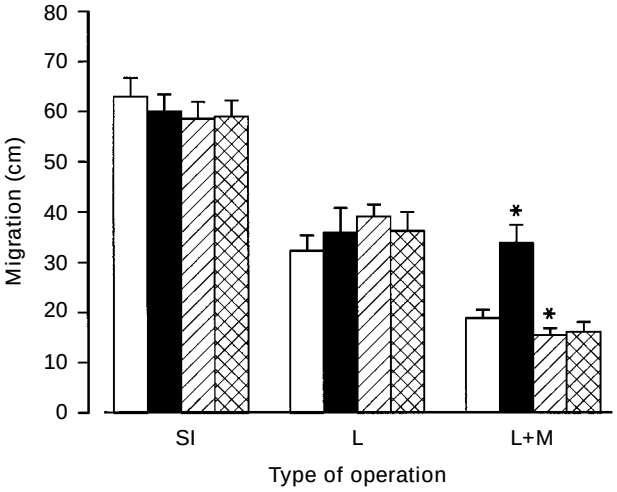

Figure 3 Effect of skin incision (SI), laparotomy (L) or laparotomy with evisceration and manipulation of the small intestine (L + M) on intestinal transit in control rats (open columns, $n \geqslant 9$) and in rats treated with L-NOARG (5 mg kg^{-1}, solid columns, $n \geqslant 9$), with L-arginine (300 mg kg^{-1}, hatched columns, $n \geqslant 9$) or with L-NOARG plus L-arginine (crossed-hatched columns, $n \geqslant 9$). Results are expressed as cm migration of Evans blue and shown as mean ± s.e.mean. $*P \leqslant 0.05$, significantly different from the transit of rats that underwent the laparotomy with evisceration and manipulation (L + M); two way analysis of variance.

Discussion

Postoperative ileus is a common complication after surgery of which the pathogenesis is still debated. In the present study, we provide evidence that in addition to adrenergic nerves, non-adrenergic nerves, releasing NO, are also involved in the pathogenesis of postoperative ileus.

In rats, gastric and small intestinal ileus predominate after laparotomy. Therefore, measurement of the small intestinal transit is a reliable indicator of postoperative ileus in rats (Cheng *et al*., 1996). By applying three different nociceptive stimuli, namely skin incision, laparotomy and laparotomy followed by mechanical stimulation of the gut, different degrees of inhibition of gastrointestinal motility were achieved. Our data demonstrate that skin incision did not affect the intestinal transit in rats whereas laparotomy delayed the intestinal transit. This effect was even more pronounced when the laparotomy was followed by an evisceration and manipulation of the small intestine and caecum. These results are in agreement with previous findings that skin incision did not alter the myoelectric gastrointestinal activity, whereas incision of abdominal muscle layers caused a transient inhibitory effect (Bueno *et al*., 1978). This inhibitory effect was complete when the peritoneum was incised and was prolonged by evisceration and manipulation of the bowel (Bueno *et al*., 1978; Dubois, 1988; Livingston & Passaro, 1990).

Adrenergic blockade by reserpine completely reversed the inhibition of the transit induced by laparotomy, confirming the involvement of adrenergic pathways in the pathogenesis of postoperative ileus (Catchpole, 1969; Dubois *et al*., 1973;

