Structure of Human Serum Albumin

We have reported the crystal structure of human serum albumin (HSA) at a resolution of 6.0 Å by the method of multiple isomorphous replacement (1). A different quaternary arrangement of the six subdomains than that reported at low resolution has become apparent at 4 Å resolution (2). The change in the electron density involves connecting the previously labeled amino- and carboxyl-terminal helices through the symmetry operation (Y, X, 1-Z) together with a concomitant formation of new termini (Fig. 1A). This connection was not revealed in the electron density at 6.0 Å mainly because of series termination effects that are usually more pronounced at lower resolution. The attachment of the tail (subdomains IIIB, IIIA, and IIIB) to the head (subdomains IA, IB, and IIA) of the molecule differs from that originally proposed and requires relabeling of certain subdomains (Fig. 1B). Further evidence supports this quaternary arrangement. The subdomains assume a heart shape, which agrees with the dark-field electron micrograph images of the genetically related human and bovine α-fetoproteins (AFP) (3). Domains I, II, and III may be superimposed (Fig. 1C), which is consistent with the homology within the amino acid sequence. The major ligand binding regions are identified within subdomains IIA (previously labeled IA) and IIIA, which is consistent with the competitive drug displacement experiments (4).

Fig. 1. (A) Illustration of the close packing of the HSA molecules along columns in the (a/2, b/2) direction viewed perpendicular to the c-axis. The individual HSA molecules are shown in yellow and blue. An outline of the quaternary arrangement of the subdomains reported at 6.0 Å is illustrated. (B) Stereoview of a simplified tracing (not α-carbons) representing the convolution of electron density within a molecule of HSA based on the interpretation of the 4.0 Å electron density. The subdomains from left to right are IIIB, IIIA, IIB, IIIB, IIIB, and IIA. The difference density illustrating the major binding location for ibuprofen within IIIA is shown. The width of the molecule from the amino- to the carboxyl-terminal domain is ~82 Å, and the maximum dimensions of the molecule from the apex of the heart to the amino- and carboxyl-terminal domains are approximately 83 and 70 Å, respectively. The depth of the molecule is roughly 30 Å. (C) A stereoview of independent tracings of the electron density within domains II (yellow) and III (blue) superimposed to illustrate the structural homology.
Deprenyl and the Progression of Parkinson’s Disease

In the absence of a comparable assessment of the two groups it is not justifiable to conclude that deprenyl retards the progression of Parkinson’s disease, however attractive this possibility is from a theoretical standpoint.

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REFERENCES

Response: Both Sudarsky and Friedhoff raise the important issue of whether or not a symptomatic effect of deprenyl, rather than a slowing of the disease process, could account for the results of our study. As pointed out by Sudarsky, since deprenyl is an inhibitor of monoamine oxidase, it might increase the synaptic persistence of endogenously released dopamine, thereby leading to some degree of symptomatic improvement. To assess this possibility, two steps were taken in our study. First, patients were carefully reevaluated 1 month after the study drug was started to see if they had improved compared to their baseline evaluation (this would have indicated a symptomatic effect). At this 1-month “wash-in” evaluation, no symptomatic improvement was observed. Even more important, when patients reached end point (that is, the need for l-dopa therapy), the study drug was stopped for an entire month (“wash-out”), after which they were carefully reevaluated. Had deprenyl been providing a symptomatic effect later in the course of treatment, one would have expected deterioration, and none was observed. While it could be argued that the wash-out period might have been too short, we are unaware of any anti-parkinsonian drugs that provide an unmitting symptomatic effect for as long as 1 month after they are discontinued.

Friedhoff raises the interesting point that...
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