## Inhibitory Interaction Between Spinal Reflexes to Primary Afferents

Recent investigations have revealed spinal reflexes depolarizing Ia, Ib and cutaneous afferents. These afferent systems display characteristic differences with respect to the types of afferents that are effective in causing depolarization and the receptive fields from which these actions are drawn[1].

Primary afferent depolarization can be recorded as a dorsal root potential (DRP) and the present investigation is based on observations of interactions between DRPs evoked from different sources. Stimulation of the sensorimotor cortex depolarizes cutaneous afferents and Ib afferents but not Ia afferents[2]. Following cortical stimulation there is a long-lasting depression of the DRP evoked from cutaneous afferents and from group I muscle afferents. Since volleys in these afferents give depolarization in afferents depolarized from cortex the depression could be due to presynaptic inhibition or to refractoriness in a common line. The present work has, however, revealed a DRP depression caused by another mechanism. The original finding was that cortical stimulation depresses the DRP evoked by group Ia volleys from flexor muscles. Further experiments revealed that volleys in the FRA (flexor reflex afferents) are also effective in depressing this Ia effect, and Figure 1 illustrates the effect of a volley in a cutaneous nerve on the DRP evoked by a train of Ia volleys from posterior biceps-semitendinosus (PBSt). Of the different afferents hitherto investigated, only Ia fibres are depolarized by Ia fibres from flexors[1] and since neither cortical stimulation nor volleys in FRA depolarize Ia fibres, it was of obvious interest to learn if there was a corresponding depression of the primary afferent depolarization in Ia fibres.

Further experiments have shown that this is the case. In Figure 2, A–C, a stimulus was applied to Ia fibres through a microelectrode inserted into the motor nucleus of gastrocnemius-soleus (G-S) and the test volley recorded in the nerve to G-S[3]. A train of Ia volleys from PBSt causes a depolarization in the G-S Ia terminals as is evidenced by the facilitation in B. Record C shows the removal of facilitation when a volley in the cutaneous superficial peroneal (SP) nerve precedes the conditioning Ia PBSt train as shown at slower speed in record D. The corresponding records E–H are intracellular from a G-S motoneurone. The unconditioned Ia EPSP is shown in E, and F shows the depression evoked by a train of Ia volleys from PBSt[4]. This depression is smaller in G when the sensorimotor cortex is also stimulated as is shown at slower sweep speed in H. Neither cortical stimulation nor volleys in the FRA have action on Ia fibres. It is postulated that the inhibition is exerted on interneurones of the reflex path from Ia to Ia. The mechanism may be postsynaptic inhibition of interneurones or depolarization of the terminals of the interneurones, i.e. presynaptic inhibition with respect to the actions exerted by impulses in interneurones. We favour the latter hypothesis for the reason that the characteristic long-lasting time course is similar to that of the action exerted from the FRA and from cortex on primary afferents.


[1] J. C. Eccles, F. Magni, and W. D. Willis, J. Physiol. *160*, 62 (1962). – J. C. Eccles, R. F. Schmidt, and W. D. Willis, Proc. XXII Inter. Congress, Vol. II, Leiden (1962). – J. C. Eccles, P. G. Kostyuk, and R. F. Schmidt, J. Physiol. *161*, 258 (1962).

[2] P. Andersen, J. C. Eccles, and T. A. Sears, Nature *194* (1962). – D. Carpenter, A. Lundberg, and U. Norrsell, Exper. *18*, 337 (1962).

[3] P. Wall, J. Physiol. *142*, 1 (1958).

[4] K. Frank and M. C. F. Fuortes, Fed. Proc. *16*, 39 (1957). – J. C. Eccles, R. M. Eccles, and F. Magni, J. Physiol. *159*, 147 (1961).


