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Baclofen alters flash-evoked potentials in Long–Evans rats

Bruce E. Hetzler *, Janie M. Ondracek [1]

Department of Psychology, Lawrence University, Appleton, WI 54912 USA

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Abstract

This experiment examined the effects of the GABA-B agonist baclofen on flash-evoked potentials (FEPs) recorded from both the visual cortex (VC) and superior colliculus (SC) of chronically implanted male Long–Evans rats. FEPs were recorded at 5, 25, 45, and 65 min following intraperitoneal injections of saline, and of 1.25, 2.5, 5.0, and 10.0 mg/kg baclofen on separate days. In the VC, the amplitude of components P_{23}, P_{37}, N_{55}, N_{150}, and P_{242} increased, while the amplitude of components N_{31} and P_{48} decreased following baclofen administration. P_{88} was unchanged. In the SC, components P_{28}, N_{49}, N_{55}, and N_{59} were reduced in amplitude, while P_{39} was unaffected by baclofen. These effects on amplitudes were dose- and time-dependent. Many peak latencies in the VC and SC were altered by baclofen, although there was no obvious pattern of change, with some decreasing, a few increasing, and others unchanged. Body temperature was recorded in a separate group of animals, with both the 5.0 and 10.0 mg/kg doses of baclofen producing significant hypothermia. The 10.0 mg/kg dose of baclofen resulted in a significant decrease in movement during the recording sessions, but not in subsequent open field observations. The results show the involvement of GABA-B receptors in the production/modulation of the various components of FEPs.

Keywords: Baclofen; Visual cortex; Superior colliculus; Flash-evoked potentials; Visual-evoked potentials; Rats; Hypothermia; Locomotion

1. Introduction

Baclofen (beta-(4-chlorophenyl)-GABA) is a lipophilic derivative of GABA that functions as a stereoselective GABA-B receptor agonist (Addolorato et al., 2000; Harrison et al., 1988). It has been used clinically since the 1970s as a centrally acting muscle relaxant and antispastic agent, suppressing both mono- and polysynaptic spinal reflexes (Bowery and Enna, 2000; Penn and Kroin, 1987). Baclofen has recently received considerable attention because of its reported ability to reduce ethanol intake in rats (see Colombo et al., 2004; Czachowski et al., 2006; Walker and Koob, 2007), reduce alcohol craving and intake, and alleviate alcohol withdrawal symptoms in human alcoholics (Addolorato et al., 2000, 2002; Flannery et al., 2004). Other reports show that baclofen can attenuate responding in rats for other drugs as well, such as heroin, nicotine, and amphetamines (Corrigall et al., 2000; Phillis et al., 2001; Xi and Stein, 1999).

One method used to characterize the effects of drugs and toxic substances on the functioning of the nervous system utilizes sensory-evoked potentials (Borbély, 1973; Dyer, 1985). Sensory-evoked potentials, which can be easily recorded from both cortical and subcortical sites in laboratory animals, are complex neural responses that are phase-locked to the stimulus presentation (Shah et al., 2004). The individual components of flash-evoked potentials (FEPs) are representations of neural pathways that are activated during the photic stimulation (Fox and Rosenfeld, 1972). Such evoked potentials are often used to assess the functional integrity of the brain (Dyer, 1985), because they provide an integrated view of neural activity and sensory processing (Sisson and Siegel, 1989).

Despite the research and clinical interest in baclofen, very few studies have examined the effects of this compound on sensory-evoked potentials. Two studies reported on the effects of baclofen on click-evoked responses recorded from the inferior colliculus (IC) of rats. One demonstrated that baclofen reduced the amplitude of the second peak in the evoked

* Corresponding author. Tel.: +1 920 832 6704; fax: +1 920 832 6962.
E-mail address: hetzlerb@lawrence.edu (B.E. Hetzler).
[1] Present address: Department of Neuroscience, School of Graduate and Postdoctoral Studies, Rosalind Franklin University of Medicine and Science, North Chicago, IL 60064 USA.

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response (Szczepaniak and Møller, 1995), while the other found that baclofen could reverse the enhancement of the IC potential brought about by acute tone exposure (Szczepaniak and Møller, 1996). Click-evoked potentials recorded from the anterior suprasylvian gyrus of pentobarbital-anesthetized cats were reduced or abolished by baclofen, and somatosensory-evoked potentials were also reduced in amplitude (Toldi and Fehér, 1985). In contrast, baclofen increased cortical somatosensory-evoked potentials in dogs (Tan, 1985), but was reported to have no effect on cortical somatosensory-evoked potentials in one study on humans, even though it depressed lumbosacral evoked potentials (Kofler et al., 1992a). In other work, late components of cortical somatosensory-evoked potentials produced by stimulation of the median nerve in patients being treated with intrathecal baclofen were depressed while the early N_{20} component was generally unchanged (Dressnandt and Conrad, 1996). Interestingly, following an accidental overdose of baclofen in one clinical case, baclofen depressed median nerve somatosensory-evoked potentials but left brainstem auditory evoked potentials unchanged (Kofler et al., 1992b).

GABA is the main inhibitory neurotransmitter in the mammalian visual system, and is believed to play a major role in information processing in the cerebral cortex (Somogyi, 1989). Past investigations of the effects of GABAergic drugs on the rat visual cortex (VC) FEP have concentrated on the late slow negative wave (N_{150}) and subsequent after-discharge (AD), usually leaving primary and secondary components without analysis. Furthermore, in these studies the results have often been conflicting/confusing (see Hetzler and Zeisset, 1997). Although one study has examined the role of the direct GABA-A agonist THIP on FEPs recorded from the rat VC (Hetzler and Zeisset, 1997), to date no study has examined the effects of baclofen on FEPs recorded from the rat VC. The effects of baclofen on visual evoked potentials were explored in one study by Kasamatsu et al. (2005), who recorded local field potentials from the VC of anesthetized and paralyzed cats in response to contrast reversal of bar gratings. They identified a fast local component and a slower distributed component in the potentials. Baclofen had a greater suppressant action on the slow component than the fast local component, perhaps reflecting localization of GABA-B receptors on distal dendrites.

To help elucidate the physiological role of GABA-B receptor sites in processing sensory information, the present study examined the effects of baclofen on FEPs recorded from both the VC and superior colliculus (SC) of Long–Evans rats. The SC, a structure involved in attention and orientation (Binns, 1999; Goldberg and Robinson, 1978), was included since the SC is one of the brain areas with the highest GABA concentration (Okada et al., 1971).

In addition to recording FEPs, body temperature was also measured in the present study. Given the involvement of central GABAergic systems in thermoregulation (e.g., Jha et al., 2001; Yakimova et al., 1996), baclofen-induced changes in body temperature would be expected, and such changes in body temperature may then result in secondary changes in evoked-potential parameters (Hetzler and Dyer, 1984; Hetzler et al., 1988). Finally, since baclofen can alter behavior in rats (e.g., Grech and Balster, 1993), we monitored gross body movement during and after the evoked-potential recording sessions.

