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A single dose of lorazepam reduces paired-pulse suppression of median nerve evoked somatosensory evoked potentials

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Abstract

Paired-pulse behaviour in the somatosensory cortex is an approach to obtain insights into cortical processing modes and to obtain markers of changes of cortical excitability attributable to learning or pathological states. Numerous studies have demonstrated suppression of the response to the stimulus that follows a first one after a short interval, but the underlying mechanisms remain elusive, although there is agreement that GABAergic mechanisms seem to play a crucial role. We therefore aimed to explore the influence of the $GABA_A$ agonist lorazepam on paired-pulse somatosensory evoked potentials (SEPs). We recorded and analysed SEPs after paired median nerve stimulation in healthy individuals before and after they had received a single dose of 2.5 mg of lorazepam as compared with a control group receiving placebo. Paired-pulse suppression was expressed as a ratio of the amplitudes of the second and the first peaks. We found that, after lorazepam application, paired-pulse suppression of the cortical N20 component remained unchanged, but suppression of the N20–P25 complex was significantly reduced, indicative of GABAergic involvement in intracortical processing. Our data suggest that lorazepam most likely enhances inhibition within the cortical network of interneurons responsible for creating paired-pulse suppression, leading to reduced inhibitory drive with a subsequently reduced amount of suppression. The results provide further evidence that $GABA_A$-mediated mechanisms are involved in the generation of median nerve evoked paired-pulse suppression.

Introduction

Stimulation with pairs of stimuli in close succession (paired-pulse stimulation) has become a common tool for investigating paired-pulse suppression (PPS). PPS describes the phenomenon whereby, at short interstimulus intervals (ISIs), cortical responses to the second stimulus are significantly reduced. PPS is quantified in terms of the amplitude of the second response divided by the amplitude of the first response. Accordingly, small amplitude ratios are associated with strong PPS, and large amplitude ratios are associated with reduced PPS. For the somatosensory system, PPS in combination with somatosensory evoked potential (SEP) recordings over the primary somatosensory cortex has been increasingly used to investigate paired-pulse behaviour, in order to obtain insights into cortical processing modes and to obtain markers of changes of cortical excitability attributable to learning or pathological states (Allison, 1962; Schwartz & Shagass, 1964; Shagass & Schwartz, 1964; Ragert *et al.*, 2004; Höffken *et al.*, 2007, 2013a,b; Lenz *et al.*, 2011; Gatica Tossi *et al.*, 2013).

Despite substantial experimental and theoretical work, the mechanisms mediating paired-pulse behaviour are not fully understood. Because of differences in PPS between cortical and thalamic cells, it has been argued that inheritance of thalamic response properties is unlikely to account for long-lasting forward suppression (Wehr & Zador, 2005). For human subjects, on the basis of multichannel SEP recordings after paired median nerve stimulation, it has been shown that PPS is generated at least rostral to the brainstem nuclei (Höffken *et al.*, 2010). There is agreement that presynaptic mechanisms play a crucial role (Hashimoto & Kano, 1998). Wehr & Zador (2005) reported that, in the rat auditory cortex, GABA receptor-mediated inhibition does not play a major role in forward suppression for ISIs of < 100 ms. For longer ISIs, synaptic depression is assumed to be responsible for the observed PPS (Wehr & Zador, 2005). In the visual cortex, suppression is also more consistent with thalamocortical synaptic depression than with inhibition (Carandini *et al.*, 2002; Freeman *et al.*, 2002). There is also evidence for the

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involvement of glutamatergic transmission in the paired-pulse phenomenon (Takahashi *et al.*, 1996; von Gersdorff *et al.*, 1997).

In the motor domain, paired-pulse transcranial magnetic stimulation has been widely used to study intracortical inhibition of the human motor cortex. These studies provided several lines of evidence for a critical role of GABAergic, presumably $GABA_A$-mediated, inhibition (Kujirai *et al.*, 1993; Ziemann *et al.*, 1996, 2001; Werhahn *et al.*, 1999; Hanajima *et al.*, 2003; Florian *et al.*, 2008), although the involvement of $GABA_B$ has also been advocated (Porter & Nieves, 2004), owing to pharmacological interventions (Florian *et al.*, 2008) or based on the timing of long-interval intracortical inhibition (Fitzgerald *et al.*, 2009).

Given the overwhelming evidence from motor cortex studies for a critical role of $GABA_A$, we sought to revisit the $GABA_A$ influence on PPS in the primary somatosensory cortex of healthy adults. We found that, after lorazepam application, PPS of the cortical N20 component remained unchanged, but suppression of the N20–P25 complex was significantly reduced, indicative of GABAergic involvement in intracortical processing.