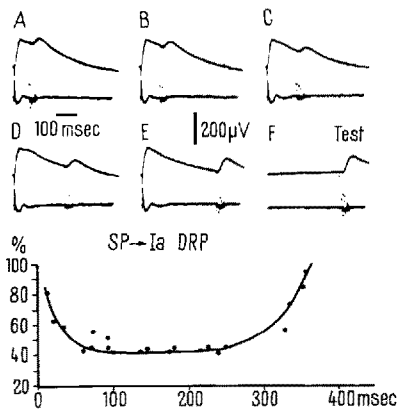


Fig. 1. The dorsal root potentials (DRP) in the upper traces were recorded from a dorsal root filament in lower L6. The filament was cut 15 mm from the entry into the cord and placed on two electrodes, one close to the entry zone and the other on the cut end. An upward deflection signals negativity of the central electrode. In the lower traces, recorded from the dorsal root entry zone in L7, negativity of the cord dorsum is upwards. Record F shows the unconditioned DRP evoked by a train of group Ia volleys from posterior biceps-semitendinosus (PBSt). In A–E stimulation of the cutaneous superficial peroneal nerve (SP) preceded the test at different intervals. The time course of the depression is shown in the graph. 100% on the ordinate is the height of the unconditioned test DRP. Time interval on the abscissa is between the arrival to the cord of the volley in the SP nerve and the first volley in the train from PBSt.

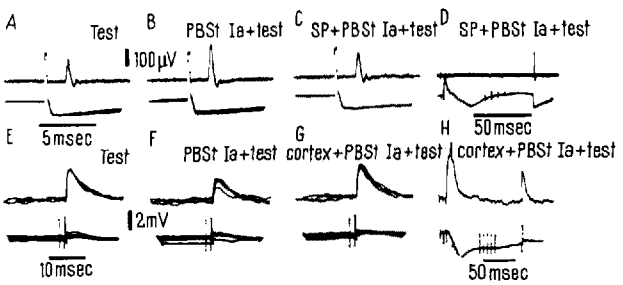


Fig. 2. Records A–D illustrate excitability measurement from Ia terminals. The testing stimulus was given through a microelectrode inserted into the motor nucleus of gastrocnemius-soleus (G-S) at the site where the maximal Ia focal potential could be recorded, and the discharge was recorded in the nerve to G-S. A shows the unconditioned test discharge. The increase in B was caused by a train of Ia volleys in the nerve to PBSt. C shows the removal of the increased excitability by a single volley in the cutaneous SP nerve. The time relationships are shown in the slow record D. Conditioning the SP nerve alone did not change the height of the test discharge. Spinal cat anaesthetized with chloraloze-urethane

E–H were obtained in another experiment and are intracellular records from a G-S motoneurone. E is the unconditioned Ia EPSP evoked from the G-S nerve. The depression in F was caused by a train of group Ia volleys in the PBSt nerve. G shows the removal of the EPSP depression by a train of stimuli to the contralateral sensorimotor cortex. The time relationships are shown in record H. Cortical stimulation alone did not change the height of the Ia EPSP.

In all records the lower traces were recorded from the S1 dorsal root entry zone. A–C and E–G are superimposed traces and D and H are single traces.

*Zusammenfassung.* Die Depolarisation der Ia Nervenfasern, welche durch eine Entladung in Ia Fasern eines Flexormuskelnerven reflektorisch ausgelöst werden kann, wird durch Reizung der sensorisch-motorischen Grosshirnrinde oder der Flexor-Reflex-Afferenten gehemmt.

Es wird vorausgesetzt, dass der Mechanismus dieser Hemmung präsynaptisch ist, und zwar durch eine Depolarisation der Endigungen der Interneuronen, welche die Wirkung von Ia- zu Ia-Afferenten übertragen.

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## Observations on the Renal Clearance and the Volume of Distribution of Polyfructosan-S, a New Inulin-Like Substance

It is well known that inulin is the only substance at present, the clearance of which is independent of its plasma concentration in all vertebrates investigated (SMITH[1]). Therefore inulin represents a standard for all other clearance substances.

Recently, we received a new inulin-like substance, Polyfructosan-S (producer: Laevosan Company, Linz, Donau, Austria), to examine the conditions of its renal excretion and the volume of distribution in man. Informative studies in dogs and rats by HARTH[2] have shown that the renal clearance and the 'space' of Polyfructosan-S (PFS) are in agreement with the corresponding values of inulin.

According to the manufacturer, PFS is a starch-like polymer, which contains about 15 to 18 fructose molecules especially. Similar to inulin the molecule is elongated, presumably with ramifications. The molecular weight is given as almost 3000. In comparison with inulin, there are a number of advantages: (1) PFS is totally soluble in cold water, (2) it is alkali-stable and (3) with weak acids it hydrolyzes only half as fast as inulin, a circumstance which is desirable insofar as inulin sometimes slightly hydrolyzes into smaller products during the dissolution of the ampuls in boiling water.

