

Table V.—Nucleic acids content of normal and tetanized skeletal muscles. The values are referred to 1 g of fresh tissue and are given as μg of NA, DNA or RNA phosphorus.

Animals	Number of experiments	Homogenates			Sarcosomes				
		Total NA	NA/N	DNA	DNA/N	RNA	RNA/N	RNA	RNA/N
Normal . . .	7	179 ± 14	10.6	44 ± 8	2.6	135 ± 7	8.0	20 ± 4	16.6
Tetanized . .	7	142 ± 12	8.4	31 ± 8	1.8	112 ± 11	6.6	24 ± 1	15.0

In the experiments which were made on animals killed under Mg sulphate anaesthesia, no difference was found between normal and tetanized muscles. The values found for ATP were about 20% higher, those for AMP about 20% lower, than those obtained in the non-anaesthetized guinea pigs. This is probably due to the fact that Mg sulphate produces inhibition of ATP splitting, while ATP synthesis is not greatly affected.

Table II shows that the oxidative capacities of tetanized muscles against succinate, dl-alanine and cytochrome c are practically not modified. Oxidative phosphorylation (Table III) is also quite normal in the earlier stage of tetanus, but decreases slightly with the progress of time. ATPase activity (Table IV) of both homogenates and sarcosomes does not show any significant modification. A striking difference was observed, however, in ATPase activity of myofibrils, which increased strongly in those isolated from tetanized muscles.

Nucleic acids (Table V) are decreased in tetanized muscles. The decrease affects both desoxyribo- and ribonucleic acids.

From this rapid survey of the results obtained, one may conclude that (1) ATP is strongly decreased in tetanized muscles; (2) ATP formation through the processes of oxidative phosphorylation is at least normal; (3) ATPase activity of myofibrils is strongly increased. (4) Nucleic acids are decreased. The most probable phenomenon responsible for the decrease of ATP thus resides in the activation of ATPase located within myofibrils.

ATP is known to exert in the muscle 2 fundamental functions: (1) it acts as a plasticizing (relaxing agent), which conditions the thread disposition of the polymeric actomyosine molecules; (2) it acts as the physiological contracting agent, its splitting being responsible for the shortening of the actomyosine threads. It has been shown (BATHE-SMITH¹, BENDALL², WEBER and PORTZEHL³) that skeletal muscle in state of rigor mortis contains a very low amount of ATP and that rigor itself is probably due to the absence of the plasticizing action of ATP. Whether a mechanism, in some manner similar to that which occurs in rigor mortis, exists in the tetanized muscle is under investigation in this laboratory.

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¹ E. C. BATHE-SMITH and J. R. BENDALL, *J. Physiol.* **106**, 177 (1947); **110**, 47 (1949).

² J. R. BENDALL, *J. Physiol.* **144**, 71 (1951).

³ H. H. WEBER and H. PORTZEHL, in *Progress in Biophysics*, edited by J. A. V. BUTLER and J. T. RANDALL, Vol. 4 (Pergamon Press Ltd., London, 1954).

Riassunto

Gli Autori hanno studiato il metabolismo ossidativo e le frazioni fosforilate dell'omogenato di muscolo e di cuore in cavie normali e in cavie trattate con tossina tetanica. Nel muscolo tetanizzato si produce una forte diminuzione di ATP, insieme con un forte aumento di AMP e con un lieve aumento di ADP. La fosforilazione ossidativa è normale, la succinossidasi, la d-amino-acidossidasi e la citocromossidasi non subiscono modificazioni, la ATPasi dell'omogenato totale e quella mitocondriale non presentano differenze significative dal normale, ma la ATPasi presente nelle miofibrille è fortemente aumentata. Anche il contenuto di acidi ribo- e desossiribonucleinici è diminuito. Gli autori concludono che la diminuzione dell'ATP è dovuta ad una aumentata demolizione piuttosto che ad una diminuita sintesi.

