Review Letter

ALBUMIN AS THE MAJOR METAL TRANSPORT AGENT IN BLOOD

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Certain serum proteins are considered as metal transport agents merely because they bind metal tightly, e.g., ceruloplasmin (which clutches copper). In some cases such an assigned role is suspect, however, since the metal, once attached, cannot readily be released. One would expect speedy uptake and delivery from a carrier. There is, however, present in serum an agent that fills this requirement admirably – serum albumin. This protein, present in the serum in larger amounts than any other protein, and of relatively low mol. wt (69 000) is usually assigned the role of maintaining colloidal osmotic pressure. Unique in its affinity to bind organic molecules such as dyes, L-tryptophan, fatty acids, etc., this molecule has also the capacity to act as a scavenger. In addition, it displays unusual attractive forces toward metal ions.

We have observed that manganous ion is cleared from plasma with extreme rapidity in the animal and only traces of the ion remain in the plasma seconds after its injection into the jugular vein of rabbits. How, then, is the Mn^{2+} carried in the blood stream? Foradori et al. [1] claim that it is associated with the β_1-globulin fraction, which they baptized 'transmanganin'. Pesendorfer et al. [2] suggested that it is bound to transferrin (the iron carrier) only. In our opinion, neither of these two groups of workers is correct. We observed that Mn^{2+} added to human or rabbit plasma in vitro combines selectively with the albumin fraction. When traces of $^{54}MnCl_2$ are mixed with serum and eluted from a Sephadex G-100 column the emergence of radioactivity coincides with that of albumin. Zn^{2+}, Ni^{2+} and Co^{2+} can compete effectively for the sites of the protein that bind manganous ion [3]. Indeed, albumin accounts for a large amount of Zn^{2+} binding by serum [4]. The Mn–albumin complex releases the metal upon ammonium sulfate fractionation while the Co–albumin complex does not. Hence, traces of $^{60}CoCl_2$ can be mixed with serum and similarly eluted and the albumin peak can be further purified by fractionation with ammonium sulfate. Only the albumin fraction shows high specific radioactivity. (When mixed with antibody to serum albumin, all $^{60}Co^{2+}$ radioactivity appears in the formed precipitin) [5]. For Co^{2+}–albumin, a Scatchard plot yields a curve that may be resolved for two classes of sites: One, where $n_1 = 2$ and $K_1 = 6.5 \times 10^3$, the other where $n_2 = 23$ and $K_2 = 1.6 \times 10^2$ [5]. In the case of Mn^{2+}–albumin, $n_1 = 1$ and $K_1 = 2.4 \times 10^4$ and $n_2 = 5$ and $K_2 = 0.5 \times 10^3$ [3].

Careful chromatography of the ^{60}Co-labeled serum (obtained by injecting ^{60}Co into the jugular vein of rabbits and bled after 20 min) employing Sephadex G-200 suggested to us that another carrier (of approx. 110 000 daltons) besides albumin might exist, albeit in much smaller amounts. This 'second carrier' when subjected to preparatory electrophoresis on 7.5% standard pore size acrylamide gel column migrates at a different rate than albumin but reacts exactly like albumin upon immunoelectrophoretic testing with antibody to albumin. That is, ^{60}Co introduced into the blood circulation of rabbits is bound mainly by an albumin-monomer and to a smaller extent by an albumin-dimer. The dimer cannot be converted to monomer by exposure to a reducing agent [6]. We believe that we have evidence that the non-convertible dimer species of albumin does occur in plasma normally in small amounts.

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