Influence of Hepatectomy on Body Temperature Change in Rats

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Abstract. Abdominal surgery, especially liver resection and transplantation, increases body temperature during and after surgery, but the precise mechanism(s) underlying this effect are not well understood. The present study thus sought to investigate this phenomenon using an experimental rat model. Specific pathogen-free male Sprague-Dawley rats, 5 weeks of age, underwent a two-thirds partial hepatectomy (PH), one-third splenectomy, or left kidney resection, and then rectum temperature was measured for 5 consecutive days after surgery. Rectum temperature increased in PH rats to a peak on day 4, but no change in temperature was detected after splenectomy and kidney resection. In the second part of the study, we examined the influence of gadolinium chloride and interleukin-1β monoclonal antibody (IL-1β mAb) on the increase in rectum temperature following PH. Treatment of rats with 20 mg/kg gadolinium chrolide or 200 μg IL-1β mAb inhibited the PH-induced increase in rectum temperature and decrease in IL-1β and prostaglandin E2, which act as pyrogens to change the thermoregulatory set point in the hypothalamus. These results suggest that abdominal surgery, especially liver resection, caused an increase in endogenous pyrogen production that results in increased body temperature.

Key Words: body temperature, hepatectomy, IL-1β, prostaglandin E2, Kupffer cell.

Introduction

As warm-blooded animals, human organs are designed to operate efficiently at a body temperature around 37°C (1), with natural variations in throughout the day remaining within 1°C. The body uses a complex mechanism for thermoregulation and generates heat through the process of metabolism, which generates the energy essential to maintain biological activities. Decreased body temperature after surgery is a well-known outcome in many patients (2, 3), because surgery is an invasive process that can induce a shock effect to the body (4, 5). In addition, the temperature of the body at rest is slightly lower than while active and most surgical suites are air-conditioned and tend to be very cold (3). Surgery also causes blood loss, which will further decrease body temperature. In some cases, surgery may be performed to remove an organ or organ system from the body. Therefore, a decrease in postoperative body temperature is caused by a combination of these factors as the body struggles to maintain temperature, while healing surgical wounds. Furthermore, body temperature after surgery may decrease in response to medication administered both before and during procedures (3, 6), while the lack of activity while the patient is on the operating table will slow metabolism and lower heat generation within the body (5).

After surgery, a patient's body temperature is maintained with heated blankets because low postoperative body temperature can cause complications if not corrected promptly. Within a few hours, the individual usually regains the ability to self-regulate body temperature as the effects of anesthesia wear off. Abdominal surgeries, especially liver resection and transplantation, can increase body temperature during surgery. It is reported that liver resection causes the activation of Kupffer cell to produce IL-1(7), which can affect changes in body temperature(8), suggesting that IL-1 from Kupffer cells increases body temperature of patients. However, there is no direct evidence that IL-1 from Kupffer cells causes increase in body temperature. Therefore, the aim of the present study was to examine the possible mechanisms by which abdominal surgery increase body temperature using an experimental rat model.

Materials and Methods

Animals. Specific pathogen-free male Sprague-Dawley rats, 5 weeks of age, were purchased from Charles River Laboratories Japan, Inc. (Atsugi, Kanagawa, Japan) and maintained in our animal facility under a controlled environment (25 ± 2°C, 55 ± 5% humidity, and 12-h dark/light cycle). All experimental procedures were approved by the Animal Care and Use Committee of Showa University (approval no.: 54001).

Surgical Operation. Two-thirds partial hepatectomy (PH) was performed according to the methods described by Higgins and Anderson (9). Briefly, rats were anesthetized by intraperitoneal injection of pentobarbital (30 mg/kg; Kyoritsu Seiyaku Corp., Tokyo, Japan). After the abdominal hair was shaved and the abdominal skin was sterilized with 70% ethanol and povidone iodine (Meiji Seika Co., Ltd., Tokyo, Japan), an incision of approximately 3 cm was made into the abdominal wall and two-thirds of the liver was removed. Afterward, each PH rat received three daily intraperitoneal injections of cefazolin sodium hydrate (40 mg/kg; Fujisawa Pharmaceutical Co., Ltd., Tokyo, Japan) to prevent postoperative bacterial infection. To prepare the partial splenectomy and kidney resection rat models, rats were pre-treated in a similar manner

and then either approximately one-third of the spleen or the left kidney was resected. Rats subjected to abdominal wall treatment only (hair removal and incision) were used as sham-operated controls. Postoperatively, these rats also received three daily intraperitoneal injections of cefazolin sodium hydrate (40 mg/kg; Fujisawa Pharmaceutical Co., Ltd.) to prevent bacterial infection.

