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POSITRON EMISSION TOMOGRAPHY STUDIES IN THE NORMAL AND ABNORMAL AGEING OF HUMAN BRAIN

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RESUME

Jusqu'à récemment, l'étude des correlations neurophysiologiques entre le veillissement normal et anormal du cerveau humain était limitée par des contraintes d'ordre méthodologique. En effet, les technologies existantes ne fournissaient que quelques paramètres -comme par exemple les électroencéphalogrammes ou la circulation sanguine cérébrale-, observés dans les structures superficielles du cerveau, pauvres et très peu précis en ce qui concernait la région. Par la suite, plusieurs techniques non invasives furent développées, qui permettent l'étude in vivo, d'une façon à la fois quantitative et régionale, d'aspects importants du fonctionnement du cerveau, jusqu'alors réputés inaccessibles. Parmi ces techniques, outre la SPECT et la RMN, la Tomographie par émission de positons semble la méthode à la fois la plus puissante et la plus prometteuse, car elle permet la mesure in vivo de paramètres biochimiques et pharmacologiques.

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INTRODUCTION

Until recently, the investigation of the neurophysiological correlates of normal and abnormal ageing of the human brain was limited by methodological constraints, as the technics available provided only a few parameters (e.g. electroencephalograms, cerebral blood flow) monitored in superficial brain structures in a grossly regional and poorly quantitative way. Lately serveral non invasive techniques have been developed which allow to investigate in vivo both quantitatively and on local basis a number of previously inaccessible important aspects of brain function. Among these techniques, such as single photon emission tomography imaging of computerized electric events, nuclear magnetic resonance, positron emission tomography stands out as the most powerful and promising method since it allows the in vivo measurement of biochemical and pharmacological parameters.

WHAT IS POSITRON EMISSION TOMOGRAPHY (PET)?

Positron emission tomography is a research tool in clinical neuroscience since it provides non invasive quantitative in vivo autoradiography in humans (Phelps and Mazziotta, 1985). Hence, following intravenous or airborne administration of trace doses of a compound labeled with a positron-emitting radiopharmaceutical, images that quantitatively represent the distribution of the tracer in a cross section of the brain can be obtained.

The detection device necessary to collect the photons is specific in that it makes use of the paired photons that result for positron annihilation to generate high resolution, quantitative tomographic cuts.

Most of the radioisotopes used have a short half-life and need to be produced in a cyclotron situated in the hospital. Among those, oxygen 15 (T = 2 min), nitrogen 13 (T = 10 min), carbon 11 (T = 20 min) and fluorine 18 (T = 112 min) may be used to replace without modification natural constituants of biological matter. Furthermore, because of their short half-lives, they give rise to high specific radioactivity labeling (low mass for high radioactivity). This point is important when the metabolism of a toxic molecule or a pharmacologically active drug is to be studied (table I).

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TABLE I

CHARACTERISTICS OF SOME SHORT-LIVED ISOTOPES

1 - positron emitters	quantitative tomographic imaging
2 - short half-life	. high statistics . low radiation dose . low mass for a high radioactivity
3 - chemical nature oxygen-15 nitrogen-13 carbon-11 fluorine-18*	replace without modification natural constituants of biological matter

Rapid radiochemistry techniques have been developed to label molecules of biological interest to measure flows and metabolisms (blood flow, oxygen, sugar, protein metabolism) and neurotransmitter systems (dopaminergic, cholinergic, serotoninergic, opiate, benzodiazepine) (Comar et al., 1982). Table II gives some of these radiopharmaceuticals currently used in many PET centres.

TABLE II

SOME RADIOPHARMACEUTICALS FOR POSITRON EMISSION TOMOGRAPHY

^{15}O-water	blood flow
^{15}O-molecular oxygen	oxygen metabolism
^{11}C-glucose ^{11}C-methyl glucose ^{11}C or ^{18}F-deoxyglucose	sugar metabolism
^{11}C-methionine ^{11}C-leucine	protein metabolism
^{11}C, ^{18}F, ^{75}Br-drugs	neurotransmitter, receptor systems
Spiperone	dopaminergic
Ro 15 1788	benzodiazepine
QNB	cholinergic
Diprenorphine	opiate
Setoperone	serotoninergic

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* fluorine may replace hydrogen in some cases.

. APPLICATIONS AND LIMITATIONS OF PET

The classical autoradiographic approach can be applied to PET in order to study in vivo variables such as local cerebral glucose utilisation (using either ^{11}C-2-deoxy-D-glucose or ^{18}F-2-deoxy-D-glucose), blood perfusion (using $H_2{}^{15}O$, ^{11}C-iodoantipyrine, etc.), intracellular pH (using ^{11}C-DMO), or blood volume (using ^{11}CO or $C^{15}O$). In addition, the short half-life of ^{15}O (2 min) led to the design of original, "dynamic steady-state" models to measure local cerebral blood flow and oxygen consumption (Jones et al., 1976).

