

## CHANGE OF STRETCH REFLEX THRESHOLD IN SPASTICITY: EFFECT OF BOTULINUM TOXIN INJECTIONS

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### INTRODUCTION

Spasticity is a motor disorder characterised by a velocity-sensitive increase in stretch reflex with exaggerated jerk reflex as a component of upper motor neuron disease (10). This kind of muscle hypertonia is an outcome of many neurological lesions. In particular it occurs after lesion of corticospinal pathways, which are inhibitory on stretch reflex circuit. The normal control of posture is mediated by interactions between descending spinal pathways, which are either inhibitory (as the reticulospinal projections) or excitatory (as the vestibulospinal projections) on motoneurons innervating antigravitary muscles (14), which are the muscles undergoing to spasticity after lesions. An increased excitation on these motoneurons can be the result of lesions, both of the reticulospinal pathway, as after spinal cord injury, and of the cortical and subcortical structures, as stroke or head injury, which result in a disfacilitation of inhibitory reticulospinal pathways.

Resistance of the muscle to stretch in spasticity is due to two components: a neurogenic component that is the increased stiffness due to both muscle shortening, in fact the muscle is contracting even at rest length because of the decreased stretch reflex threshold (9), and to a muscular component due to muscle transformation: change of muscle fibres types consequent to paresis (4), change in muscle metabolism, substitution of muscle tissue with connective one and changing in motoneuronal firing rates (6, 7).

The decreased stretch reflex threshold in the spastic muscle has been demonstrated many years ago. In this work the authors quantified the hypertonus giving a score to the muscle stretch resistance (1 is a light spasticity, 4 is a very severe spasticity). Then they recorded the electromyographic (EMG) activity of elbow flexors during stretch and calculated the stretch reflex threshold. An higher decrease in stretch reflex threshold was recorded in more severe spasticity (score 4, high resistance to stretch) (15).

The role of stretch reflex threshold regulation in impaired motor control in hemiparetic subjects was studied by Levin and Feldman (11). They demonstrated a negative relationship between static stretch reflex excitability and the level of clinical spasticity.

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The chronic transformation of muscle spasticity was studied by Hufshmidt and Mauritz (8). They were able to separate the mechanical component of spasticity (both viscous and plastic, and elastic components) from the reflex component of muscle resistance to stretch and observed that only after one year of illness the mechanical components differ from normal ones, while the stretch reflex was out of normal range from the beginning.

The changing of stretch reflex threshold and gain has been studied by Thilmann et al. (18) recording the stretch reflex after 1-3 months by stroke and after 1 year. They confirm a progressive increase of the stretch reflex gain and decreased threshold from the beginning of the disease and a stabilisation about one year after the stroke, when the myogenic component of resistance to stretch, on respect to the neurogenic one, is increased.

The aim of the work is addressed on studying the neurogenic component of spasticity. In particular we want to answer the questions: *a)* How do the stretch reflex in spasticity undergoes to modifications as time goes by?, *b)* Are the threshold changes reversible with therapy? *c)* Do Botulinum Toxin injections, which have potent anti-spastic effect (3, 17), modify the stretch reflex threshold?

#### METHODS

In 20 subjects affected by muscle spasticity due to cerebral ictus, the stretch reflex threshold of wrist flexors was measured. They were affected by spasticity of right ( $n = 8$ ) or left ( $n = 13$ ) arm due to ischemic ( $n = 17$ ), hemorrhagic ( $n = 2$ ) or head injury ( $n = 2$ ), occurred from one to sixty-one months before (Tab. I). Five of them were examined by three months after injury and again

Tab. I - Case report.

case	sex	age (years old)	disease	time from the beginning of the disease (months)	side of hemiplegia
CL1	f	74	ischemic	32	left
CL2	m	58	ischemic	9	left
CG3	m	61	hemorrhagic	15	right
PP5	f	62	ischemic	29	right
FM6	f	51	ischemic	1	right
BB7	f	31	head injury	30	left
BA8	m	69	ischemic	34	left
PM10	m	63	ischemic	11	right
FR11	m	59	ischemic	47	left
AL12	m	22	head injury	36	left
MS16	m	69	ischemic	11	left
DA17	m	39	ischemic	61	left
SL18	m	50	ischemic	8	left
BE20	m	61	ischemic	30	left
UL24	m	58	ischemic	37	left
BG25	m	64	ischemic	6	left
ZE12	m	53	hemorrhagic	3	right
ML16	f	41	ischemic	2	right
GG11	m	58	ischemic	2	right
TR14	m	61	ischemic	1	left