Acetylcholine, Cholinergic Drugs, and Cortical Electrical Activity

It appears certain that acetylcholine (Ac) has some part to play at the level of the central nervous system, but this role has by no means been entirely clarified or put in its true context (FELDBERG¹).

The conclusions which may be drawn after analysis of the results obtained in the series of investigations, which have appeared on this subject since 1937, cannot be definite. A certain number of facts are, however, available for discussion.

It is possible to influence cortical electrical activity either by cholinergic or anti-cholinergic drugs; and the modifications obtained are very similar to functional physiological states which can be induced in the normal animal. In fact, the modifications induced by anti-cholinesterasic drugs, such as eserine and DFP, closely resemble the state of activation of the cortex (WESCOE and co-workers², FUNDERBURK and CASE³, BRADLEY and ELKES⁴), whereas those induced by atropine and other anticholinergic drugs resemble the state of rest or sleep (FUNDERBURK and CASE³, LONGO and coworkers⁵).

On the other hand, BONNET and BREMER⁶ have been able since 1937 to demonstrate a cortical action of Ac when injected by the carotid route, which was described as an increase in the amplitude and frequency of the

¹ W. FELDBERG, *Brit. Med. Bull.* **6**, 312 (1950).

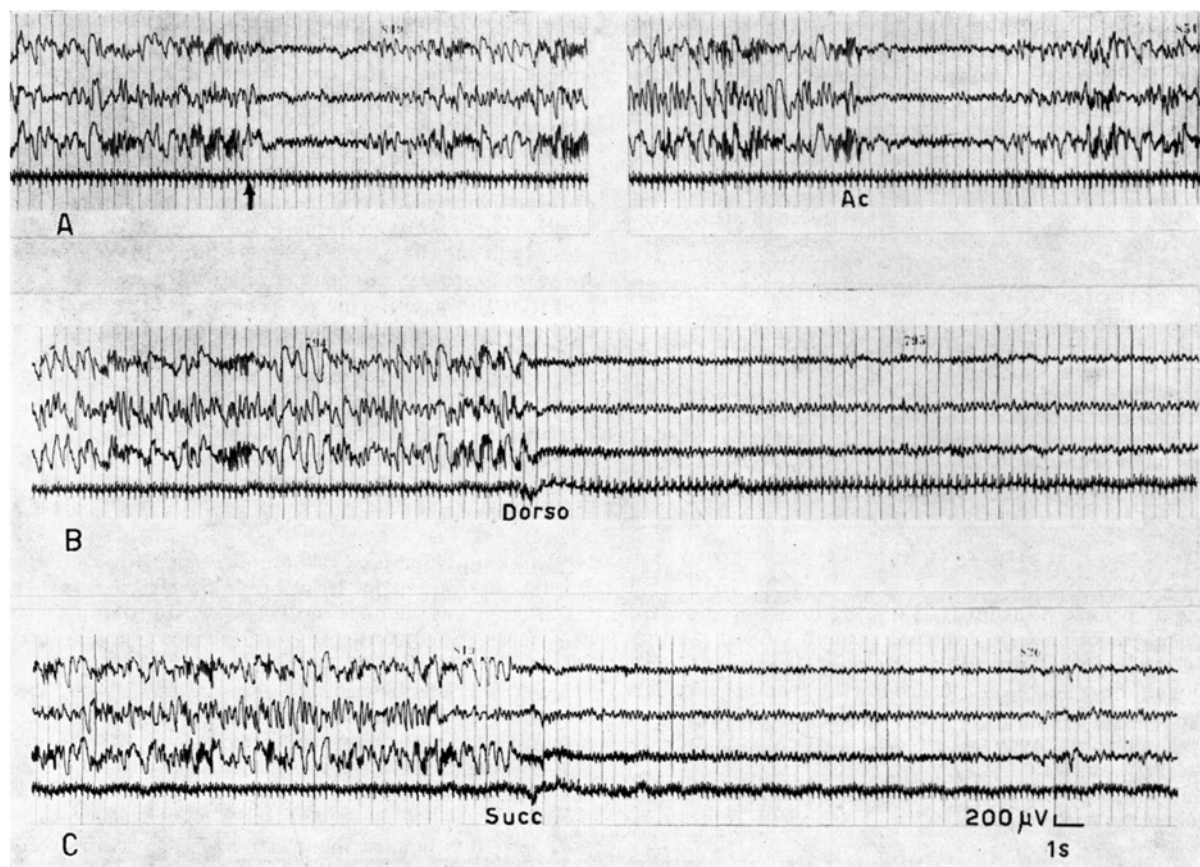
² W. C. WESCOE, R. E. GREEN, B. P. MC NAMARA, and S. KROP, *J. Pharmacol.* **92**, 63 (1948).

