On the Mechanism of the Increase of Blood Non-Protein Nitrogen in Eclampsia, Convulsion etc.*

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(Received for publication, May 24, 1952)

Although many disputes have been made regarding the quantitative behaviour of non-protein nitrogen of blood (N.P.N.) in eclampsia patients, it is now generally believed to increase. Also the increase of N.P.N. after delivery and operation has been reported by many authors. With respect to the mechanism of N.P.N. increase, Amano1)2) suggested that it is probably due to the stimulation of some cerebral center controlling the protein metabolism, because he found in dogs no increase of N.P.N. after convulsion by strychninum nitricum in contrast with a marked increase after that by picrotoxin. Akiyama3) inferred that the rise of N.P.N. in eclampsia is partially caused by the renal insufficiencies and muscular contraction, but mostly by some "convulsion toxin" which acts on the cerebral center of the protein metabolism. Eufinger4) put forward also similar opinion that the amount of N.P.N. is raised after eclampsia convulsions by an abnormal metabolic product rather than by the renal insufficiency. To acquire more accurate knowledge in this connection the experiments regarding N.P.N. after operation, delivery and convulsion have been undertaken which are dealt with in this account.

Experiments and Discussion

N.P.N. Increase due to the Eclampsia Convulsion, Delivery and Operation

At first, N.P.N. was estimated before and after eclampsia convulsion in 3 cases. N.P.N. increased slightly (+4.2—+5.6 mg/dl) as had been observed by Wada.5)
Further, in 4 cases of artificial abortion (5 to 7 months preg.) and 2 cases of normal labor, the amount of N.P.N. was seen to rise after delivery by +4.3 to +12.2 mg/dl, the average being +10.5 mg/dl, in accord with the results of Hohlweg, Gibuns, Shinoda, Nakai, Kuji, Wada and others.

But when phenobarbital, a hypnotic acting on the cerebral trunk, (0.15 to 0.2 g. a day) was given before as well as after delivery, N.P.N. showed almost no change (-2.0 to -1.7 mg/dl) in 4 cases of artificial abortion and in one of 2 cases of normal labor. In the remaining one of normal labor, N.P.N. increased only slightly (+1.2 mg/dl) in 3 hours after delivery. In this case the administration of phenobarbital was discontinued just after labor, and N.P.N. increased distinctly (+8.3 mg/dl) after 34 hours from delivery, but after subsequent re-administration of phenobarbital it decreased within 24 hours to a value +2.2 mg/dl above the one before delivery.

As to N.P.N. after operation, Nakayama and many other investigators reported that it begins to increase markedly soon after the operation, and after having reached the maximum in 2 to 3 days, becomes reduced to the normal in 7 days. In my 5 cases (Doléris op., panhysterectomy, excision of Fallopian tubes, abdominal cesarean section and supravaginal amputation of uterus) there occurred an increase of +5.4 to +14.1 mg/dl, +9.6 mg/dl on an average, but almost none (-1.3 to +1.9 mg/dl), when phenobarbital (0.2 g. a day) was given. In a case of abdominal cesarean section, in which phenobarbital was not given after the operation, it showed a high value on the second day and on administering the drug again on the third day, returned to the preoperative value.

From the above findings it might be said that N.P.N. increases after all of eclampsia convulsion, labor and operation, and that the increase in labor and operation at least is ascribable to the excitement of the cerebral trunk. Moreover, to study the mechanism of N.P.N. increase the writer carried out the following experiments:

1. A 10% solution of cardiazol, a convulsion drug acting on the cerebral trunk, (0.2 to 0.3 cc.) was intravenously injected to rabbits. 7 animals (weighing over 2 kg.) showed clonic, tonic convulsion and N.P.N. increased distinctly (+7.2 to +17.2 mg/dl, average +14.4 mg/dl), but in 3 animals, which exhibited no convulsion despite of almost the same dose of cardiazol, no change of N.P.N. (-0.2 to +1.1 mg/dl) happened.