*Methods and Materials.* Since PFS and inulin form the same products by hydrolysis, the chemical analysis of both substances in plasma and urine is identical. Consequently, only successive studies in comparing PFS to inulin, with an interval of at least 1 day (for a complete removal) were possible. To diminish the limit of experimental error, the basal conditions in water and salt metabolism were kept constant in each case. Three days before the clearance studies were performed, the persons to be examined were put on a diet, which contained either 40 to 60 or about 150 mval sodium per day, and 0.5 to 1.0 g protein per kg body weight per day; the water balance was compensated. The clearance and 'space' ratios PFS/inulin were determined in 12 subjects (3 normal, 1 with healing acute glomerulonephritis, 4 with chronic glomerulonephritis, 3 with chronic pyelenophritis, 1 with essential hypertension), whereas the behaviour of PFS clearance after elevation of PFS plasma level was studied in 6 other subjects (2 normal, 1 with healing acute glomerulonephritis, 3 with chronic glomerulonephritis). No person examined had evidence of hypoproteinemia, endocrinopathy, heart failure or fluid retention. Determinations of the clearance and the volume of distribution of PFS and inulin, respectively, were performed simultaneously in 2 or 3 consecutive periods, lasting always 30 min. We used an 'inflow' procedure[3,4] with physiologically active extracellular fluid volume calculated by difference method. By means of a modified calibrated infusion technique, an equilibration of the clearance substances between plasma water and rapidly diffusible interstitial fluid (NICHOLS et al.[5], COTLOVE[6], MERTZ[7], MERTZ and EPPLER[8]) was hastened by a constant priming infusion over 20 min. Then the infusion rate was reduced and maintained constant at a value amounting to 1/4 of the initial rate for the continuous infusion. Equilibration was achieved about 40 to 50 min after the continuous infusion was started. In experiments in which the plasma level of PFS was elevated, we measured the clearance values as soon as a new equilibrium was reached.

For PFS and inulin analyses in urine and plasma, we used the method described by ROE et al.[9].

*Results and Conclusions.* In spite of the fact that only the successive method of comparison could be used, the clearance (C) and volume of distribution (VD) values of both substances are in good agreement. The mean values of $C_{PFS}$ and $C_{In}$ amounted to $101.6 \pm 27.7$ (range from 62 to 152) and $100.8 \pm 23.5$ (range from 64 to 142) ml/min and 1.73 $m^2$ body surface, respectively. We found a clearance ratio PFS/inulin of $1.016 \pm 0.099$. There is no difference in the variation of the values between normals and persons with renal diseases. We calculated a VD ratio PFS/inulin for the entire group of $1.005 \pm 0.093$. PFS clearances of patients with renal disease and of normal controls are independent of PFS plasma concentration over a range from 21.5 to 85.2 mg/100 ml. The mean deviation amounted to $-0.8 \pm 4.0\%$ of the control value. In all experiments PFS was non-toxic and produced no pyrogenic action.

Considering the standardization of the experimental conditions in each individual, the variability of the clearance ratio and of the 'space' ratio PFS/inulin has to be related mainly to endogenously changing glomerular filtration rate and extracellular fluid volume, respectively. Further studies about the usefulness of the PFS clearance are necessary. A complete description will be presented elsewhere[10]. According to the present data, it is suggested that PFS may be qualified as a substance for the deter-

[1] H. W. SMITH, *The Kidney. Structure and Function in Health and Disease* (Oxford University Press, New York 1951).
[2] O. HARTH, personal communication (Physiologisches Institut, Universität Mainz).
[3] D. P. MERTZ, Ärztl. Forschung *11*, I/8 (1957).
[4] D. P. MERTZ, Z. klin. Med. *156*, 35 (1959).
[5] G. NICHOLS Jr., N. NICHOLS, W. B. WEIL, and W. M. WALLACE, J. clin. Invest. *32*, 1299 (1953).
[6] E. COTLOVE, Amer. J. Physiol. *176*, 396 (1954).
[7] D. P. MERTZ, Klin. Wschr. *34*, 887 (1956); *Die extracelluläre Flüssigkeit* (Biochemie und Klink), (G. Thieme, Stuttgart 1962).
[8] D. P. MERTZ und F. EPPLER, Klin. Wschr. *37*, 588 (1959).
[9] J. H. ROE, J. H. EPSTEIN, and N. P. GOLDSTEIN, J. biol. Chem. *178*, 839 (1949).
[10] D. P. MERTZ und H. SARRE, in preparation.