after six months, to study the evolution of spasticity. Finally 16 out of 20 subjects were submitted to antispastic therapy with Botulinum toxin. All patients gave their informed consent to participate to this study. The effect of the therapy was evaluated applying the Ashworth scale (1) to quantify the hypertonus and measuring elbow's and wrist's angular Range of Motion (ROM) before and after treatment. The stretch reflex threshold of wrist flexors was recorded before and 10-30 days after the injection.

#### *Stretch reflex threshold examination.*

To measure the stretch reflex threshold, an isokinetic instrument (Kin-Com, Chattanooga) with an electromyographic device was used. The subject was set on a comfortable chair and asked to be relaxed; the forearm was fixed on the horizontal plane and the hand was fixed on the level of the machine, with the wrist articular angle aligned with the fulcrum of the instrument. The level moved to make a wrist angular excursion of  $70^\circ$ , from  $35^\circ$  of flexion to  $35^\circ$  of extension, at 8 different velocities: 5, 10, 20, 40, 50, 100, 150 and  $200^\circ/\text{sec}$ . During the passive wrist extension the flexors' and the extensors' surface EMG activity was recorded, applying two surface electrodes on the muscle (Fig. 1, left side). The EMG and angular excursion were recorded to be printed and analysed off-line.

The stretch reflex was visualised on EMG recordings as a sudden increase in activity. From EMG observations the velocity stretch reflex threshold is defined as the lower velocity at which the reflex is evoked, the angular stretch reflex threshold as the angular excursion at which the reflex appears (Fig. 1, right side).

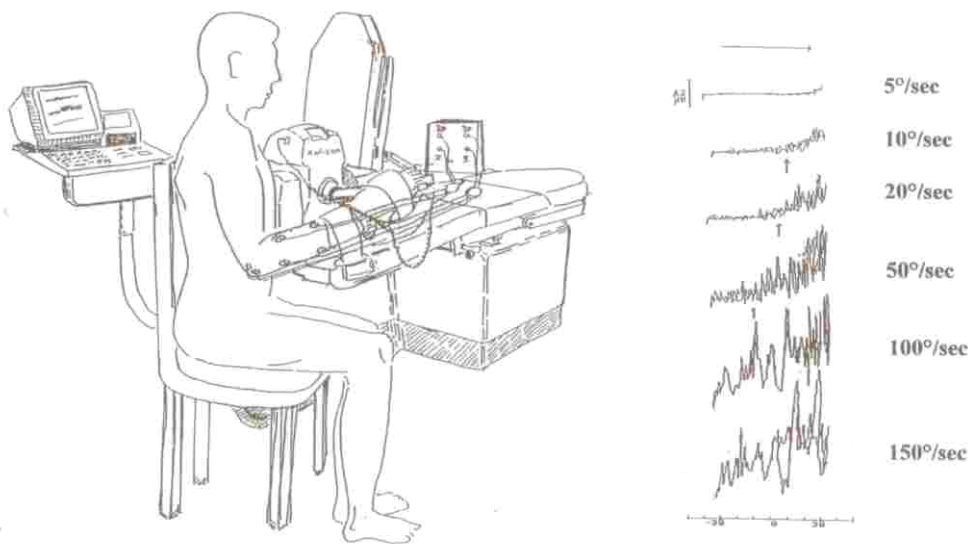


Fig. 1 - Drawing of the recording apparatus.

On the left the subject submitted to the stretch reflex threshold examination is set on a chair with the forearm fixed on the horizontal plane and the arm is passive moved by the Kin-Com machine's level, at with the hand of the subject is fixed. During eight different velocities movements, the wrist extensor and flexor muscle EMG activity is recorded by a two channel EMG recorder. All the data (motion velocity, displacement angle and EMG activity) were recorded on the computer and then printed and analysed off line. On the right the EMG activity of wrist flexor muscles during six different velocity passive angular movements from  $35^\circ$  of wrist flexion to  $35^\circ$  of extension are shown. The stretch reflex is identified by a sudden increase of EMG activity (arrows) and the angular threshold is the lower displacement at which the reflex appears, while the velocity threshold is the lower velocity at which the reflex appears; in this case it is  $10^\circ/\text{sec}$ .