2. 8 rabbits were intravenously injected a 0.1% strychnine solution, a peripheral convulsion drug, (0.3 to 0.4 cc.) to produce tonic, clonic convulsion. By this convulsion N.P.N. was also raised though little (+0.2 to +14.0 mg/dl, average +6.4 mg/dl), disagreeing with the result of Amano, who said that there is no increase after convulsion caused by
strychnine in dogs. In the same rabbits, 4 or 5 days later, convulsion was induced with strychnine (0.3 to 0.6 cc.) again after 30 minutes from preceding subcutaneous injection of 0.5 cc. of 10% phenobarbital, entailing almost no change of N.P.N. (-3.6 to +6.4 mg/dl, average +0.3 mg/dl). Since subcutaneous injection of mere phenobarbital does not alter the value of N.P.N., the N.P.N. increase by strychnine convulsion is mostly ascribed to the excitation of cerebral center.

To decide whether this center is localized in cortex or trunk, strychnine convulsion was induced in 5 animals which had been subcutaneously injected 30 minutes before with 0.2 to 0.3 g. chloratum hydratum, a cortical hypnotic. Hereby greater increase (+10.7 to +20.0 mg/dl, +14.8 mg/dl on an average) of N.P.N. took place than when strychnine alone was used. The rise of N.P.N. after strychnine convulsion thus looked to spring mostly in the shock of the cerebral trunk. So, in order to find in which part of the cerebral trunk the controlling center of N.P.N. is situated, an attempt was made to cause strychnine convulsion after having poured some anesthetics in hypothalamus, where the nuclei of autonomic nerves gather. Namely, taking 3 rabbits to the end in view, a very small hole was made in the skull which allowed a needle to arrive at nuclei hypothalamicus ventromedialis and hypothalamicus lateralis. The convulsion was given rise to in 15 minutes after pouring a drop of 10% phenobarbital either in nucleus hypothalamicus ventromedialis or in nucleus hypothalamicus lateralis. N.P.N. increased by +3.3 mg/dl on an average (-1.5 to +9 mg/dl) in the former case, and by +3.8 mg/dl on an average (+1.6 to +7.5 mg/dl) in the latter. The elevations reached only half of the height in the convulsion by mere strychnine (+6.4 mg/dl on an average), offering a proof that phenobarbital prevents hypothalamus from excitation. The inhibitory effect of phenobarbital here was not so distinct as when the drug was injected subcutaneously. This was probably because hypothalamus on the opposite side was not soaked with phenobarbital within so short time as 15 minutes, the interval till applying strychnine, and, hence a similar experiment was repeated moreover on 5 rabbits after prior treatment with 3% procainum hydrochloricum, without resultant increase of N.P.N. (when nucleus hypothalamicus ventromedialis was anesthetized -1.5 to +0.5 mg/dl, average -0.3 mg/dl; when nucleus hypothalamicus lateralis was anesthetized, -3.8 to +4.5 mg/dl, average +0.4 mg/dl) as expected. In these cases the minimum dose of strychnine requisite for developing convulsion was 0.53 cc. in averages, far greater than the mean minimum 0.3 cc. in the case with strychnine alone, and also greater that those after subcutaneous injection of 10% phenobarbital solution (0.45 cc.) and of chloratum hydratum (0.42 cc.).

Judging from what were observed, it is regarded as justified to suspect
that, in regulation of N.P.N. amount, cerebral trunk, particularly hypothalamus plays the most cardinal part.

Change in N.P.N. due to Direct Hypothalamus Invasion

Nucleus hypothalamicus ventromedialis or lateralis was punctured with a needle, employing 3 rabbits each, but the N.P.N. did not undergo any noticeable change (in the former case -0.7 to +3.8 mg/dl, mean +1.0 mg/dl and in the latter case -0.4 to +1.7 mg/dl, mean +0.7 mg/dl).

