Primary and secondary antibody responses following intraventricular, intravenous and subcutaneous administration of antigen

Primary antibody response					Secondary antibody response				
Amount of antigen injected (mg)	No. of rabbits[a]	Mean peak antibody titer (log_2) 5 days	8 days	11 days	Amount of antigen injected (mg)	No. of rabbits[a]	Mean peak antibody titer (log_2) 5 days	8 days	11 days
				Intraventricular injection					
0.1	3/5	0.6	1.4	1.0	1	4/5	1.6	1.0	0.8
1	5/6	0.4	1.5	2.0	1	5/6	3.2	2.5	1.8
10	6/7	0.6	1.8	2.2	10	7/7	4.3	4.0	3.4
				Intravenous injection					
0.1	2/6	0	0	0.4	1	5/6	1.8	1.6	1.2
1	2/5	0	0	0.6	1	5/5	2.2	2.3	1.5
10	8/8	0.4	2.0	2.7	10	8/8	3.7	3.8	3.0
				Subcutaneous injection					
0.1	0/6	0	0	0	1	0/6	0	0	0
1	1/7	0	0	0.3	1	2/7	0.3	0.4	0.3
10	5/8	0	0.4	1.5	10	5/8	2.3	1.8	1.0

[a] Numerator, number of rabbits with anti-human γ-globulin antibody; denominator, number of rabbits in group.

demonstrable antibody when injected intracorneally or intravitreously than when injected by other parenteral routes.

The mechanism by which foreign protein reaches immunologically competent cells from the cerebrospinal fluid is unknown. It was demonstrated in dogs that when radioiodinated human serum albumin is injected intrathecally, a cisternal fluid-plasma equilibrium is established in 16–20 h[5]. DUPONT et al.[6] suggested that red blood cells and albumin are cleared from the cerebrospinal fluid by separate mechanisms. They postulated that red blood cells are phagocytized by the mesothelial cells which line the subarachnoid space. SIMMONDS[7] demonstrated that the bilateral ligation of the cervical lymphatics does not affect the 'absorption rate' of the red blood cells from the brain cavity. Similar results were obtained on clearance of colloidal Au-198 particles from the cerebrospinal fluid[6]. However, these observations do not rule out the lymphatic pathways for the passage of soluble protein from the cerebrospinal fluid into the circulation.

The present study does not offer evidence on the immunological competence of choroid plexus cells. However, the possibility that choroid plexus may be a route by which protein particles cross the brain-blood barrier must be taken into account. It seems probable that choroid plexus may play a role by furnishing the site where the intraventricularly injected antigen meets the blood-borne immunologically competent cells. Indirect evidence in support of this hypothesis is the formation of 'round space aggregates of cells', resembling lymphoid follicles, in the choroid plexus of animals developing experimental allergic encephalomyelitis[8,9].

Résumé. Des lapins ont été immunisés avec de petites quantités de γ-globuline humaine par voie intraveineuse, sous-cutanée et par le ventricule latéral du cerveau. L'expérience met en évidence que l'immunisation par voie intraventriculaire est la plus efficace pour la production des anticorps.

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Postsynaptic Inhibition in Motoneurones Evoked from the Lower Reticular Formation

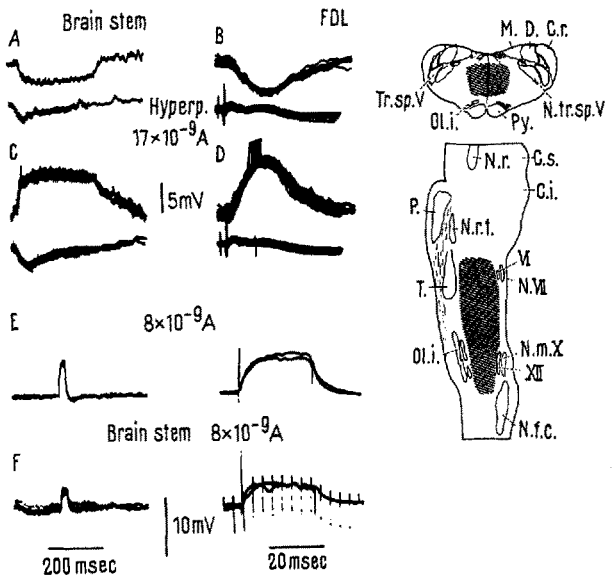
Powerful descending inhibition can be evoked from the lower reticular formation[1]. Stimulation of this region can give presynaptic inhibition through primary afferent depolarization and also inhibition of reflex paths at an interneuronal level[2], but there has been no clear demonstration of postsynaptic inhibition of motoneurones. Although hyperpolarizing responses can be evoked in motoneurones from the lower brain stem[3,4], it has been reported that these responses can neither be reversed on hyperpolarization of the membrane nor are they associated with the conductance changes typical of inhibitory postsynaptic potentials (IPSP)[3]. It will presently be demonstrated that large IPSPs can be evoked in motoneurones from the lower brain stem.