Materials and methods

Subjects

We investigated two groups of right-handed subjects: the target group (lorazepam) consisted of 13 subjects (six females and seven males; mean age, 24.6 years; standard deviation, $\pm$ 2.5 years); the control group (placebo) consisted of 10 subjects (five females and five males; mean age, 25.9 years; standard deviation, $\pm$3.6 years). All subjects underwent clinical neurological investigations to exclude somatic illness before their participation, and gave their written informed consent. The study was approved by the local Ethics Committee, and was performed in accordance with the Declaration of Helsinki.

Paired-pulse stimulation

To study changes in PPS, we applied a paired-pulse protocol described in a recent review and systematic analysis by Höffken *et al.* (2013a,b). It consists of paired electrical median nerve stimulation with an ISI of 30 ms. Nerve stimulation of the right side was performed with a block electrode on the wrist (pulse width of rectangular pulse of 0.2 ms; repetition rate of paired stimuli of 2 Hz). To verify the correct positioning of the stimulation electrode, subjects had to report a prickling sensation in the thumb, index, and middle finger. The stimulation intensity was chosen at 2.5-fold of the somatosensory threshold, and was kept constant for each subject before and after administration of drug. In all subjects, the stimulation intensity evoked a small twitch of the thenar muscles. During stimulation, subjects were seated in a comfortable chair and were instructed to relax but to stay awake with eyes closed.

Electroencephalography signals were recorded continuously with Ag–AgCl electrodes (resistance, < 5 kΩ) between C3′ and Fz as the reference. C3′ is located over the left primary somatosensory cortex (SI), 2 cm posterior to C3, according to the 10/20 system. The electroencephalography signals were amplified with a bandwidth of 0.1–1000 Hz and digitized at 2.5 kHz with the BrainAmp Amplifier (Brainproducts, Munich, Germany). The electrical potentials were segmented in epochs from – 50 ms to 200 ms, baseline-corrected, and averaged. Latencies and peak-to-peak amplitudes of the cortical N20 and the N20–P25 response components were compared before and after drug administration. PPS was calculated as a ratio of the amplitude of the second response peak (*A*2) and the amplitude of the first response peak (*A*1), i.e. *A*2/*A*1 (Fig. 1). Analysis was performed by a blinded coworker who was not involved in data recording, using BRAINVISION ANALYZER (Brainproducts). A repeated-measures ANOVA with the within-subjects factor 'course: before/after' and the between-subjects factor 'group' (lorazepam group vs. control group) was performed.

When repeated-measures ANOVAS were used, all *F*-ratios associated with the repeated-measures factors were assessed by the use of degrees of freedom corrected with the Wilks' lambda procedure for controlling type I error. All statistical analyses were performed with SPSS 17 (SPSS, Chicago, IL, USA).

Ectroencephalography recordings were performed in two sessions: the first session was used to obtain baseline data (before), and the second session started 75 min after intake of lorazepam (after). Each session contained a total number of 1000 paired-pulse stimuli. Medication consisted of a waver either of placebo or of 2.5 mg of lorazepam, and was administered in a pseudorandomized and double-blinded manner. Immediately after the end of the recording, blood samples were taken to quantify the plasma level of lorazepam.

Results

In repeated-measures ANOVA with the within-groups factor before–after and the between-subjects factor group (lorazepam group vs. control group), analysis of latencies and peak-to peak amplitudes of both the N20 and the N20–P25 components revealed no significant change between the groups before and after lorazepam intake (F = 1.757, P = 0.179; Table 1). In the placebo group, the