Next, the writer estimated the change of N.P.N. 15 minutes after giving a drop of Hinterin (posterior pituitary hormone), which is conceded to bear close relation with eclampsia, in hypothalamus in a similar manner. No increase of N.P.N. was found (-0.7 to +1.8 mg/dl, average -0.1 mg/dl) in 3 cases when nucleus hypothalamicus ventromedialis was reached by the hormone, but a slight increase (-3.8 to +7.5 mg/dl, average +2.1 mg/dl) in 5 cases when nucleus hypothalamicus lateralis was reached.

In the third, a drop of a 0.1% acetylcholine solution was applied to the hypothalamus as above and N.P.N. was determined 15 minutes after. When nucleus hypothalamicus ventromedialis was reached by the agent, there was even a slight decrease of it (+4.5 to -8 mg/dl, average -5.8 mg/dl), but a slight increase (+3.0 to +6.0 mg/dl, average +4.6 mg/dl) in all cases when nucleus hypothalamicus lateralis was reached. Namely, the N.P.N. increase is considered to ensue from the excitation of nucleus hypothalamicus lateralis.

In short, it is concluded that N.P.N. increases after operation, labor and convulsion by the stimulation of diencephalon, in particular of hypothalamus.

Cobb-Bailey, Go, Iwata, Tsukahara and others considered corpora quadrigemina of diencephalon to be the convulsion center, since Sherrington had mentioned that it is the most important part of the brain. Later Takahashi successfully demonstrated an epilepsy-like convulsion by heating corpora quadrigemina, and Miyoshi also considered the epilepsy convulsion to be due to the excitation of corpora quadrigemina. And at present many authors are of the opinion that the convulsion center exists in the cerebral trunk. As eclampsia convulsion closely resembles epilepsy convulsion, the former must also have a bearing on cerebral trunk. Consequently my experimental deduction that the control center of N.P.N. lies in hypothalamus especially in nucleus hypothalamicus lateralis and its neighbourhood supports the opinion of Kushima and coworkers who pointed to the cerebral trunk, and, among other parts, the hypothalamus as the center of eclampsia convulsion.
SUMMARY

1. Blood non-protein nitrogen (N.P.N.) increases after the convulsion in eclampsia, delivery and operation.
   a) The rise of N.P.N. after delivery and operation is prevented by phenobarbital.
   b) N.P.N. rises in rabbits remarkably after convulsion by cardiazol but only slightly after convulsion induced by strychnine. And in the latter case, no increase of N.P.N. is noticed at all when the rabbits are treated in advance with phenobarbital.
   c) If rabbits are treated before the strychnine convulsion with chloratum hydratum instead of phenobarbital, N.P.N. increase is not inhibited, but rather accelerated. To sum up, the behaviour of N.P.N. is mostly controlled by a cerebral center and this center is localized in the cerebral trunk.

2. Increase of N.P.N. hardly takes place when convulsion is caused by strychnine after previous treatment with phenobarbital or procainum hydrochloricum of hypothalamus, especially of nucleus hypothalmicus ventromedialis or lateralis, in other words, the center in question is most probably in hypothalamus.

3. When posterior pituitary hormone (Hinterin) or acetylcholine is dropped in nucleus hypothalmicus ventromedialis, no change in N.P.N. is observed. However, if nucleus hypothalmicus lateralis is stimulated in the same manner, N.P.N. increases though slight. Accordingly, the controlling center of N.P.N. must be sought in nucleus hypothalmicus lateralis and its neighbourhood.

4. The two facts that the controlling center of N.P.N. lies in hypothalamus and that N.P.N. increases after eclampsia convulsion give a support to the claim of Kushima that the center of eclampsia convulsion is situated in hypothalamus.

I am very grateful to both Profs. Shinoda and Kushima who were kind enough to give me instruction and guidance.

References

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