Changes in visual evoked potentials by amitriptyline in patients with endogenous depression

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The recent development in cortical evoked potential study on psychotropic drugs as well as quantitative pharmacoelectroencephalography has been brought about by the increasing need for an objective and quantitative method of evaluating the action of a psychotropic drug on the human CNS, and for a technique to predict the therapeutic efficacy and to determine the optimal doses in patients. However, concerning tricyclic antidepressants only a few have been written. Shagass et al11 reported that imipramine and tranylcypromine returned the recovery function of somatosensory evoked potentials (SEP) toward normal and diminished the SEP amplitude in patients with psychotic depression. They also found that amitriptyline reduced the SEP amplitude which tended to occur along the entire time course of the response11. Recently, Saletu11 studied the SEP profiles of antidepressants in normal volunteers and suggested that tricyclic antidepressants had both stimulatory properties and inhibitory qualities, indicated by a latency decrease in the early peaks and a latency increase in the late response as well as an attenuation of the amplitude, respectively.

We studied both the changes of amplitude-ratio of visual evoked potentials (VEP) after an overloading mental task using a modification of Kadobayashi’s addition task method and the changes of amplitude and latency of the baseline VEP before the task by successive oral administration of amitriptyline (AMP) in patients with monopolar endogenous depression. We also studied the relationship between changes of the amplitude-ratio after the task and baseline VEP changes by administration of AMP, and the dose-dependences of these VEP changes.

The subjects consisted of three with monopolar depression, one with bipolar depression, and eight with involutional melancholia. The age ranged from 27 to 65 years. Seven were male and five were female. None of them received any kind of medication before the visit to our clinic.

VEP recordings were performed 3-5 times consecutively in each patient; the first recording was made before treatment, the second a week after the initial administration of AMP, the third two weeks after the administration, and the last at the time of remission. In some cases additional recordings were occasionally done between the third and last.
recordings. AMP was freely given orally according to the clinical state of each patient. The initial dose ranged from 20 to 150 mg per day, and was increased weekly to a maximum of 75-250 mg per day. After a remarkable clinical improvement the doses were gradually reduced. At the time of remission all subjects except one were still given AMP of 20-175 mg. Nearly all subjects were given hypnotics (benzodiazepine derivatives), and in six cases antianxiety agents were administered.

For the procedure of VEP recording and the loading-mental-task-method we employed a modification of Kadobayashi's addition task method, the details of which were reported elsewhere. We took the last VEP of the initially recorded three VEPs as the baseline VEP (C). After giving a short addition task of a 20-second duration two VEPs were recorded, i.e., one minute after the task (T) and four minutes after the task (B). Then an overloading mental task was given. This was an addition task of a 15-minute duration, and the addition problems were given at a faster pace than in Kadobayashi's original. One minute after the task a VEP (A1) was recorded and thereafter a series of VEPs were recorded at an interval of two minutes (A2, A3, A4, A5, A6). The amplitude-ratio was calculated by dividing the amplitude of the positive peak appearing at about 100 msec ($P_{100}$) from the onset of the VEP after the overloading mental task by that of the baseline VEP (C). The mean amplitude-ratio was the mean value of the six amplitude-ratios obtained during eleven minutes after the task in each subject. The amplitude and latency of $P_{100}$ and $N_{40}$ (the negative peak appearing at about 40 msec) of the baseline VEP before the task were also determined for each subject.

Fig. 1 (A) illustrates longitudinal changes of the amplitude-ratios after the task by successive oral administration of AMP in a patient. Curve I represents that of pretreatment, which shows a marked reduction as in many patients with monopolar endogenous depression reported previously. As shown in curve II this reduction was diminished by successive administration of AMP of 150 mg per day for one week and the amplitudes returned to nearly the same level as that of the baseline VEP before the task. But as is shown in curve III, re-reduction of the amplitude-ratios took place instead of further augmentation of them by increasing the dose to 200 mg per day for one week in spite of remarkable clinical improvement. This re-reduction was often seen in the case of continuous high dose administration of AMP (above 150 mg per day). Curve IV represents the amplitude-ratios at the time of remission, showing the augmentation of the amplitude-ratio especially at $A_4$.

