

## *Comments on early inhibitions*

by

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### **SUMMARY**

COMMENTS ON EARLY INHIBITIONS

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*The author's early work on the retina contained the observation that the first effect of a flash tended to be an inhibition of the discharge in the optic nerve. This was called « pre-excitatory inhibition ». The present article is a review of a number of other cases in which early inhibitions have been observed. It is being maintained that their common denominator is a need for more complex messages to be written out on a « clean state » for which some time is required as well as for a uniform background holding chance variations of the active population of neurons in check.*

In thinking of how information is transmitted and organized and also when reasoning teleologically and asking about the purpose of a motor act we are inclined to consider excitation only and neglect inhibition. Perhaps I should give some typical examples of useful teleological questions to illustrate what I mean : why do we have two kinds of visual receptors instead of one only ? The answer to the why-question is that the two kinds of receptors serve two different purposes, daylight and night vision. Why do the bees execute the curious « *Schwänzeltanz* », observed by Y. FRISCH ? His answer was, as is well known, that by their manner of dancing they indicate direction to a source of honey (v. FRISCH, 1953). These two examples are chosen to show that teleological questions are likely to lead to sound experimental work and new biological insight. As I have pointed out elsewhere (GRANIT, 1972) how- and why questions supplement one another and blend well. Without the support of a teleological answer many observations are likely to be trivial, unless saved by a particularly penetrating analysis of the mechanisms concerned.

Now, as to the role of inhibition there lay in the heritage of SHERRINGTON the general understanding that one of its main purposes was to curb and transform an excitatory process so as to produce the necessary differentiation, precision and modelling of our experience. We possess numerous instances, especially from the field of vision, to show that inhibition really plays such a role.

My task in this lecture is to place before you some evidence from the experimental literature indicating that inhibitions also are used, as it were, to clean a field for a change of action, thus suggesting that the nervous organizations on occasion are in need of such operations. This statement can be reformulated in a slightly different way : cessation of a neural discharge may well be a necessary prelude to the generation of a new pattern.

In my early work on the retina I was very much impressed by the fact that a flash of light produced inhibition as its first effect. It is not my intention to review later work on retinal microphysiology in relation to inhibition but to return to a comment I made at the time as to the general sensory significance of this observation. The reason for this is that the same phenomenon has turned up since in other contexts. My statement was : « *from the point of view of sensation, it would be advantageous to an organism continuously subjected to light stimuli if each fresh stimulus entering the field were accompanied by changes which can first clear the ground, as it were making way for the new effect, before it is presented to the higher centres as another shower of impulses* » (GRANIT, 1947).

This teleological notion has independently been raised by SEARS (1973) in a different context (see below) and I myself have re-iterated it in my *Murlin Lecture* at Rochester, since published in an abbreviated version in the Edmonton Symposium on Control of Posture and Locomotion (GRANIT, 1973). At Rochester N.Y. Dr. DOTY responded to it by drawing my attention to an interesting experience from his work on swallowing. This is a complex reflex lasting over 500 msec and engaging two dozen motoneuron pools in a sequence ending up in the mobilization of oesophageal and gastro-oesophageal components. The reticular half-center for swallowing « *first inhibits almost all participating ipsilateral motoneurons, including those of the constrictors. Excitation is then delivered ipsilaterally to the leading complex* » (DOTY, RICHMOND and STOREY, 1967). For the retinal effect I introduced the term pre-excitatory inhibition and here, again, it seems appropriate.

Swallowing is a case in which a teleological explanation of the early inhibition makes some sense. The path must be swept clean before action. Another matter is then by what mechanism the initial silencing of the motoneurons is being achieved. This question embodies an ordinary neurophysiological research project. Is there any point at all in adding an explanation of a teleological nature? The most obvious answer is that teleological explanations implicate evolutionary theory. In this case it means that it has been an asset for the organisms, which have developed swallowing in the complex manner of the vertebrates, to have it initiated by an inhibition clearing the path. This development has had survival value. Thus the teleological hypothesis leads the experimenter straight into developmental physiology. It is further possible to investigate whether there are specific common elements in mechanisms initiated by pre-excitatory inhibition, considered teleologically. Why need these particular paths be cleared before action? How common are the cases covered by our teleological explanation? The most general answer to the need for such teleological questions is that they contribute a necessary element of understanding and stimulate research and thinking. For this reason I feel perfectly justified to consider cases of pre-excitatory inhibition teleologically.