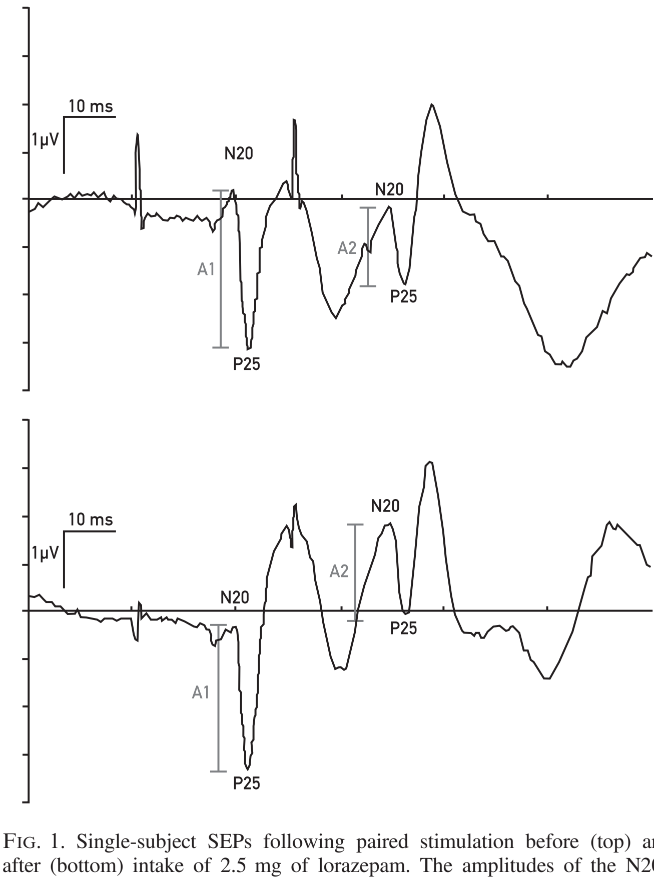

FIG. 1. Single-subject SEPs following paired stimulation before (top) and after (bottom) intake of 2.5 mg of lorazepam. The amplitudes of the N20–P25 complex (*A*1 and *A*2) are marked.

TABLE 1. Amplitude and excitability parameters (means and standard errors of the mean) and *P*-values of *t*-tests of differences after administration of placebo or lorazepam

Parameter	Group	Mean	SD	Unit	*t*-value	*P*-value
*A*2/*A*1	Placebo	−0.057	0.079		−2.879	0.009
	Lorazepam	0.220	0.056			
*A*1	Placebo	−0.146	0.415	μV	0.911	0.373
	Lorazepam	−0.595	0.277	μV		
*A*2	Placebo	−0.130	0.147	μV	−1.258	0.223
	Lorazepam	0.194	0.193	μV		
N20*	Placebo	−0.013	0.238	μV	0.651	0.522
	Lorazepam	−0.232	0.226	μV		
N20†	Placebo	−0.121	0.315	μV	0.584	0.566
	Lorazepam	−0.324	0.173	μV		
P25*	Placebo	0.192	0.350	μV	0.832	0.415
	Lorazepam	−0.179	0.274	μV		
P25†	Placebo	−0.235	0.592	μV	0.075	0.941
	Lorazepam	−0.286	0.360	μV		

*A*1, amplitude of the first response peak; *A*2, amplitude of the second response peak; SD, standard deviation.
*Components of the SEP after the first of the paired stimuli.
†Components of the SEP after the second of the paired stimuli.

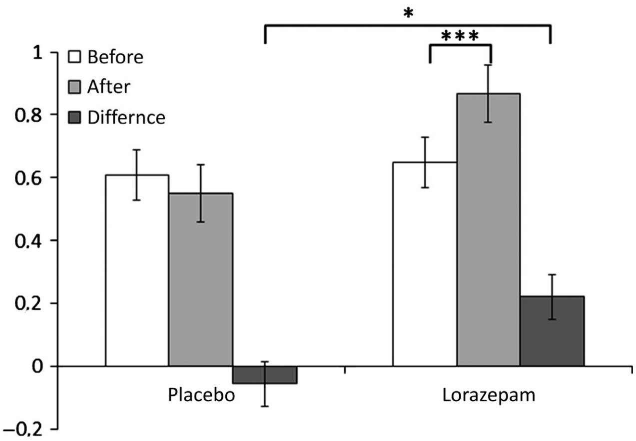

FIG. 2. Mean paired-pulse ratios before (white) and after (light grey) lorazepam administration for the placebo group (left) and the lorazepam group (right). Error bars show the standard errors of the mean. Note the significant increase in the *A*2/*A*1 ratio in the lorazepam group (****P* = 0.003), which was also significantly different from placebo (**P* = 0.026).

amplitudes of the first response of the N20 component were 1.76 ± 0.79 mV before intake and 1.75 ± 0.76 mV after intake, and the amplitudes of the second response were 1.53 ± 0.89 mV before intake and 1.41 ± 0.66 mV after intake (*t*-test: *P* = 0.95 and *P* = 0.71, respectively). Similarly, the amplitudes of the first and second N20–P25 components did not differ significantly before intake (2.86 ± 1.06 mV and 1.64 ± 0.81 mV, respectively) and after intake (2.72 ± 0.78 mV and 1.51 ± 0.71 mV, respectively) (*t*-test: *P* = 0.73 and *P* = 0.4, respectively).