### *Botulinum toxin injections.*

In the clinical assessment particular attention was given to: arm position at rest, resistance to muscle passive stretch in different directions, residual voluntary motion; the results of these observations, in fact, indicate the muscles to be treated. Botulinum toxin type A (Botox, Allergan), was reconstructed with saline to obtain a concentration of 100 UI in 1 ml. The injections were done in selected muscles, with EMG guide, using a recording needle (2). For each case, injections on different muscles (from two to five) of forearms were done, with a total amount of toxin, for treatment, ranging between 50 and 200 UI. The muscles more frequently injected were the flexor carpi (both ulnaris and radialis) and the flexors digitorum (both profundus and superficialis); more proximal muscles were injected only in five cases: pectoralis major, biceps brachii, brachioradialis and pronator terens.

## RESULTS

The velocity stretch reflex threshold of wrist flexors in the spastic forearm was ranging from 5 to 150°/sec. There is a negative correlation between velocity stretch reflex threshold and the age of pathology (Fig. 2), being lower the threshold in the older spasticity. If we compare the mean value of velocity threshold in subjects affected by ictus cerebri since six months ( $60.0 \pm 54.0^\circ/\text{sec}$ , range 20-150°/sec,  $n = 7$ ) with that of subjects affected by spasticity by more than 1 year ( $10.5 \pm 10.8^\circ/\text{sec}$ , range 5-40°/sec,  $n = 10$ ), it results significantly higher in the young spasticity ( $p < 0.05$ ).

In five subjects, being affected by mild spasticity (Ashworth scale value from 0 to 2) of right ( $n = 4$ ) or left ( $n = 1$ ) arm, one-three months after stroke, the velocity

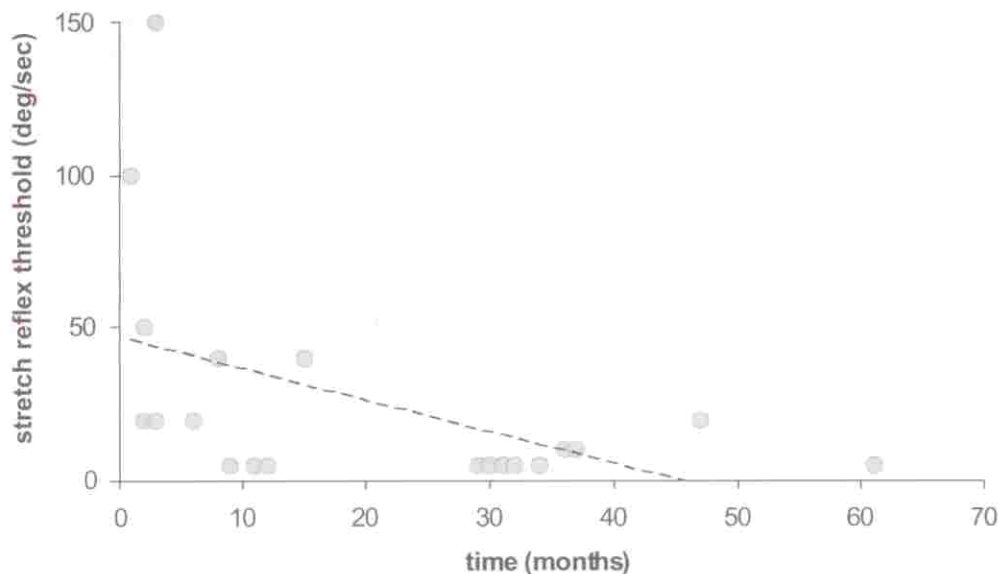


Fig. 2 - Change of stretch reflex threshold with aging of the disease.

In abscissa the time from the beginning of the disease in months, on ordinate the velocity stretch reflex threshold recorded, expressed in degree/second. A significant negative correlation was found (the regression line is  $x = 47.3 - 1.03 y$ ;  $R^2 = 0.28$ ;  $p < 0.05$ ).

