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USE OF MICRODIALYSIS TO STUDY DRUG DISTRIBUTION OF ANTIVIRAL COMPOUNDS

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Microdialysis is a method by which it is possible to sample the extracellular space of virtually any organ in the body, in experimental animals and in man. Samples can be obtained as 5 - 60 min (or more) fractions for several days without disturbance of fluid and electrolyte balance. A unique property is the possibility to follow, e.g. brain extracellular concentrations in experimental animals for long periods of time in one and the same animal. This presentation reviews the method with emphasis on application to antiviral drugs. With microdialysis samples are obtained from the unbound fraction of drug in the extracellular fluid and therefore provides an estimate of how much drug is available to the cells for uptake and subsequent metabolism. The information thus obtained is comparable to the medium concentration in in vitro studies of antiviral effects in cell culture systems. In this sense microdialysis can be said to bridge, at least partially, the information gap between in vitro and in vivo studies. We have applied the method to study the distribution to the brain of several antiviral compounds directed against herpes virus and HIV. We have shown in rats that acyclovir and zidovudine enters the brain to such an extent that the concentration is 20 - 40 % of free plasma concentrations. On the other hand, ddC could not be detected in brain extracellular fluid and, with the detection limit of the assay, did not reach concentrations above 10 % of the plasma concentration, possibly much lower. Several new compounds, some of which are in clinical trials, have been investigated and 3'-fluorothymidine (alovudine) has been studied in special detail. In rats and monkeys this drug enters the brain to the same extent as zidovudine. A detailed study of the mechanism of maintenance of the blood brain barrier concentration gradient suggests that the flow of cerebrospinal fluid and, possibly, active transport out from the brain are the main causes.