monia secretion and fixed base excretion associated with the development and recession of alkalosis from forced breathing. The results appear to be out of harmony with the base regulatory theory of ammonia production.

10051

Automaticity of Central Neurones After Nicotine Block of Synapses.

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The discovery that central neurones manifest a rhythmic electrical potential in the absence of deliberate sensory stimulation suggested that these cells possess an automatic beat homologous to that of the cardiac nodal cells. The possibility of nerve impulses, either from receptors or injured nerves or from closed circuits of interneurones* with long maintained activity, had not, however, been excluded. The persistence of a marked potential rhythm in the frog's olfactory bulb for hours after its complete removal and at a time when its only neural connections—the olfactory nerves and cerebral hemispheres—were electrically dead[1] seemed to eliminate any action of impulses from receptors or injured neurones. Since, however, stimulation of the olfactory nerves of such a preparation increases the bulb potentials or even reinitiates them after they have stopped and since this enhancement may persist for many minutes or hours following a brief stimulation[2] the existence of trapped impulses in closed circuits remained a definite possibility. This has been urged especially by Lorente de No.[3] In the present experiments it is shown that when synaptic conduction is blocked by nicotine the rhythmic slow potential waves of the isolated bulb are increased rather than abolished. It may be concluded, therefore, that the activity rhythm originates in single neurones and is immediately independent of any maintained or recurrent bombardment by conducted nerve impulses.

Nicotine has long been used to block synaptic transmission in

* This word is suggested as a condensation of "internuncial neurones" parallel to Sherrington's use of "motoneurone."

1 Gerard, R. W., and Young, J. Z., *Proc. Roy. Soc. B*, 1937, **122**, 343.

2 Libet, B., and Gerard, R. W., *Am. J. Physiol.*, 1938, **122**, 128 (P) and unpublished.

3 Lorente de No, R., *Am. J. Physiol.*, 1935, **113**, 505.

autonomic ganglia[4] and is also known to exert a curarizing action.[5,6] We have found no reference, however, to a similar effect on central synapses, though Langley[7] reported some experiments indicating its occurrence. The following facts evidence such a central blockade at all synapses tested:

1. Local application of 0.1% nicotine to the exposed spinal cord in the frog abolishes in 15 min. cross reflex responses to stimulation of the central end of a cut sciatic. Peripheral sciatic stimulation remains effective. Langley[7] published a similar observation. Even after strychninization, reflex block is produced by nicotine. Stronger nicotine (0.5%) abolishes motor responses to electrical stimulation of the cord itself though the lower concentrations do not.

2. Local application of 0.5% nicotine to the exposed optic lobes in a freshly amputated frog head abolishes the wink reflex elicited by touching the eye or nostril.

3. This same application eliminates, within 6 min, visual action potentials in the optic lobes, evoked by shining light in the eyes, while leaving unchanged the action potentials in the optic nerve. It also prevents the changes in olfactory bulb potentials otherwise produced by stimulation of the olfactory nerves.

4. Nicotine (2.5 mg per kilo) blocks tactile action potentials in the thalamus and somaesthetic radiations in the cat, evoked by touching hairs of a contralateral leg, within 4 min of its intravenous injection. At this concentration, the nicotine effect begins to wear off in 20 min and electric responses are again normal in an hour.

5. When the curarizing action of nicotine is prevented by clamping the vessels to the cat's leg, crossed and uncrossed spinal reflexes to it are abolished a few seconds after intravenous injection of the drug, when the motor nerve still gives good responses. Similar results are obtained for jaw and wink reflexes from the brain stem. Convulsive motor discharges may accompany synapse block.

6. Phrenic nerve action potentials continue after nicotine has abolished the other responses mentioned (see also [6]). Bursts continue at the usual frequency and intensity but are no longer spaced at regular intervals. Asphyxia still increases these discharges and eventually abolishes them. Stronger nicotine (10 to 13 mg per kilo) stops phrenic discharges while leaving cortical potentials slower (2 to 4 rather than 6 per second) and more regular than before.

[4] Langley, J. N., and Dickinson, W. L., *Proc. Roy. Soc. B*, 1889, **46**, 423.

[5] Rosenthal, *Centralb. f. Medicin. Wissensch.*, 1863, **1**, 47.

[6] Gold, H., and Modell, W., *J. Pharm. and Exp. Therap.*, 1936, **57**, 310.

[7] Langley, J. N., *J. Physiol.*, 1901, **27**, 233.

It seems clear, therefore, that the phrenic nerve cells can discharge nerve impulses when afferent connections are blocked—presumably even synapsing ones from the medullary respiratory center.† Similarly, in the isolated olfactory bulb the neurones maintain their rhythm in the absence of impinging nerve impulses, for the rhythm is preserved, actually enhanced and made more regular, even after half an hour's soaking in 0.5% nicotine. Since large regular waves from a cell mass are possible only with considerable synchronization of individual units, this interaction is also possible in the absence of transmitted nerve impulses.

The chemical and physical control of the activity of the single neurone and of the coördination of the group has been discussed[8,9] and additional studies on the frog (Libet and Gerard) and cat (Dubner and Gerard) will soon be published.

We are indebted to Mr. O. Sugar for assistance in some of the cat experiments.

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Preparation of Cocarboxylase.

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From the reaction mixture which I have recently described[1] the synthetic cocarboxylase (thiaminpyrophosphate) may be obtained in crystalline form by the following procedure: 500 mg sodium pyrophosphate are placed in a Pyrex test-tube and heated until all of the water of crystallization is removed. One cc of orthophosphoric acid (cp 85%) is placed in another large Pyrex tube and heated until a slight amount of solid deposit forms on the side of the tube. Then the pyrophosphate is added and the mixture gently heated until solution takes place. After cooling 500 mg vitamin B_1.HCl are added. The tube is placed in an oil bath of 155°, kept there for 3 min and constantly stirred. Then the tube is removed and after cooling the solid mass is dissolved in 10 cc of cold water. Cold

† The alternate possibility, that these synapses remain functional, is being further explored.

8 Gerard, R. W., *Cold Spring Harbor Symposia*, 1936, **4**, 292.

9 Blake, H., and Gerard, R. W., *Am. J. Physiol.*, 1937, **119**, 692.

1 Tauber, H., *J. Am. Chem. Soc.*, 1938, **60**, 730.