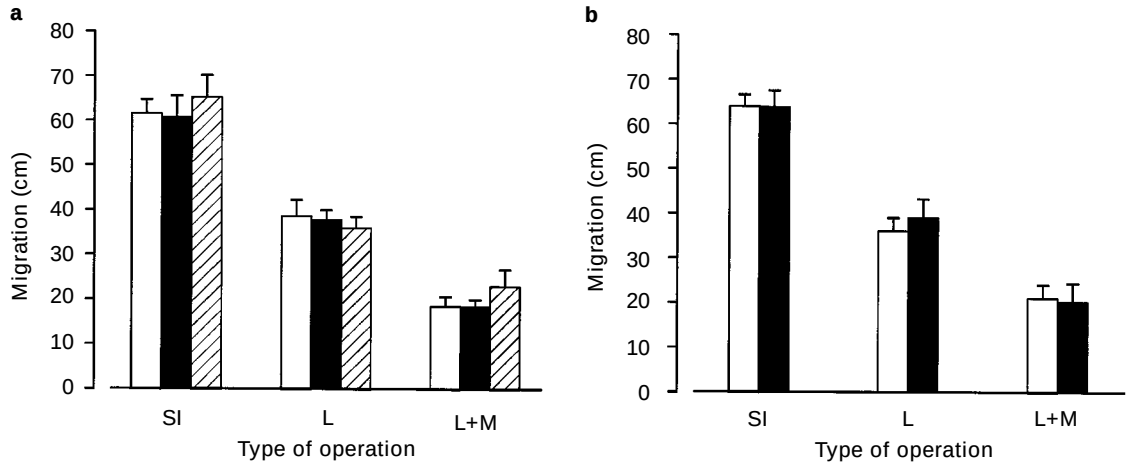

Figure 4 Effect of skin incision (SI), laparotomy (L) or laparotomy with evisceration and manipulation of the small intestine (L + M) on intestinal transit (a) in control rats (open columns, $n = 11$) and in rats treated with S-methylisothiourea (SMT) 0.01 mg kg^{-1} (solid columns, $n = 10$) or with SMT 1 mg kg^{-1} (hatched columns, $n \geqslant 9$) and (b) in control rats (open columns, $n = 10$) and in rats treated with aminoguanidine (AG) 15 mg kg^{-1} (solid columns, $n = 10$). Results are expressed as cm migration of Evans blue and shown as mean ± s.e.mean. One way analysis of variance followed by the Bonferroni test showed no statistical differences between the different treatment groups with the same operation.

Dubois, 1988; Livingston & Passaro, 1990). However, the delayed transit after laparotomy with manipulation was only partially reversed by reserpine. These results suggest the activation of a non-adrenergic pathway following more intense nociceptive and/or mechanical stimulation as previously described by several investigators (Abrahamsson *et al*., 1979; Glise & Abrahamson, 1980; Bojö *et al*., 1992). The neurotransmitter released by these non-adrenergic nerves is still unclear. Since NO is an inhibitory NANC neurotransmitter in the gastrointestinal tract (Bult *et al*., 1990; Boeckxstaens *et al*., 1990; Boeckxstaens & Pelckmans, 1996), we investigated its putative role in the pathogenesis of postoperative ileus. Treatment of the rats with L-NOARG, a nitric oxide biosynthesis inhibitor, did not affect the transit after the skin incision or the laparotomy but reversed the additional inhibition of the gastrointestinal transit induced by evisceration and manipulation, an effect prevented by concomitant administration of L-arginine, the substrate of NO synthase. Treatment with L-arginine alone, had no effect on the transit after skin incision or laparotomy. However, L-arginine slightly, but significantly increased the additional inhibitory effect of evisceration and manipulation. These findings support a role for an enhanced release of NO after mechanical stimulation of the gut. In addition, treatment of the rats with reserpine plus L-NOARG completely reversed the inhibition of the transit induced by laparotomy with evisceration and manipulation, indicating that both the adrenergic and nitrergic nerves are involved in the pathogenesis of postoperative ileus. The exact source of increased NO production after mechanical stimulation of the gut is not clear. NO can be synthesised from L-arginine by two isoforms of NO synthase: the constitutive enzyme and the inducible enzyme. In order to identify the isoform of NO synthase involved, we investigated the effect of two selective inhibitors of inducible NO synthase: SMT (Szabó *et al*., 1994; Southan *et al*., 1995; Aranow *et al*., 1996) and AG (Wu *et al*., 1995; 1996). In our study, SMT and AG had no effect on the intestinal transit after skin incision and laparotomy with or without manipulation even though these drugs were used in a concentration range shown to inhibit selectively the inducible isoform *in vivo* (Szabó *et al*., 1994; Wu *et al*., 1995). Possibly the time between the operation and the measurement of the intestinal transit (1.5 h) was not sufficient to express the inducible NO synthase, as Knowles *et al*. (1990) found that the induction of the enzyme in the liver after endotoxin challenge was maximal after six hours. Therefore, our results in this model of postoperative ileus of the rat, suggest that the enhanced release of NO is most probably produced by the constitutive rather than by the inducible NO synthase.

In conclusion, we confirmed the involvement of an adrenergic pathway in the pathogenesis of postoperative ileus and showed that mechanical and/or nociceptive stimulation of the gut triggers an additional non-adrenergic pathway. This non-adrenergic pathway is mediated by nitrergic nerves releasing NO synthesised by the constitutive rather than by the inducible isoform of NO synthase.

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