POSSIBLE USE OF FERROMAGNETIC MATERIALS FOR TARGETED DRUG TRANSPORT

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Various aspects of the problem of targeted drug transport in the body have been widely discussed in recent years. Targeted transport systems are mainly constructed by binding a drug (or a "microcontainer" containing the drug) with a transporting substance, which has affinity for components of the target organ [2]. The principle of magnetic drug transport, which has been developed most recently [5], differs in that a finely dispersed ferromagnetic material, with no specific affinity for any particular tissue component, but capable of retention in a particular region of the body through the action of an external magnetic field, is used as the transporting component. Magnetic drug transport systems require no transporting substance that is specific for a target organ and they enable drugs to be concentrated on the basis of the same carrier in a finite volume in virtually any part of the body.

Magnetic carriers for drugs must be reliably held by a magnetic field in the blood stream and must be small enough to prevent capillary embolism. These two demands are to some extent conflicting: Magnetic properties of particles of the carrier, responsible for its ability to be retained by a magnetic field in the lumen of a blood vessel, are improved by an increase in the content of ferromagnetic material in the carrier and an increase in its particle size. However, an increase in the content of ferromagnetic material leads to a decrease in concentration of the drug in the carrier, and an increase in particle size increases the risk of capillary embolism. For instance, when particles measuring 3-5 μm are used about 80% of them are retained in rabbit lung capillaries [5]. The degree of dispersion of the ferromagnetic material used also is important, for large particles, not undergoing biological decomposition, can lead to the development of definite side effects.

In the present investigation on model systems the ability of magnetic carriers of different types to be retained by an external magnetic field in a large blood vessel in an experimental animal (the marginal vein of the rabbit's ear) was studied. All carriers were made from nontoxic materials.

EXPERIMENTAL METHOD

A colloidal solution of Fe_3O_4 was obtained by the method described previously [4]. Specimens with a content of dry substance of 15-50% and an Fe_3O_4 content of 3-10% respectively were obtained.

Magnetic microspheres were obtained from partially oxidized Sephadex G-25 (fraction with diameter <10 μm) were generally provided by M. Ya. Gen (Institute of Chemical Physics, Academy of Sciences of the USSR).

The surface of the iron particles was modified with (3-aminopropyl)triethoxysilane by the method in [6]. Aldehyde-dextran was covalently bound with the resulting preparation [1] with a degree of oxidation of 20%. Binding was carried out at pH 9.0 for 12 h. Binding of [^{131}I]albumin with the magnetic microspheres and modified iron was carried out at pH 9.0 for 6 h. Colloidal Fe_3O_4 particles were activated for binding of [^{75}Se]methionine with an excess of BrCN at pH 10.0 for 10 min, frozen in liquid nitrogen, and freeze-dried. The product was treated with a solution of [^{75}Se]methionine at pH 8.0 for 18-20 h at 20°C and then for 20 min at 90-100°C. Unbounded methionine was removed by centrifugation at 40,000g.

Experiments in vivo were carried out on chinchilla rabbits. Suspensions of ^{131}I-labeled carriers were injected in a volume of 0.1-0.2 ml (1000-1100 counts/sec) and of ^{75}Se-labeled carriers in a volume of up to 0.15 ml

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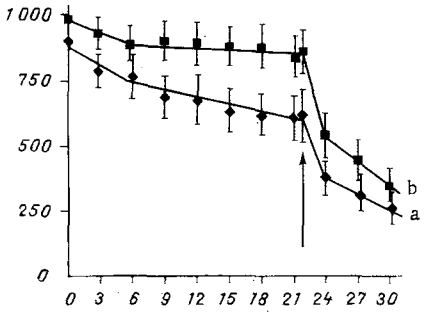

Fig. 1

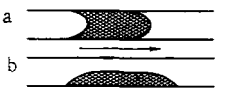

Fig. 2

Fig. 1. Retention of magnetic Sephadex (a) and of preparation of iron particles 10 nm in diameter (b) in marginal vein of rabbit ear by a magnetic field. Abscissa, time (in min); ordinate, radioactivity (in counts/sec, allowing for efficiency of counter). Arrow indicates removal of magnet.

Fig. 2. Movement of drop of colloidal solution of Fe_3O_4 with increased viscosity in blood vessel in absence of magnetic field (a) and its stabilization and retention by a magnetic field (b). Arrow shows direction of blood flow.