NEWSOM-DAVIS and SEARS (1970) studied sudden loading during voluntary breathing manoeuvres by recording the electromyogram of an intercostal muscle. A sudden obstruction, inserted during the singing of a tone, gave an immediate inhibition whose latent period was of the order of 22 msec. A load-compensating reflex followed after 50-60 msec. The short latency of the inhibition suggested that it was induced by the GOLGI tendon organs of the intercostal muscle because recurrent inhibition has not been found in the respiratory motoneurons. Like many other muscles the intercostals are lacking tendon jerks (monosynaptic spindle reflexes) and so the tendon organ inhibition can act unopposed. The subsequent load compensation is likely to have been a cortically induced gamma-spindle response because it disappeared when a 1 % lignocaine solution was injected into the rib angles in order to block the gamma motoneurons. Commenting on the early inhibition SEARS (1973) thought one of its purposes being to give the central station time for selecting the adequate response to the disturbance, a notion similar to mine.

The same purpose may in the limb muscles be served by the inhibitory pause that interrupts an initial load compensation by the monosynaptic tendon jerk and which, as we know today, does give the cortical motoneurons their chance to influence the compensatory action to a change of load on a muscle. The most clear-cut evidence stems from the work of EVARTS (1973) on the monkey. The cortical pyramidal cells responded in 35 msec to a sudden increase of loading and influenced the muscle 10 msec later. The segmental monosynaptic excitation preceded these events with a latency of merely 12 msec. The inhibitory pause that followed it must have been a composite effect consisting of afterhyperpolarization, recurrent inhibition and GOLGI tendon organ inhibition. These components blend in action and together prevent — if I may say so — the less intelligent segmental monosynaptic response from handling a challenge whose full implications it cannot anticipate.

While in the swallowing reflex the teleological explanation merely required that the neuronal path be swept clear of interference, the two last cases have carried the basic notion one step further in the specification of purposiveness. This they have done by adding the notion that the ground is cleared in order to make time and room for a central effect which by engaging a larger number of neurons becomes capable of interpreting the full significance of the added obstruction. This formulation is closer to my original one (above), seeing that the retina itself is a nervous centre. It differs from the general idea that the swallowing reflex merely requires a silent background for the action of its two dozen motoneuron pools. Apparently this vital reflex cannot proceed in an orderly manner if the membrane potentials of the 24 pools of motoneurons vary in an unpredictable manner. The whole « machinery » is too delicately poised to be given over to chance. Hence the need for a uniform background to which the simplest answer is silence.

An interesting case is provided by reciprocal innervation. Here the teleological explanation is of long standing. There are clearly situations in which it is advantageous, e.g. that the extensors should be inhibited while the flexors contract. I need not expostulate with my colleagues about the teleology involved in reciprocal innervation. From the present point of view this case is included merely because in reaction time studies of agonist excitation and reciprocal antagonist inhibition, the latent period of the inhibition is shorter than that of excitation. HUFSCHMIDT and HUFSCHMIDT (1954) found the inhibition of the antagonist precede agonist excitation by some 15-20 msec, and EVARTS (1966) confirmed this finding in the monkey.

If reciprocal innervation is assumed to be a mechanism for exclusive mobilization of one partner of a pair around a joint, it is teleologically logical that the antagonist partner should be silenced from the very beginning of the motor act. It seems pointless to have the ground cleared for action *after*, instead of *before*, action. Furthermore, muscle receptors have complex effects upon all motoneurons around a joint, including any antagonist of their own muscle. These can hardly be desirable. Again the idea of the need for a clean field in order to facilitate prediction of the effect seems teleologically sound. But it is not merely a question of behaviour of the motoneurons actually engaged in the contraction, as was the case in swallowing, because the agonists themselves are not preliminarily silenced. It is rather a matter of keeping away possible complications from the opposing partner of a reciprocally connected pair.