2. Materials and methods

2.1. Animals

Twenty-three adult, male Long–Evans hooded rats (Harlan, Indianapolis, IN), about 4 months old and weighing 365–400 g at the time of surgery, were used in the study of evoked potentials and behavior. A separate set of 10 male Long–Evans rats, weighing 350–384 g were used to study body temperature. The rats were housed individually in standard cages in a room with a light/dark cycle (light from 06:00 to 18:00 h) and climate control (temperature about 22 °C and humidity about 50%). Purina Lab Chow (St. Louis, MO) and tap water were provided *ad libitum*. All procedures were approved by the Lawrence University Animal Care and Use Committee.

2.2. Electrode implantation surgery

At least 1 week before adaptation, recording electrodes in the VC and the SC were implanted while the animals were under the effect of pentobarbital anesthesia. The rats first received an intraperitoneal (ip) injection of atropine sulfate (0.06 mg) to minimize respiratory distress during anesthesia. They were then anesthetized with an ip injection of 50 mg of sodium pentobarbital/kg body weight. The VC electrode (0–80 × 1/8 in. stainless steel screw) was placed 6 mm posterior to bregma and 3 mm lateral to the right of the midline. Similar screw electrodes placed over the ipsilateral and the contralateral frontal cortex provided for a recording reference and grounding, respectively. SC recordings were made from a twisted pair of nichrome wires (each 250 μm in diameter), insulated to the tip, with a vertical intertip distance of 1 mm. With the skull surface of the animal located in a horizontal plane (König and Klippel, 1963), the bipolar SC electrode was implanted 6.5 mm posterior to bregma and 1.5 mm lateral to the left of the midline and then lowered 4.7 mm below the surface of the skull. All electrodes were led to a 5-hole plastic cap (Wire Pro #223-1605), and the whole assembly was secured to the skull with additional screws and dental acrylic. After surgery, animals were handled briefly on a daily basis before testing.

At the conclusion of the experiment, placements of the SC electrodes were histologically verified (Hetzler et al., 1981). Results for the SC are reported for those 18 animals in which the lower member of the electrode pair penetrated the superficial layer of the SC (Dyer and Annau, 1977). VC recordings from five animals were unusable because of problems with the cap or amplifiers.

2.3. Chemicals

(±)Baclofen (Sigma Product No. B-5399, St. Louis, MO) was dissolved in 0.9% saline to obtain the different concentrations, which were injected ip in a volume of 2 ml/kg. Doses of 1.25, 2.5, 5.0, and 10.0 mg baclofen/kg body weight were used. The

goal was to utilize a range of dosages commonly found in rat studies (Munzar et al., 2000; Smith et al., 1999; Petry, 1997).

2.4. Evoked potential procedure

Evoked potentials were amplified with Tektronix 122 preamplifiers (Tektronix, Beaverton, OR) with high and low filter settings of 1.0 kHz and 0.8 Hz for both the VC and the SC. Amplified waveforms were averaged (2000-Hz sample rate, 400 ms epoch, $n=100$) by an IBM PS/ValuePoint computer connected to a Modular Instruments M100 Mainframe containing the following modules: M202 Fast A/D, M210 Memory, and M214 Data Acquisition Timer. Fifty milliseconds of the epoch occurred before the application of the evoking stimulus. Evoking stimuli were presented with an interstimulus interval of 2 s. Data collection was controlled with an S-215 Signal Averager program (Modular Instruments, West Chester, PA).

Recordings were obtained while animals were located inside a shielded recording chamber with dim background illumination of about 3 lux. The testing box, which was located inside the shielded chamber, measured 10×10×10 in. and was constructed of white Plexiglas on three sides, the top, and the bottom, whereas the front panel was clear. Shielded Microdot cables (Microdot Connectors, South Pasadena, CA), which are designed to reduce artifacts associated with cable movements (Fox and Rosenfeld, 1972), were attached to the top of the chamber with a mercury swivel, allowing freedom of movement. Flash stimuli were presented by a Grass Model PS22C photostimulator (Grass Instrument Division, Astro-Med, West Warwick, RI) with an intensity setting of 8 (measured as 133 lux-s using a Model DR-1600 Photometer with a Model D-1500-2B Multiprobe; Gamma Scientific, San Diego, CA). The flash lamp of the photostimulator was placed in a small sound-attenuating chamber to eliminate the auditory click present with each flash. The flash lamp was positioned outside the shielded recording chamber and was visible to the rat through a clear Plexiglas window.

The animals were given 2 days of familiarization to the testing procedures, followed by 2–3 days of rest before actual data collection. On each testing day, 30 min prior to testing, the animal received one drop of 1% ophthalmic atropine in each eye to maintain constant pupil dilation (Gelatt, 1981). Twenty-five min after the eye drops were given, the animal was injected ip on separate days with physiological saline (0.9% sodium chloride, 2 ml/kg), 1.25, 2.5, 5.0, or 10.0 mg baclofen per kg of body weight (2 ml/kg). The animal was then immediately placed in the testing chamber. The sequence of injections was counterbalanced, and the animals were given 2 days of rest between tests.

Evoked potentials were collected simultaneously from the VC and the SC at 5, 25, 45 and 65 min following injection. In addition, gross body movement was measured by two intersecting photocell sensors (S23-01; Coulbourn Instruments, Allentown, PA) that were positioned diagonally in the cage corners 3.5 cm above the floor of the cage. Electronic counters tallied the number of beam interruptions. Immediately after testing, the animal was placed in a restraining tube, and a rectal thermistor probe (YSI No. 402; Yellow Springs Instruments, Yellow Springs, OH) was inserted 10 cm into the rectum. A rectal temperature reading (YSI 49TA Tele-Thermometer;

