LETTERS TO THE EDITOR

INFLUENCE OF INTRATHECAL BACLOFEN ON SILENT PERIODS IN DYSTONIA

We read with great interest the article by Siebner et al.[7] reporting prolongation of silent periods induced by transcranial magnetic stimulation (TMS-SP) in a patient with generalized dystonia who received high-dose continuous intrathecal baclofen therapy. They discuss their findings as further evidence for the role of intracortical $GABA_B$-ergic interneurons in the generation of TMS-SP. Recently, we examined the TMS-SP before and after intrathecal baclofen bolus application in a 56-year-old woman with generalized dystonia. She had initially developed severe retrocollis 6 years earlier, but within 1 year, dystonic symptoms spread; prior to intrathecal baclofen application, she presented with severely disabling oromandibular, lingual, cervical, and axial dystonia, and with additional involvement of left upper and lower extremities. Dystonia movement severity score[2] was 45 (score range 0–120), and dystonia disability severity score[2] was 12 (score range 0–30). Family and drug history, cerebral magnetic resonance imaging, and laboratory tests were unremarkable. Oral medication including high-dose baclofen, trihexyphenidyl, sulpirid, and tetrabenazine had failed to improve symptoms significantly.

The TMS-SP were recorded from the right and left abductor digiti minimi (ADM) muscles while the patient contracted the target muscle on command for 5 s with near-maximum force. The TMS (Magstim 200, Magstim Co. Ltd., Spring Gardens, Whitland, UK) was applied with a round coil (14 cm outer diameter) over the vertex and adjusted slightly as needed. Current direction was clockwise for preferential activation of the right hemisphere, and anti-clockwise for the left hemisphere. Stimulus intensity was 60, 80, and 100% of stimulator output. Recordings were obtained with standard electrodiagnostic equipment (Viking, Nicolet Biomedical, Madison, Wisconsin) with sweeps of 500 ms, and filters set at 30 and 3,000 Hz.

In baseline recordings, TMS-SP were shorter in right than left ADM. Two hours after lumbar bolus application of 50 μg baclofen, soleus H reflexes were abolished, documenting the spinal efficacy of baclofen.[6] The TMS-SP increased on the right side compared to baseline, yet remained shorter than the left TMS-SP (Table 1). At this dose, there was no clinical effect of intrathecal baclofen, but the patient refused further test bolus applications in spite of information that higher doses might be effective.

Our observation is of interest because it may point to an additional spinal site of action of intrathecal baclofen affecting TMS-SP. The fate of a drug administered intrathecally depends on its physical and chemical properties, and on various pharmacodynamic and pharmacokinetic forces acting in parallel with cerebrospinal fluid (CSF) movement and gravity.[1] For baclofen, there is a lumbar to cervical concentration gradient of 4.1:1 following continuous infusion, and a similar lumbar CSF clearance following bolus application.[3] Hence, a cortical effect of intrathecal baclofen seems unlikely at that time, unless a combination occurred of (1) rapid cephalad bulk flow following bolus application giving rise to a temporarily higher CSF concentration of baclofen, plus (2) very high individual sensitivity. Indeed, the latter has been reported in spinal spasticity.[4] Alternatively, intrathecal baclofen may influence TMS-SP via a spinal action. Although the origin of TMS-SP is primarily cortical,[5] spinal mechanisms are involved as well.[8] This spinal contribution may be individually sensitive to intrathecal baclofen, at very low dose and predominantly unilateral in our patient, possibly based on a

Table 1. Silent periods (ms) in abductor digiti minimi muscle induced by TMS with incremental intensity before and after 50 μg intrathecal bolus injection of baclofen.

TMS (% intensity)	Before		After	
	Right	Left	Right	Left
60	39.0	63.0	31.3	70.0
80	45.8	101.5	59.0	116.0
100	81.0	152.0	112.5	141.5

TMS, transcranial magnetic stimulation.

nonstructural dysfunction on one side. Such a spinal effect of intrathecal baclofen may be surpassed at higher doses by a cortical effect on $GABA_B$-ergic intracortical interneurons.[7]

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REPLY

The findings by Kofler and colleagues raise the question whether the duration of the TMS-evoked silent period (TMS-SP) is a reliable marker of intracortical inhibitory activity. In normal subjects, it has been shown that spinal inhibition contributes to the early part of the TMS-SP, whereas the late part of the SP appears exclusively cortical in origin.[1,4] Therefore, the duration of the SP is thought to reflect merely the activity of cortical inhibitory circuitry.[1,2,4] However, this may not be the case in individuals with a shortened duration of the SP. In Dr. Kofler's case, the duration of the SP was markedly reduced in the right ADM muscle before baclofen bolus injection. Hence, one may hypothesize that spinal inhibition made a substantial contribution to the duration of the SP in this particular muscle. Under these circumstances, a baclofen-related increase in the activity of inhibitory spinal circuitry may result in a prolongation of the TMS-SP. In accordance with this notion, the SP of the left ADM muscle, which was considerably longer than that of the right ADM muscle, did not show any consistent changes after intrathecal baclofen bolus injection.

Recently, we reported a selective prolongation of the SP during high-dose continuous intrathecal baclofen therapy (CIBT) in a patient with generalized dystonia.[3] We did not observe any changes in the duration of the SP at daily dosages of 700 μg baclofen or less.[3] Following the line of reasoning stated above, it is likely that differences in the duration of the SP at baseline (i.e., before baclofen administration) between our patient and the patient studied by Kofler et al. account for the discrepant behavior of the SP. Because our patient already showed a normal duration of the SP before CIBT, we assume that the duration of the SP was exclusively determined by the activity of cortical inhibitory circuits. Thus, a baclofen-related reinforcement of spinal inhibition was masked by the longer-lasting cortical inhibition. An additional $GABA_B$-ergic effect at a cortical level may explain the prolongation of the SP at high dosages of intrathecally administered baclofen in our patient.[3]

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