Invest Clin 14 (2): 82-86, 1973

VENEZUELAN EQUINE ENCEPHALOMYELITIS VIRUS INFECTION: EFFECT ON DOPAMINE METABOLISM OF MOUSE BRAIN. PRELIMINARY COMMUNICATION

Ernesto Bonilla * and Slavia Ryder **

ABSTRACT

Inoculation of VEE virus to mice produces an increase in brain dopamine and homovanillic acid. This rise possibly results from an increase in the levels of L-Tyrosine hydroxylase.

It is a known fact that Parkinson's disease can follow an acute encephalitis. Although the majority of cases are idiopathic, it has been suggested that those patients have experienced subclinical encephalitis (3). As a specific dopamine deficiency has been demonstrated in Parkinson's disease (4) we considered it of interest to study the effects of Venezuelan equine encephalomyelitis (VEE) virus infection on dopamine metabolism specially following recent reports suggesting that specific effects on monoamine metabolism might be the consequence of virus infection (7-9).

Albino mice, three to four weeks old, were inoculated intraperitoneally with 0.03 ml (containing 100 LD50) of the Guajira strain of VEE virus (10). The animals were killed by cervical dislocation on the sixth day after inoculation, when paralysis of the limbs was evident. Brains were weighed and stored frozen at −70°C, until analysed for dopamine (DA) and homovanillic acid (HVA) content (11). The brains of three mice were pooled for each determination. Sham inoculation was omitted because no difference was found in determinations on non-inoculated mice which thereafter were used as controls.

As shown in Table 1, VEE virus infection produces an increase in brain DA and HVA concentration ($p < 0.001$). If the animals are harvested (in groups of 27 mice) and tested for contents of DA and HVA daily after inoculation, the increase is evident beginning on day 5, when most of the mice show signs of encephalitis (tremor, ataxia, paralysis of the limbs), but

* *Section of Clinical Neurochemistry.*

** *Section of Virology, Instituto de Investigación Clínica, Facultad de Medicina, Universidad del Zulia, Apartado 1151, Maracaibo, Venezuela.*

GROUPS	N° OF MICE	DOPAMINE (µg/g OF BRAIN)	HOMOVANILLIC ACID (µg/g OF BRAIN)
CONTROLS	129	0.69 ± 0.10	0.12 ± 0.01
INFECTED	129	1.52 ± 0.12	0.18 ± 0.02

Table 1.– Concentration of Dopamine and Homovanillic acid in brains of mice infected with Venezuelan Equine Encephalomyelitis Virus. The mice were killed on the sixth day after inoculation.

not before, suggesting a possible relationship between multiplication of VEE virus and concentration of DA and HVA. Such a relationship has been found for HVA and herpes simplex virus (7).

Encephalitis developed after intracerebral inoculation of **Schizotrypanum cruzi** in mice did not produce any change in the brain levels of DA and HVA (Bonilla L and Bonilla E, unpublished results). It looks as if such changes are typical of different viral infections since they have not being found in several bacterial and protozoal infections examined (9).

The observed rise in brain DA and HVA concentrations could be explained in terms of an increase in the levels of tyrosine hydroxylase, the rate limiting step in catecholamine synthesis (6). The increment in enzyme protein could be due to an increased synthesis and/or to a reduction of its rate of proteolytic degradation. The rise in HVA concentration was smaller when compared with the increase in DA; therefore a retarded outflow of HVA from brain to blood is probably not the cause of our findings. On the contrary, an inflammatory process tends to accelerate the transport through the blood-brain barrier (1). This effect would explain the differences observed in the increments of DA and HVA seen in VEE virus infection; normally, a high production of DA will be accompanied by a similar increase of HVA (provided there is not an inhibition of monoaminooxidase). If in VEE virus infection there is an increase outflow of HVA together with an increase production of DA, the levels in brain HVA, although high, will not reach the higher values observed if an impairment of the outflow were not present.

