Lipids in brain tumors

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Relatively few studies have been performed on lipids of brain tumors. The pioneer study of Brante\(^2\) showed that brain tumors in general have a lipid content lower than normal brain and contain esterified cholesterol, which is absent from normal adult brain tissue. Phospholipids are also present in small amounts.\(^3\) The presence in brain tumors of free fatty acids, triglycerides, and cholesterol esters, and certain lipids absent from normal brain, has been detected in our laboratory.\(^7\) Azarnoff and coworkers\(^1\) demonstrated that human glioblastomas, astrocytomas, and other intracranial tumors are capable of incorporating \(^1^4\)C-acetate into cholesterol in contrast with normal brain tissue which is known to synthesize cholesterol only to a limited extent. Paoletti, et al.\(^9\) demonstrated that the Zimmerman ependymoma can convert various precursors into cholesterol much more efficiently than normal brain of the same animals.

A typical feature of brain tumors is the presence of desmosterol (24-dehydrocholesterol), which differs from cholesterol only by an extra double bond in the lateral chain. This sterol is the last precursor of cholesterol in one of its biosynthetic possible routes. However, in the liver desmosterol does not accumulate, despite high levels of cholesterol synthesis; in brain during maturation, however, large amounts of desmosterol are found as well as in human glial tumors.\(^4,11\)

In recent experiments, large quantities of desmosterol were detected in brain tumors of the rat induced in our laboratories by nitrosourea derivatives according to Druckrey, et al.\(^3\) In ethylnitrosourea-induced oligodendrogliomas, desmosterol accounted for 10% to 15% of the total sterols.\(^12\) Desmosterol was considerably higher in some neurinomas, which is not surprising since these tumors are quite malignant and fast-growing when compared with human neurinomas. The presence of consistent pools of desmosterol in brain tumors is connected with both the high sterol biosynthetic rate and with a blockade of desmosterol transformation into cholesterol.

The ability of human brain tumors to synthesize both desmosterol and cholesterol from mevalonate was checked in vitro and compared with that of normal brain tissue. The results\(^6\) indicate that the incorporation of mevalonate in the unsaponifiable lipid fraction is very low for the slow-growing neurinomas, which do not synthesize cholesterol, while the most notable difference between glial tumors and normal brain is at the sterol level only. In fact, normal brain incorporated less radioactivity into sterols, and most of it was detected in cholesterol. The reverse was found in glial tumors, which showed a high sterol synthesis, and the ratio between synthesized desmosterol/cholesterol was higher in the glioblastomas than in other less malignant gliomas.

Comparable results were obtained by incubating in vitro an experimental ependymoblastoma, which, after 1 hour of incubation, contained a twofold increase of radioactivity in desmosterol than in cholesterol. Desmosterol accumulation in brain tumors may be magnified by Triparanol administration. This drug, inhibiting desmosterol reductase, induces accumulation of desmosterol in blood but not in mature brain. This was demonstrated in mice with experimental
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brain tumors, in which doses of Triparanol, not affecting brain sterols, induced accumulation of desmosterol in the tumors. Similar results were obtained in patients with brain tumors.

It is likely that desmosterol found in glioblastomas is not derived from blood, and this is supported by experiments showing that blood sterols and tumor sterols represent two different pools that do not equilibrate: first of all, desmosterol in human brain tumors never reaches the concentrations in blood. Moreover, biosynthetic experiments in vivo before and after Triparanol treatment show a completely different distribution of radioactivity in the desmosterol of blood and brain tumor.

These data demonstrate a sterol difference between plasma and glioblastoma and between glioblastoma and brain, and constitute the biochemical rationale for a sterol analysis of the cerebrospinal fluid (CSF) for the diagnosis of brain tumors. This method was proposed by Paoletti, et al., and is based on a short Triparanol treatment in patients suspected of having a brain tumor, with subsequent analysis of the CSF sterols. Desmosterol, which is not detectable in normal CSF and hard to detect in untreated tumor patients, becomes significantly higher (after Triparanol treatment) when a brain tumor is present, giving a correct diagnosis in 80% of the patients.

References

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