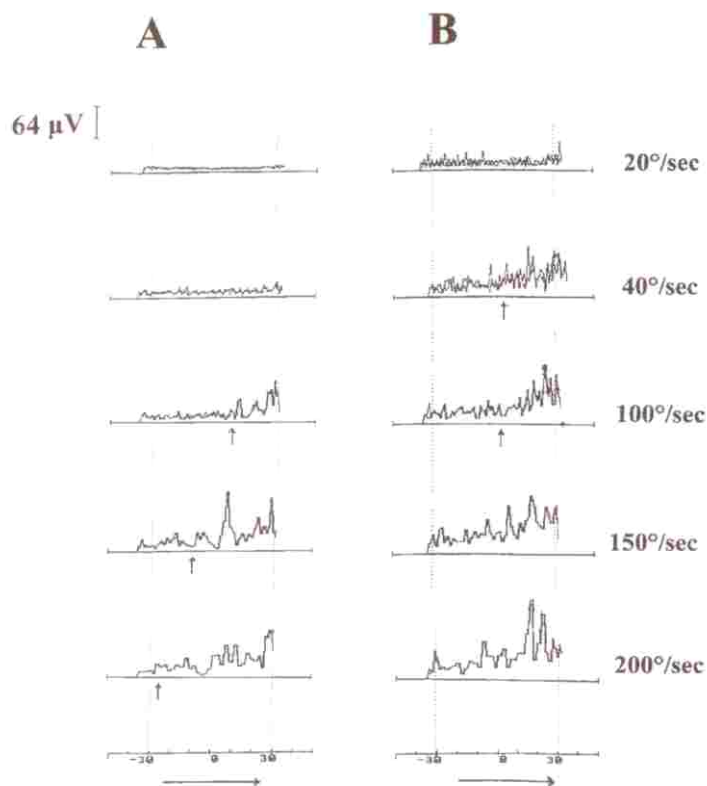


Fig. 3 - Change of stretch reflex threshold with time.

Flexor's EMG activity during passive extension from 35° of wrist flexion to 35° of extension at different increasing velocities from top to bottom in a subject affected by right hemiparesis with forearm spasticity (case FM6) one month after stroke: A and six months after: B. Arrows indicate the stretch reflex threshold. The velocity threshold was 100°/sec after one month and decreased to 40°/sec after six months.

stretch threshold resulted: 20°/sec in 2 subjects, 50°/sec, 100°/sec and 150°/sec in the other three subjects. Then they were tested after six-eight months and the stretch velocity threshold was unchanged in 2 and decreased in 3 of them, from 150 to 40°/sec, from 100 to 40°/sec (Fig. 3) and from 50 to 20°/sec.

Sixteen subjects affected by heavy spasticity of the right ( $n = 4$ ), or left ( $n = 12$ ) arm were treated with Botulinum toxin. In 14 out of 16 subjects we observed a decreased spasticity as detected by a decrease of at list 1 point in the Ashworth value of elbow and/or wrist spasticity. In the other two cases no antispastic response to Botulinum toxin was observed. The mean hypertonus Ashworth value before and after treatment was respectively  $2.4 \pm 1.0$  and  $1.6 \pm 1.1$  in elbow flexors,  $2.0 \pm 0.7$  and  $1.1 \pm 0.3$  in wrist flexors; both the differences being significant ( $p < 0.05$ ).

In five subjects no limitation of passive ROM was observed in elbow and wrist joints. In two subjects only wrist passive ROM limitation of respectively 45 and 50° were present before the treatment, but they disappeared after. In the remaining 7 subjects some passive ROM limitations were observed in the two articulations, both before and after treatment, but they decreased from  $62,9 \pm 33,9^\circ$  before to  $50,0 \pm 41,9^\circ$  after ( $n = 7$ ) in elbow, difference being statistically not significant and from  $53,9 \pm 15,6^\circ$  before to  $23,3 \pm 18,2^\circ$  after ( $n = 9$ ), for wrist articulation, the differences being statistically significant ( $p < 0.05$ ).

