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THE ROUTE OF ABSORPTION OF INTRAPERITONEALLY ADMINISTERED COMPOUNDS[1]

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ABSTRACT

LUKAS, GEORGE, SHIRLEY D. BRINDLE AND PAUL GREENGARD: The route of absorption of intraperitoneally administered compounds. J. Pharmacol. Exp. Ther. **178**: 562–566, 1971. Although the i.p. route is widely used for the administration of compounds to animals, it has not been established whether absorption from the peritoneal cavity occurs through the portal or the systemic circulation. This problem has now been investigated in two species by two experimental approaches. The initial (10 seconds to 5 minutes) rates of appearance of radioactivity in the liver and in the systemic circulation of the rat after the administration of labeled compounds were compared. The substances studied (atropine, caffeine, glucose, glycine and progesterone) represented a variety of physicochemical and biochemical properties. The appearance of radioactivity in the portal vein and in the inferior vena cava of the dog after administration of glucose was also investigated. The results demonstrate that compounds administered i.p. are absorbed primarily through the portal circulation and, therefore, must pass through the liver before reaching other organs.

Absorption of compounds from the peritoneal cavity may entail passage into the portal or into the systemic blood circulation. Although the i.p. route is widely used for the administration of compounds to animals, it has not been established which of these pathways is primarily involved in the absorption process (Yamada, 1960; Horita, 1961; Kruger *et al.*, 1962; Schanker, 1962). This problem has now been investigated in the rat and in the dog by determining the initial (10 seconds to 5 minutes) rates of appearance of radioactivity in the portal and in the systemic circulation after the administration of labeled compounds. The results demonstrate that compounds administered i.p. are absorbed primarily through the portal circulation and, therefore, must pass through the liver before reaching other organs.

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MATERIALS AND METHODS. Atropine-^{3}H (490 mc/mmol, randomly labeled, Nuclear-Chicago Corporation, Des Plaines, Ill.) was obtained as an amorphous solid in the free base form (5.88 mg). It was dissolved in 2 ml of 0.02 N HCl and was diluted with water to 200 ml.

Caffeine-^{3}H (10.1 c/mmol, randomly labeled, Nuclear-Chicago Corporation) was obtained as a solution of 0.096 mg in 1 ml of water. It was diluted with water to 50 ml.

Glucose-6-^{3}H (176 mc/mmol, New England Nuclear Corporation, Boston, Mass.) was obtained as a solution of 1.02 mg in 1 ml of 90% aqueous ethanol. It was diluted with water to 25 ml.

Glycine-2-^{3}H (200 mc/mmol, New England Nuclear Corporation) was obtained as a solution of 0.74 mg in 2 ml of 0.1 N HCl. It was neutralized with 0.5 ml of a 4% aqueous $NaHCO_3$ solution and was diluted with water to 10 ml.

Progesterone-7α-^{3}H (10 c/mmol, New England Nuclear Corporation) was obtained as a solution of 0.031 mg in 1 ml of benzene. The solvent was evaporated at 37°C in a stream of N_2 and the residue was dissolved in 10 ml of propylene glycol.

Rats. Experiments were carried out with adult female Royal Hart rats (180–200 g) under ether anesthesia. The animals were placed, back down, in a decapitator (Harvard Apparatus Company, Inc., Millis, Mass.). Compounds were administered

TABLE 1

Compounds used in the study of i.p. absorption

Compound	Solubility	Charge at pH 7
Atropine	Water	Basic
Caffeine	Water	Nonionic
Glucose	Water	Nonionic
Glycine	Water	Zwitterionic
Progesterone	Lipoid	Nonionic

i.p. or s.c. and at various times afterwards, the animals were divided transversely just above the diaphragm. Blood from the thoracic cavity was collected in heparin-treated beakers. The radioactivity in 0.1-ml aliquots of plasma was determined in a Packard Tri-Carb liquid scintillation spectrometer with Bray's solution (Bray, 1960).

The liver from each animal was removed, rinsed exhaustively with water (or with methanol in the experiments with the water-insoluble progesterone) to remove any contaminating peritoneal fluid, blotted between filter papers, weighed and homogenized with 2 volumes of 0.02 N HCl. Liver radioactivity was determined by counting 0.5-ml aliquots of the homogenates. The observation that slices of liver taken at different depths parallel to the surface contained comparable concentrations of radioactivity indicates that the radioactivity in the liver did not result from contamination by the visceral peritoneal membrane.

