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Positron emission tomography studies of sleep and sleep disorders

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Abstract Using positron emission tomography (PET) it is possible to perform an in vivo study of cerebral physiological and biochemical processes in man. Employing this technique in sleep studies, decreased cerebral metabolic rates for glucose during slow wave sleep compared with those seen during wakefulness were first demonstrated, whereas similar rates of cerebral glucose metabolism were observed during paradoxical sleep and wakefulness. More recently, regional modifications of cerebral blood flow during sleep have also been demonstrated. During slow wave sleep, cerebral blood flow is decreased particularly in the prefrontal cortex. Rapid eye movement sleep is characterized by activation of the pons, thalami, amygdaloid complexes and a number of cortical areas (e.g. the anterior cingulate cortex). Although data remain incomplete, a variety of sleep disorders, including narcolepsy, fatal familial insomnia and continuous spike-and-wave discharges during slow sleep have been investigated. These results are briefly reviewed.

Key words Positron emission tomography · Sleep disorders · Energy metabolism · Cerebrovascular circulation

Introduction

Positron emission tomography (PET) is one of the most powerful tools available for the investigation in vivo of brain haemodynamics, metabolism and neurotransmission in man [35]. It allows non-traumatic analysis of a large number of biochemical parameters for the entire brain. However, there are some disadvantages associated with PET: relatively low temporal and spatial resolution, irradiation of the subject (even though this is minimal) and high cost. Nevertheless, these drawbacks should not be allowed to discourage the use of this technique, particularly in such areas as sleep research where certain phenomena (e.g. dreams) can be investigated only in live humans.

As one of the main challenges in neuroscience is to map the human brain comprehensively [44], the importance of sleep, a heterogeneous state in which the human brain spends approximately one-third of its life span, should not be overlooked. From this perspective, PET studies are likely to contribute significantly to the future development of this field.

Although focused mainly on PET data, this review will also discuss results obtained with complementary techniques, including autoradiography, the Kety-Schmidt method and single photon emission computed tomography (SPECT).

PET studies of physiological sleep

Global modifications of energy metabolism during sleep

The first contribution of PET to sleep research was the demonstration of the considerable variations in energy metabolism that occur during sleep. Cerebral glucose metabolism, measured by the [^{18}F]-fluorodeoxyglucose (FDG) autoradiographic method, was initially investigated [34].

In normal subjects who maintained stage 2 sleep during the FDG uptake period, a non significant (11%) decrease in cerebral glucose metabolism was observed [23]. When sleep stages 2 and 3 were mixed during the FDG uptake periods, cerebral glucose metabolism was 23% lower than when awake [6]. When stages 3 and 4 slow wave sleep were present, a dramatic 40% decrease (compared with the waking level) in cerebral glucose metabolism was observed [21].

These results were in agreement with the 5% and 25% decreases in cerebral oxygen consumption reported with the Kety-Schmidt technique in normal subjects during light and deep low sleep, respectively [19, 20]. They also concurred with observations made previously in animals. Cerebral glucose metabolism, measured by the deoxyglucose (DG) autoradiographic method, was 30% lower in monkeys in slow wave sleep (SWS) than in awake controls [14]. Likewise, in cats, there was an inverse correlation between cerebral glucose metabolism and the amount of SWS observed during the DG uptake period [36].

It is very difficult (if not impossible) to study rapid eye movement (REM) sleep in animals because their REM sleep periods are too short to satisfy the experimental requirements (i.e. 45 min of cerebral steady state) of the DG method. In contrast, human REM sleep episodes are long enough for reliable investigation with PET and FDG analyses. In normal subjects, cerebral glucose metabolism during REM sleep was shown to be similar to (+ 3% [21]) or slightly lower than the waking level [6]. Similar observations were made concerning cerebral blood flow and oxygen consumption. Using the Kety-Schmidt technique, Madsen et al. [20] showed no significant differences in cerebral blood flow and oxygen utilization between REM sleep and wakefulness measurements.

The fluctuations in energy metabolism during sleep probably reflect the modified firing patterns of large populations of neurones. Indeed, in animals in SWS, three rhythms (spindles, theta and slow rhythms) are generated by thalamic cells and thalamo-cortical and intracortical networks. These rhythms are all characterized by prolonged periods of hyperpolarization interspersed with short firing bursts [42]. The predominance of hyperpolarization periods over firing bursts probably leads to an overall decrease in energy metabolism.

In contrast, during REM sleep, the tonic bombardment of the thalamus by the mesopontine reticular formation causes the resumption of a tonic firing pattern at the thalamic and cortical levels [41]. This cascade of events results in an increase in levels of cerebral energy metabolism over those seen when awake.

Regional modifications of energy metabolism and related parameters during sleep

The above observations have prompted the investigation of the homogeneity of distribution of changes in cerebral activity (i.e. whether or not some cerebral structures are affected more than others).

