Alpha [11C] Methyl-L-Tryptophan Positron Emission Tomography In Epilepsy

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Advances in positron emission tomography (PET) techniques have allowed the measurement and imaging of serotonin synthesis, transport and receptor binding in the living human brain.

Both the imaging and pathological studies in patients with epilepsy, as well as studies derived from experimental models of epilepsy provide evidence that endogenous serotonin plays a significant role in epileptogenesis. This review summarizes the advances in alpha-Methyl tryptophan PET imaging in patients with different types of epilepsy.

Key words: Epilepsy; Positron-emission tomography; Alpha-(11C)methyl-L-tryptophan; Diagnostic imaging - methods; Experimental models

INTRODUCTION

Epilepsy is a heterogeneous group of disorders of various etiologies characterized by recurrent, usually spontaneous paroxysmal clinical events known as epileptic seizures. Epileptic seizures are signs and symptoms of cerebral dysfunction, resulting from paroxysmal hyperexcitable or hypersynchronous discharges of neurons involving predominantly the cerebral cortex. Data derived from experimental models of epilepsy indicate that targeting serotonin synthesis may provide important clinical and pathophysiological clues. The development of new probes for positron emission tomography (PET) in epilepsy has the potential to improve the identification of the epileptogenic focus for clinical purposes and to advance our understanding of the neurochemical processes underlying epilepsy.

The serotonergic system

In the human brain, the serotonergic system originates from the raphe nuclei that give widespread projections to all areas of the central nervous system (2). In keeping with its diffuse anatomical distribution, serotonin seems to modulate different functions and it has been implicated in a variety of neurological disorders, including epilepsy. This has prompted the development of noninvasive methods for studying the serotonergic system in the living human brain. Various approaches have been proposed, targeting different aspects of serotonergic transmission such as the 5-$HT1_A$ and 5-$HT2_A$ receptors (18,22,28), the serotonin transporters (43) and the serotonin vesicular uptake sites (6). Among these methods is the measurement of serotonin synthesis which estimates the activity of the presynaptic serotonergic transmission (3).

Regulation of serotonin synthesis

Serotonin is synthesized from the neutral amino acid L-tryptophan which is hydroxylated to 5-hydroxytryptophan and then rapidly decarboxylated to serotonin. The first of these reactions is catalyzed by the enzyme *tryptophan hydroxylase* (TPH) which is restricted to serotonergic neurons (29). TPH utilizes two substrates, L-tryptophan and molecular oxygen, as well a reduced pterin as an electron donor. In physiological conditions, TPH is not saturated by any of its substrates (3). As a consequence, an increase in their concentration will lead to an increase in serotonin synthesis. Such an effect has been demonstrated in several species for tetrabiopterin (34); oxygen (11,14,38); and tryptophan (5,14,52). Similarly a reduction in the body and presumably brain tryptophan results in a decrease in the brain serotonin synthesis (39). Serotonin synthesis can also be influenced by neuronal firing. Electrical stimulation of the dorsal raphe over the range of frequencies at which serotonin are known to fire (2-20 Hz) increases the level of serotonin in the dialysate. Although the mechanism underlying this process is unknown, it has been postulated that neuronal firing increases V_{max} of TPH (4) and enhances tryptophan uptake into serotonergic neurons (12).

Alpha-methyl tryptophan as a tracer of serotonin synthesis

Alpha-methyl tryptophan (α-MTrp) is an artificial amino acid and analogue of tryptophan (45). The ligand reflects the uptake of tryptophan into the brain and in physiological conditions it is thought to relate to the synthesis of serotonin (15). Several lines of evidence support the validity of α-MTrp as a tracer for measuring the rate of serotonin synthesis. First, labeled α-MTrp is found at high tracer concentrations in serotonergic cell bodies of the raphe nuclei and at an ultrastructural level it co-localizes with TPH and endogenous serotonin in the perykaria and dendrites of the raphe nuclei as well as in the axon terminals of the serotonin target zones such as the cerebral cortex (9,15,33). Second, labeled α-MTrp follows the serotonin biosynthetic pathway and leads to the formation of α-Methyl-serotonin (α-M-5HT) which is trapped irreversibly into the serotonergic neuron (9,13,15). Third, labeled α-MTrp uptake is consistently affected by drugs

that affect serotonin synthesis (i.e. the TPH inhibitors or $5HT1_A$ agonist) (39,49); or serotonin release and reuptake (35,40,47,51). Finally, changes in plasma tryptophan and an increase in oxygen saturation correlate well with the rate of the α-MTrp trapping (14, 39).