Dogs. Two male mongrel dogs were anesthetized with sodium pentobarbital (Nembutal) (35 mg/kg i.v.). The abdominal cavity was opened through a midline incision and the portal vein exposed. A polyethylene catheter (PE 60) was inserted, *via* a distal branch, into the lumen of the portal vein in such a way that samples of blood could be withdrawn without obstructing flow through the vessel. The inferior vena cava was similarly cannulated and the two catheters were exteriorized. Both catheters were fitted with three-way stopcocks and two heparin-treated 10-ml syringes were attached to the free ends of each stopcock. When it was time to take a sample from the inferior vena cava or the portal vein one syringe served to clear the dead space fluid from the catheter and the other (with a turn of the stopcock) to obtain the test sample. At various time intervals after i.p. administration of glucose-6-^{3}H, 2-ml samples of blood were collected simultaneously from the two veins. Plasma radioactivity was assayed as described above.

Treatment of data. All measured values were corrected for quenching by the internal standard technique. Concentrations of radioactive compounds were calculated as microcuries per kilogram of tissue or per liter of plasma and are given as the mean ± standard error. The statistical significance of the differences between groups of data was evaluated according to Student's t test.

RESULTS. The route of absorption of an i.p. administered compound might conceivably depend on its physicochemical and biochemical properties. Therefore, a variety of compounds, listed in table 1, were selected for this study.

Figure 1 shows the results of absorption studies in the rat with radioactive atropine. Atropine was present in the liver at a fairly high concentration within 10 seconds (the earliest time studied) after its administration i.p. A longer time interval was required for the appearance of appreciable quantities of the drug in the systemic blood of these same animals. These data strongly suggest that atropine injected into the peritoneal cavity was absorbed through the portal rather than the systemic circulation. The concentration of atropine in the liver remained significantly higher ($P < .02$) than that in the plasma throughout the five-minute experimental period. In contrast, after s.c. administration of

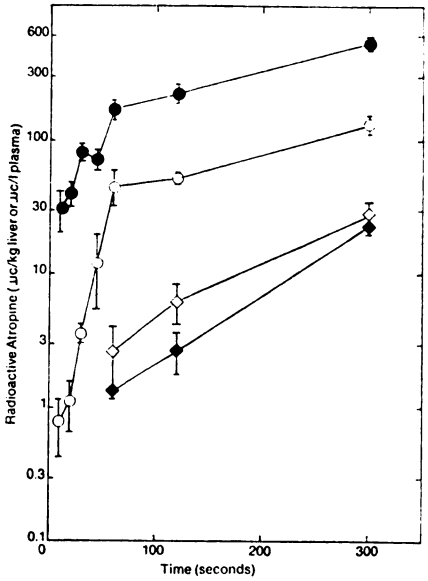

FIG. 1. Radioactive atropine in liver (●——●) and plasma (○——○) after i.p. administration and in liver (◆——◆) and plasma (◇——◇) after s.c. administration of 248.8 μc/kg (147 μg/kg) to rats. Each point represents the mean value ± standard error for seven animals (i.p.) or three animals (s.c.).

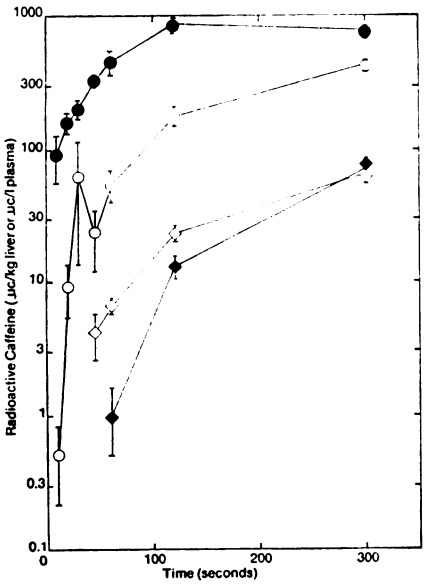

FIG. 2. Radioactive caffeine in liver (●——●) and plasma (○——○) after i.p. administration and in liver (◆——◆) and plasma (◇——◇) after s.c. administration of 275.6 μc/kg (5.3 μg/kg) to rats. Each point represents the mean value ± standard error for six animals (i.p.) or three animals (s.c.).