³ H. W. FUNDERBURK and T. J. CASE, *E.E.G. Clin. Neurophysiol.* **3**, 213 (1951).

⁴ P. B. BRADLEY and J. ELKES, *J. Physiol.* **120**, 14P (1953).

⁵ V. G. LONGO, G. P. VON BERGER, and D. BOVET, *J. Pharmacol.* **111**, 349 (1954).

⁶ V. BONNET and F. BREMER, *C. r. Soc. Biol.* **126**, 1271 (1937).



A. Analogy between cortical response (arousal reaction) to hand clap (arrow) and to the endocarotid injection of $0.2 \mu\text{g}$ of Acetylcholine (Ac). – B and C. More sustained arousal reaction to tactile stimuli: touching the back (Dorso) and to endocarotid injection of Succinylcholine ($5 \mu\text{g}$). Normal rabbits. Leads from top to bottom: Left frontoparietal. Left parieto-occipital. Right fronto-parietal. Control electrocardiogram.

spontaneous cortical potentials with prolongation of the afterdischarge of responses arising from the acoustic area after sound stimuli. MORUZZI¹ confirmed these results and in addition described a lowering of the threshold of faradic excitability of the cortex.

As far as the mechanism of action is concerned, it may be that acetylcholine interacts at the cortical level in consequence of a non-specific generalized impulse originating in the thalamus (diffuse projection thalamic system), and that this could be responsible for the fast activity that can be recorded in the cortex during the "arousal reaction". The same activity can be induced by administering eserine by the intravenous or intracarotid route (FUNDERBURK and CASE², BREMER and CHATONNET³) or by the deposition of Ac on the cortex treated with anti-cholinesteratic drugs (CHATFIELD and DEMPSEY⁴). MILLER and co-workers⁵, using strong concentrations of Ac *in loco*, were able to observe superimposition of spikes over this fast activity; spiking, however, was abolished after the cutting of thalamic radiations.

It could thus be argued that this fast activity is of acetylcholinergic origin: this may be shown by the fact that under the influence of atropine and other parasympatholytic drugs the fast waves in the cortex are no longer induced (LONGO¹).

A description is given of the results obtained by centrifugal intracarotid injection of acetylcholine in the rabbit, whose cortical activity was recorded.

In order to avoid any action on the reflexogenic carotid area, the vagus nerve was first cut and the superior cervical ganglion removed; enervation of the carotid body by the HEYMANS² method was then carried out; a cannula of polyvinyl resin was introduced into the internal carotid and ligatured above the bifurcation. Small doses of heparin were administered in order to keep the cannula clear. All the products were diluted in physiological saline and the quantity of liquid injected was kept constant (0.2 cm^3). Several central injections of saline were always made during the performance of the single experiments.

The electro-encephalographic changes can be recorded in the normal rabbit or in the rabbit curarized with Flaxedil and given artificial respiration to avoid artefacts induced by movements. A similar reaction to that induced by external stimuli (arousal reaction) is seen

¹ G. MORUZZI, Arch. Int. Physiol. 49, 33 (1939).

² H. W. FUNDERBURK and T. J. CASE, E.E.G. Clin. Neurophysiol. 3, 213 (1951).

³ F. BREMER and J. CHATONNET, Arch. Int. Physiol. 57, 106 (1949).

