References and Notes

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Factors Involved in the Effect of Serotonin on Evoked Electrocortical Potentials

Serotonin, when it is injected into the common carotid artery, causes a transitory inhibition of the (ipsilateral) transcallosal response (Marrazzi *et al., 1, 2*). Marrazzi *et al.* conclude that serotonin inhibits the ipsilateral cortical synapses. However, the question arises whether serotonin may not exert its inhibiting effect upon the cortical synapses indirectly—that is, via subcortical or even extracerebral receptors such as the carotid sinus receptors. Bonvallet *et al.* (*3*) have demonstrated that an increase in excitation in the pressoreceptors leads to an inhibitory picture in the electroencephalogram, and Heymans *et al.* (*4*) have shown that serotonin has an excitatory effect upon the pressoreceptors in the sinus.

In cats anesthetized with dial-urethane (0.45 ml/kg), the right carotid sinus was denervated. Fine metal canulae were inserted into the common carotid artery on both sides, approximately 1 inch below the carotid sinus. Optically evoked potentials were recorded in the conventional manner from both visual areas. A short light flash was applied every 6.3 seconds. The standard procedure was to give ten control stimuli and then to inject the serotonin and to record another 50 responses. Injections into the innervated (left, *I*) artery and into the denervated (right, *D*) artery were alternated at intervals of not less than 30 minutes. Each injection yielded two sets of records, an ipsilateral (with respect to site of injection, *I*) one and a contralateral one (*C*). Thus four sets of records were available from each pair of injections, referred to as *II,* (innervated, ipsilateral), *IC* (innervated, contralateral); *DI* (denervated, ipsilateral); and *DC* (denervated, contralateral). We averaged the results in each of these four groups after we had converted the measured values to ratios with respect to unity, and we calculated the area between the curve connecting the (averaged) peaks of the responses and the straight line representing the mean of the (preinjection) control values for the four experimental situations. Areas below the control were designated as "minus," indicating inhibition, those above as "plus," indicating facilitation. Our results are based on 27 experiments with 1.25, 5.0, and 10.0 μg of serotonin per animal.

As is shown in Fig. 1, denervation of the carotid sinus does not abolish the effect of intracarotid injection of serotonin. However, quantitative differences between *II* and *DI* indicate that part of the cortical effect is induced from the carotid sinus and conveyed to the cortex via nervous pathways. Since effects are obtained from the denervated carotid on the ipsilateral (*DI*), as well as on the contralateral cortex (*DC*), the drug evidently excites receptor sites which have a bilateral modulating effect upon the optic cortex (*5*). Such receptors are in all probability located in the reticular core. Finally, differences between the ispi- and contralateral records point toward participation of a cortical receptor site sensitive to serotonin. From this evidence we conclude that the following three factors play a part in bringing about the cortical effect: (*x*) a nervous influence induced by stimulation of carotid sinus receptors, conveyed from there to the brain stem and from there via ascending unspecific diffuse systems to the ipsilateral and the contralateral cortex (*5*); (*y*) a bilateral nervous influence via ascending unspecific systems, activated by the drug at receptor elements located in the brain stem; (*z*) a direct influence of the drug in question on the cortical (*5*) synapses on the side of the injection. We further assume that the effects of these components add algebraically to bring about the cortical effect. The following equations indicate the way in which these factors are combined in the four experimental situations:

$$II: x + y + z \quad (1)$$

$$IC: x + y \quad (2)$$

$$DI: y + z \quad (3)$$

$$DC: y \quad (4)$$

$$\therefore \quad IC + DI - DC = II \quad (5)$$

The values obtained indicate that Eq. 5 is well satisfied by our experiments, although there is a residue of positive or negative sign. On the basis of Eqs. 2, 3, and 4, the time course of factors *x*, *y*, and *z* as $f(t)$ was calculated from the values of *IC, DI,* and *DC* at any time *t*. Figure 1 shows the result in smoothed average curves (ten values each). Furthermore, Fig. 1 shows that the curve $\Sigma\ (xyz)_t$ follows closely curve II_t. This is another indication that our assumptions and equations are valid.

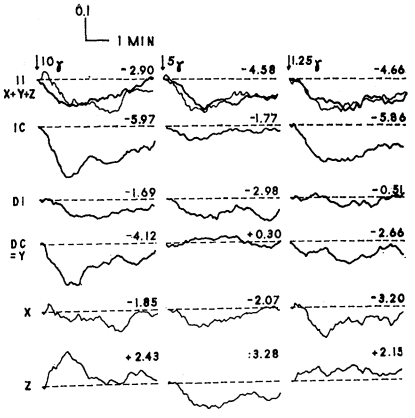

Fig. 1. Effect of serotonin (10, 5 and 1.25 μg) on optic potentials. The numbers at the top of each curve indicate the areas between preinjection values (dashed horizontal lines) and the peak-to-peak distance of the primary positive and negative response (solid lines). The abbreviations *II, IC, DI,* and *DC* indicate the different experimental situations described in the text; *x, y,* and *z* are the factors calculated on the basis of Eqs. 2, 3, and 4. All curves are smoothed averages (10 values) from mean values of 10 (10 μg), 9 (5 μg), and 8 (1.25 μg) experiments. The heavy line in the top section is II_t; the thin line is $(x+y+z)\ t$. Note the good coincidence. Abscissa: time; ordinate: one-tenth relative amplitude.

The method described here thus allows one to "fractionate" drug effects and to gain insight into the intimate mechanisms involved in the action of "centrally active" chemicals.

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5. *Cortical* here may be taken to mean "cortical or geniculate body, or both."

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