Treatment of rats with agents. PH rats received either 200 μg of interleukin-1β monoclonal antibody (IL-1β mAb) or 20 mg/kg gadolinium chloride intravenously 4 days after surgery. The dose of gadolinium chloride used in this study showed no toxicological effects when injected intravenously into rats (10, 11). Both agents were purchased from R & D System, Inc. (Minneapolis, MN, USA) as preservative-free reagents.

Measurement of rectum temperature. Rectum temperature was measured using a thermal probe connected to a digital thermometer (Tateyama Kagaku Industry Co., Ltd., Toyama, Japan). Rats were anesthetized with an intraperitoneal injection of pentobarbital (30 mg/kg; Kyoritsu Seiyaku Corp.). A thermistor probe (Tateyama

Kagaku Industry Co., Ltd.) was then inserted about 2 cm into the rectum and left in place for 1 min to record the temperature.

Assay for interleukin (IL)-1β and prostaglandin (PG) E2. Serum IL-1β and PGE2 levels were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's recommendations. The ELISA test kits for IL-1β were purchased from R & D Systems and those for PGE2 from Cayman Chemical Company (Ann Arbor, MI, USA). The minimum detectable levels of these ELISA kits were 5.0 pg/ml for IL-1β and 7.8 pg/ml for PGE2.

Statistical analysis. All data are expressed as the mean ± SE of five rats. Significant differences between control and experimental groups were identified by analysis of variance followed by the Bonferroni test. A probability (*P*) value < 0.05 was considered statistically significant.

Results

Influence of abdominal surgery on core body temperature

Rats that underwent PH underwent a rectum temperature measurement once a day (from 11:00 to 12:00) for 5 consecutive days. As shown in Fig. 1, the rectum temperature of PH rats significantly increased on day 1, plateaued by day 4, and declined thereafter. To then examine whether splenectomy and kidney resection also caused an increase in body temperature, the rectum temperature of rats in the splenectomy and kidney resection groups was measured 4 days after surgery. As shown in Fig. 2, there were no significant differences in rectum temperature between rats in the splenectomy (36.4 ± 0.10°C) and kidney resection (36.4 ± 0.08°C) groups and controls (36.0 ± 0.31°C).

Influence of gadolinium chloride and IL-1β mAb treatment on rectum temperature of PH rats

We next examined whether gadolinium chloride or IL-1β mAb treatment suppressed the increase in rectum temperature following PH. Preliminary experiments confirmed that intravenous injection of either gadolinium chloride or IL-1β mAb into non-treated

rats caused no changes in rectum temperature (data not shown). Rats in the PH group received an intravenous injection of gadolinium chloride 4 days after surgery and rectum temperature was measured 2 h later, and as shown in Fig.3A, the injected rats showed a significantly suppressed increase in rectum temperature (37.1 ± 0.11°C) induced by PH, compared with non-treated controls (36.0 ± 0.32°C). Similar experiments to examine the influence of IL-1β mAb injection on PH rats showed an inhibition of the PH-induced increase in rectum temperature (37.3 ± 0.06°C) compared to sham-operated controls (36.0 ± 0.32°C) (Fig. 3B).

Influence of gadolinium chloride or IL-1β mAb treatment on PGE2 and IL-1β levels in PH rats

The third set of experiments was designed to examine the influence of PH on the production of endogenous pyrogens, which increase the core body temperature of mammals. Furthermore, we also examined the influence of pyrogen suppression on changes to core body temperature. Briefly, serum was obtained from PH rats before and after treatment with gadolinium chloride or IL-1β mAb, and then assayed for both PGE2 and IL-1β by ELISA. As shown in Fig. 4A & B, gadolinium chloride treatment

significantly decreased serum levels of both PGE2 (314.10 ± 22.57 pg/ml) and IL-1β (13.00 ± 2.52 pg/ml), which were increased by PH (PGE2: 480.77 ± 25.80 pg/ml; IL-1β: 40.45 ± 9.51 pg/ml). The data in Fig. 5 (A & B) also showed that IL-1β mAb treatment decreased serum PGE2 levels (351.00 ± 27.62 pg/ml), which were increased by PH (469.20 ± 30.16pg/ml). On the other hand, kidney resection did not influence serum pyrogen levels (Fig. 6), with PGE2 and IL-1β levels in serum obtained from rats 4 days after kidney resection (PGE2: 413.50 ± 31.89 pg/ml ; IL-1β: 6.93 ± 3.58 pg/ml) nearly identical to those obtained before surgery (PGE2: 416.70 ± 12.82 pg/ml; IL-1β: 6.90 ± 3.47 pg/ml).