Neuropharmacology is another field of application of PET, due to the unique possibility of measuring the local concentrations of labeled drugs in brain tissue. This approach has been applied to drugs such as phenytoin and valproate, in order to study their pharmacokinetics in both normal and abnormal tissue (Baron et al., 1983). Labeled drugs have also been used as specific radioligands in order to study in vivo different central neurotransmitter receptors such as the dopamine, serotonin, benzodiazepine and opiate receptors (Baron and Mazière, 1986). Using appropriate ligands administered in trace amounts, one can demonstrate in vivo that they bind specifically to their brain receptors, showing a specific regional distribution of the tracer. For example, the neuroleptic high affinity antagonist ligand, spiperone, has been shown to accumulate more in the striatum than in the cerebellum. The dose-dependent inhibition or displacement of the ligand by an unlabeled competitor, the stereospecificity of this displacement and the saturability of the in vivo ligand accumulation itself, all correlate with the known pharmacological properties of the dopamine receptor.

Another unique advantage of PET is to provide the time course of the tracer in any given region of the brain with a temporal resolution of less than one second. This is a considerable advantage over classical autoradiography, since it allows the actual local measurement of the rate constants of the radiopharmaceutical. Hence, a combination of PET and the Sokoloff method using labeled 2-deoxy-D-glucose to measure local cerebral glucose utilisation can be applied to pathological conditions such as cerebral ischaemia. The local tracer accumulation curve can be fitted to a three-compartment model in order to determine the actual rates of both transport across the blood-brain barrier and phosphorylation and, hence, the rate of local glucose utilisation (Huang et al., 1980, Baron and al., 1984). This interpretation assumes a constant relationship between the behaviour of glucose and that of the glucose analogue. Recent developments have shown that this relationship, the so-called "lumped constant", can be measured regionally by PET using an additional study with ^{11}C-methyl-glucose (Gjedde et al., 1985). A different approach to the measurement with PET of glucose utilisation uses the regional cerebral kinetics of intravenously administered ^{11}C-D-glucose (Raichle et al., 1977), a method which avoids the problem of the "lumped constant" but which is subject to errors due to the rapid metabolism of labeled glucose in brain, blood and peripheral organs.

The kinetic approach has also been applied to the essential amino acids L-methionine and L-leucine, both labeled with ^{11}C (Bustany et al., 1981; Phelps et al., 1984). These authors demonstrated that in baboons the behaviour of ^{11}C-L-methionine in brain could be accurately described by a three-compartment model including plasma, a free-methionine pool in tissue (essentially de novo protein incorporation), while other possible fates of the

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tracer (e.g. demethylation, transmethylation) were negligible (Bustany and Comar, 1985). Since the breakdown of proteins in brain is a slow process relative to the duration of the study (~45 min), the return of protein-incorporated ^{11}C-L-methionine back to the free pool can be neglected and the model simplified to a three rate-constant situation similar to that of the 2-deoxyglucose Sokoloff paradigm. Accordingly, ^{11}C-L-methionine has been used to infer the rate of local protein synthesis in human brain in vivo (Bustany and Comar, 1985).

The brain kinetics of radioligands can be used to estimate quantitative parameters of specific binding to brain receptors in vivo, although there is as yet no general model that describes faithfully each particular radioligand-receptor interaction (Mintun et al., 1984; Syrota et al., 1984; Baron and Mazière, 1986). In addition, these models are limited in that they are not designed to provide both the affinity constant (K_d) and the receptor density (B_{max}). The interpretation of in vivo clinical PET studies of radioligands has so far relied on semi-quantitative indexes of specific binding. Thus, for example, the striatum/cerebellum radioactive concentration ratio has been used to assess dopaminergic receptor function in the striatum using labeled spiperone derivatives (Wong et al., 1984; Baron et al., 1985; Mazière et al., 1985). The validity, under certain conditions, of this index has, however, been amply demonstrated (Wong et al., 1984).

Another promising application of PET has been developed over the last eight years at McMaster University (Canada), where the function of the presynaptic dopamine terminals has been studied using ^{18}F-labeled 6-fluoro-L-DOPA (Garnett et al., 1983). Through elegant experimental validation studies, these authors were able to demonstrate that this compound behaves as an L-DOPA analogue, undergoing specific re-uptake at dopamine terminals in brain tissue (a process that results in its accumulation in the striatum and, to a lesser extent, in the frontal cortex). On the other hand, this compound is much less subject to further metabolism than L-DOPA, and is therefore suitable for the study of the regional brain kinetics of dopaminergic processes in vivo.

