Factors Affecting the Uptake of ^{99m}Tc-Sulfur Colloid by the Lung and Kidney

William C. Klingensmith III, Min-Fu Tsan, and Henry N. Wagner, Jr.

Johns Hopkins Medical Institutions, Baltimore, Maryland

Occasionally patients injected with ^{99m}Tc-sulfur colloid (TSC) for liver–spleen imaging show increased uptake by the lungs or kidneys. In animals, increased lung uptake of TSC can be produced by injecting endotoxin intraperitoneally. Using an intraperitoneal endotoxin model, we studied the effect of heparin on dose–response curves for TSC uptake by the lungs and kidneys. Over a dose range of 1 μg to 10 mg of endotoxin, TSC uptake by the lungs increased progressively; heparin had no effect. In the kidneys, endotoxin in doses from 1 μg to 1 mg resulted in an increased TSC uptake which was less marked than that in the lungs and which was also unaffected by heparin. However, at a dose of 10 mg of endotoxin, a marked increase occurred in TSC uptake by the kidneys, and this could be prevented by heparin. Although the increased TSC uptake by the kidneys at lower doses of endotoxin and by the lungs at all doses is probably not related to intravascular coagulation, the marked increase in TSC uptake by the kidneys at 10 mg of intraperitoneal endotoxin probably is related to intravascular coagulation, possibly by entrapment in fibrin deposits in the renal capillaries.

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Intravenously injected radiocolloids, such as ^{99m}Tc-sulfur colloid (TSC), usually distribute within the body according to regional blood flow and phagocytic activity and are commonly used to study the structure and regional phagocytic activity of the liver and spleen. Occasionally, increased TSC uptake is observed in the lungs (*1–6*) or kidneys (*7–9*); this effect is usually related to the patient's disease rather than to such technical factors as macroaggregation of the radiopharmaceutical before injection. Studies of the mechanism of increased lung uptake of TSC in man have yielded data arguing against the presence of a plasma factor (*1,5*) and suggesting a gradual accumulation of TSC in the lungs with time (*2,5*). In animals, intraperitoneal endotoxin causes increased lung uptake of TSC: autoradiography indicates that this uptake is intracellular rather than within the capillary or arteriolar lumen (*10*). However, the evidence to date is insufficient to establish or exclude any one mechanism.

In the case of colloidal carbon, animal studies have shown that injection of thromboplastin (*11*) or production of extensive burns (*12*) caused a marked increase in uptake of colloidal carbon by the lungs, and that pretreatment with heparin will prevent this increased uptake. In view of these findings, we investigated the effect of heparin on endotoxin-induced uptake of TSC by the lungs and the kidneys over a wide dose range. We postulated that, if intravascular coagulation and fibrin formation played a role in lung or renal accumulation of colloid, heparin administration would have an inhibitory effect.

METHODS AND MATERIALS

Sprague–Dawley male rats weighing 250–350 gm (Charles Rivers, Wilmington, Mass.) were injected intraperitoneally with lipopolysaccharide-B *E. coli* endotoxin (Difco Laboratories, Detroit, Mich.) over a dose range of 1 μg to 10 mg. Approximately half

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For reprints contact: William Klingensmith III, Nuclear Medicine Service, V.A. Hospital, 1055 Clermont St., Denver, CO 80220.

the animals at each dose level were given 1,000 units of heparin intravenously 1–2 min after the endotoxin injection. (A number of animals were heparinized before the endotoxin injection, but many of these died of intraperitoneal hemorrhage after the peritoneal puncture. Those that survived showed the same findings as the animals given heparin 1–2 min after the intraperitoneal injection of endotoxin.) Four hours after injection of endotoxin the animals were injected intravenously with 10–20 μCi of ^{99m}Tc-sulfur colloid (Union Carbide, Rye, N.Y.) and killed with ether 15 min later. Both lungs, both kidneys, the spleen, and the liver were weighed and their ^{99m}Tc contents were measured in a scintillation well counter. The amount of activity in the lungs, kidneys, and spleen was expressed as the ratio of the counting rate per gram in these organs with the counting rate per gram in the animal's liver (*11,13*). Each data point represents an average of five animals and a minimum of two.