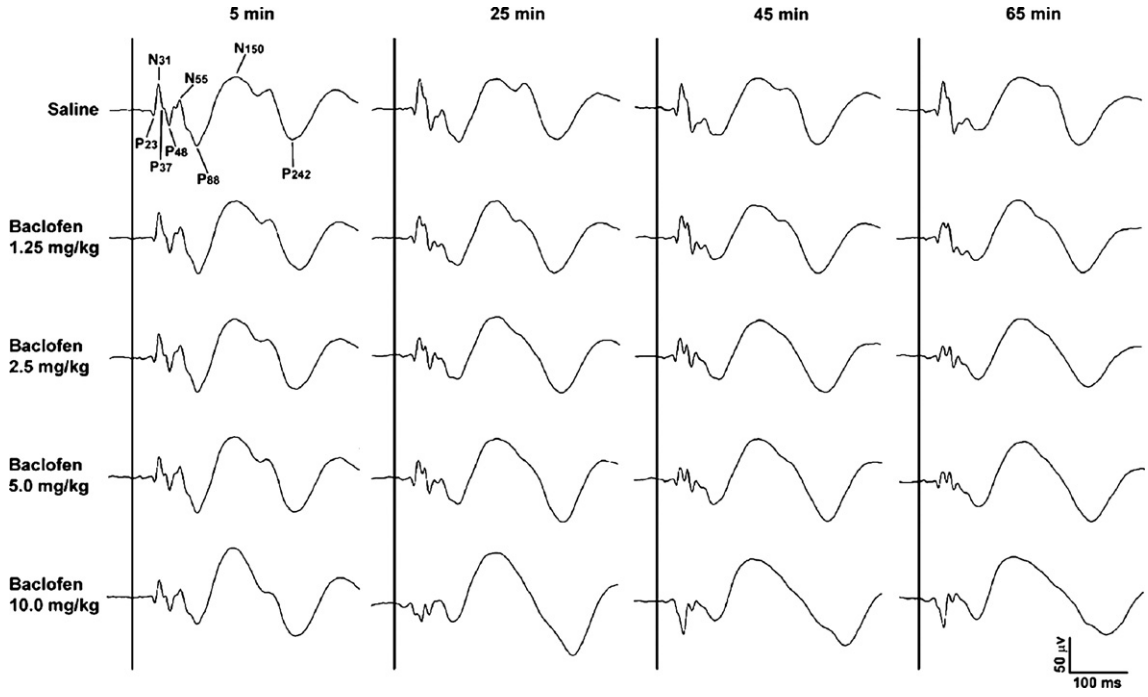

Fig. 1. Group average visual cortex (VC) flash-evoked potential (FEP) waveforms ($n=18$) for each dose of baclofen and each time interval. Vertical lines represent onset of the evoking stimulus. Individual FEP components are named by polarity and latency from the onset of the evoking stimulus. The effects of baclofen varied with the component and time interval. In general, the amplitudes of components P_{23}, P_{37}, N_{55}, N_{150}, and P_{242} were increased by baclofen, while the amplitudes of components N_{31} and P_{48} were decreased by baclofen. Amplitude of component P_{88} was unchanged.

Yellow Springs Instruments) was then taken. Ambient temperature (22 °C) was controlled by a wall thermostat, and was recorded at the conclusion of each test. Although body temperature was recorded at this time, a problem with the meter rendered those readings unreliable. Therefore, a separate body temperature study was conducted later.

2.5. Open field behavior

Following body temperature measurement, each animal was observed for three minutes in a 0.92 meter-square open field, with walls 46 cm high. The field was constructed of standard plywood, and was painted gray. The Plexiglas floor of the apparatus was divided into 36 equal squares, 15 cm on each side. Overhead fluorescent lights provided illumination of approximately 635 lux. On each testing day, the animal was placed in the same middle square of the open field, and allowed to explore for three minutes. Line crossings (movement of all four limbs of the rat across a line) were recorded, and general qualitative observations were made of each animal's behavior.

2.6. Body temperature

Prior to testing, the animals were given 2 days of adaptation to the testing procedures, followed by one day of rest. During testing, animals were injected ip every third or fourth day with physiological saline (0.9% sodium chloride, 2 ml/kg), 1.25, 2.5, 5.0, or 10.0 mg baclofen/kg of body weight. The volume of the injection was 2 ml/kg. The sequence of injections was counterbalanced. Animals were placed in restraining tubes after the injection, and rectal thermistor probes (YSI No. 402) were inserted 10 cm into the rectum. Temperature readings (YSI 44TA Tele-Thermometer) were taken 15, 25, 35, 45, 55, and 65 min after the injections. The rats were restrained continuously during the 1 h sessions so that the probes remained in place. Ambient temperature was 23.5 °C.

Table 1
Effects of time-related factors on flash evoked potentials (FEPs)

Component	Saline 5 min vs.			Baclofen 5 min vs.		
	25 min	45 min	65 min	25 min	45 min	65 min
VC amplitude						
P_{23}	—	—	—	↑(10)	↑(10)	↑(10)
N_{31}	—	—	—	↓(10)	↓(10)	↓(2.5,10)
P_{37}	↓	↓	↓	↑(10)	↑(10)	↑(10)
P_{48}	↑	↑	↑	—	—	↓(10)
N_{55}	↓	↓	↓	↓(1.25)	—	↓(1.25)
P_{88}	(↓	↓	↓)+	(↓	↓	↓)+
N_{150}	—	—	—	—	—	—
P_{242}	(↑	↑	↑)+	(↑	↑	↑)+
VC latency						
P_{23}	—	—	—	↑(10)	↑(10)	—
N_{31}	—	—	—	—	↓(5)	↓(5,10)
P_{37}	—	—	—	↓(2.5,5,10)	↓(1.25,2.5,5,10)	↓(1.25,2.5,5,10)
P_{48}	—	—	—	—	—	—
N_{55}	—	—	—	—	—	—
P_{88}	(↓	↓	↓)+	(↓	↓	↓)+
N_{150}	—	↓	—	—	—	↓(10)
P_{242}	—	—	—	↑(10)	↑(5,10)	↑(2.5,5,10)
SC amplitude						
P_{28}	(↑	↑	↑)+	(↑	↑	↑)+
P_{39}	(↑	↑	↑)+	(↑	↑	↑)+
N_{49}	—	↓	↓	↓(2.5,5,10)	↓(1.25,2.5,5,10)	↓(1.25,2.5,5,10)
N_{55}	—	—	—	↓(1.25,2.5,5,10)	↓(1.25,2.5,5,10)	↓(1.25,2.5,5,10)
N_{59}	—	—	—	—	—	—
SC latency						
P_{28}	↓	↓	↓	↓(1.25,2.5,5,10)	↓(1.25,2.5,5,10)	↓(1.25,2.5,5,10)
P_{39}	—	↑	—	—	↓(2.5,5,10)	↓(2.5,5,10)
N_{49}	—	—	—	↓(1.25,2.5,5,10)	↓(1.25,2.5,5,10)	↓(1.25,2.5,5,10)
N_{55}	—	—	—	↓(10)	↓(2.5,10)	↓(1.25,2.5,5,10)
N_{59}	—	—	—	—	—	—

Each row presents a simplified summary of the effects of time-related factors for one FEP component, named by polarity and latency from the onset of the evoking stimulus. Following significant analyses of variance for the main effects of time and/or baclofen × time interactions, Dunnett's tests were used to compare values from the 25, 45, and 65 min recording intervals with values from the 5 min interval. The results of these tests are shown separately for saline and for baclofen. FEP = Flash Evoked Potential, VC = Visual Cortex, SC = Superior Colliculus, ↑ = increase, ↓ = decrease, — = no change, (1.25,2.5,5,10) = change was observed only at this(these) dosage(s) of baclofen (mg/kg), + = main effect of time was significant, but the baclofen × time interaction was not significant. See also Figs. 2, 3, 5, and 6.

2.7. FEP component identification

Fig. 1 presents group average FEP waveforms for the VC, while Fig. 4 presents group average FEP waveforms for the SC. Components studied in the present experiment are identified in the 5 min saline traces. Following the component identification procedure described in Hetzler and Theinpeng (2004), in the present study FEP components were designated by their polarity and by their latency from the onset of the light flash. Baseline-to-peak amplitudes and peak latencies were obtained for nine VC components (P_{23}, N_{31}, P_{37}, P_{46}, N_{55}, P_{88}, N_{150}, and P_{242}; see Fig. 1). Components P_{28}, P_{39}, N_{49}, N_{55}, and N_{59} were similarly analyzed in the SC waveforms (see Fig. 4). The baseline-to-peak amplitudes consisted of the difference between the mean voltage of 50 ms of prestimulus activity and the peak voltage. Peak latencies were measured from the onset of the evoking stimulus.