Discussion

Surgical procedures are well accepted to be able to lower core body temperature by 0.5–1.5°C, owing, in part, to cold operating rooms, decreased muscular activity, and restricted cutaneous vasodilation (3, 6). Although abdominal surgery is known to cause transient increases in body temperature, the mechanisms that drive these fluctuations in body temperature are not well understood (5). The aim of the present study was therefore to identify possible mechanisms through which abdominal surgery increases body temperature using experimental rat models.

The present results clearly showed that PH, but not splenectomy or kidney resection, increased rectum temperature. The mammalian liver reportedly possesses the unique ability to regenerate to nearly its original size after PH or injury (12, 13). The proliferative signals responsible for liver regeneration are conveyed by a complex network of cytokines and growth factors, which induce hepatocytes to proliferate (12). In a study to identify cell types and mediators that stimulate hepatocyte proliferation, Goss et al. (13) showed that Kupffer cells, resident macrophages in the liver, obtained from PH rats were significantly activated relative to macrophages obtained from the spleen, peritoneum, and airways. This group also observed that Kupffer cells from PH

rats produced much higher levels of both IL-1 and PGE2 in response to lipopolysaccharide stimulation *in vitro* (13).

Increases in body temperature induce changes to the thermoregulatory set point in the hypothalamus, via the direct action of many types of mediators, which include IL-1β, tumor necrosis factor, and IL-6 (8, 14). These endogenous pyrogens trigger the synthesis and release of other mediators, most notably PGE2, in the preoptic nuclei of the anterior hypothalamus (15, 16) and in vascular endothelial cells, among other regions (1). Preoptic neurons bearing E-prostanoid receptors alter their intrinsic firing rate in response to PGE2 stimulation, evoking an elevation in the thermoregulatory set point (1). Together with these reports, the present data might indicate that PH in rats activates Kupffer cells to produce IL-1β and PGE2, which, in turn, raise the thermoregulatory set point in the hypothalamus and subsequently, the body temperature.

We then asked how exactly the PH procedure, but not splenectomy or kidney resection, could increase body temperature. To do this, we first examined the influence of inhibiting Kupffer cell activation on body temperature fluctuations using gadolinium chloride, which can inhibit calcium ion uptake and calcium-dependent cellular

responses such as nuclear factor kappa-B (NF-κB) activation responsible for protein production, including IL-1 and PGE2 (10, 11 17). The present data clearly showed that gadolinium chloride treatment prevented the PH-induced increases in body temperature in rats and also suppressed the serum levels of both PGE2 and IL-1β, which play essential roles in modulating body temperature and which were raised by PH. Furthermore, IL-1β mAb treatment of PH rats inhibited the increase in both body temperature and PGE2 production. These results strongly suggest that PH activated Kupffer cells, and that these cells, in turn, increased production of the endogenous pyrogens IL-1β and PGE2 to induce a net increase in body temperature. This speculation is supported by the observation that kidney resection did not cause changes to serum levels of the endogenous pyrogens IL-1β and PGE2.

In conclusion, the increase in body temperature induced by PH, but not by splenectomy and kidney resection, could be attributed, at least in part, to Kupffer cell activation.

Conflict of interest

The authors declare no conflict of interest regarding this work.

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Figure legends

Fig. 1. Influence of partial hepatectomy on body temperature fluctuations in rats. Rats underwent a 2/3 partial hepatectomy on day 0. Rectum temperature was measured before surgery (day 0) and at 1, 2, 3, 4, and 5 days after surgical operation. The data are expressed as the mean ± SE of five rats.

Fig. 2. Influence of partial hepatectomy, partial splenectomy, and kidney resection on body temperature. Groups of rats underwent a 2/3 partial hepatectomy, one-third splenectomy, or left kidney resection on day 0. The rectum temperature was measured on day 4. The data are expressed as the mean ± SE of five rats.

NC: Normal Control; SC: Sham Control; PH: Partial hepatectomy, PS: partial splenectomy, KR: kidney resection.

Fig. 3. Influence of treatment with gadolinium chloride (GC) or interleukin-1β monoclonal antibody (IL-1β mAb) on body temperature of partial hepatectomized (PH) rats. PH rats were intravenously injected with either 20 mg/kg GC or 200 μg IL-1β mAb on day 4 and rectum temperature was measured 2 h later. The data are

expressed as the mean ± SE of five rats. NC: Normal Control; SC: Sham Control; PH: Partial hepatectomy.