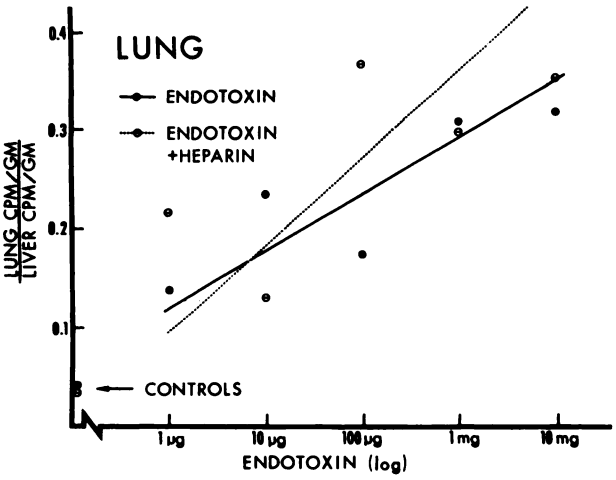

FIG. 1. Dose–response curves of lung uptake of ^{99m}Tc-sulfur colloid 4 hr after intraperitoneal administration of endotoxin, with and without heparin. Uptake progressively increases with increasing doses of endotoxin, and this effect is unaffected by heparin. Straight lines represent least-squares fits through data points, with and without heparin, excluding control values.

RESULTS

Lung uptake of TSC after intraperitoneal administration of endotoxin increased progressively with increasing doses of endotoxin over a range of 1 μg to 10 mg (Fig. 1). Each mean lung uptake, both with and without heparin, was significantly greater than the mean control level ($p < 0.05$). There was no significant difference between the heparinized and nonheparinized animals at any dose level including the controls. The relative standard deviations of the data points for the lungs were larger than those for the kidneys although the measurements for the two organs were made in the same animals.

Renal uptake after 1 μg to 1 mg of intraperitoneal endotoxin also showed a significant increase above control values at all dose levels ($p < 0.05$) and heparin had no effect on this (Fig. 2). This increase in the kidneys was not as marked or progressive as in the lungs. At a dose of 10 mg of endotoxin, however, there was a marked increase in renal uptake of TSC, and this could be prevented by treatment with heparin ($p < 0.05$) (Fig. 3).

No significant change from control levels was found for the spleen at any dose of endotoxin, with or without heparin.

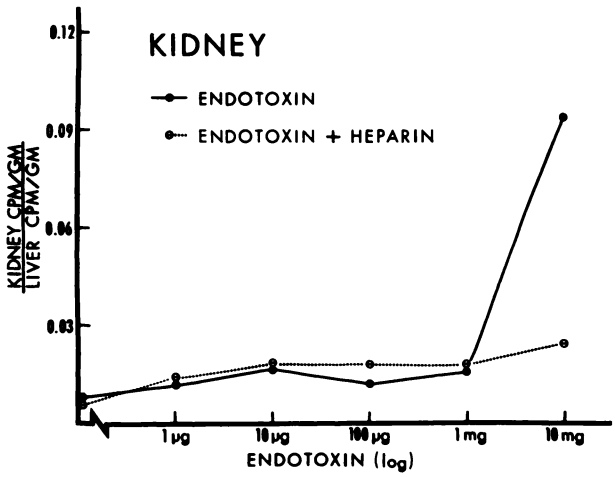

FIG. 2. Dose–response curves of renal uptake of ^{99m}Tc-sulfur colloid 4 hr after intraperitoneal administration of endotoxin, with and without heparin, show mild relatively nonprogressive increase in uptake with increasing doses of endotoxin up to 1 mg, and this is unaffected by heparin. At 10 mg renal uptake increases markedly. This is preventable by heparin.

DISCUSSION

The incidence of increased lung uptake of TSC in liver–spleen studies ranges from 1.6% (*3*) to 8% (*6*). This finding has been reported in association with a number of diseases, including metastatic carcinomas (*1–3*), malignant lymphomas (*2,3*), infection (*3,4*), histiocytosis X (*5*), amyloidosis (*14*), and mucopolysaccharidosis type II (Hunter) (*6*). In nonreversible progressive diseases, the presence and degree of increased lung uptake correlate with a poor prognosis and usually indicate the terminal phase of the disease (*1–5,14*). In the case of mucopolysaccharidosis type II, increased lung uptake may be present on serial studies for years, although the intensity of lung uptake tends to increase as the disease progresses (*6*). In reversible conditions, such as infection, increased lung uptake resolves on followup liver–spleen studies as the patient's condition improves (*3,4*).