2.8. Data analysis

VC, SC, photocell, and body temperature data were subjected to two factor (i.e., baclofen dose and time) repeated measures analyses of variance. When a significant main effect, or drug × time interaction, was found, individual means were compared with the Dunnett test. The saline treatment and 5-min recording interval data served as the basis for comparisons in the Dunnett tests for the VC, SC, and photocell data. That is, the 25-, 45-, and 65-min data were compared to the 5-min data, while each dosage of baclofen was compared to the saline treatment. In the body temperature study, the saline treatment and 15-min recording interval data were used as the basis for comparisons. Open field line crossings data were subjected to a repeated measures analysis of variance in which drug treatment was the repeated factor. A significant main effect was followed by the Dunnett test. In all analyses, statistical significance was assumed when $P<.05$ for two-tailed comparisons.

Changes in evoked potential amplitudes and latencies resulting from time-related factors are summarized in Table 1, but are not further discussed in the Results section. Likewise, significant drug × time interactions are described only in relation to the main effects of the drug.

3. Results

3.1. Visual cortex: amplitude

Group mean evoked potentials for each dose of baclofen and each testing time interval are displayed in Fig. 1, where it is

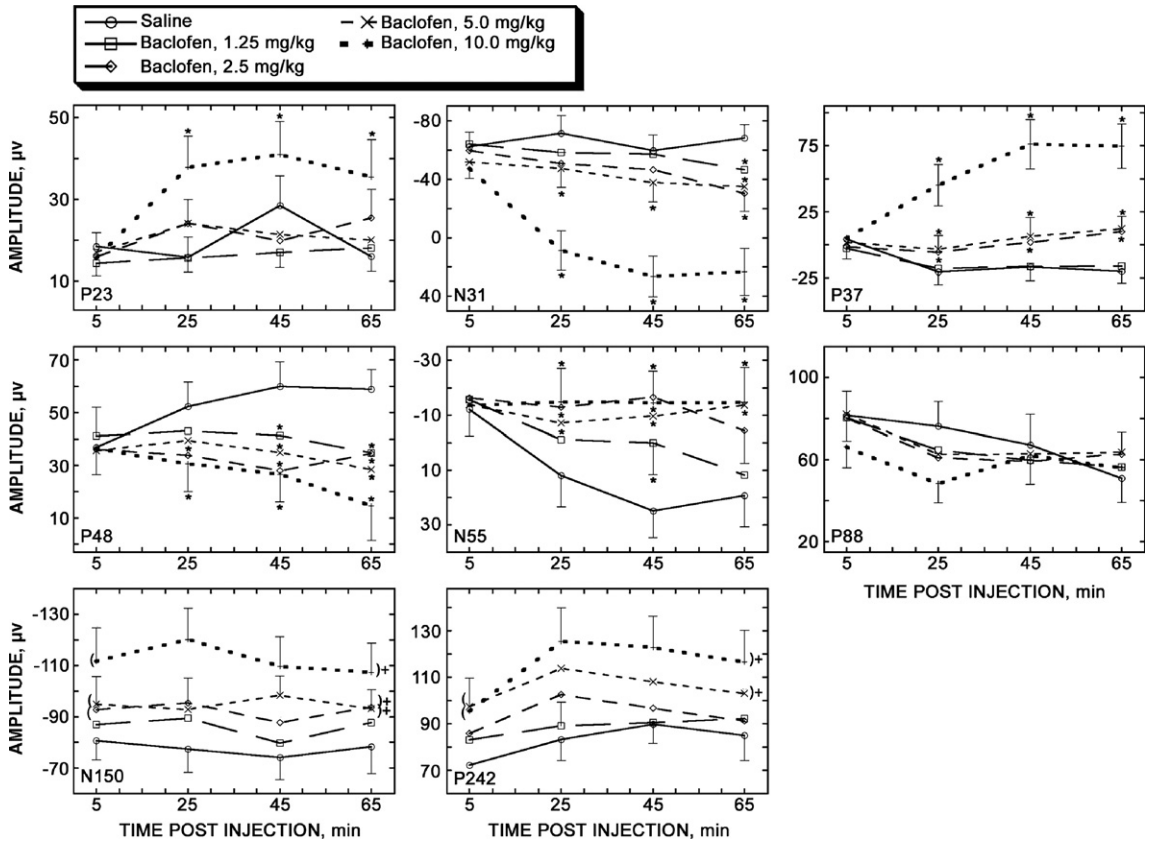

Fig. 2. Peak amplitudes of VC FEP components ($n=18$) as a function of baclofen dosage and time interval. Each panel illustrates the results for one FEP component, named by polarity and latency from the onset of the evoking stimulus. Vertical bars above or below the mean values represent + or −1 S.E.M., respectively. *$P<.05$ when compared to the saline value by a two factor repeated measures ANOVA followed by Dunnett's test comparisons at individual time intervals. $^{+}P<.05$ when compared to the saline value by a two factor repeated measures ANOVA followed by Dunnett's test comparisons (i.e., the main effect of baclofen was significant, but the baclofen × time interaction was not significant).

apparent that the effects of baclofen varied with the component, with the most dramatic effect being the elimination of component N_{31} when the highest dose of baclofen was administered. In general, baclofen decreased the amplitude of components N_{31} and P_{48}, but increased the amplitude of components P_{23}, P_{37}, N_{55}, N_{150}, and P_{242}. No significant effect of baclofen was observed on component P_{88}. ANOVA results for the main effect of baclofen for each component were as follows:

P_{23}: $F(4,68)=4.56$, $P<.001$
N_{31}: $F(4,68)=20.79$, $P<.001$
P_{37}: $F(4,68)=25.50$, $P<.001$
P_{48}: $F(4,68)=6.04$, $P<.001$
N_{55}: $F(4,68)=6.97$, $P<.001$
P_{88}: $F(4,68)=0.97$, $P=.430$
N_{150}: $F(4,68)=13.00$, $P<.001$
P_{242}: $F(4,68)=13.42$, $P<.001$

Significant drug × time interactions were also present for components P_{23}, N_{31}, P_{37}. P_{48}, and N_{55}.

Baseline-to-peak amplitude data are presented for each component in Fig. 2. In comparison to saline, component P_{23} was augmented by the 10 mg/kg dose of baclofen at the 25, 45, and 65-min intervals. In marked contrast, the subsequent negative component N_{31} was reduced in amplitude at the 25, 45, and 65-min intervals by both the 5.0 and 10.0 mg/kg baclofen doses, and also reduced at the 65-min intervals by the two lowest baclofen doses. In fact, N_{31} was reduced to such an extent by the 10.0 mg/kg dose of baclofen that it became positive at this dose.

P_{37} (the small positive inflection between N_{31} and P_{48}) was enhanced at the 45 and 65 min intervals by the 2.5, 5.0, and 10.0 mg/kg doses of baclofen, and enhanced at the 25 min interval by the 10.0 mg/kg dose as well. This enhancement at the 10.0 mg/kg dose resulted in an amplitude that was even greater than that for components P_{23} and P_{48}. The baclofen-related reduction in amplitude of component P_{48} was almost the mirror image of the enhancement of component P_{37}. That is, P_{48} was significantly reduced by all doses of baclofen at the 45 and 65 min intervals, and also reduced in amplitude at 25 min by both the 2.5 and 10.0 mg/kg doses.