A similar observation was made for the lorazepam group. For the N20 component, there was no significant difference between the before and after sessions for the first amplitude (1.51 ± 0.97 mV and 1.27 ± 0.69 mV, respectively; *t*-test, *P* = 0.34) or the second amplitude (1.29 ± 0.58 mV and 0.87 ± 0.51 mV, respectively; *t*-test, *P* = 0.11). For the N20–P25 component, neither the first response amplitudes (3.14 ± 1.36 mV before intake, and 2.54 ± 1.07 mV after intake; *t*-test, *P* = 0.09) nor the second response amplitudes (1.84 ± 0.64 mV before intake, and 2.04 ± 0.91 mV after intake) differed between the before and after sessions (*t*-test, *P* = 0.35). In contrast, ANOVA showed a significant effect for the within-subjects factor before–after × group (*F* = 3.097, *P* = 0.038). Although no significant change in the *A*2/*A*1 ratio was found in the placebo group (0.61 ± 0.28 and 0.55 ± 0.28, *P* = 0.49), we found a significant increase in the lorazepam group (0.65 ± 0.24 and 0.87 ± 0.33; *t*-test, *P* = 0.003), indicating that PPS was decreased after intake of lorazepam. This increase in the *A*2/*A*1 ratio after lorazepam intake was also significantly different from what was seen in the placebo group (0.55 ± 0.28 vs. 0.87 ± 0.33; *t*-test, *P* = 0.026; Fig. 2; Table 1).

The plasma level of lorazepam ranged between 16 ng/mL and 127 ng/mL. There was no correlation between concentration and electrophysiological parameters.

Discussion

Our study addressed the putative role of GABAergic transmission in the generation of paired-pulse behaviour in the somatosensory cortex. Using paired median nerve stimulation to record SEPs in the human somatosensory cortex, we demonstrated that a single dose of the $GABA_A$ agonist lorazepam modulates PPS of the cortical N20–P25 component, but not of the N20 component. Although numerous studies have demonstrated suppression of a response to a stimulus that follows a first one after a short interval, the underlying mechanisms remain elusive. There is agreement that PPS is most likely an intracortical phenomenon that is not present in a comparable form at a downstream level. Also, because of the suppressive nature of the paired-pulse behaviour, GABAergic contributions were advocated early on. However, data from animal research that have allowed detailed analysis of cellular and synaptic processes in mediating paired-pulse behaviour have created a complex picture (Wehr & Zador, 2005).

In contrast, studies in human individuals have to rely on more indirect approaches. For many years, paired-pulse transcranial magnetic stimulation has been widely used to study intracortical inhibition of the human motor cortex. The combination of paired-pulse transcranial magnetic stimulation with the application of agonists and/or antagonists of well-known transmitter systems has generated a considerable amount of information that, indeed, supports a role of GABAergic mechanisms in the generation of PPS (Kujirai *et al.*, 1993; Ziemann *et al.*, 1996, 2001; Werhahn *et al.*, 1999; Hanajima *et al.*, 2003; Di Lazzaro *et al.*, 2006; Florian *et al.*, 2008). Most studies have supported the involvement of $GABA_A$, but have also demonstrated that different forms of intracortical inhibition, such as short-interval intracortical inhibition, long-interval intracortical inhibition, and short-interval interhemispheric inhibition, might be mediated by different mechanisms (Florian *et al.*, 2008). PPS has been documented for the motor cortex (Ziemann *et al.*, 1996, 2001; Werhahn *et al.*, 1999; Hanajima *et al.*, 2003; Di Lazzaro *et al.*, 2006; Florian *et al.*, 2008), the auditory cortex (Percaccio *et al.*, 2005; Wehr & Zador, 2005), the somatosensory cortex (Allison, 1962; Schwartz & Shagass, 1964; Shagass & Schwartz, 1964; Ragert *et al.*, 2004; Höffken *et al.*, 2007, Lenz *et al.*, 2011), the visual cortex (Musselwhite & Jeffreys, 1983; Höffken *et al.*, 2008, 2009, 2013a,b), and higher cortical areas such as the dorsolateral prefrontal cortex (Fitzgerald *et al.*, 2009), implying that PPS is a ubiquitous cortical phenomenon that is not limited to a particular area. On the other hand, there are also significant differences in the properties of PPS across areas and modalities. For the somatosensory cortex, paired median nerve stimulation creates significant suppression up to

100 ms, whereas, for the visual cortex, suppression has been demonstrated for up to 200 ms or more (Höffken *et al.*, 2008). In contrast, for the motor cortex, transcranial magnetic stimulation-induced suppression evokes many forms of inhibition, such as short-interval intracortical inhibition and long-interval intracortical inhibition, which do not have an obvious equivalent in sensory cortices. In an early study of the effects of lorazepam on motor cortex excitability, corticocortical inhibition showed a tendency towards more inhibition, whereas corticocortical facilitation was almost completely suppressed (Ziemann *et al.*, 1996). In another study, in which GABAergic mechanisms were explored after application of the GABA uptake blocker tiagabine, PPS of the motor evoked potential at an ISI of 160 ms was more pronounced, whereas paired-pulse facilitation at an ISI of 10 ms was increased (Werhahn *et al.*, 1999).

