Short report

The effect on plasma prolactin levels of interictal epileptiform EEG activity

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SUMMARY Because of the known effects of seizures on plasma prolactin, the plasma prolactin levels were measured before and after generalised interictal epileptiform activity was provoked in the EEG in five epileptic patients. The findings were compared with those obtained in five normal subjects and three epileptic patients who were also exposed to flicker stimulation, but who did not develop a photoconvulsive EEG response. There was no significant difference in baseline prolactin values, and levels did not change with photic stimulation or in response to the presence of generalised epileptiform activity in the EEG.

A marked increase in plasma prolactin level is known to occur in many patients shortly after a tonic-clonic seizure¹⁻⁵ and may sometimes occur also following partial seizures.⁵⁻⁷ However, the effect on plasma prolactin of interictal epileptiform EEG activity is unknown. Epileptiform EEG discharges (that is, abnormal paroxysmal activity consisting of spike, polyspike or sharp wave discharges with or without associated slow waves) may occur without obvious clinical accompaniments in many patients with epilepsy. Nevertheless such EEG discharges may be accompanied by an increase in reaction time, or by complete failure to respond to a stimulus.⁸ Indeed, some authors consider that generalised spike-wave activity is always accompanied by impaired performance.⁹ The likelihood of discerning some impairment of cerebral function during the occurrence of epileptiform activity depends upon the testing technique used. In particular, simple motor tasks are relatively little affected by generalised spike-wave EEG activity, whereas choice reaction time, signal detection, and short-term memory tasks are more sensitive.⁸

We have examined the effect of interictal epileptiform EEG activity on plasma prolactin levels because any change in prolactin levels under these circumstances might provide further support for the belief that interictal generalised epileptiform EEG discharges are of functional significance. At the same time, it would detract from the possible importance of measuring plasma prolactin levels when attempting to determine in epileptic patients whether clinical attacks of uncertain nature represent seizures. Finally, any increase in prolactin level with subclinical generalised interictal epileptiform EEG discharges might provide further insight to the basis of the prolactin response accompanying seizures.

Methods

Spontaneous interictal epileptiform EEG activity occurs unpredictably, and this would preclude the taking of blood samples for baseline purposes before the occurrence of such activity. Accordingly we had to use some means of provoking a generalised epileptiform discharge in the EEG, and this was achieved by photic stimulation. The subject lay on a couch in a quiet, darkened room while a 16-channel EEG was recorded for one hour. A Grass intermittent photic stimulator was then used to cause rhythmic flash stimulation while the EEG was recorded bipolarly from a wide region of the scalp including the parietal and occipital areas. Flash stimuli were delivered at 1, 3, 6, 9, 12, 15, 18 and 21 Hz. At each flash rate the EEG was recorded with the subject's eyes

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open for about 5 seconds, and with the eyes closed for a further 5 seconds. The EEG was then recorded for a further hour while the subject rested quietly. If any epileptiform activity occurred, either during the resting record or with photic stimulation, the subject was observed carefully for any behavioural changes and was also asked to repeat a sequence of numbers or nonsensical statement to determine whether external awareness was impaired. In none of the subjects whom we studied were clinical changes detected by these simple methods.

We studied five normal volunteer subjects (two men, three women; aged between 22 and 37 years), and eight patients with a known seizure disorder (one man and seven women; aged between 16 and 47 years). The patients were selected in that they had been found to have a photoconvulsive response in EEGs recorded previously.

Once the EEG electrodes had been attached to the scalp, a heparin lock was placed in an accessible vein in the arm to permit blood samples to be taken at selected intervals of time. Samples were obtained at the commencement of EEG recording and then 1 hour later, following which photic stimulation was performed; further blood samples were obtained immediately after flicker stimulation, and then at 15 minute intervals for the following hour, while the EEG was recorded continuously. Blood was collected into EDTA containing tubes for measurement of prolactin level. Plasma was promptly separated from blood cells at 5°C, frozen, and stored at -70°C until assayed. Prolactin determination was performed by radioimmunoassay using kits provided by the National Pituitary Agency, all assays being performed at the same time. No patient received any drugs during the 2 to 3 hour period of the study. Those already receiving anticonvulsant drugs continued their normal routine, and took their usual morning dose before the study, which was always

commenced at approximately 9 am. All subjects voluntarily gave their written consent to participate in the study, which had the approval of the Committee of Human Research at this medical centre.

Results

None of the normal subjects had any epileptiform activity in their resting EEGs or during photic stimulation. Among the eight epileptic patients known from previous EEGs to have a photoconvulsive response, seven had generalised tonic-clonic seizures and one had complex partial seizures. One of the patients with tonic-clonic seizures also had absence attacks. In three patients, the tonic-clonic seizures were sometimes provoked by flickering lights. All patients but one were receiving one or more anticonvulsant drugs at the time of study; four patients were taking carbamazepine, three were receiving phenobarbitone, and one each was receiving valproic acid, phen-suximide and phenytoin. Only five of these epileptic patients had a photoconvulsive response during the present study, that is generalised epileptiform activity provoked by the flicker stimulation and with spikes having a discharge frequency unrelated to that of the flashing light. Among these five, the total duration of epileptiform activity provoked by flicker stimulation varied between 17 and 32 seconds, while the longest discharge occurring at any one time was between 5 and 7 seconds. There were no clinical or behavioural changes during these discharges.