The limitations of PET should, however, be emphasized. As said earlier, most positron emitters require for their production the availability of a medical cyclotron in the hospital very close to the positron tomograph. In addition, labeling methods are sometimes difficult to develop, and many pharmaceutical compounds cannot, as yet, be labeled. Finally, the need for appropriate spatial and temporal data sampling has led to the development of sophisticated, high-cost positron cameras. To run such equipment, and to analyse the data correctly requires a large team of highly trained people. These considerations help explain why PET centres are so few, why they drain a large amount of public funds, and why they have been restricted so far to clinical research applications. It therefore follows that the research protocols need be very rigorous and methodologically sound in order to optimise the cost-benefit ratio of PET.

PET IN NORMAL AGEING AND DEMENTIA

The potential of the above applications of PET, summarized in table III, to the in vivo study of ageing of the brain in humans are obvious, since a better understanding of the regional functional correlates of ageing are at hand, as well as a means to perform longitudinal studies and to quantitate the effect of therapy.

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TABLE III

INVESTIGATION OF DEMENTIA WITH PET

Oxygen consumption Glucose utilisation	neuronal function and reactivity to cognitive stimulation
Perfusion	vascular factors
Precursors Specific receptors	neurotransmission systems
Protein synthesis	degeneration and repair mecanisms (plasticity)

Several reports have appeared that suggested that normal ageing is associated with a small but significant reduction in overall brain oxygen consumption (Frackowiak et al., 1980; Pantano et al., 1984) and glucose utilisation (Kuhl et al., 1982), while other reports, sometimes from the same laboratories, claim no significant change in these parameters (Frackowiak et al;, 1983; Duara et al., 1983, 1984; Hawkins et al., 1983; De Leon et al., 1984). These descrepancies illustrate differences in selection criteria for normality and are consistent with previous findings using the Kety-Schmidt technique (Smith, 1984; Pantano et al., 1984), indicating that very healthy aged people may -through hypothetic compensatory mecanisms- maintain normal cerebral metabolic rate despite neuronal loss while more "normal" ageing entails a small reduction in cerebral metabolism. Differences in environmental set-up during study may also account, in part, for these discrepancies, as age-related visual and auditory declines have been shown to affect brain metabolic activity (Smith, 1984). The symmetrical metabolic reductions of normal ageing preferentially affect the prefrontal, perisylvian and parieto-occipital cortex (Pantano et al., 1984; Kuhl et al., 1982; Chawluck et al., 1985). Data concerning white matter indicate a decrease in glucose utilisation but a preservation of oxygen consumption, suggesting possible alterations in the oxidative phosphorylation process of glial cells with ageing.

More than 15 PET studies of cerebral metabolic rate in Alzheimer's type dementia (DAT) have now appeared. Despite some variability in patient inclusion criteria and in PET methodology, they all concur in showing a decreased overall brain metabolism of both oxygen and glucose that is correlated with the severity of dementia, although early forms of DAT may be spared (Frackowiak et al., 1981; Foster et al., 1983, 1984; De Leon et al., 1983; Benson et al., 1983; Friedland et al., 1983, 1985; Chase et al., 1984; Haxby et al., 1985; Alavi and De Leon, 1985; Kuhl et al., 1985; Chawluck et al., 1985, Cutler et al., 1985a,b). These studies have also disclosed that this metabolic impairment preferentially affects the parieto-temporo-occipital cortex with relative preservation of the primary visual and sensory motor cortex, prefrontal cortex, anterior cingulum, basal ganglia, thalamus and cerebellum. Due to inadequate spatial resolution, there is little information of the medial-temporal cortex and hippocampus. A final important aspect of DAT has been the significant prevalence of right-left metabolic asymmetry, particularly affecting the parieto-temporo-occipital cortex. Satistically significant clinical correlations have been demonstrated between these focal metabolic impairments (Foster, 1983, 1984; Chase, 1984; Haxby, 1985), indicating an association between left

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parieto-temporal metabolism and verbal tasks on the other hand. Patients with predominant memory impairment show symmetrically depressed cortical metabolic rate. The parietal/cerebellum metabolism ratio has emerged as the index best correlated with severity of dementia (Kuhl et al., 1985). However, precise correlations between the severity of the specific intellectual alterations and the focal metabolic impairment are lacking, although Cutler et al. (1985) recently reported interesting temporal dissociations.

The measured regional metabolic rate essentially reflects the density of synaptic contacts and their functional activity and much less the other energetic expenditures of neurons and those of glial cells. The regional metabolic histological alterations, suggesting that its basis are more structural than actually functional and hence possibly indicating irreversibility. The ability of PET to show histopathology in vivo remains however of great interest but needs a definitive confirmation.