In this and in our previous studies (Höffken *et al.*, 2007; Lenz *et al.*, 2012), we did not use a subtraction approach, but used raw amplitudes. In our view, the use of subtraction implicitly assumes that the response behaviour for single or paired stimulation is linear; that is, all of the later components present after single stimulation will show up identically under a paired-stimulation condition. In contrast, we took a more non-linear view, whereby new inputs, here the second stimulus, can override, reset or modulate components that are present under single stimulation. Therefore, in our view, the use of raw amplitudes involves fewer assumptions than does the subtraction approach. Moreover, in some of our previous studies, we had correlated paired-pulse ratios with perceptual measures, which revealed significant correlations, whereby the amount of PPS was linked to individual tactile performance behaviour (Höffken *et al.*, 2007; Lenz *et al.*, 2012). Such behaviour strongly supports the assumption that raw amplitude analysis provides a meaningful measure of intracortical excitability.

In our data, we found that, with an ISI of 30 ms, the response amplitudes of the first and second responses of the N20 and the N20–P25 components were not significantly altered. In contrast, the amplitude ratios of the N20–P25 component were significantly increased, indicative of reduced suppression. To explain these, on first glance, counterintuitive observations, we assume that the $GABA_A$ agonist lorazepam most likely enhances inhibition within the network of interneurons responsible for creating PPS. As a result, the inhibitory drive is reduced, thereby reducing the amount of suppression. Interestingly, no such effects were observed for the N20 component of the SEPs. Further studies are needed to explore whether PPS evoked at ISIs shorter or longer than 30 ms shows a similar pharmacological dependency as demonstrated for 30 ms (Werhahn *et al.*, 1999; Wehr & Zador, 2005).

There is general agreement that the N20 component originates mainly in the granular layer (layer IV) of Brodmann's area 3b, which occupies the posterior bank of the rolandic fissure (Allison *et al.*, 1989, 1991; McLaughlin & Kelly, 1993; Urbano *et al.*, 1997; Balzamo *et al.*, 2004). The origin of the P25 component is less clear. It has been proposed that the P25 component reflects the depolarization of the superficial portion of apical dendrites located in cortical layers 2 and 3 (Mitzdorf, 1985; Vaughan & Arezzo, 1988; Allison *et al.*, 1991; McLaughlin & Kelly, 1993; Nicholson Peterson *et al.*, 1995). Other studies have suggested a radially oriented source that is usually identified as Brodmann's area 1 at the apex of the postcentral gyrus (Arezzo *et al.*, 1979; Allison *et al.*, 1989, 1991; McCarthy *et al.*, 1991). Despite these discrepancies, there is agreement that the N20 component reflects thalamocortical input to SI, whereas the N20–P25 component represents intracortical processing (Wolters *et al.*, 2005). Such a dissociation is compatible with our finding of a lack of GABAergic modulation of the N20 component. It should be noted that, owing to the cephalic channel recording used in this study, it is possible that the P25 potential is modulated by an N30 potential of frontal origin, further complicating the discussion of the origin of the P25 component.

By the use of magnetoencephalography to record somatosensory evoked magnetic fields, a GABAergic contribution has been studied following lorazepam administration (Huttunen *et al.*, 2008). These authors reported that, for ISIs of of 20 ms, the drug had no effect on PPS or recovery for the N20 m deflection, but that the P35 m deflection was attenuated and did not recover at ISIs of 100 ms (Huttunen *et al.*, 2008). The lack of recovery at ISIs of 100 ms is difficult to reconcile with the early components seen in electrical SEPs, which all show recovery.

Although our data show clear involvement of $GABA_A$-mediated mechanisms in the generation of median nerve evoked PPS, research findings from the motor cortex and other areas make it highly likely that other mechanisms are also involved. For example, for the visual cortex, noradrenergic modulation of PPS has recently been demonstrated (Höffken *et al.*, 2012). Apparently, more studies are needed, including animal studies, to unravel the mechanisms of paired-pulse behaviour.

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Abbreviations

*A*1, amplitude of the first response peak; *A*2, amplitude of the second response peak; ISI, interstimulus interval; PPS, paired-pulse suppression; SEP, somatosensory evoked potential.

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