Fig. 4. Influence of treatment with gadolinium chloride (GC) on serum levels of interleukin (IL)-1β (A) and prostaglandin E2 (B) in partial hepatectomized (PH) rats. PH rats were intravenously injected with 20 mg/kg GC on day 4. Serum samples were obtained 2 h later and PGE2 and IL-1β levels were examined by ELISA. The data are expressed as the mean ± SE (pg/ml) of five rats. NC: Normal Control; SC: Sham Control; PH: Partial hepatectomy.

Fig. 5. Influence of treatment with interleukin (IL)-1β monoclonal antibody (IL-1β mAb) on serum levels of IL-1β (A) and prostaglandin E2 (B) of partial hepatectomized (PH) rats. PH rats were intravenously injected with 200 μg IL-1β mAb on day 4. Serum samples were obtained 2 h later and the contents of both PGE2 and IL-1β were examined by ELISA. The data are expressed as the mean ± SE (pg/ml) of five rats. NC: Normal Control; SC: Sham Control; PH: Partial hepatectomy; N.T.: Not Tested; mAb: monoclonal antibody.

Fig. 6. Influence of kidney resection on serum levels of interleukin (IL)-1β and prostaglandin (PG) E2. The left kidney was removed from each rat and serum samples were obtained 4 days later. IL-1β and PG E2 levels were examined by ELISA. The data are expressed as the mean ± SE (pg/ml) of five rats. NC: Normal Control; SC: Sham Control; KR: kidney resection.

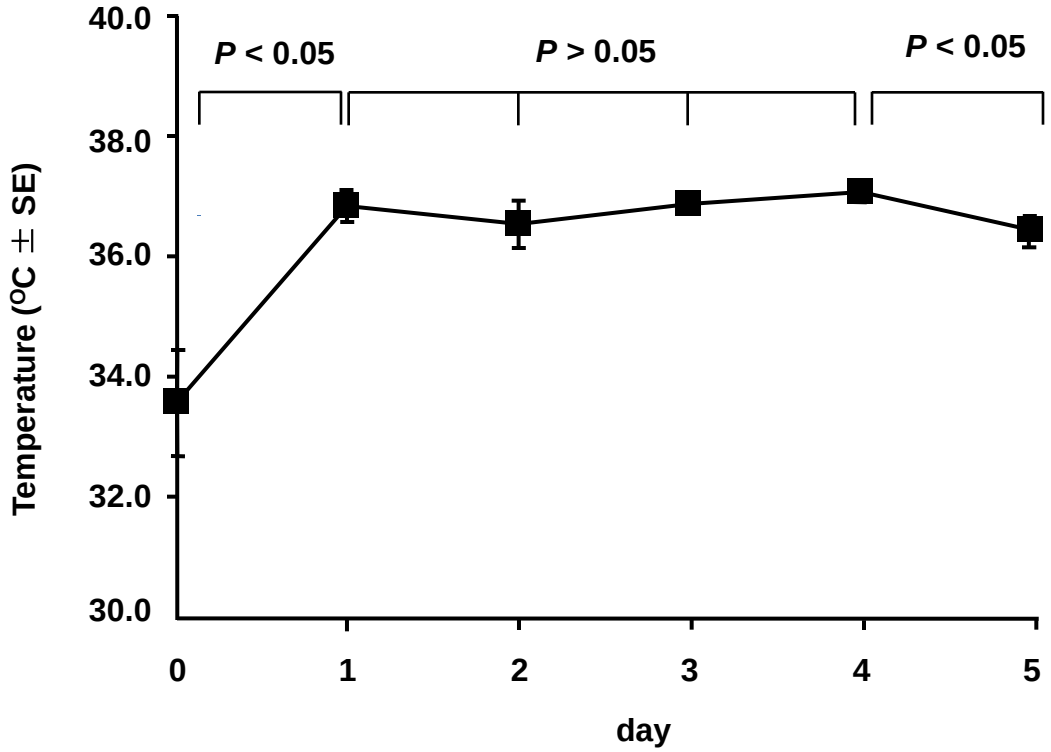

40.0
38.0
36.0
34.0
32.0
30.0
Temperature (°C ± SE)
P < 0.05
P > 0.05
P < 0.05
0
1
2
3
4
5
day