Component N_{55} was enhanced by the 2.5, 5.0, and 10.0 mg/kg doses at 25, 45, and 65 min, and also at the 45 min interval by the 1.25 mg/kg dose. While P_{88} was unaffected by baclofen, both N_{150} and P_{242} were enhanced. For component N_{150}, the 2.5, 5.0, and 10.0 mg/kg doses resulted in significant amplitude enhancement, while component P_{242} was enhanced by both the 5.0 and 10.0 mg/kg doses.

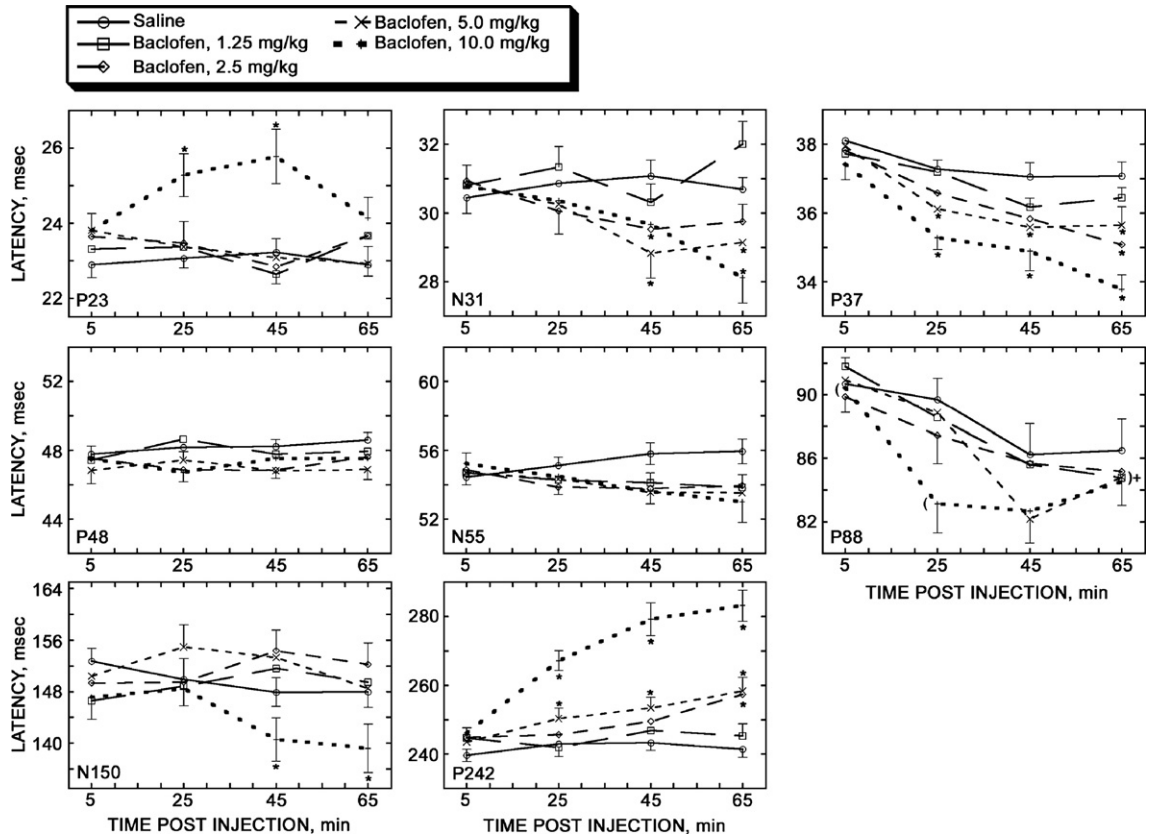

Fig. 3. Peak latencies of VC FEP components ($n=18$) as a function of baclofen dosage and time interval. Each panel illustrates the results for one FEP component, named by polarity and latency from the onset of the evoking stimulus. Vertical bars above or below the mean values represent + or − 1 S.E.M., respectively. *$P<.05$ when compared to the saline value by a two factor repeated measures ANOVA followed by Dunnett's test comparisons at individual time intervals. $^{+}P<.05$ when compared to the saline value by a two factor repeated measures ANOVA followed by Dunnett's test comparisons (i.e., the main effect of baclofen was significant, but the baclofen × time interaction was not significant).

3.2. Visual cortex: latency

The VC latency data are displayed in Fig. 3. The highest doses of baclofen significantly altered the latency of most of the VC components.

P_{23}: $F(4,68)=5.58$, $P=.001$
N_{31}: $F(4,68)=3.84$, $P=.007$
P_{37}: $F(4,68)=9.96$, $P<.001$
P_{48}: $F(4,68)=1.78$, $P=.142$
N_{55}: $F(4,68)=2.18$, $P=.081$
P_{88}: $F(4,68)=2.55$, $P=.047$
N_{150}: $F(4,68)=3.51$, $P=.012$
P_{242}: $F(4,68)=30.69$, $P<.001$

Significant drug × time interactions were also present for components P_{23}, N_{31}, P_{37}, N_{150}, and P_{242}.

The highest dose of baclofen (10 mg/kg) significantly increased the latency of component P_{23} at both the 25 and 45 min time intervals, but N_{31} latency was significantly decreased at the 45 min interval by both the 2.5 and 5.0 mg/kg doses of baclofen, and decreased at the 65 min interval by both the 5.0 and 10.0 mg/kg doses. The 5.0 and 10.0 mg/kg doses of baclofen significantly decreased the latency of component P_{37} at the 25, 45, and 65 min intervals, and the 2.5 mg/kg dose decreased P_{37} latency at the 65 min interval as well.

Neither component P_{48} nor component N_{55} were significantly altered in latency by any dose of baclofen, but P_{88} latency was reduced by the 10.0 mg/kg dose of baclofen. The 10.0 mg/kg dose of baclofen also significantly decreased the latency of component N_{150}, at both 45 and 65 min. Finally, component P_{242} was significantly increased by baclofen at 25, 45, and 65 min by both the 5.0 and 10.0 mg/kg doses, and at 65 min by the 2.5 mg/kg dose.

3.3. Superior colliculus: amplitude

Group mean SC evoked potentials are displayed in Fig. 4. Baseline-to-peak amplitude data for each of these components are presented in Fig. 5. There were significant depressant effects of baclofen on the amplitude of 4 out of the 5 components measured.

P_{28}: $F(4,68)=12.82$, $P<.001$
P_{39}: $F(4,68)=1.00$, $P=.412$
N_{49}: $F(4,68)=27.38$, $P<.001$
N_{55}: $F(4,68)=14.34$, $P<.001$
N_{59}: $F(4,68)=6.30$, $P<.001$

Significant drug × time interactions were also present for components N_{49} and N_{55}.