All twelve patients favorably responded to AMP, showing a remarkable improvement, and all except one who received only a small dose of the drug showed a decrease in amplitude-ratio reduction or an increase in amplitude-ratios at least once in the course of treatment. These VEP changes caused by the administration of AMP depended mainly on the dose and they reached a level of statistical significance only when a dose of more than 75 mg per day of AMP was administered. Fig. 1 (B) shows this relationship. Only when a dose above 75 mg per day was given, there did exist a significant difference between the mean amplitude-ratios before and after the administration of the drug (indicated on the left side of the figure). With the dose under 75 mg per day this value decreased, but it was
Fig. 1 (A) Longitudinal changes of the amplitude-ratios after an overloading mental task by administration of AMP in a patient. The ordinate: the value of amplitude-ratios after the task expressed as percentage. The abscissa: each amplitude-ratio at each time point within eleven minutes after the task, e.g. A₁ represents the amplitude-ratio at one minute after the task. Each curve therefore represents the amplitude-ratios within the eleven minutes after the task on each dose of AMP. Note remarkable augmentation of the amplitude-ratios after the task by AMP.

Fig. 1 (B) Comparison of the mean amplitude-ratio after the task between on high and low doses of AMP. The ordinate: the mean amplitude-ratio after the task expressed in terms of percentage.

The amplitude of P₁₀₀ of the baseline VEP before the task was reduced by administration of AMP in many subjects. A negative correlation was seen between the dose and the amplitude \( (r=-0.58, \ p<0.001) \) except one in whom the opposite tendency was seen. On the other hand, the latency of P₁₀₀ tended to become longer, but the changes were not correlated to the dose. For comparison with Saletu’s findings in normal subjects that the latencies of early peaks of SEP decreased by AMP, we tried to determine the latency and amplitude of N₄₀ of VEP, but failed to identify the N₄₀ in our depressive subjects who were given AMP.

It is of interest to see the correlation between the changes of VEP after the
overloading mental task and the changes of the baseline VEP before the task. As is shown in Fig. 2, there is a high negative correlation \((r=-0.61, p<0.001)\), provided that as the mean amplitude-ratio after the task we take only the ratio above 80% which is considered to be affected by the amplitude-augmenting action of the drug. As to the latency we could not see any relationship.

Previously we reported a more noticeable decrease in amplitude-ratios after the overloading mental task in depressive patients using a modification of Kadobayashi's method than that of normal controls matched in age and sex\(^9\). We considered this amplitude decrease to be due to the lowered excitability of the brain of depressive patients caused by the overloading mental task as Callaway\(^9\) noted. Our results that AMP diminished the amplitude-ratio reduction or caused the amplitude-augmentation might be related to the stimulatory effect of AMP on the brain of depressive patients. If this inference is correct, this is the first report on the stimulatory effect of AMP on patients detected by measuring cerebral evoked potentials, although Shagass et al\(^9\) has already reported on the normalization of SEP recovery function by imipramine and tranylcypromine in patients, and Saletu\(^9\) has also reported on the decrease in latency of early peaks of SEP by AMP in normal subjects.

This stimulatory effect of AMP appeared only in the dose of more than 75 mg per day, thus being consistent with the view of Saletu\(^9\) that changes in cerebral evoked potentials by psychotropic drugs are dose-dependent. On the other hand, when minor doses were given, only inhibitory qualities, as indicated by the decrease of the amplitude-ratios after the task, were observed.

The amplitude change of the baseline VEP by AMP in our study is in accordance with Shagass's findings\(^9\) that AMP decreased the amplitude of SEP along the entire time course of the response, and also with Saletu's findings\(^9\) that amplitude in the late response of SEP was decreased by AMP in normal subjects. Thus it might be considered that AMP causes the suppression of amplitude of cerebral evoked potentials in man regardless of the difference in sensory modality used. We could not find a consistent change in latency in the patients on a clinical dose of AMP, while Saletu\(^9\) reported the decrease in latency of late responses of SEP in normal subjects on a minor dose of the drug. Recently, Hendrickson et al\(^9\) also reported that AMP did not cause any changes in latency of auditory evoked potentials and SEP in patients with senile depression. These differences between depressive patients and normal subjects might imply the difference in the drug action on CNS between these two groups. Recently, Allison et al\(^9\) reported the possibility of extraneural origin of early peaks of VEP, and this might be the reason why the early peaks of VEP \((N_{10})\) could scarcely be identified in our depressive subjects on a clinical dose of AMP.

From the last finding in our study that a negative correlation was seen between the mean amplitude-ratio of \(P_{100}\) after the overloading mental task and the amplitude of the baseline VEP on AMP, it might be suggested that in depressive patients both the stimulatory and the inhibitory effect of AMP occurred simultaneously, relating each other.
Further investigation is now being undertaken to confirm these findings in a large number of subjects and to simplify the method for clinical application.

REFERENCES


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