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Review

Cerebral microdialysis in glioma studies, from theory to application

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ABSTRACT

Despite recent advances in the treatment of solid tumors, there are few effective treatments for malignant gliomas due to the infiltrative nature, and the protective shield of blood–brain barrier or blood–tumor barriers that restrict the passage of chemotherapy drugs into the brain. Imaging techniques, such as PET and MRI, have allowed the assessment of tumor function in vivo, but they are indirect measures of activity and do not easily allow continuous repeated evaluations. Because the biology of glioma on a cellular and molecular level is fairly unknown, especially in relation to various treatments, the development of novel therapeutic approaches to this devastating condition requires a strong need for a deeper understanding of the tumor's pathophysiology and biochemistry. Cerebral microdialysis, a probe-based sampling technique, allows a discrete volume of the brain to be sampled for neurochemical analysis of neurotransmitters, metabolites, biomarkers, and chemotherapy drugs, which has been employed in studying brain tumors, and is significant for improving the treatment of glioma. In this review, the current concepts of cerebral microdialysis for glioma are elucidated, with a special emphasis on its application to neurochemistry and pharmacokinetic studies.

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1. Introduction

Gliomas account for the vast majority of adult malignant brain tumors and are typically divided into four histopathologic grades based on the degree of malignancy. High-grade gliomas (HGGs) account for 60–75% of all gliomas, and include World Health Organization (WHO) grade III anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), mixed anaplastic oligoastrocytoma (AOA) and grade IV glioblastoma multiforme (GBM) [1]. These tumors may develop at all ages, while the peak incidence is in the fifth and sixth decades of life [2]. Surgical resection can greatly reduce tumor bulk; however, complete excision is virtually impossible due to the infiltrative nature of these tumors. As the blood–brain barrier (BBB) acts as a protective shield which supplies brain tissue with nutrients and restricts the passage of foreign substances into the brain, chemotherapy drug delivery to the brain has been constrained due to the existence of the protective BBB. Therefore, although adjuvant radiotherapy and chemotherapy partly improves survival, death occurs inevitably from either recurrent or progressive disease [3]. For example, GBM is the most common primary intracranial neoplasm in adults. Despite multimodal therapy (surgery, radiotherapy and chemotherapy), most of these patients die within 18 months of diagnosis [4,5].

Local invasion is the hallmark of malignant gliomas and is the major cause of recurrence and morbidity. Unlike most other tumors that metastasize to distant organs via the lymphatic and vascular systems, malignant glioma very rarely metastasizes outside the central nervous system (CNS) [1,6]. In this sense, malignant glioma may be regarded as a "local" tumor. However, surgical resection is rarely curative because glioma cells diffusely invade and permeate into the surrounding brain parenchyma and may even cross the midline to the contralateral brain (Fig. 1) [7,8]. The tumor marginal region exhibits increased angiogenesis, and tumor cells in this region are more migratory and resistant to apoptosis, which contributes to treatment resistance and relapse [9]. More extensive resection can eliminate more tumor cells and may thereby enhance the efficacy of subsequent adjuvant therapies and enhance the survival benefit [10,11]. However, increasing impairment of neurological function is a major concern, resulting in tradeoffs between the efficacy of surgery and the quality of patients' lives.