Intracellular recordings have been made from motoneurones in precollicular decerebrate cats either with intact spinal cord or with the spinal cord transected at

Th XII, except for the ventral quadrant ipsilateral to the side of recording. All the experiments were made under Flaxedil. There was frequently evidence of excitatory postsynaptic potentials but, in 77 of the 85 investigated flexor and extensor motoneurones, the dominating effect of brain stem stimulation was a hyperpolarization. 19 of the motoneurones were analysed with passage of current through the recording microelectrode, and in all of them an inward membrane current gave reversal to a depolarization. This shows that IPSPs are evoked from the brain stem as illustrated in the Figure. The IPSPs in A and B are evoked from the brain stem and the nerve to the flexor digitorum longus (FDL) respectively. The corresponding lower recordings, taken during the passage of a hyperpolarizing current, show the reversal to depolarization (C, D).

Pulses of current were also passed through the recording microelectrode and a compensating bridge[5] was employed to measure the membrane potential changes, as shown at two sweep speeds in E before and, in F, during stimulation of the brain stem. The reduced size of the potential in F shows that there is a large increase in membrane conductance during the IPSP. During stimulation of the brain stem the mono- and polysynaptic EPSPs are markedly decreased, but at least in part this may be due to presynaptic inhibition since dorsal root potentials are evoked at the strengths required to give IPSPs. There is also a reduction of the IS and SD component of the antidromically evoked spike potentials; presumably a result of the increased membrane conductance.

The hatched areas in the right-hand drawings of the Figure give the approximate transverse and longitudinal distribution of the region from which IPSPs are evoked in flexor and extensor motoneurones at low strengths of stimulation. There is a good correspondence with MAGOUN's inhibitory centre[1]. Controls taken at the beginning of the experiments, before curarization of the animals, showed that, at the stimulus intensities required to evoke IPSPs, there was a collapse of the ipsilateral decerebrate rigidity. Primary afferent depolarization as well as inhibition of interneurones of different reflex paths may play a role in the pronounced descending generalized motor inhibition from MAGOUN's inhibitory centre. Further studies are required to find out whether these different effects originate from selective regions of the brain stem, but in all likelihood the main action is through postsynaptic inhibition of motoneurones[7].



Precollicular decerebrate cat under Flaxedil. A–D: gastrocnemius-soleus motoneurone. The upper traces show the potentials recorded intracellularly with a K-citrate microelectrode (resistance 3.5 MΩ). Intracellular potential change in a positive direction is shown as an upward deflection. The lower traces were recorded from the dorsal root entry zone in lower L6 against an indifferent electrode in the muscle. Upward deflection denotes negativity of the central electrode. Record A shows a steady increase in membrane potential elicited by repetitive stimulation (150/sec) of the medial reticular formation of the medulla. Record B shows the IPSP produced in the same motoneurone by strong stimulation of the nerve to the flexor digitorum longus. Records C and D show the reversal of both these responses when the membrane was hyperpolarized by an inward current ($17 \cdot 10^{-9}$ A) applied through the recording microelectrode. E–F: posterior biceps-semitendinosus motoneurone. Change in membrane potential induced by rectangular pulse of depolarizing current ($8 \cdot 10^{-9}$ A) (E) and its depression (F) by repetitive stimulation (280/sec) of the medullary reticular formation. On the right-hand side are drawings of transverse and parasagittal section of the brain stem showing the region of the medial reticular formation whose repetitive stimulation produced IPSPs in both extensor and flexor motoneurones of the ipsilateral hindlimb (abbreviations as in [6]). The inhibitory region (hatched) covers mainly the nucleus reticularis pontis caudalis, gigantocellularis, ventralis and lateralis of Meessen and Olszewski as well as the region of the medial longitudinal fasciculus.

Riassunto. La stimolazione della formazione reticolare mediale del tronco dell'encefalo con intensità di corrente efficace a inibire la rigidità da decerebrazione produce un notevole aumento del potenziale di membrana in motoneuroni spinali estensori e flessori. Questa risposta è invertita dal passaggio di una corrente iperpolarizzante ed è associata ad un notevole aumento della conduttanza della membrana simile a quella che si ha durante i potenziali inibitori post-sinaptici (IPSP) prodotti negli stessi motoneuroni dalla stimolazione di afferenze primarie.

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[7] *Note added in proof:* In a paper appearing since our manuscript was submitted LLINAS and TERZUOLO (J. Neurophysiol. *27*, 579 (1964)) now report that true postsynaptic inhibition can be evoked from the bulbar reticular formation in extensor α-motoneurones.