

Mediators of Inflammation, 6, 73–74 (1997)

## Systemic inflammatory response syndrome (SIRS) induced by carbon tetrachloride in rats

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WE have observed the symptoms of systemic inflammatory response syndrome (SIRS) in male rats intoxicated by carbon tetrachloride (CCl<sub>4</sub>). Severe hypothermia, tachypnoea and increase in the heart beat/min were diagnosed. These symptoms developed in the first hour of intoxication. The hepatic dysfunction was characterized by elevated bilirubin levels. In the sera we have measured increases in the activity of secretable (group II) phospholipase A<sub>2</sub> sPLA<sub>2</sub> (2,8x) and 6-ketoprostaglandin F<sub>1α</sub> (KPGF) (1,44x). Supposedly the free radicals derived from CCl<sub>4</sub>—mainly trichloromethyl—could induce the prompt reaction of SIRS and the release of sPLA<sub>2</sub> as well as the formation of KPGF. Our findings show that in the early phase of CCl<sub>4</sub> intoxication the symptoms of SIRS can be related to elevation of sPLA<sub>2</sub> and the products of cyclooxygenase II.

**Key words:** Acute CCl<sub>4</sub> intoxication, SIRS, sPLA<sub>2</sub>, 6-ketoprostaglandin F<sub>1α</sub>

### Introduction

Actual response of the living organism to various injuries depends not only on the type of the noxa but also on the reactivity of the body. Based on several observations, a new concept, the systemic inflammatory response syndrome (SIRS) was introduced in 1992.<sup>1</sup> SIRS was defined as an acute response to different forms of stress, e.g. infection, tissue necrosis, combustion etc. The characteristics of SIRS were determined by the existence of (1) hypothermia or hyperpyrexia, (2) high pulse rate, (3) increased respiratory frequency, (4) leukocytosis or leukopenia. If two of these signs have been developed the syndrome is manifested. Carbon tetrachloride (CCl<sub>4</sub>) is the most potent halogenated hydrocarbon. In the hepatic microsomes it is activated to free radicals, mainly trichloromethyl (CCl<sub>4</sub>-CCl<sub>3</sub>) bound covalently to proteins, nucleic acids or lipids. Free radicals can mediate numerous toxic effects including membrane damage, diffuse fatty degeneration and necrosis of the hepatocytes in zone III of the liver acinus.<sup>2</sup> Some consequence of the acute CCl<sub>4</sub> intoxication can develop within a few hours.<sup>3</sup> The liver is deeply involved in the processes. Hepatocytes are stimulated by pro-inflammatory cytokines, e.g. TNF<sub>α</sub>. At the same time they also secrete acute phase proteins.<sup>4</sup> The elevation of serum bilirubin is an early marker of acute toxic hepatic failure.<sup>5</sup> Different non-specific stimuli can induce the release of

secretable (group II) phospholipase-A<sub>2</sub> (sPLA<sub>2</sub>), initiating the production of arachidonic acid and a cascade of enzymatic reactions, e.g. cyclooxygenase mediated prostaglandin synthesis.

### Experiments

Male Wistar rats (200–220 g bodyweight) were treated with a single CCl<sub>4</sub> dose of 1.25 ml/kg between 08.00 and 09.00 h. Controls received saline in the same volume and time. In the first hour of intoxication body temperature decreased from 36.3°C to 31.6°C. A tachypnoea was registered, respiratory frequency augmented from 68 to 110/min and heart beat/min increased from 341 to 368. The rise in serum bilirubin levels reflected liver lesions in the animals. Furthermore elevated activities of sPLA<sub>2</sub> were found in sera (2,8x) by using: 1-stearoyl-2-(1-<sup>14</sup>C)arachidonyl,L-3-phosphatidylcholine (Amersham) as substrate, and increased amounts of 6-ketoprostaglandin F<sub>1α</sub> (KPGF) production (1,4x) were measured in aortic tissue specimens.<sup>6</sup>

Results are given in Table 1.

### Discussion

In our experiments three symptoms of SIRS, hypothermia, tachypnoea and increased pulse rate were observed in the 60 min of acute CCl<sub>4</sub> intoxication of rats. Vadas and Pruzansky demonstrated that secretory non-pancreatic

**Table 1.** Changes induced by CCl<sub>4</sub> in rats (mean ± SE)

Experimental animals	Controls saline (n = 15)	CCl <sub>4</sub> (60 min) (n = 10)
Body temperature °C	36.3 ± 0.7	31.6 ± 0.3 (P < 0.001)
Respiratory frequency/min	68 ± 3.5	110 ± 5 (P < 0.001)
Heart beat/min	341 ± 10.4	368 ± 8.7 (NS)
Serum PLA <sub>2</sub> U/l	0.001 ± 0.0012	0.0028 ± 0.0035 (P < 0.001)
6-keto-PGF <sub>1α</sub> in aortic tissue pg/mg protein	182 ± 41.0	263 ± 89.7 (P < 0.001)
Serum bilirubin μmol/l	3.13 ± 0.13	3.84 ± 0.42 (NS)

P vs controls.

PLA<sub>2</sub> correlated with markers of multi system organ injury and SIRS.<sup>7</sup> We also found elevated sPLA<sub>2</sub> activities serving a further support to our suggestion that acute CCl<sub>4</sub> intoxication is also a form of SIRS. The products of sPLA<sub>2</sub>, platelet activating factor (PAF) and arachidonic acid, the source of prostanoids may have secondary but very important mediating role in the completion of the multiple organ failures. The increased levels of KPGF reflected an increased prostanoid synthesis by cyclooxygenase II.<sup>8-10</sup> Liver lesion, hypothermia, tachypnoea and tachycardia manifested together represent a real form of multi-organ failure. The conclusion of our observation is that during acute CCl<sub>4</sub> intoxication a form of SIRS is manifest.

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ACKNOWLEDGEMENT. This work was supported by a grant from the Ministry of Public Welfare and the Health Scientific Committee (T 02 425/93).

Received 27 October 1996;  
accepted 28 October 1996