There were three patients in whom a photoconvulsive response failed to occur, one of whom was the patient with complex partial seizures. Another of these patients had tonic-clonic seizures that in the past had occasionally been provoked by flashing lights. These three patients were therefore considered separately when our data was analysed.

We found no difference in baseline prolactin values between the three groups of subjects (normal volunteers; patients with photoconvulsive response; patients without photoconvulsive response) when the data were analysed using a one-way analysis of variance. In evaluating the response to flicker stimulation and to the epileptiform activity provoked by this means, the values for prolactin levels were analysed using a repeated measures analysis of variance to determine whether there were any differences over time or between groups, or any differences in the way the group values changed with time. No differences occurred in any of these factors. The findings are shown in the figure. The increase in plasma prolactin that occurred about 45 minutes after flicker stimulation in the epileptic patients without photoconvulsive response related predominantly to a surge in prolactin level in one patient at this time, but which never-

Fig Changes in plasma prolactin as a percentage of baseline level, at selected intervals following flicker stimulation in three groups of subjects. Baseline value represents the mean of the value immediately after insertion of the heparin lock and the value obtained 1 hour later, immediately before flicker stimulation was commenced. Each point represents the mean for that time-period for each subject group. The open triangles represent data from normal subjects (n:5); filled circles, epileptic subjects with a photoconvulsive response (n:5); open circles, epileptic subjects without a photoconvulsive response (n:3).

theless remained within normal limits. Such surges of prolactin are well described and may occur, for example, in relation to sleep.¹⁰

Discussion

Several recent studies have shown that a transient increase in serum or plasma prolactin frequently follows generalised tonic-clonic seizures,¹⁻⁵ electroconvulsive therapy,^{11,12} and partial seizures of both the simple and complex varieties.⁵⁻⁷ Among patients with seizures arising from the temporal lobe, secondary generalisation of the EEG discharge is not necessary for a maximal increase in postictal prolactinaemia to occur.⁶ These studies have not addressed the issue of whether a similar elevation of circulating prolactin occurs after generalised interictal epileptiform EEG discharges. Such "subclinical" EEG discharges may resemble the activity recorded over the scalp during a clinical seizure, and they may be associated with a transitory impairment of cognitive function which is detectable by psychological testing procedures.⁸ It is therefore of considerable interest that these discharges (at least when provoked by a flashing light as in our study) are not accompanied by any change in plasma prolactin levels. Similarly, we found no difference in baseline plasma prolactin level between our group of normal subjects and the patients with epilepsy. Pritchard *et al*⁷ found that among patients with complex partial seizures, interictal serum prolactin values were slightly higher in those with mesiobasal temporal lobe spike discharges, whereas there was no significant difference between subjects with unilateral and those with bilateral temporal lobe spike foci.

Many physiological stimuli affect the circulating prolactin level, including physical activity, and it is possible that the convulsive activity of tonic-clonic seizures contributes to the prolactin response accompanying them. However, a prolactin response may also follow complex partial seizures in which there are no convulsive components.^{6,7} The absence of a consistent change in circulating growth hormone level following seizures¹ suggests that the other hormonal responses are not stress-related, but does not entirely exclude this possibility since different types of stress are known to produce different hormonal changes.¹³

It is possible that the prolactin response relates to generalised neuronal discharges involving hypothalamic stimulation. If this is the case, however, our finding that there is no prolactin response following generalised interictal epileptiform discharges implies that these discharges involve different diencephalic structures from those involved by ictal discharges, despite their similar morphology at the scalp and the

cognitive impairment that may occur with both. Patients with myoclonic or akinetic seizures do not develop a postictal hyperprolactinaemia,⁶ perhaps because the seizures are brief and provide an inadequate stimulus to interfere with anterior pituitary function.⁶ This seems unlikely to be the explanation for the lack of prolactin response to the generalised epileptiform EEG discharges induced in our patients by photic stimulation, since the total duration of such activity was up to 32 seconds, with individual discharges lasting for 5 to 7 seconds.

Binnie *et al*¹⁴ reported that patients were often referred for video-monitoring to determine whether or not known epileptiform EEG discharges were accompanied by clinical changes, and found that the video-recordings frequently revealed brief minor seizures that had previously escaped clinical detection. Such a finding, and the occurrence of cognitive impairment in association with a paroxysmal change in electrocerebral activity, suggest that the presence of epileptiform activity may have greater clinical significance than has previously been recognised. Nevertheless, our findings suggest that the presence of epileptiform activity should not be equated with occurrence of seizures in general, although the hormonal accompaniments of minor seizures remain poorly defined at the present time and merit further study.

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