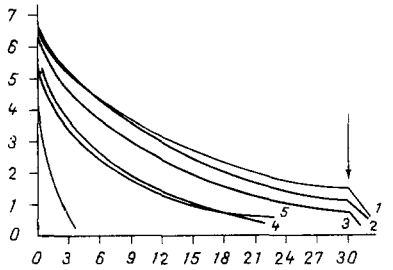

Fig. 3. Retention of colloidal solution of Fe_3O_4 (50% of dry substance), stabilized by magnetic field, in marginal vein of rabbit's ear. 1-3) Radioactive label ([^{75}Se]methionine) covalently bound with surface of colloidal particles; 4, 5) [^{75}Se]methionine dissolved in magnetic colloid without covalent binding; 6) control (radioactive label bound covalently with surface of particles, magnetic field absent). Ordinate, radioactivity (in thousands of counts/sec). Remainder of legend as to Fig. 1.

(up to 6000 counts/sec). The preparations were injected into the marginal vein of the rabbit's ear in its upper part. A cylindrical samarium-cobalt magnet was placed in the lower part of the ear (5-7 cm from the site of injection), giving H = 1.5 kG, ΔH = 0.5 kG/cm in the region of the vein. On the other side of the ear opposite the magnet a detector of an RD-1600 gamma-counter (Finland) was mounted. Preliminary tests showed that with this arrangement the magnet did not affect counting efficiency. Control experiments were conducted under the same conditions without the magnet.

EXPERIMENTAL RESULTS

The results are evidence that granules of magnetic Sephadex are well retained in the lumen of a blood vessel by the action of a magnetic field (Fig. 1a). The same also applies to preparations made from iron particles 10 nm in diameter (Fig. 1b), aggregating in a magnetic field, as was shown by experiments in vitro, up to a diameter of 1 μm or more. After removal of the magnet, particles of both types were quickly washed out of the vessel wall by the blood flow and were irreversibly dispersed over the animal's body. Large magnetic par-

ticles are thus retained sufficiently reliably by a magnetic field in the lumen of a large vessel, but in the absence of the magnetic field they are quickly eliminated from the circulation. Particles of colloidal size (Fe_3O_4, diameter 50 nm) pass freely through the capillary network, but a decrease in size of the particles has a very adverse effect on the relations between their magnetic and hydrodynamic properties, and individual particles of this size are no longer held up by the magnetic field in the blood stream. However, they can be combined into a relatively stable aggregate, the dimensions of which are comparable with those of the large particles used previously.

The behavior of a concentrated magnetic colloid with increased viscosity in the marginal vein of the rabbit's ear was then studied. This colloid, when injected into the vessel, moved along it in a compact "drop" and was distributed in the zone of action of the magnetic field on the surface of the vessel wall (Fig. 2), from which it was subsequently gradually washed out by the blood flow as a result of disintegration into the initial particles. Wash-out curves are illustrated in Fig. 3. Retention not only of the particles, but also of the solution present in the spaces between them was observed, as was demonstrated by a similar experiment using [^{75}Se]methionine label, present in a colloidal solution of magnetite in the free state. In the absence of a magnetic field the drop of magnetic colloid passed readily along the vein (Fig. 3). Activity in the rabbit's opposite ear, not exposed to the action of the magnetic field (control) remained at 170-250 counts/sec throughout the experiment. An aggregate which is unstable in the absence of a magnetic field can thus be stabilized by a magnetic field and retained in a blood vessel for a desired time.

It can be concluded from these results that carriers for targeted magnetic transport of drugs can be constructed both on the basis of relatively large particles containing ferromagnetic material, and on the principle of binding particles of ferromagnetic material of colloidal size into more or less stable aggregates. The drug preparations in this case can be included in the composition of the aqueous phase and incorporated into the structure of the particle or aggregate, or bound chemically with the structural base of the aggregates. The principles underlying the obtaining of ferromagnetic material of colloidal dimensions and modification of its surface for various purposes have already been sufficiently worked out [3] and they can be applied to the synthesis of magnetic carriers for targeted drug transport.

In our opinion two promising methods for the use of "magnetic" drug transport can be proposed: 1) concentration of a drug circulating in the blood stream in large vessels and capillaries in a particular part of the body; 2) retention of a drug injected into the region of action of the magnetic field in a concentrated state. The type of carrier and its concrete properties must correspond to the method of its administration and the type of drug carried by it.

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