Two major critiques have been raised. The first is that the trapping of the labeled α-MTrp relates to tryptophan incorporation into proteins and that only its conversion to metabolite can be utilized in the calculation of serotonin synthesis (21). Several studies have previously shown that α-MTrp is not incorporated into proteins (16,32) and that its uptake is not affected by the protein synthesis inhibitor cycloheximide (49). In addition, the unidirectional uptake of α-MTrp does not correlate with the permeability surface area product of tryptophan or tryptophan incorporation into proteins (17). The second criticism arose from the observation that in anesthetized monkeys only a small proportion of labeled α-MTrp is converted into α-M-5HT at 180 min post-injection, suggesting that trapping is only a measure of the brain uptake of tryptophan (44). It is important to emphasize that the α-MTrp model is based on the brain tissue trapping of labeled α-MTrp and not necessarily on its conversion to a metabolite. The trapping constant is highly correlated to the conversion of tryptophan into serotonin but not with the tryptophan incorporation into proteins (31). Furthermore, both rat and human tissue time activity are fitted by an irreversible three-compartment model rather than a two-compartment model (13), suggesting that α-MTrp does not trace just the tryptophan transport from the plasma into the brain rather it traces tryptophan conversion into serotonin (17).

In physiological conditions, measurement of the unidirectional uptake of α-MTrp is a valid approach for the determination of brain serotonin synthesis rates (13). However, in pathological conditions where inflammatory processes occur, the induction of the indolamine 2,3-dioxygenase results in the synthesis from L-tryptophan of metabolites of the kynurenine pathway (54).

Serotonin in epilepsy

Studies in experimental models of epilepsy have suggested an inhibitory role of serotonin on epileptiform discharges (37,46,53). Electrical stimulation of the raphe nuclei increases the release of serotonin and inhibits kindled amygdaloid seizures (30). High frequency epileptiform discharges induce an increase of microdyalisate levels of serotonin in rats treated with 4-aminopyridine (27). In contrast, the inhibition of serotonin synthesis by irreversible TPH inhibitors or depletion of forebrain serotonin by lesions of the midbrain raphe increase seizure susceptibility (29). In human tissue, enhanced serotonergic innervation in the epileptogenic area of patients with cortical dysplasia has been described (50). In addition, increased levels of serotonin and of its metabolite 5-hydroxyindole acetic acid (5-HIAA) have also been reported in epileptogenic lesions resected for seizure control (41).

α-[11C]-MTrp PET in patients with intractable epilepsy and cortical dysplasia

Several studies have demonstrated that α-MTrp is able to identify regions of cortical dysgenesis with high specificity (19,24,25). In our series, 7 patients with cortical dysplasia were studied, 57% of which showed a focal increase of α-MTrp uptake within the epileptic focus defined by ictal scalp EEG and MRI (19). The sensitivity of α-[11C]-MTrp PET, in terms of lobar localization has been reported to be lower than [18F]-fluorodeoxyglucose (FDG) PET. However, the regions of reduced metabolism on [18F]-FDG PET are widespread and extend beyond the structural abnormality. In contrast, the increased uptake of α-[11C]-MTrp PET has been demonstrated to be highly co-localized to the area of neocortical seizure onset defined on electrocorticography (24). Furthermore, in those patients with histologically proven cortical dysplasia, the occurrence of increased α-MTrp uptake was higher compared to those with non-specific pathological changes (i.e. gliosis) (24). This high specificity provides the opportunity to use α-[11C]-MTrp PET to re-evaluate patients who underwent epilepsy surgery for further resections (25).

α-[11C]-MTrp PET in patients with intractable epilepsy and tuberous sclerosis

Several studies have demonstrated the unique ability of α-[11C]-MTrp PET to successfully identify the epileptogenic area among multiple dysplastic lesions in patients with tuberous sclerosis (1,7,20,26). Initial studies showed that α-MTrp differentiated between epileptogenic and nonepileptogenic tubers in about 2/3 of the patients (7). In our series, we studied 8 patients, 50% of which showed focal increased uptake of α-MTrp in the epileptogenic area (20). The main advantage of α-MTrp is to show locally increased uptake in and around the epileptogenic tuber, while showing normal or decreased uptake in non-epileptogenic tubers (1,20). We observed a correlation between focal increases in α-MTrp uptake and interictal spike frequency, suggesting that increased α-MTrp uptake relates to epileptogenicity (20). These findings are not related to nonspecific changes in perfusion or metabolism as indicated by a lack of changes in interictal markers of blood flow such as [15O]-H2O or with markers of metabolism such as [18F]-FDG (20). However, the relationship between a-MTrp uptake and interictal spike frequency has not been confirmed by other studies (24).