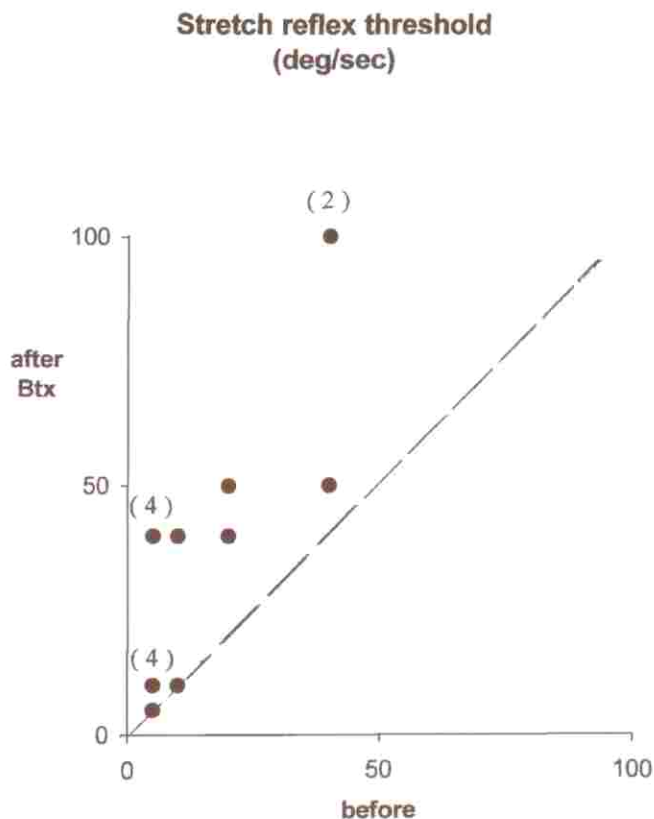


Fig. 4 - *Change of stretch reflex threshold after Botulinum toxin injection.*

In abscissa the velocity stretch reflex threshold (degree/second) before, in ordinate after the antispastic treatment with Botulinum toxin. Three points indicate more than one case: brackets numbers. The sketched line is the bisector of the angle between abscissa and ordinate: the two points following it indicate no change in stretch reflex threshold in that cases; the other points are in the upper space, indicating a decrease of stretch reflex threshold after the treatment.

In all the subjects except the two cases which didn't respond to Botulinum toxin, the stretch reflex threshold increased after the treatment (Fig. 4). Both subjects with heavy spasticity and very low threshold and subjects with milder spasticity and higher threshold showed an increase of stretch threshold with the decrease of spasticity, after the Botulinum toxin injections (Fig. 5).

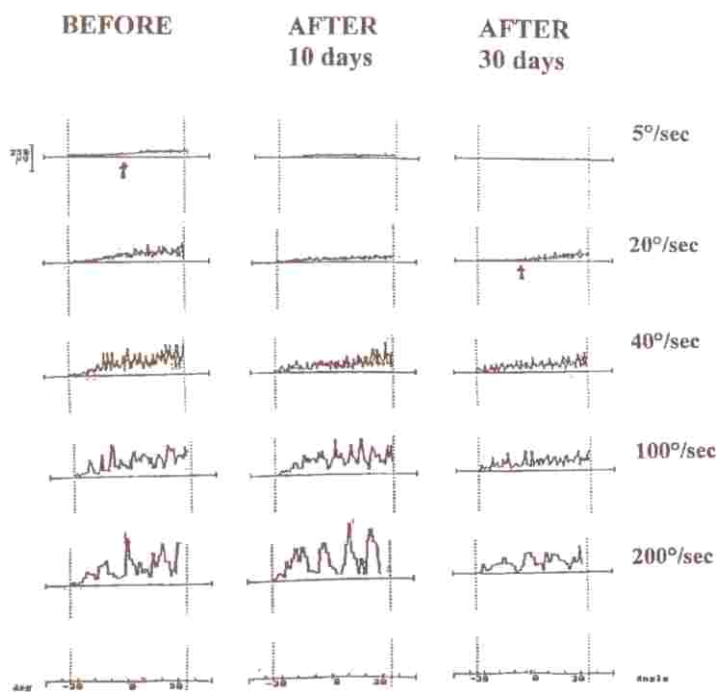
The mean velocity stretch reflex threshold was  $14,1 \pm 13,8^\circ/\text{sec}$  before Botulinum Toxin injection, and  $37,2 \pm 29,4^\circ/\text{sec}$  ten-thirty days after the treatment, the difference being statistically significant (paired t-test,  $n = 14$ ,  $p < 0.05$ ).