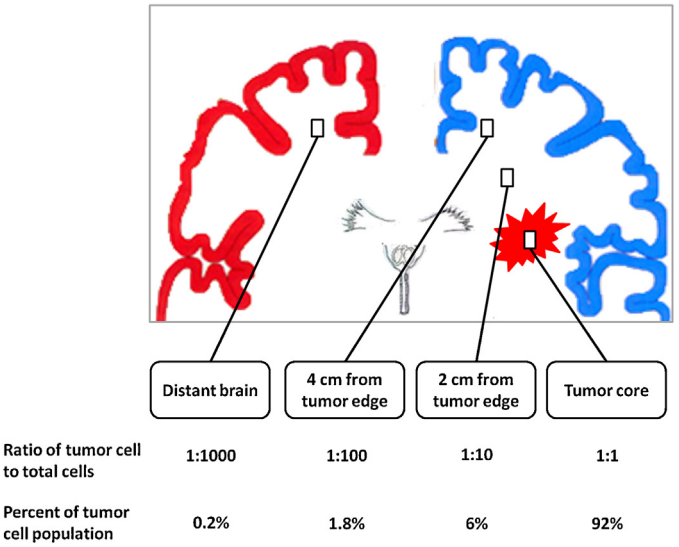

Fig. 1. The pathological model for glioma local invasion. The glioma cells migrate along preexisting brain structures. As a consequence of such extended tissue invasion, surgical resection is usually non-curative and followed by cell survival and regrowth from invasion zones beyond the resection margins.

On the other hand, as gliomas are very invasive, tumor cells such as GBM cells extend at least as far as areas of T2-weighted abnormality on magnetic resonance imaging (MRI) [12,13]. Tumors frequently recur close to the resection margin, which is attributed to the increased tumor cell density along the margin. Traditionally, biochemical studies of gliomas have been limited to animal models [14] and in vitro studies [15]. Imaging techniques such as positron emission tomography (PET) and MRI have allowed the assessment of tumor function in vivo [16–19], but they are indirect measures of activity and do not easily allow repeated evaluation over an extended time-course. As a result, the biology of malignant glioma on a cellular and molecular level is fairly unknown, especially in relation to various treatments [20]. In this case, the development of novel therapeutic approaches to this devastating condition requires a strong need for deeper understanding of the tumor's pathophysiology and biochemistry, which is significant for improving the treatment of glioma.

Cerebral microdialysis is an effective method with which to monitor CNS anticancer drug disposition, basic pathophysiologic metabolism, bioactive compounds and the changes in neurotransmitters in the brain. The method provides a unique opportunity to allow the simultaneous determination of unbound concentrations of drugs at several tissues and to directly and continuously measure glioma biochemistry. This approach provides advantages over other sampling methods (e.g., whole tissue homogenization) including sampling from discrete anatomic compartments such as the brain extracellular fluid (ECF) or ventricular cerebrospinal fluid [21], sampling from normal brain or brain tumor tissue, and the acquisition of unbound or pharmacologically active drug moieties. Therefore, microdialysis is an attractive methodology and has been employed in studying anticancer drug penetration within brain tumors, particularly in the case of HGGs [22–25]. By sampling multiple sites in the same tumor, the variability of neurochemical biomarkers or PK features of an antineoplastic drug can be estimated. Moreover, by inserting catheters at the macroscopic tumor margin rather than the tumor core, researchers are likely to be sampling from more highly invasive tumor tissue because a distinct "invasive" subpopulation of glioma cells is apparent at the periphery of tumors [26].

In the following review, a comprehensive overview of the use of cerebral microdialysis for studies in glioma is provided with a special emphasis on its application to neurochemistry and pharmacokinetic studies.

2. Cerebral microdialysis

2.1. Principles of cerebral microdialysis

The cerebral microdialysis system consists of a stereotaxic apparatus, a probe, a pump and vials in which the perfusate is collected. The system can be connected to an automated sampler/collector or to online (or even online bedside) analysis, and small, portable pumps for continuous use have been developed.

Briefly, the basic principle of microdialysis is to mimic the function of a capillary blood vessel by perfusing a thin dialysis probe with physiological fluid after inserting it into the tissue of interest by means of a guide cannula. The probe containing a dialysis membrane with a specific molecular weight cutoff is implanted in the physiological region of interest. The continuous transfer of soluble molecules from the ECF into the probe occurs by means of a semipermeable membrane covering the tip of the probe. The driving force for analyte movement is the concentration gradient established between two compartments, the interstitium and the probe. Small molecules in the ECF that are not present in the perfusate diffuse across the membrane based on their concentration