Until recently, regional distribution of cerebral activity was assessed by the use of multiple regions of interest, placed in as many cerebral structures as possible. This method was cumbersome and lacked anatomical precision. Furthermore, statistical analyses usually involved multiple comparisons of non-independent parameters, thus increasing the risk of type I error.

For these reasons, and because study populations were small, reports of attempts to describe regional variations in cerebral activity have been inconsistent. During SWS, the decrease in the rate of glucose metabolism appears particularly prominent in thalamic nuclei [6, 21]. This result is in accordance with data obtained in animal experiments [14, 36]. Accordingly, cerebral blood flow was reported to be particularly decreased in the brain stem, thalamus and basal ganglia [3]. However, reductions in cerebral blood flow were also noted in frontal, cingular and insular cortices [3].

Results of measurements of glucose metabolism [21] and cerebral blood flow [18] in subjects in REM sleep have shown apparent increases in temporal and occipital activity. It was suggested that this posterior brain activity is related to oneiric activity in sleeping subjects [18, 21].

More recently, the use of multiple cerebral blood flow estimations and new modes of statistical analysis have permitted more detailed descriptions of the functional neurophysiology of sleep in man. In such experimental protocols, cerebral blood flow (used as a marker of neuronal activity) is qualitatively estimated in different cerebral states by the infusion of ^{15}O-radiolabelled water. The use of successive water injections is made possible by the short half-life of ^{15}O (123 s). Furthermore, analysis with statistical parametric mapping (SPM [9]) has enabled researchers to successfully identify the significant regional variations in cerebral blood flow that occur in different cerebral states. Thus, SPM may be used to identify regionally specific effects and to produce statistical parametric maps that give a representation of significant regional modifications in cerebral blood flow.

In a sleep study where this technique was used, six ^{15}O-radiolabelled water injections (2 when awake, 2 in SWS and 2 in REM sleep) were given to volunteers undergoing continuous polygraphic monitoring for 1 night. Preliminary results in six subjects showed that blood flow in the prefrontal cortex was significantly decreased relative to wakefulness during slow sleep (4 subjects were scanned during deep SWS and 2 in stage 2 sleep) [25]. The final results of this study have been submitted for publication[1]. Similarly, Hetta et al. [10] reported a significant decrease in prefrontal cerebral blood flow in deep

[1] Note added in proof: Final results can be found in: Maquet P, Degueldre C, Delfiore G, Aerts J, Péters JM, Luxen A, Franck G (in press) Functional anatomy of human slow wave sleep. J Neurosci

SWS after a similar statistical analysis [46] was used with up to only three injections per night (7 scans).

Maquet et al. [26] showed REM sleep to be characterized by a significant activation of central core structures (pontine tegmentum and thalamus), both amygdaloid complexes and two cortical areas with prominent amygdalar afferents (anterior cingulate cortex and right parietal operculum). Cerebral areas receiving few amygdalar projections (prefrontal cortex, parietal cortex and precuneus) were significantly less active than the rest of the brain. These results require confirmation by further experimental observations but suggest a functional interplay between amygdaloid complexes and the cortex during REM sleep. It is possible that these functional amygdalo-cortical relationships participate in the processing of some memory traces. They may also be responsible for dreaming activity.

PET studies of sleep disorders

Introduction

There are two factors that should be considered when interpreting the results of PET studies in sleep disorders. Firstly, some patients have true sleep disorders (e.g. narcolepsy and nocturnal myoclonus) whereas in others, abnormal sleep is a characteristic of the disease (e.g. fatal familial insomnia and continuous spike-and-wave discharge during slow sleep). There are other disorders in which sleep disturbances occur but are not one of the core features of the disease (e.g. depression). In the present paper, only the first two categories will be discussed. Likewise, PET studies of sleep deprivation are not covered, despite their relevance to conditions such as sleep apnoea syndrome and to insomnia, shift work-related incidents and sleep-related traffic accidents. Furthermore, anecdotal case reports of PET studies in single patients with sleep disturbances are not reviewed.

Secondly, the state of vigilance of subjects in whom PET studies were performed should be considered. Very few studies have been carried out in sleeping patients, mainly because of technical difficulties. Thus, the majority of investigators studied sleep disorders in patients who were awake during the procedure.

Narcolepsy

Early observations using ^{133}Xe inhalation and the Kety-Schmidt technique indicated brain stem and cerebellar blood flows in 13 awake narcoleptic patients to be lower than those in normal controls [29]. After the onset of sleep (3 of 13 in REM sleep), cerebral blood flow paradoxically increased at both the hemispheric and brain stem/cerebellar levels. Interestingly, during visual dreaming and hypnagogic hallucinations, regional blood flow was increased in temporo-parietal areas. This observation reflects cerebral glucose metabolism data during normal REM sleep [18, 21].

