Evento	Salão UFRGS 2018: SIC - XXX SALÃO DE INICIAÇÃO CIENTÍFICA DA UFRGS
Ano	2018
Local	Campus do Vale - UFRGS
Título	Pharmacological GLT-1 downregulation impacts on [18F]FDG PET signal: potential astrocytic role
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Pharmacological GLT-1 downregulation impacts on [^{18}F]FDG PET signal: potential astrocytic role

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Introduction and Objective: The positron emission tomography scan using the radiopharmaceutical [18F] Fluorodeoxyglucose ([18F] FDG-PET) allows the determination of the tissue glucose consumption rate and its topographic location. This technique has become one of the most important tools in the investigation of the encephalon, with applications in both research and diagnosis of various cerebral and psychiatric disorders. Since its inception, 40 years ago, this test has its results in the brain interpreted as a direct product of neuronal activity, neglecting the contribution of glial cells, although strong evidence points to an important contribution of astrocytes in cerebral glucose metabolism. In this way, we used clozapine to pharmacologically down-regulate GLT-1, the main trigger to glucose uptake in astrocytes, to investigate the potential participation of these cells on glucose brain metabolism and [18F]FDG-PET results.

Methods: Adult male Wistar rats received clozapine in the drinking water for six weeks as a strategy for reducing GLT-1. *In vivo* glucose brain metabolism was longitudinally accessed using [18F]FDG microPET before and after the treatment. Cortical immunocontent and expression of glutamate transporters GLT-1 and GLAST were assessed. Moreover, the cortex was also used for preparing an adult astrocytic culture, which was analyzed for [3H]D-Aspartate and [3H]2-deoxyglucose uptake.

Results: The clozapine treatment significantly reduced [18F]FDG metabolism specifically in the cortex of adult rats. The immunocontent and expression of the glutamate transporter GLT-1 were also significantly reduced in the same region. A similar trend was seen in the cortical adult primary astrocytic culture, with a reduction tendency of GLT-1 density, D-aspartate uptake and 2-Deoxyglucose uptake.

Conclusion: This work provides the first PET evidence that downregulation of the astrocytic glutamate transporter GLT-1 reduces [18F]FDG signal in cortical layers. These early results raise the need for a reevaluation in the way the brain [18F]FDG-PET data are interpreted and suggests that astrocytes should be integrated in the [18F]FDG-PET data interpretation.