Fig. 1

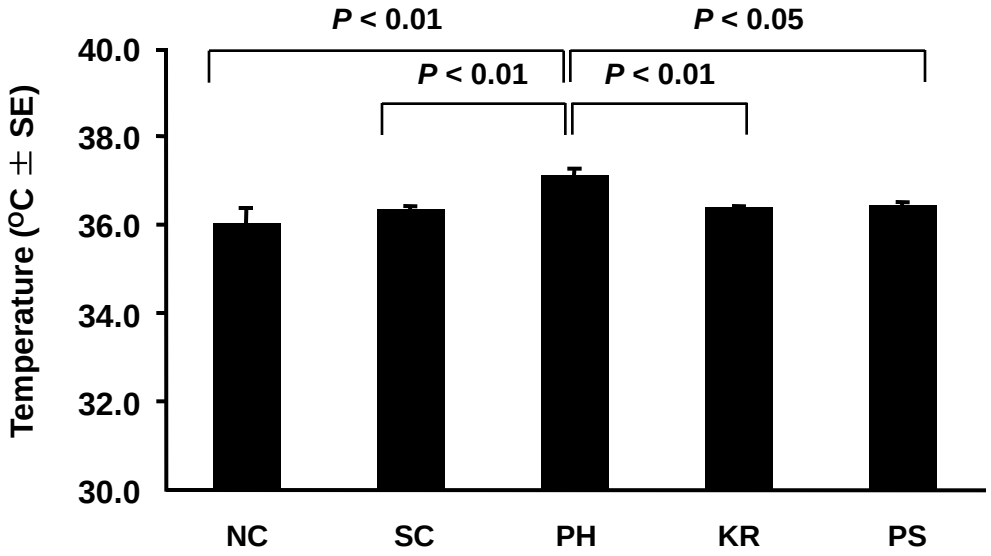
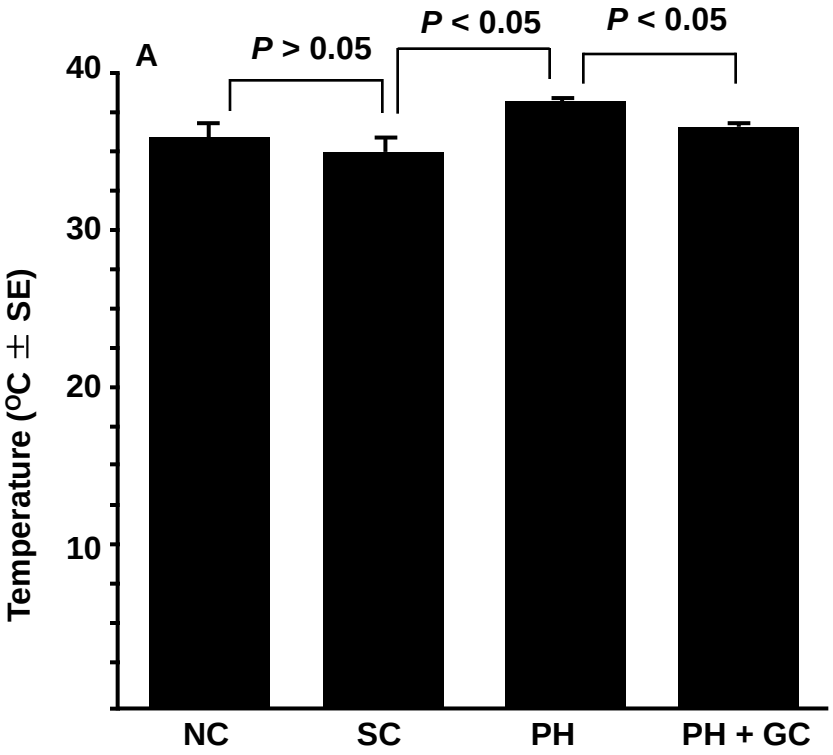

P < 0.01
P < 0.05
P < 0.01
P < 0.01
40.0
38.0
36.0
34.0
32.0
30.0
Temperature (°C ± SE)
NC
SC
PH
KR
PS