Our results could also be explained in terms of a decrease in the levels of dopamine-b-hydroxylase. However, it is known that different pharmacological or physiologic stresses which produce increased neuronal activity elevate tissue levels of dopamine-b-hydroxylase and tyrosine hydroxylase (5). Besides, in spite of the large amount of dopamine-b-hydroxylase normally found in the neostriatum, the noradrenalin content in this region is relatively low. This contrast with the fact that 80% of cerebral dopamine is located in the striatum (2), suggesting that the main pathway in this structure is not concerned with the formation of noradrenaline. This being the case, any important increase in brain dopamine is not necessarily due to a decrease in dopamine-b-hydroxylase.

Experiments are in progress to determine whether the biochemical changes are limited to DA and HVA or to other monoamines, and assays of tyrosine hydroxylase and dopamine-beta-hydroxylase during viral infection will be done to test our hypothesis.

Whatever the mechanism underlying these observations, it is clear that VEE virus infection produces an increase in the activity of dopaminergic neurons. This effect could initiate the sequence of events leading to a destruction and loss of these cells and finally, to the development of parkinsonism.

AGRADECIMIENTO

Al técnico químico Carlos Valbuena por su excelente trabajo técnico.

Infección con el virus de la encéfalomielitis equina venezolana: efecto sobre el metabolismo de la dopamina en el cerebro del ratón. Comunicación preliminar.

Bonilla E and Ryder S (Instituto de Investigación Clínica, Facultad de Medicina, Universidad del Zulia, Maracaibo, Venezuela). **Invest Clin** 14(2): 82-86, 1973.- En ratones inoculados con el virus de la EEV se produce un incremento de la concentración de dopamina y del ácido homovanílico en el cerebro. Este aumento posiblemente es debido a una elevación en los niveles de la hidroxilasa de la tirosina.

REFERENCES

1– BAKAY L: The cerebral uptake of tritiated tetracycline from blood and cerebrospinal fluid under normal conditions and in experimental pneumococcal meningitis. J Neuropath 21: 424-436, 1962.

2– BERTLER A, ROSENGREN E: Ocurrence and distribution of dopamine in brain and other tissues. Experientia (Basel) 15: 10–11, 1959.

3– CALNE DB: Parkinsonism: physiology, pharmacologyy and treatment. (Arnold E, ed) London, 1970, p 25.

4– EHRINGER H, HORNYKIEWICZ O: Verteilung von Noradrenalin und Dopamin (3 Hydroxytyramin) im Gehirn des Menschen und ihr Verhalten bei Erkrankungen des extrapyramidalen systems. Klin Wochschr 38: 1236–1239, 1960.

5– KOPIN IJ: Control of synthesis, tranport and release of dopamine-betahydroxylase and tyrosine hydroxylasee, in New Concepts in Neurotransmitter Regulation (Mandell AJ, ed) Nex York, Plenum Press, 1973, pp 21–31.

6.– LEVITT M, SPECTOR S, SJOERDSMA A, UDENFRIEND S: Elucidation of the ratelimiting step in NE biosynthesis in the perfused guinea pig heart. J Pharmacology 148: 1–8, 1965

7– LYCKE E, ROOS BE: Effect on the monoamine metabolism of mouse brain by experimental herpes infection. Experientia (Basel) 24: 687–689, 1968.

8– LYCKE E, MODIGH K, ROOS BE: The monoamine metabolism in viral encephalitides of the mouse. I. Virological and biochemical results. Brain Res 23: 235–246, 1970.

9– LYCKE E, ROOS BE: The monoamine metabolism in viral encephalitides of the mouse. II. Turnover of monoamines in mice infected with herpes simplex virus. Brain Res 44: 603–613, 1972.

10– SOTO–ESCALONA A, FINOL LT, RYDER S: Estudio de un brote de encefalitis venezolana en el Distrito Páez, Estado Zulia, en octubre de 1968. Invest Clin 10 (31): 45–57, 1969.

11– SPANO PF, NEFF NH: Procedure for simultaneous determination of dopamine, 3–methoxy–4–hydroxyphenylacetic acid, and 3,4–dihydroxyphenylacetyc acid in brain. Anal Biochem 42: 113–118, 1971.