P_{28} amplitude was significantly depressed by the 2.5, 5.0, and 10.0 mg/kg doses of baclofen, but P_{39} was not altered by baclofen. N_{49} amplitude was depressed at the 25, 45, and 65 min

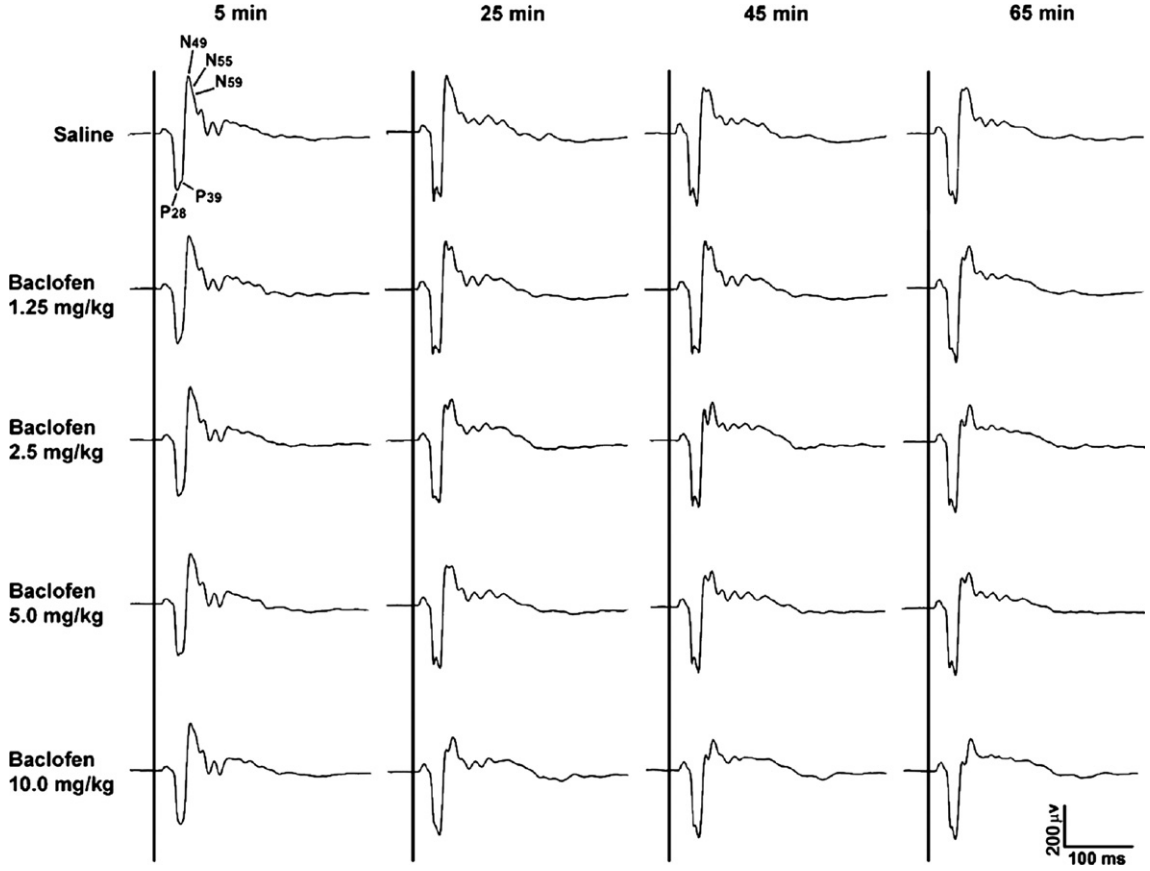

Fig. 4. Group average superior colliculus (SC) FEP waveforms ($n=18$) for each dose of baclofen and each time interval. Vertical lines represent onset of the evoking stimulus. Individual FEP components are named by polarity and latency from the onset of the evoking stimulus. The effects of baclofen varied with the component and time interval. In general, the amplitudes of components P_{28}, N_{49}, N_{55} and N_{59} were decreased by baclofen. The amplitude of component P_{39} was unchanged.

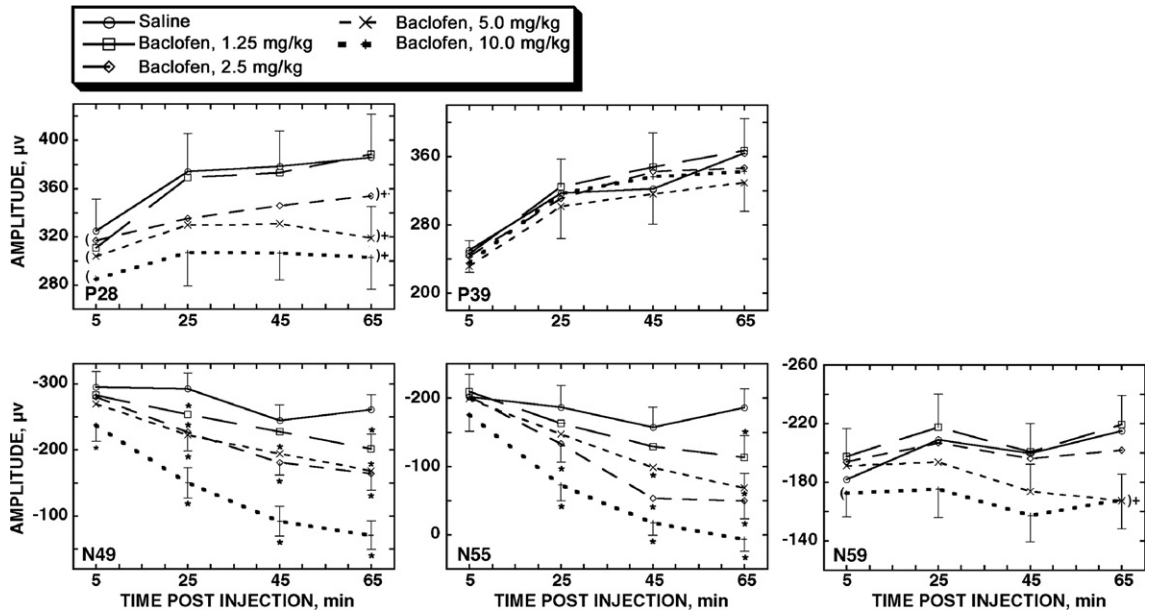

Fig. 5. Peak amplitudes of SC FEP components ($n=18$) as a function of baclofen dosage and time interval. Each panel illustrates the results for one FEP component, named by polarity and latency from the onset of the evoking stimulus. Vertical bars above or below the mean values represent + or −1 S.E.M., respectively. *$P<.05$ when compared to the saline value by a two factor repeated measures ANOVA followed by Dunnett's test comparisons at individual time intervals. $^{+}P<.05$ when compared to the saline value by a two factor repeated measures ANOVA followed by Dunnett's test comparisons (i.e., the main effect of baclofen was significant, but the baclofen × time interaction was not significant).

intervals by all baclofen doses, with the exception of the 45 min interval for the 1.25 mg/kg dose. N_{49} amplitude was also depressed at the 5 min interval by the 10.0 mg/kg dose. All baclofen doses depressed the amplitude of component N_{55} at the 65 min interval, while the 2.5, 5.0 and 10.0 mg/kg doses depressed this component at 45 min, and the 2.5 and 10.0 mg/kg doses depressed N_{55} at 25 min. Finally, the amplitude of component N_{59} was significantly depressed by only the 10.0 mg/kg baclofen dose.