Fig. 2


A
P > 0.05
P < 0.05
P < 0.05
40
30
20
10
Temperature (°C ± SE)
NC
SC
PH
PH + GC

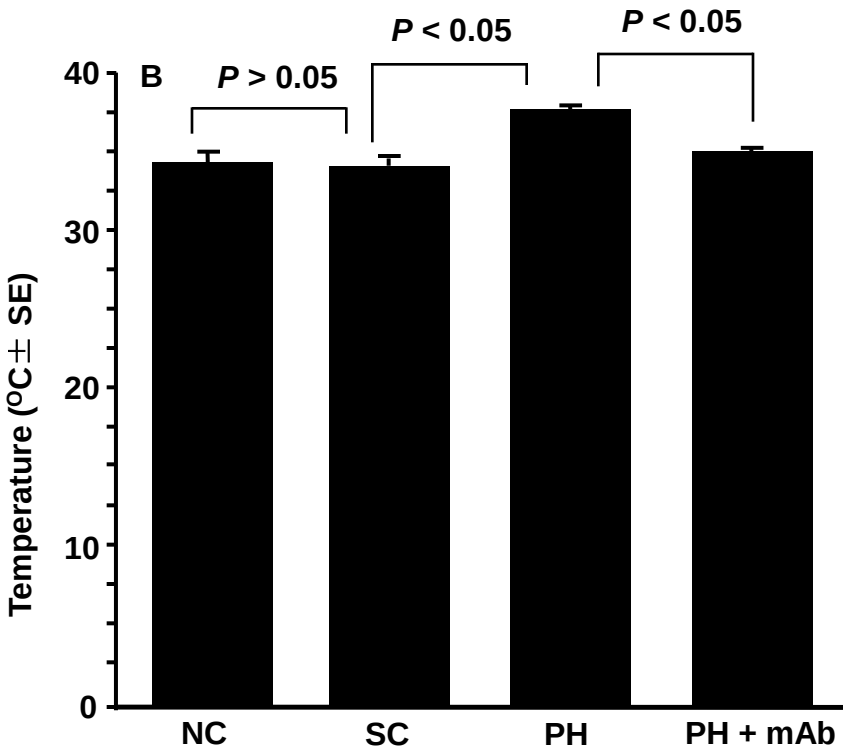

B
P > 0.05
P < 0.05
P < 0.05
40
30
20
10
0
Temperature (°C ± SE)
NC
SC
PH
PH + mAb

