THE NERVE-MODULUS FOR ANESTHETICS

FOR some years this laboratory has examined the quantitative effects of local anesthetics upon nerve action-potentials. Full details of apparatus and methods will be published elsewhere. It was found that for sciatic nerve of *R. Pipiens*

$$T \log R = Z$$

when:

T is the elapsed time in minutes between the application of the anesthetic and a decrease in action potential of 80 per cent.

R is the ratio $\frac{\text{molarity—minimum effective molarity}}{\text{minimum effective molarity}}$

Z is a constant.

We propose to call the quantity Z the nerve-modulus for local anesthetics. It was found closely to approximate 5.50 for five local anesthetics of unrelated chemical structures.

In the determination of local anesthetic-potency it is a common practice to use the minimal effective concentration (Mm) as a criterion of potency. Mm is frequently determined by successively testing solutions of decreasing concentrations. Because the relationship between block-time and molarity is hyperbolic the experimental determination of the minimum effective concentration presents practical difficulties. The use of the modulus Z renders this procedure unnecessary as from it the minimum effective concentration can be readily calculated.

Thus

$$\text{Log } R = \frac{Z}{T}$$

$$R = \log^{-1} \frac{Z}{T}$$

and

$$R = \frac{M_1 - Mm}{Mm}$$

$$Mm = \frac{M_1}{1 + \log^{-1} \frac{Z}{T}}$$

or more conveniently (and because $Z = 5.50$)

$$Mm = \frac{M_1}{1 + \text{antilog} \left(\frac{5.50}{T}\right)}$$

Thus in comparing an anesthetic with procain the ratio:

$$\frac{M_1 \left(1 + \log^{-1} \frac{Z}{T_2}\right)}{M_2 \left(1 + \log^{-1} \frac{Z}{T_1}\right)} = P$$

When:

M_1 = molarity of procain
M_2 = molarity of anesthetic tested
T_1 = block-time for procain
T_2 = block-time for anesthetic tested
Z = modulus or 5.5
P = potency (relative to procain)

Consequently the minimum effective concentration of procain and the unknown may be compared without the determination of the Mm of either. When anesthetics differing widely in potency are compared it is not usually possible to use equimolar concentrations in testing them, because an effective concentration of one will be either too concentrated or too dilute for the other.

The modulus permits direct comparison of solutions of unlike molarities. To correct the block-time for differences in nerve-diameters the standard nerve diameter was arbitrarily taken as 500 micra. The block-time for a given molarity was found to vary as the square of the diameter of the nerve. Therefore it is a simple matter to correct an observed block-time to that for a standard nerve of 500 μ. In practice a concentration of anesthetic is selected that causes 80 per cent. block in from 3.5 to 12 minutes. Higher concentrations give inaccurate results because when excess anesthetic is present the molar/time relationship is not valid. Lower concentrations yielding long block-times are inconvenient for the same reason that renders the determination of Mm difficult. When a number of determinations of T have been made for one or more values of M the times are corrected to standard diameter, averaged, and Mm calculated. The validity of Mm can then be checked by direct experiment. When this is done, 45 minutes is arbitrarily taken as the time in which a decrease in the action potential must be observed in order for the concentration to be considered minimal. In the five anesthetics tested Mm calculated from Z closely corresponded with the experimentally determined values.

For anesthetics having prolonged action such as Nupercain the calculated Mm was found to exceed the determined Mm. These anesthetics block nerve-conduction for much longer periods than those for which the modulus was found to hold, recovery-time in some instances being as long as 3 or 4 hours contrasted with 30 minutes or less for anesthetics such as cocain and procain. The modulus proves useful in making rapid preliminary tests of new compounds. When it is found that the recovery time after 80 per cent. block is longer than 30 minutes, the calculated Mm should be checked by direct experiment before attempting to use the modulus to calculate the relative potency P. Further experiments are in progress.

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THE QUANTITATIVE RELATIONSHIP OF RIBOFLAVIN TO CATARACT FORMATION IN RATS

NUTRITIONAL cataract in rats due to avitaminosis was first described by Day, Langston and O'Brien.[1]

[1] P. L. Day, W. C. Langston and C. S. O'Brien, *Amer. Jour. Ophth.*, 14: 1005, 1931.