TABLE 2

Liver/plasma ratios of various compounds after i.p. and s.c. administration in the rat

Compound	Route	Liver/Plasma Ratio at:						
		10 sec	20 sec	30 sec	45 sec	60 sec	120 sec	300 sec
Atropine	i.p.	39.1	36.2	22.4	5.8	3.7	4.2	4.0
Caffeine	i.p.	177.0	17.0	3.2	14.2	7.6	4.9	1.8
Glucose	i.p.	77.0	105.1	17.6	10.6	2.7	1.3	1.4
Glycine	i.p.	67.5	12.3	10.8	4.2	2.6	3.3	2.7
Progesterone	i.p.	56.4	120.0	60.6	134.5	13.1	11.3	
Atropine	s.c.					0.50	0.43	0.83
Caffeine	s.c.					0.15	0.58	1.14
Glucose	s.c.							0.78
Glycine	s.c.					0.17	0.24	0.68

atropine, the concentration of the drug in plasma was greater than that in liver, although the difference was not significant ($P > .05$). Higher levels in plasma than in liver would be expected after s.c. injection, since this route obviously excludes the possibility of portal absorption. The fact that, after s.c. administration, atropine could not be detected in either liver or plasma at times earlier than 60 seconds (see fig. 1) indicates that absorption was relatively slow after the s.c. route of injection.

Results similar to those observed with atropine were seen with each of the other four compounds studied, namely caffeine (fig. 2), glucose, glycine and progesterone.

In table 2, the liver/plasma concentration ratio after i.p. administration is compared with that after s.c. administration. The data demonstrate clearly that, after i.p. administration, the ratio is very high initially and decreases rapidly towards unity and that, after s.c. administration, the ratio is very low initially and increases gradually toward unity.

The effect of dosage on absorption was studied with caffeine. When 275.6 μc/kg of radioactive caffeine were administered in a dose of 5.3 mg/kg, *i.e.*, in an amount 1000 times that used in the experiments shown in figure 2, the rate of appearance of radioactivity in liver and plasma was similar to that observed at the lower dosage.

The effect of saline vehicle *vs.* water vehicle on absorption was studied with atropine. Administration of atropine in 0.9% NaCl gave results similar to those obtained after administration of atropine in water.

The distribution of radioactivity was determined in five rats 30 seconds after i.p. administration of 430 μg/kg of atropine. Total recovery of the administered radioactivity in the animals averaged 105.7 ± 2.9%. The amount of radioactivity in the liver corresponded to about 4% of the radioactivity administered, whereas other tissues contained only negligible amounts of radioactivity at that time. The remainder of the radioactivity (an apparent 100.3 ± 5% of the dose) was still in the peritoneal cavity and was recovered from there by repeated rinsing.

Figure 3 shows the concentration of radioactivity in the plasma obtained from the portal vein and from the inferior vena cava of a dog at various times after i.p. administration of labeled glucose. The radioactivity appeared in the portal vein almost immediately after administration. A much longer period was required to detect radioactivity in the inferior vena cava. Thus, 45 to 60 seconds after the injection of the glucose, the amount of radioactivity in the portal blood was approximately 3 μc/l, whereas that in the blood from the inferior vena cava was still undetectable (<0.3 μc/l). Most of the radioactivity which did finally appear in the

inferior vena cava presumably passed first through the liver, the heart and the arteries. Similar results were obtained in an experiment with a second dog.

Kountz *et al.* (1964) have measured the venous flow rates in various blood vessels of the dog. They have found that, in dogs weighing approximately 25 kg, the average rates of flow in milliliters per minute were as follows: portal vein, 586; and inferior vena cava, 1032. Thus, the possibility is ruled out that the large difference in radioactivity in the two vessels was due to different degrees of dilution (resulting from different flow rates) of the glucose absorbed from the peritoneal cavity. The observed difference in the amounts of radioactivity therefore constitutes valid evidence of the differential rates of absorption of glucose by the two routes.

Discussion. Compounds absorbed from i.m. or s.c. sites enter the systemic circulation through the superior or the inferior vena cava. The heart distributes the compounds into the entire body through the arteries, and only 28% of the cardiac output reaches the liver (Gaines *et al.*, 1966), the major site of detoxication of many exogenous substances. Thus, large portions of unaltered compounds are able to reach various organs. However, absorption from i.m. or s.c. sites is relatively slow.