As physiologists we are interested in how inhibition can precede excitation in a simple reaction time experiment, considering that PHILLIPS and his colleagues (LANDGREN, PHILLIPS and PORTER, 1962 ; KERNELL and WU, 1967) have shown that the only difference in time of arrival of excitatory and inhibitory impulses from the cortical colonies of pyramidal cells to the motoneurons is a delay corresponding merely to one additional synapse in the inhibitory path. Thus excitation and inhibition from the motor area to the reciprocally connected pair *could* arrive virtually at the same instant. In order to explain the result either excitation must be delayed or inhibition speeded up by some more direct route to the motoneurons. It is well known from studies of reaction time that excitation, indeed, is delayed by comparison with the possible minimum. I need merely refer to LUSCHEI, SASLOW and GLICKSTEIN (1967) for the experiments which have shown that an early electromyographic response with a latency of some 30 to 50 msec may slip through the system, while the reaction time to a click is of the order

of 80 msec and to light still longer, 150-160 msec. Fundamentally, there is nothing to prevent inhibition from being faster than excitation, by this or some other route. Measuring the reaction time imposes complex central processing for the acting agonist in response to the demand for specificity, speed and precision, while the antagonist merely need be thrown out of action as fast as possible. Thus, for instance, the command for inhibition to the antagonist may not require the cortical motor potential, preceding segmental excitation. However, the problem is open for experimental analysis.

In a recent paper KRANZ, ADORJANI and BAUMGARTNER (1973) studied the effect of a mild nociceptive electrical stimulation of the skin of the fingers and found it to produce an inhibition « *on most motoneurons* ». The tested ones were those of mm. *I dors. interosseus*, *ext. digit. indicis*, *flexor digit. prof.* The effect was ipsilateral only and did not occur in the absence of a perception of pain. It was ascribed to the delta group of fibres.

HAGBARTH (1960) and HAGBARTH and FINER (1963) had less stereotyped results with nociceptive reflexes from the lower limb. Thus stimulation of the plantar surface of the hallux excited *tensor fasciae femoris*, *sartorius*, *rectus femoris*, *tib. ant.*, *per. long.* and *ext. brev. digit.* It inhibited *glutaeus max.*, *vastus med.* and *lat.*, *gastroc.*, *soleus* and *flexor brev. digit.* HAGBARTH gives a value of 35-40 msec for the inhibition. To judge from his curves the earliest excitatory latencies are around 50-60 msec but, since excitation begins slowly, HAGBARTH is uncertain about the precise value.

The work with FINER was more concerned with the well-known excitatory and inhibitory skin areas of the leg (HAGBARTH, 1952) and their plasticity. These were stimulated at pain level with an electrical shock of 20 msec duration. The early area-dependent response was inhibition followed by rebound or, alternatively, excitation succeeded by a silent period. Either initial response had a latency of 60-80 msec. However, the question of precise latencies for excitation and inhibition was not specifically raised, as the authors were interested in demonstrating that during a month of stimulation with totally 500 stimuli an initial inhibition did not change into excitation. The plasticity actually observed referred to a delayed centrally organized response. The early segmental one only showed some habituation.

The common denominator in these experiments is that early inhibitions, even when preceded by a brief excitatory response, are early enough to stay premature action and give time for a defense reaction determined at a higher level (midbrain, cerebellum according to HAGBARTH and FINER). The human response to a painful skin stimulus is not identical with that of the spinal cat. A preliminary reflex organization responds « *meaningfully* » to the site of the stimulus (the HAGBARTH reflex area) but inhibition is inserted at an initial stage to make possible an adjustment to body posture that is of less importance for the fingers. Other central adjustments are required for them. But in both cases an early inhibition is needed to clear the ground and give higher stations time to elaborate the more complex response that can be written out only on a clean slate.

It is not my intention to go on indefinitely collecting examples that can be fitted to the original teleological hypothesis but I cannot leave out one very interesting example. This is from the work of SCHMIDT (1965) in which he reports that there is in the *Necturus* a « *short burst of efferent inhibitory impulses to the receptor preceding each active gill movement* » in respiration.