PET was used to investigate dopamine D2 postsynaptic binding during wakefulness in narcolepsy, following reports of increased dopamine D2 binding in the brains of deceased narcoleptic patients at autopsy [2, 16]. In vivo imaging of narcoleptic patients by SPECT [13, 40] or PET [15, 28] consistently showed no significant variations in dopamine D2 binding [37]. The suggestion that increased dopamine D2 binding may be observed only in elderly patients with narcolepsy who have undergone prolonged treatment [15] has not been confirmed by other studies [37]. This premise nevertheless provides a possible explanation for the discrepancies seen in postmortem results.

Periodic leg movements/nocturnal myoclonus syndrome

It has been suggested that periodic leg movements/nocturnal myoclonus syndrome might be related to decreased central dopaminergic activity: patients respond to dopaminergic agonists [5] and their condition worsens when dopamine antagonists are given [1]. Some attempts have been made to test this hypothesis in vivo using SPECT and [^{123}I]-IBZM (iodobenzamide; a dopamine D2 receptor ligand) with semiquantitative analysis. Staedt et al. [39] showed the ratio of dopamine D2 binding in the basal ganglia to that in the cortex to be significantly decreased relative to ten healthy control subjects. This pilot study requires confirmation by quantitative analysis with controls for the effects of age and duration of disease.

Fatal familial insomnia

This prion disease is characterized by insomnia and dysautonomia and invariably causes death [17]. Four awake patients were investigated using PET and FDG analysis. In all patients, a prominent hypometabolism was observed in the anterior part of the thalamus [33]. In two patients exhibiting only the two characteristic signs, thalamic hypometabolism alone was seen in one. In the other patient, it was accompanied by a frontal, anterior cingulate and temporal polar hypometabolism. In the other two patients (who presented with a more complex clinical picture) the hypometabolism was widespread and involved many cortical areas, basal ganglia and the cerebellum. It is not known whether this widespread hypometabolism is indicative of the more advanced stages of the disease or whether it indicates two forms of this disorder, one thalamic and the other disseminated.

The Landau-Kleffner syndrome and related disorders

The Landau-Kleffner syndrome and the syndrome of continuous spike-and-wave discharges during slow wave sleep

(CSWS) were originally described, and are still considered, separately. The former combines an acquired aphasia with spike-and-wave discharges that are activated by SWS, behavioural disturbances and, sometimes, epileptic seizures [4]. The latter is characterized by continuous spike-and-wave discharges during SWS, usually combined with global intellectual deterioration and epileptic seizures [43]. These two syndromes share many common features, including onset during childhood, deterioration of cognitive function (previously acquired normally), seizure type, EEG pattern, pharmacological reactivity, and regression of neuropsychological symptoms, EEG abnormalities and seizures before the end of adolescence. Structural lesions that might be detected by computed tomography or magnetic resonance imaging are also absent [11, 27].

Early studies with PET described metabolic abnormalities that predominantly involved the temporal lobes [8, 22, 38]. Focal or regional areas of hypometabolism and hypermetabolism were reported. These observations resulted in a confused situation in which the pathophysiology of the syndrome remained unclear. SPECT studies provided similar results [7, 30–32, 45]. Furthermore, an isolated case of normal distribution of cerebral blood flow was seen in one of these studies [12].

Recently, cerebral glucose metabolism was investigated using PET and FDG in seven patients (asleep and awake) [24]. The results showed variable cerebral metabolism in CSWS patients. Regional increases as well as decreases in cerebral glucose metabolism were both observed. Furthermore, metabolic patterns in individual patients may change over time.

Notwithstanding these uncertainties, four basic metabolic characteristics appear to be displayed by these patients:

1. A higher rate of metabolism in the cortical mantle than in the thalamic nuclei. This metabolic pattern is characteristic of an immature brain.

2. Focal or regional metabolic abnormalities of the cortex, suggesting a focal origin of the spike-and-wave discharges.

3. Metabolic disturbances predominantly involving associative cortices. This suggests deterioration of cognitive function only.

4. Thalamic nuclei remain symmetrical despite significant cortical asymmetries, suggesting that cortico-thalamic neurones either do not participate in the generation of spike-and-wave discharges or are being inhibited by pathological mechanisms.

These findings suggest that CSWS is brought about by an alteration in the maturation of one or more associative cortices. Thus, the pathological processes involved would be expected to cause "imperfect" neuronal wiring and thus an imbalance of inhibitory and excitatory drives. This would lead to deterioration in associated higher cerebral functions and would create conditions conducive to the production of neuronal discharges. Discharges expressed during waking would be activated during slow wave sleep because of the physiological reinforced synchronization of neuronal firing characteristic of that type of sleep [42].

Conclusions

PET may prove valuable in the exploration of many aspects of cerebral haemodynamics, metabolism and neurotransmission during sleep under both physiological and pathological conditions. Although the contribution of this technique to the development of this field has so far been modest, future research should confirm its usefulness in sleep research.

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