⁴ P. D. CHATFIELD and F. W. DEMPSEY, Amer. J. Physiol. 135, 633 (1942).

⁵ F. R. MILLER, G. W. STAVRAKY, and G. A. WOONTON, J. Neurophysiol. 3, 131 (1940).

¹ V. G. LONGO, Rendiconti Ist. Sup. Sanità (in press).

² C. HEYMANS, J. J. BOUCKAERT, and L. DAUTREBANDE, C. r. Soc. Biol. 109, 556 (1932).

after the injection of acetylcholine in doses varying, according to the sensitivity of the animal, from 0.1 to 1.0 μg . The drug also induces motor responses proportional to the dose, varying from torsion spasm towards the injected side, to flight movements.

Product	Dose provoking arousal reaction on the ECG when injected endo-carotid*.
Acetylcholine bromide	0.1-0.5
Tetramethylammonium iodide . .	0.5-1
Decamethonium iodide	2-5
Succinylcholine chloride	3-7
d-Tubocurarine chloride	10-20
Tetraethylammonium iodide . . .	Ineffective (200)
Hexamethonium bromide	Ineffective (200)
Flaxedil iodide.	Ineffective (200)

* Total dose expressed in μg of weight of free base.

The atropinized rabbit (1-3 mg/kg) does not show the "arousal reaction" to external stimuli (FUNDERBURK and CASE¹); intra-carotid injections of Ac can only give the awakening reaction picture on the tracing with larger doses (5-10 μg). The motor reaction, however, is always present, even when the cortical reaction is completely absent.

The results described above, which illustrate an action of acetylcholine achieved with doses even inferior to

¹ H. W. FUNDERBURK and T. J. CASE, E.E.G. Clin. Neurophysiol. 3, 213 (1951).

those needed to produce pharmacological effects at the level of the autonomic ganglia or the neuro-muscular junction, support the conception of a cholinergic mechanism of "activation" at the level of the central nervous system.

Experiments carried out with other drugs, however, have shown that the same cortical response could be obtained with other cholinergic substances, using higher doses. The results obtained are tabulated. It will be observed that the active products have, in common with Ac, a quaternary nitrogen, linked with methyl groups, and that the stimulating properties occur independently of the type of cholinergic action shown in other systems.

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Résumé

L'injection endocarotidienne centrifuge d'acétylcholine provoque chez le lapin, déjà sensible à la dose de 0,1-0,5 μg , une réponse motrice consistant en un spasme de torsion du côté injecté et, aux doses élevées, en une réaction de fuite.

Le tracé électroencéphalographique correspondant montre une réaction analogue à la «réaction d'arrêt» provoquée par des stimuli extérieurs.

A côté de l'acétylcholine, d'autres substances exercent des effets semblables: hydrate de tétraméthylammonium (1-2 μg); décaméthonium (2-5 μg); succinylcholine (3-7 μg); d-tubocurarine (5-10 μg). L'hydrate de tétraéthylammonium, l'hexaméthonium, et le Flaxédil sont par contre sans effet jusque à la dose de 200 μg .

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genommen sind, so ist es zu begrüßen, dass in einem Anhang Hinweise zum Anpacken der Aufgaben sowie ihre Lösungen gegeben werden.

Während sich in den angelsächsischen Ländern viele hervorragende Mathematiker mit dem weitverzweigten Gebiet der modernen Statistik beschäftigen, ist es auf dem europäischen Festland noch etwas still geblieben. Leider halten hier Vorurteile und mangelndes Interesse die meisten Mathematiker davon ab, sich auf eine Materie einzulassen, die für theoretische und für praktische Forschung gleichermaßen aussichtsreich ist. Die vorliegende Aufgabensammlung ist dazu berufen, helfend einzugreifen. Der Leser, der sich in die Methoden der mathematischen Statistik einarbeiten möchte, kann sich sein Studium viel anregender gestalten. Auch zur Verwendung in einem Seminar für vorgerückte Studenten kann das Buch bestens empfohlen werden.

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