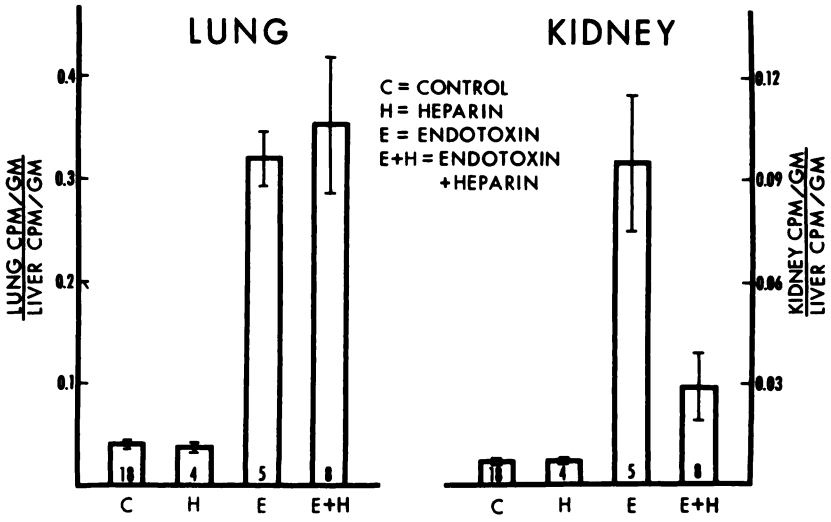

FIG. 3. Mean (± s.e.m.) for lung and kidney uptake of ^{99m}Tc-sulfur colloid in control (C) and experimental animals given 10 mg of intraperitoneal endotoxin (E), with and without heparin (H). Heparin without endotoxin has no effect on colloid uptake. Both lung and kidney uptakes show large response at 10 mg of endotoxin. Heparin does not affect this increased uptake in lungs, but greatly reduces it in kidneys.

The incidence of increased renal uptake of TSC is much less than that of increased lung uptake. Only three cases have been reported during routine liver–spleen imaging, and all three of these patients were in congestive heart failure (*8,9*). However, increased TSC uptake by the kidneys is a common finding in renal transplants undergoing rejection if the imaging is done so that the bone marrow is visualized (*7*).

The mechanism of increased TSC uptake by the lungs and kidneys is not known. In the lungs, TSC macroaggregation and increased phagocytic activity in the pulmonary capillary bed have been proposed as mechanisms. The possibility of macroaggregation after injection has been tested by mixing TSC with heparinized plasma or serum from patients who have had increased lung uptake and then either examining the result microscopically (*1*) or injecting the mixture into animals and quantifying the amount of lung uptake (*5*). The results have been negative, but the use of plasma or serum is an inadequate test if intravascular coagulation plays a part in the macroaggregation.

In the case of increased TSC uptake by the kidneys, macroaggregation is an unlikely cause, since the macroaggregates would only reach the renal capillary bed after passing through the pulmonary capillary bed. Entrapment of the TSC in fibrin deposits has been proposed as a possible mechanism (*7*), and it has been shown that radioiodine-labeled fibrinogen (*15*) and TSC (*7*) accumulate in renal transplants during rejection.

In the present study, relatively large doses of endotoxin were used, but the rat is one of the most endotoxin-tolerant animals (*16*). The uptake of TSC by the lungs increased progressively with increasing doses of endotoxin, but was unaffected by heparin. This finding suggests that the mechanism of increased lung TSC uptake induced by endotoxin is neither entrapment by fibrin deposits nor in vivo macroaggregation involving coagulation. Other possible mechanisms include increased phagocytic activity in the pulmonary capillary bed and adherence of TSC to damaged endothelium. Microcirculation studies have shown that, following the injection of endotoxin, damaged endothelium can first be detected by the progressive adherence of intravenously injected colloidal carbon to its surface and that, with time, the endothelial cells swell and the colloidal carbon appears within the cells, suggesting phagocytosis (*17*).

The increased uptake of TSC by the kidney, although significantly different from control levels at all doses of endotoxin, was neither as marked nor as progressive as that in the case of the lung. Over an endotoxin dose range of 1 μg to 1 mg, heparin had no effect on the increased renal uptake and the considerations with respect to mechanisms in this dose range are similar to those for the lungs. The large increase in TSC uptake by the kidneys at 10 mg of endotoxin and its prevention by heparin suggest that coagulation and fibrin in particular are involved at this dose level. A single large dose of intraperitoneal endotoxin may mimic two smaller doses of intravenous endotoxin and produce a generalized Shwartzman reaction. This reaction results in intravascular coagulation and fibrin deposition; it is most prominent in the vascular bed of the kidneys (*18*) and can be prevented by heparin (*19*).

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