Fig. 3

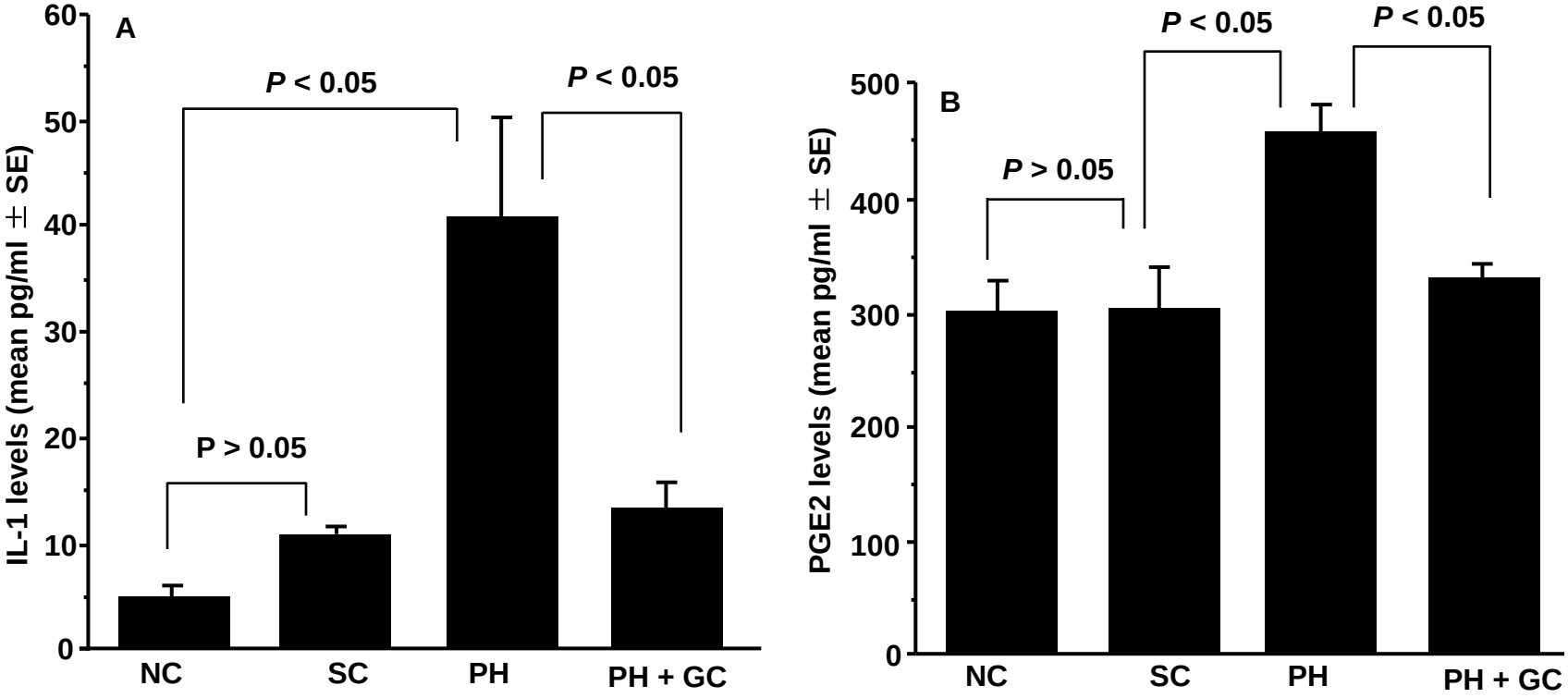

A
IL-1 levels (mean pg/ml ± SE)
60
50
40
30
20
10
0
P < 0.05
P < 0.05
P > 0.05
NC
SC
PH
PH + GC
B
PGE2 levels (mean pg/ml ± SE)
500
400
300
200
100
0
P < 0.05
P < 0.05
P > 0.05
NC
SC
PH
PH + GC

Fig. 4

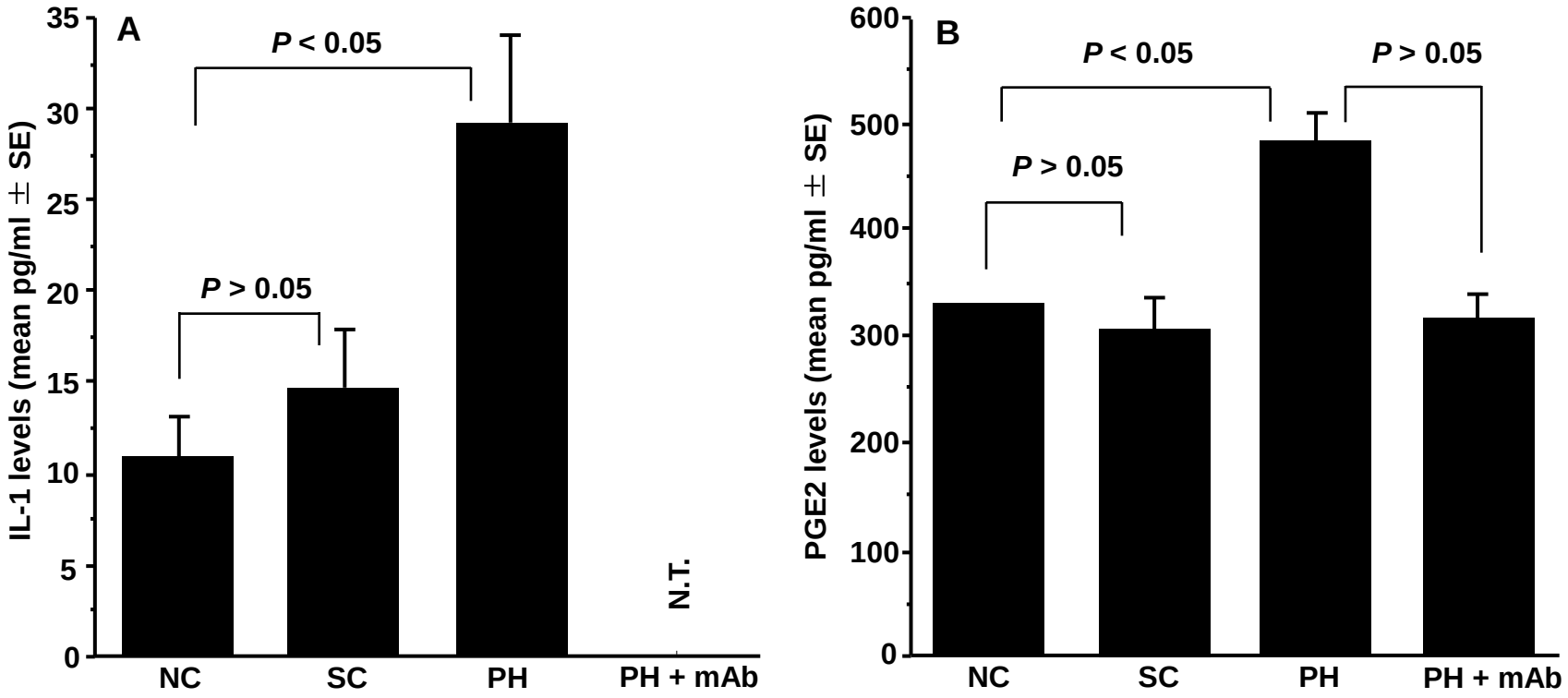

A
P < 0.05
P > 0.05
IL-1 levels (mean pg/ml ± SE)
35
30
25
20
15
10
5
0
N.T.
NC
SC
PH
PH + mAb
B
P < 0.05
P > 0.05
P > 0.05
PGE2 levels (mean pg/ml ± SE)
600
500
400
300
200
100
0
NC
SC
PH
PH + mAb