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## BIBLIOGRAPHY

- DOTY R.-W., RICHMOND W.-H. & STOREY A. (1967). *Effect of medullary lesions on coordination of deglutition*. *Exp. Neurol.*, **17** : 91-106.
- EVARTS E.-V. (1966). *Pyramidal tract activity associated with a conditioned hand movement in the monkey*. *J. Neurophysiol.*, **29** : 1011-1027.
- EVARTS E.-V. (1973). *Motor cortex reflexes associated with learned movements*. *Science*, **179** : 501-503.
- FRISCH K. v. (1953). *Aus dem Leben der Bienen*. 1 vol., Springer, Göttingen, Heidelberg.
- GRANIT R. (1947). « *Sensory Mechanisms of the Retina* », 1 vol. (pp. 62-63), Oxford Univ. Press.
- GRANIT R. (1972). *In defense of teleology*. In « *Brain and Human Behavior* » (Eds. A.G. KARCZMAR and J.C. ECCLES), 1 vol., Springer, Berlin, Heidelberg, New York.
- GRANIT R. (1973). *Demand and accomplishment in voluntary movement*. In « *Control of Posture and Locomotion* » (Eds. R.B. STEIN *et al.*), 1 vol., Plenum Press, New York.
- HAGBARTH K.-E. (1952). *Excitatory and inhibitory skin areas for flexor and extensor motoneurons*. *Acta physiol. scand.*, Suppl. 94.
- HAGBARTH K.-E. (1960). *Spinal withdrawal reflexes in the human limb*. *J. Neurol., Neurosurg. Psychiat.*, **23** : 222-227.
- HAGBARTH K.-E. & FINER B.-L. (1963). *The Plasticity of Human Withdrawal Reflexes to Noxious Skin Stimuli in Lower Limbs*. *Progr. Brain Res.*, **1** : 65-81.
- HUFSCHMIDT H.-J. & HUFSCHMIDT T. (1954). *Antagonist Inhibition as the Earliest Sign of a Sensory-Motor Reaction*. *Nature (London)*, **174** : 607.
- KERNELL D. & WU CHIEN-PING (1967). *Post-synaptic effects of cortical stimulation on forelimb motoneurons of the baboon*. *J. Physiol. (London)*, **191** : 673-690.
- KRANZ H., ADORJANI C. & BAUMGARTNER G. (1973). *The effect of nociceptive cutaneous stimuli on human motoneurons*. *Brain*, **96** : 571-590.
- LANDGREN S., PHILLIPS C.G. & PORTER R. (1962). *Cortical fields of origin of the monosynaptic pyramidal pathways to some alpha motoneurons of the baboon's hand and forearm*. *J. Physiol. (London)*, **161** : 112-125.
- LUSCHEI E., SASLOW C. & GLICKSTEIN M. (1967). *Muscle potentials in reaction time*. *Exp. Neurol.*, **18** : 429-442.
- NEWSON-DAVIS J. & SEARS T.A. (1970). *The proprioceptive reflex control of the intercostal muscles during their voluntary activation*. *J. Physiol. (London)*, **209** : 711-738.
- SCHMIDT R.S. (1965). *Amphibian acoustico-lateralis efferents*. *J. cell. comp. physiol.*, **65** : 155-162.
- SEARS T.-A. (1973). *Servo control of the intercostal muscles*. In « *New Developments in Electromyography and Clinical Neurophysiology* » (Ed. J.E. DESMETS) vol. 3, pp. 404-417.

## RÉSUMÉ

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#### Commentaires sur l'inhibition précoce

Le travail initial de l'auteur sur la rétine comportait cette observation que le premier effet d'un éclair tend à être une inhibition de la décharge dans le nerf optique ; ce qui fut appelé « *pre excitatory inhibition* ». Cet article-ci passe en revue un certain nombre d'autres cas dans lesquels une inhibition précoce a été observée. On maintient que leur commun dénominateur est la nécessité pour les messages suffisamment complexes d'être transcrits sur des « places nettes », ce qui exige aussi bien un délai qu'un arrière-plan uniforme tenant en arrêt les variations aléatoires de la population active des neurones.