## DISCUSSION

The results of recording the EMG activity during stretch of wrist flexors indicate that a decrease of stretch reflex threshold characterizes the neurogenic component of spasticity, confirming previous studies on elbow flexors (8, 11, 15). The decreased threshold is present soon after the stroke but there is a progressive decreasing in the first year after acute disease (9, 18) as confirmed by the negative correlation between

Fig. 5 - Decrease of stretch reflex threshold after Botulinum toxin treatment.

Flexor's EMG activity during passive extension from 35° of wrist flexion to 35° of extension at different increasing velocities from top to bottom in a subject affected by left emiparesis with forearm spasticity (case FR11) before, 10 days and thirty days after stroke. Arrows indicate the stretch reflex threshold. The velocity stretch reflex was 5°/sec before the treatment and decreased, reaching the value of 20°/sec thirty days after the antispastic treatment.



stretch reflex threshold and age of the pathology (Fig. 2). This phenomenon could be explained by plastic readapting of spinal synaptic network: as many cortical and brainstem inputs on interneurons and motoneurons are lost after neuronal lesions, the lost synapses are replaced by a sort of sprouting of the integer inputs which are the afferent fusul inputs. These processes need some time and this fact could explain the progressive decrease of stretch reflex threshold after stroke (18). Muscle spasticity can be treated by local injections of Botulinum toxin (Btx) (17). This drug is a potent neurotoxin synthesized by the anaerobic bacterium *Clostridium botulinum*. There are seven known serotypes of Btx and the type A is commercially available to be used as antispastic treatment. The toxin blocks the release of Acetylcholine at the neuromuscular junction (3).

In addition to the effect on muscle contractile fibres, there is experimental evidence that Btx acts even on intrafusal muscle fibres (16). In rats injections of Btx into the masseter reduces muscle spindle afferent discharge in jaw muscle even before muscle tension is modified (5). A similar decrease in afferent discharge and stretch sensitivity occurs in muscle spindles of extraocular eye's muscles (12).

Recently an indirect neurophysiologic demonstration of Btx effects on intrafusal fibres in human being has been published. Comparing M, H reflexes amplitude and the responses to tendon tapping amplitude before and after two different antispastic treatments: Btx A or phenol nerve infiltration, they demonstrate that after Btx but not after phenol, there is a decrease in tendon reflex, that is in the fusul sensitivity effect (13).

All these studies suggest that the Btx blockade of Acetylcholine release at motor ending is earlier and more intensive in gamma than in alpha motoneurons. These observations explain the results of the present experiments demonstrating that the decreased stretch reflex threshold observed in spasticity can be reversed by injections of Btx in the spastic muscles (Fig. 5). The stretch reflex threshold recording after Btx injection in the spastic muscles and the confrontation with pre-treatment value, can quantify the intrafusal effect of Btx injection. The observation of an increase of stretch reflex threshold only in the muscles responsive to Btx antispastic treatment confirms that the antispastic effect of the drug is mainly due to the intrafusal action of the drug.

#### SUMMARY

Spasticity is a disorder of hypertonus associated with neurological diseases, characterized by a decrease in stretch reflex threshold.

Stretch reflex threshold of wrist flexors has been recorded in subjects affected by forearm spasticity due to acute neurological lesions, occurred from one to sixty-one months before. In all the subjects a decreased stretch reflex threshold was recorded and a negative correlation between stretch reflex threshold and time of the disease resulted.

In five subjects affected by mild spasticity the velocity stretch reflex threshold was tested one-three months after stroke and then six months later. In three cases a further decrease in stretch reflex threshold was recorded.

Sixteen subjects affected by heavy forearm spasticity (quantified by Ashworth scale), were treated with Botulinum toxin injections to reduce spasticity. Fourteen of 16 subjects were responsive to the antispastic therapy: a decrease of at least 1 point in the Ashworth scale was detected after the treatment. In all the responsive cases an increase of stretch reflex threshold was recorded.

The results confirm that the stretch reflex threshold is decreased in spastic muscles; it decreases progressively in time after the acute lesion. In addition, these results demonstrate that the decreased stretch reflex threshold can be reversed with Botulinum toxin injections. It is known that Botulinum toxin reduce the presynaptic release of Acetylcholine of neuromuscular synapses, but there are experimental evidences that it acts even on spindle's fibres, decreasing the sensitivity of intrafusal muscle fibres. This effect explains how Botulinum toxin increases the stretch reflex threshold in spastic muscles.

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