Fig. 5

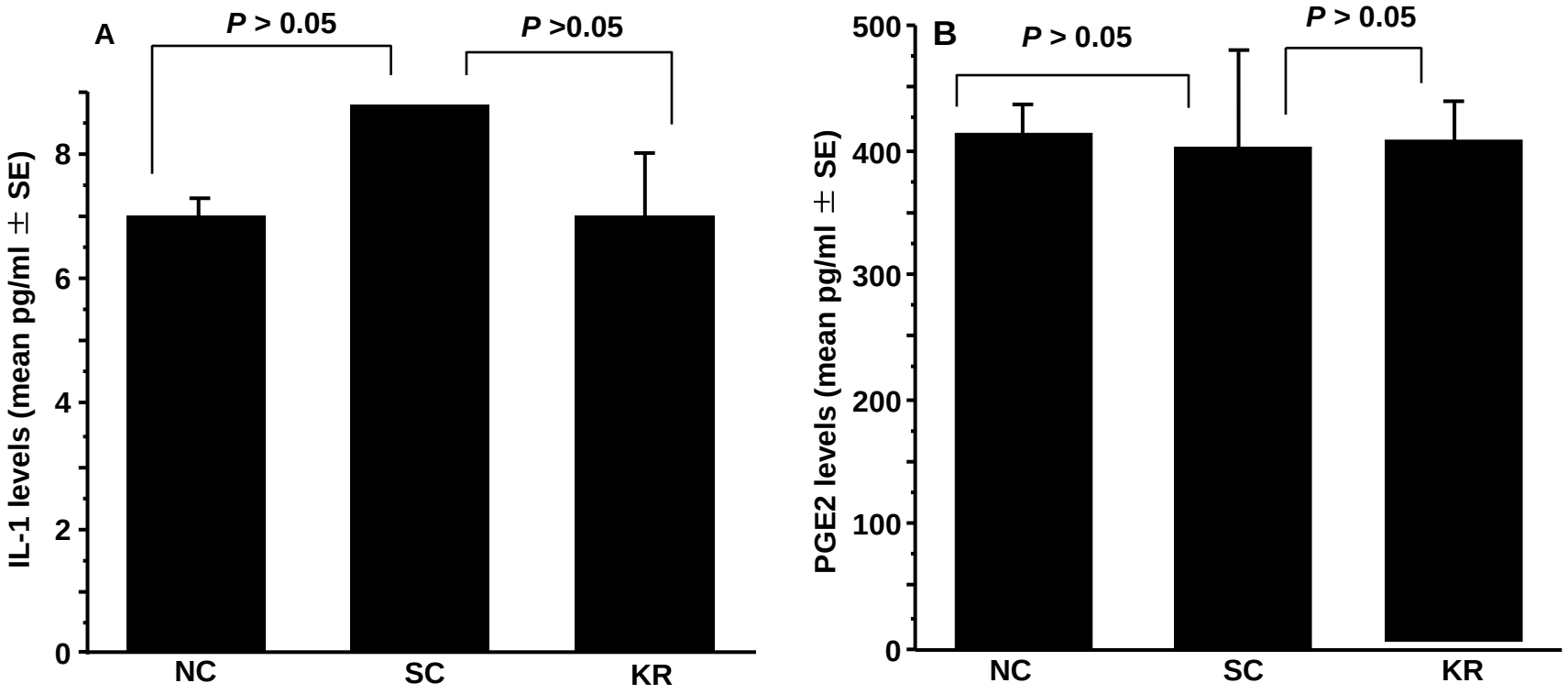

A
P > 0.05
P >0.05
IL-1 levels (mean pg/ml ± SE)
0
2
4
6
8
NC
SC
KR
B
P > 0.05
P > 0.05
PGE2 levels (mean pg/ml ± SE)
0
100
200
300
400
500
NC
SC
KR

Fig. 6