Intraperitoneal administration leads to a different situation. In man, and probably in many other mammalian species, the total surface of the peritoneal membrane is extremely large, approximating that of the skin (Sweet and Miller, 1966). When i.p. administered compounds are exposed to this large membrane surface, one would expect rapid absorption to occur. Indeed, in many instances the pharmacologic or toxic effects elicited by i.v. injected drugs can be approximated more closely by i.p. than by i.m. or s.c. administration.

The visceral peritoneum (the membrane covering most abdominal organs), the mesentery and the omentum drain into the portal system of veins, whereas the parietal peritoneum (the membrane lining the abdominal wall) as well as the lymphatics drain into the systemic circulation (Lockhart *et al.*, 1960; Romanes, 1964). Therefore, the rapid absorption after i.p. administration could conceivably follow two pathways, the first entering the liver and the second

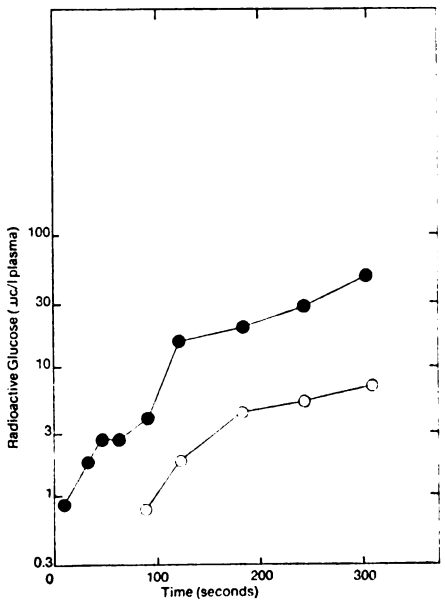

Fig. 3. Radioactive glucose in the portal vein (●——●) and in the inferior vena cava (○——○) of a dog after i.p. administration of 20 μc/kg (20.4 μg/kg).

bypassing it. However, the slow rate of lymph flow normally results in relatively little lymphatic absorption (De Marco and Levine, 1969). Furthermore, the surface of the membranes draining into the portal vein is so much larger than that of the parietal peritoneum that absorption would be expected to occur predominantly through the portal pathway.

The consequence of portal absorption is that compounds must pass through the liver before they reach the heart. Consequently, they should be found in the liver before they can be detected in systemic blood. However, any comparison of concentration differences in various tissues or fluids more than a few minutes after i.p. administration provides little direct information on the route of absorption because the compound is rapidly distributed into the entire blood volume. Rather, the initial rate of appearance of the compound in portal and systemic blood or in tissues supplied by such blood should be compared. The present results demonstrate that all compounds studied appear in the liver 10 to 20 seconds after i.p. administration and that there is a short but significant time lag before they can be detected in systemic blood. In contrast, s.c. administration leads to a slower rate of ab-

sorption and to the appearance of the compounds in systemic blood prior to their appearance in the liver. Cannulation of the portal vein and the inferior vena cava of the dogs and simultaneous sampling of the blood flowing in those veins corroborate our conclusions from the absorption studies in the rat. Thus, our experimental findings are in good agreement with what might be predicted on theoretical grounds from anatomical considerations.

One would predict from the present findings that a drug might be metabolized very differently depending on whether it is administered i.p. or by some other parenteral route. Indeed, there are numerous examples in the literature of drugs that are less effective after i.p. administation than when given by other parenteral routes. Such examples include reserpine (Westermann, 1962; Bhagat, 1964; Rosecrans, 1967; Mueller and Shideman, 1968), dopamine, tryptamine and serotonin (Westermann, 1962), phenelzine and phenipramine (Horita, 1961), diisopropyl fluorophosphate and paraoxon (Westermann, 1962; Ramachandran, 1966; Natoff, 1967). Conversely, parathion is more toxic by the i.p. than by the s.c. route (Holtz and Westermann, 1959; Gaines *et al.*, 1966), in keeping with the fact that it is converted by mammalian liver to the more potent paraoxon. These and other examples of the influence of the route of administration on drug effect can be explained by the present demonstration that i.p. administered compounds must pass through the liver before reaching other organs.

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