3.4. Superior colliculus: latency

SC latency data are presented in Fig. 6. There were significant main effects of baclofen on the latency of 3 out of the 5 components measured.

P_{28}: $F(4,68)=1.46$, $P=.225$
P_{39}: $F(4,68)=3.50$, $P=.012$
N_{49}: $F(4,68)=4.35$, $P=.003$

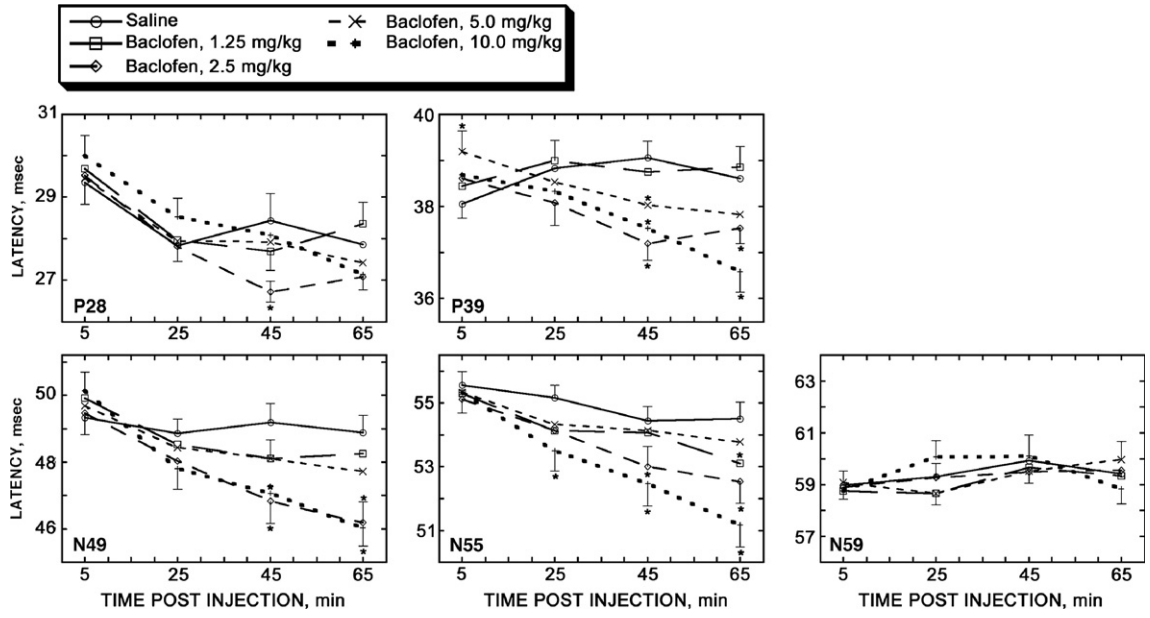

Fig. 6. Peak latencies of SC FEP components ($n=18$) as a function of baclofen dosage and time interval. Each panel illustrates the results for one FEP component, named by polarity and latency from the onset of the evoking stimulus. Vertical bars above or below the mean values represent + or −1 S.E.M., respectively. *$P<.05$ when compared to the saline value by a two factor repeated measures ANOVA followed by Dunnett's test comparisons at individual time intervals.

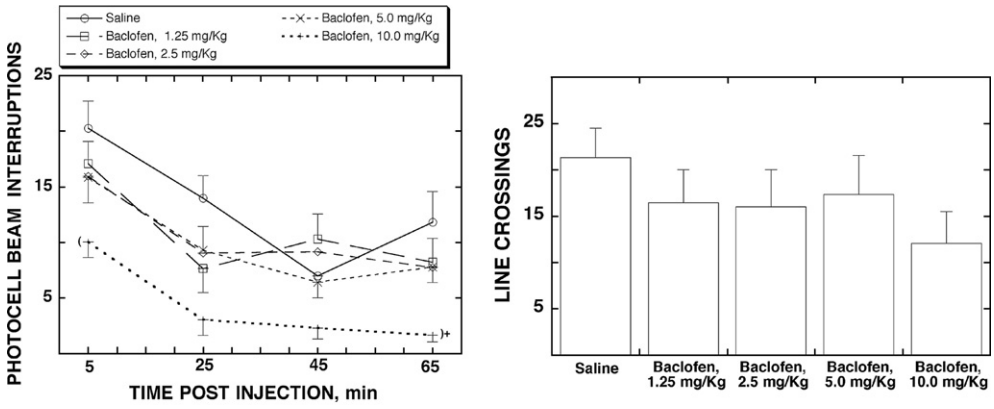

Fig. 7. This figure illustrates the effects of baclofen on body movement. Left panel: body movement ($n=23$) as measured by photocell beam interruptions during the 3.5-min evoked potential test sessions. Data are presented as a function of baclofen dosage and time interval. Vertical bars above or below the mean values represent + or −1 S.E.M., respectively. $^{+}P<.05$ when compared to the saline value by a two factor repeated measures ANOVA followed by Dunnett's test comparisons (i.e., the main effect of baclofen was significant, but the baclofen × time interaction was not significant). Right panel: mean line crossings ($n=23$) during a 3-min open field test session that followed evoked potential collection. Data are presented as a function of baclofen dosage. Vertical bars above the mean values represent +1 S.E.M. No significant effects of baclofen were observed in a repeated measures ANOVA.

N_{55}: $F(4,68)=4.14$, $P=.005$
N_{59}: $F(4,68)=0.18$, $P=.949$

Significant drug × time interactions were also present for components P_{28}, P_{39}, N_{49}, and N_{55}.

For component P_{28}, there was a transient decrease in latency at 45 min when the 2.5 mg/kg dose was given. In contrast, for component P_{39} the 5.0 mg/kg dose transiently increased latency at the 5 min interval but decreased latency at the 45 min interval. The 2.5 and 10.0 mg/kg doses decreased the latency of components P_{39}, N_{49}, and N_{55} at both the 45 and 65 min intervals. Additional decreases in latency were observed for component N_{55} at 65 min following administration of the 1.25 mg/kg dose, and at 25 min following administration of the 10.0 mg/kg dose.

3.5. Body movement

Fig. 7(left panel) presents the mean number of photocell beam interruptions recorded during 3.5 min of evoked potential recording for each recording session. The 10.0 mg/kg dose of baclofen resulted in significantly fewer photocell beam interruptions than were observed following saline administration [$F(4,88)=8.37$, $P<.01$]. The drug × time interaction was not significant. The mean number of line crossings during the 3-min observation period following evoked potential testing is shown in the right panel of Fig. 7. Although there was a tendency for baclofen to decrease activity, the effect did not reach statistical significance: [$F(4,88)=1.12$, $P=.352$].