However, the recent demonstration of a prefrontal cortex hypometabolism in the "subcortical dementia" of progressive supranuclear palsy (D'Antona et al., 1985) has stimulated interest, because it indicates that purely subcortical degenerative lesions may, as a result of deafferentation, cause both distant cortical metabolic dysfunction and intellectual impairment. This observation is consistent with both the neuropsychological and the cortical metabolic effects of lesions located either in the thalamus or in the subcortical cholinergic systems (Baron et al., 1986; London et al., 1984). In addition, stereotaxic electrocoagulation of the nucleus basalis of Meynert in the baboon revealed a marked metabolic depression of the ipsilateral cerebral cortex (Kiyosawa et al., 1987).

Since subcortical neuronal lesions are thought to play a major role in the development of the dementias of DAT, Parkinson's disease (PD) and Hutington's chorea, these observations are of some importance. Although there is a striking similarity in the pattern of metabolic alterations in PD dementia and DAT (Kuhl et al., 1985), a marked bifrontal hypometabolism has occasionaly been reported in advanced cases of DAT (Fackowiak et al. 1981; Benson et al., 1983). Hence, an in vivo approach to the cortical and subcortical features in the various clinical subgroups of dementia may be at hand.

There is only one brief report of a ^{11}C-L-methionine PET study of DAT patients (Bustany and Comar, 1985). These preliminary findings suggest that early DAT is already reflected in 20 % decrease in protein synthesis rate in the cerebral cortex, while more advanced cases show up to 75 % decrease, particularly in parieto-temoral and/or frontal cortex. Hence the cortical protein synthesis rate may well be a very sensitive parameter in DAT, perhaps altered much earlier than glucose utilisation, in line with the hypothesis that DAT is primarily a disease of nucleic acids (Mann, 1982).

As yet, no PET studies of central receptors in DAT have appeared. It must be stressed that no reliable PET method has yet been developed to investigate the muscarinic receptors in the cerebral cortex. Using both ^{11}C-methyl-spiperone and ^{76}Br-bromospiperone, a highly significant loss of striatal dopaminergic receptors has been demonstrated in normal ageing (Wong et al., 1984; Baron et al., 1986). These studies not only confirm in vivo the results obtained post-mortem but also serve to illustrate the reliability and the sensitivity of these PET methods. Furthermore, a highly significant loss of ^{76}Br-bromospiperone binding sites in the striatum of 7 patients with

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PSP has been demonstrated in vivo (Baron et al., 1986), providing an explanation for the lack of benefit from L-DOPA and DA agonists in this condition despite reduced nigro-striatal dopaminergic function. Such methods will be important for our better understanding of the effects of normal ageing on the dopaminergic systems, particularly if coupled to the ^{18}F-fluoro-DOPA method (Leenders et al., 1984).

CONCLUSION

Positron emission tomography demonstrates correlations between brain metabolism and clinical symptoms of dementia:

- I -

The magnitude of the decrease in whole brain oxygen and glucose consumption, which preferentially affects the parieto-temporo occipital cortex, correlates with the severity of dementia in Alzheimer's disease.

- II -

In senile dementia of Alzheimer's type, an association has been demonstrated between:

- decrease in right parieto-temporal metabolism and impairment in visuo-spatial tasks,

or

- decrease in left parieto-temoral metabolism and impairment in verbal tasks.

- III -

Prefrontal cortex hypometabolism in the "subcortical dementia" of progressive supranuclear palsy indicates that subcortical degenerative lesions cause distant cortical metabolic dysfunction and intellectual impairment.

- IV -

Stereotaxic electrocoagulation of the nucleus basalis of Meynert in the baboon results in a marked metabolic depression of the ipsilateral cerebral cortex.

Since 1) the nucleus basalis of Meynert is the major source of cholinergic input to the cortex and 2) this systems influences behaviour and is involved in several demential processes, this animal model may be interesting for better understanding and treatment of dementia in humans.

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POSITRON EMISSION TOMOGRAPHY STUDIES IN THE NORMAL AND ABNORMAL AGEING OF HUMAN BRAIN

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SUMMARY

Until recently, the investigation of the neurophysiological correlates of normal and abnormal ageing of the human brain was limited by methodological constraints, as the technics available provided only a few parameters (e.g. electroencephalograms, cerebral blood flow) monitored in superficial brain structures in a grossly regional and poorly quantitative way. Lately serveral non invasive techniques have been developed which allow to investigate in vivo both quantitatively and on local basis a number of previously inaccessible important aspects of brain function. Among these techniques, such as single photon emission tomography imaging of computerized electric events, nuclear magnetic resonance, positron emission tomography stands out as the most powerful and promising method since it allows the in vivo measurement of biochemical and pharmacological parameters.

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