It has been postulated that the mechanism of increased uptake of α-MTrp in the epileptogenic tuber may be related to the synthesis, from L-tryptophan, of quinolinic acid and other metabolites of the kynurenine pathway. Local application of quinolinic acid induces epileptiform discharges (48). Conversely, there is evidence to suggest that NMDA antagonists can suppress hyperexcitability *in vivo* and exert anticonvulsant effects in several animal models of epilepsy (10). Studies on the regional distribution of tryptophan and its metabolites in the genetically epilepsy-prone rat model of partial epilepsy have shown a significant increase of kynurenine, serotonin and 5-HIAA in the cortex. Furthermore, high levels of quinolinic acid and low levels of TPH in epileptogenic dysplastic tissue with increased α-MTrp uptake on PET have been described suggesting that in at least some cases, increased α-MTrp uptake is mainly due to enhanced kynurenine metabolism (8). However, in a human brain tissue study, no differences were found in the concentrations of quinolinic acid between epileptognic and non-epileptogenic regions and the cerebrospinal fluid concentrations of quinolinic acid were significantly lower in patients than in controls (23).

α-[11C]-MTrp PET in non-lesional (cryptogenic) focal epilepsy

Patients with no detectable lesion on MRI present a difficult problem in localization and usually have the least favorable surgical outcome. Increased focal uptake of α-MTrp in a proportion of such patients is a valuable addition to current methods of investigation. In our study, we reported that 3 of 11 (27%) patients with no detectable lesion on MRI showed focal increased uptake of α-MTrp correlating with the ictal EEG findings (19). It appears that α-[11C]-MTrp PET has a lower sensitivity for the localization and lateralization of epileptic foci in patients with crytpogenic focal epilepsy.

α-[11C]-MTrp PET in mesial temporal lobe epilepsy

Increased α-MTrp uptake has been described in 7 patients with mesial temporal lobe epilepsy with normal hippocampal volumes. In contrast, α-[11C]-MTrp PET in patients with hippocampal atrophy failed to show changes in α-MTrp uptake (36). It is possible that partial volume effects limit the accuracy of α-MTrp PET imaging in the latter setting. The increased α-MTrp uptake in patients with temporal lobe epilepsy might be related to augmented neurogenesis. Recently, increased cell proliferation in the dentate gyrus of adult rats via a 5HT1A receptor dependent mechanism has been reported in the pilocarpine model of epilepsy (42).

CONCLUSION

Although the basis for increased α-MTrp uptake in patients with epilepsy has not been completely elucidated and is likely to be different depending on the etiology, available evidence suggests that α-MTrp is a useful tracer in the presurgical evaluation of patients with epilepsy. Depending on the nature of the epileptogenic lesion, α-[11C]-MTrp PET will display different specificity, with the highest shown for the dysplastic lesions of tuberous sclerosis or cortical dysplasia. The role of α-[11C]-MTrp PET in temporal lobe epilepsy and in cryptogenic neocortical epilepsy remains controversial.

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ALFA [11C] METIL-L-TRIPTOFAN POZITRONSKA EMISIJSKA TOMOGRAFIJA KOD EPILEPSIJE

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SAŽETAK

Prednosti tehnike pozitronske emisijske tomografije (PET) omogućile su mjerenje i slikovnu dijagnostiku sinteze serotonina, transport i povezivanje receptora u mozgu živoga čovjeka. Slikovna dijagnostika i patološke studije o pacijentima koji boluju od epilepsije i studije nastale iz eksperimentalnih modela epilepsije pružaju dokaze da endogeni serotonin ima važnu ulogu u epileptogenezi. Ovaj pregledni članak sažima prednosti alfa-metil triptofan PET vizualizacije u pacijenata koji boluju od različitih tipova epilepsije.

Ključne riječi: Epilepsija; Pozitronska emisijska tomografija; Alfa(11C)metil-L-triptofan; Slikovna dijagnostika - metode; Eksperimentalni modeli