Behavioral observations were also made during this 3-min observational time. Following administration of either saline or the 1.25 mg/kg dose of baclofen, the animals scurried to the perimeter of the maze. They tended to walk around the periphery before finally stopping in a corner. They were alert and active, and almost always reared up against a wall or in a corner. With the 2.5 mg/kg dose of baclofen, the rats ran around the perimeter once or twice, and then crouched in a corner for the remainder of the time, again very similar to the behavior observed with saline. At the 5.0 mg/kg dosage level, it became apparent that some of the animals were more sensitive to the effects of baclofen than others. While some behaved in a manner similar to that following saline, others waddled around, looking up frequently, and still others went immediately to a corner, remaining there. The amount of rearing decreased. After the administration of the 10.0 mg/kg dose, most of the animals could not rise up on their hind legs to ambulate. Often they would drag themselves to a corner and lay there. When moving, they appeared disoriented, venturing into the center, cutting corners, or doubling back on themselves. On the other hand, 5 of them did not move at all for the entire 3 min.

3.6. Body temperature

Fig. 8 presents body temperature data for 10 rats. Both the main effect of baclofen [$F(4,36)=5.92$, $P<.05$] and the

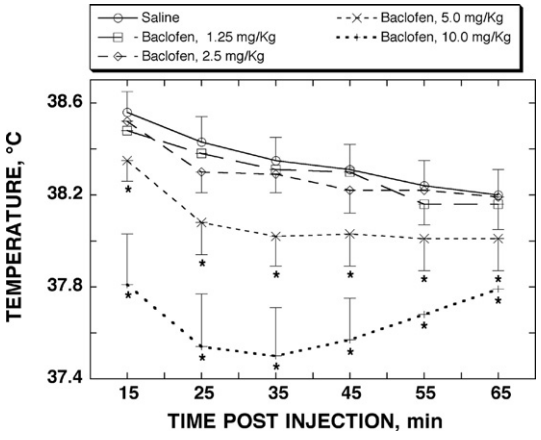

Fig. 8. Body temperature ($n=10$) as a function of baclofen dosage and time interval. Body temperature was measured with a rectal thermistor probe. Vertical bars above or below the mean values represent + or −1 S.E.M., respectively. $*P<.05$ when compared to the saline value by a two factor repeated measures ANOVA followed by Dunnett's test comparisons at individual time intervals.

baclofen × time interaction [$F(20,180)=2.11$, $P<.05$] were significant. Both the 5.0 and the 10.0 mg/kg doses of baclofen significantly decreased body temperature at all time intervals compared to saline.

4. Discussion

Although the visual pathways use excitatory neurotransmitters (i.e., glutamate/aspartate) for transmitting information, at each excitatory synapse local GABA-releasing cells gate and modify the responses produced in the post-synaptic cells (Somogyi,1989). In the adult rat VC, GABA terminals are found in every layer, with the greatest density of synaptic contacts occurring in layer IV (Beaulieu et al., 1992), and electrophysiological studies have demonstrated that synaptic inhibition in the rat VC is mediated by both GABA-A and GABA-B receptors (e.g., Shao and Burkhalter, 1999; Murakoshi et al., 1993).

The GABA-A receptor directly controls a Cl^- ionophore, and has interacting binding sites for benzodiazepines, barbiturates, neurosteroids, picrotoxin, and ethanol (Paul, 1995; Faingold et al., 1998). GABA-B receptors are G-protein coupled, and are located both pre- and postsynaptically. The presynaptic receptors are apparently coupled to voltage-gated Ca^{+2} channels, with their activation leading to a reduction in Ca^{+2} conductance. In contrast, activation of the post-synaptic receptors produces a slow inhibitory post-synaptic potential as a function of the opening of K^+ channels and the resulting increase in K^+ conductance (Bowery, 1989; Kamatchi and Ticku, 1990). These GABA-B receptors thereby both reduce neurotransmitter release presynaptically, and decrease neuronal excitability postsynaptically.

In the present study, the GABA-B agonist baclofen produced significant effects on FEPs recorded in both the VC and the SC. While the effects of baclofen on VC FEPs could originate within the cortex itself, since GABA plays a major role in information processing in the cerebral cortex (Somogyi, 1989), it is also possible that the actions of baclofen in other brain regions could have secondary effects on the cortical FEPs (Herr and Boyes, 1995). For example, VC FEP component P_{23} is presumed to be the correlate of the presynaptic geniculate volley (Siegel and Sisson, 1993), and is often unaltered in amplitude by pharmacological manipulations (e.g., Hetzler and Theinpeng, 2004). The increased amplitude observed in the present study following administration of the 10 mg/kg dose of baclofen could result from actions of baclofen in the cortex, but could also be secondary to effects of baclofen in the retina (Moller and Eysteinsson, 2003) or dorsal lateral geniculate nucleus of the thalamus (Crunelli et al., 1988; Zhu and Lo, 1999).

The most striking effect of baclofen in the VC was the virtual elimination of component N_{31}, which was diminished to such an extent by baclofen that it became positive. N_{31} represents a geniculocortical synaptic process produced by glutamate/aspartate release in Layer IV of the VC (Meeren et al., 1998; Siegel and Sisson, 1993), and therefore reflects the initial excitatory post-synaptic potential (epsp) in cortical neurons following visual input. The elimination of component N_{31} could therefore result from activation of presynaptic GABA-B receptors on the geniculocortical axon endings, reducing the release of glutamate, or activation of post-synaptic GABA-B receptors on the dendrites of cortical cells, producing a slow hyperpolarization. The effects of baclofen on local field potentials in the VC of the cat (Kasamatsu et al., 2005) support the involvement of post-synaptic GABA-B receptors, but evidence for baclofen-induced reduction of glutamate release in the cortex is mixed. Using mouse and rat slice preparations that contained the somatosensory cortex and ventrobasal thalamus, Gil et al. (1997) found that baclofen selectively reduced intracortical epsps without affecting thalamocortical epsps. In contrast, Porter and Nieves (2004) demonstrated that presynaptic GABA-B receptors are present at thalamocortical synapses onto both inhibitory and excitatory neurons in thalamocortical slice preparations of the mouse "barrel" cortex, and that baclofen depressed glutamate-related epsps in both inhibitory and excitatory neurons. Clearly, more research detailing the modulation of thalamocortical input by GABA-B receptors is warranted.

Component P_{37}, a small positive inflection between N_{31} and P_{48}, is rarely examined in rat FEP studies. In the present study, the effect of the 10.0 mg/kg dose of baclofen on this component was so profound at the 45 and 65 min intervals that P_{37} became the most prominent early component. A similar occurrence was observed by Hetzler and Zeisset (1997) with the component they identified as Pn, which was greatly augmented in amplitude by the GABA-A agonist THIP. It would therefore appear that GABA receptors play an important role in the generation/modulation of this component.

P_{48} and N_{55} are two of the so-called secondary components, which are thought to result from connections between the SC, brain stem, and diffuse thalamic projections (Creel et al., 1974). In the saline condition, both components become more positive over repeated testing on a single day, but baclofen appears to prevent this time-related process, keeping amplitudes near what they are in the 5 min saline condition.

Although baclofen had no significant effect on the last of the secondary components (P_{88}), baclofen did produce an enhancement of both late components N_{150} and P_{242}. N_{150} reflects secondary (or rebound) activation of cortical pyramidal cells (Meeren et al., 1998), and is generally viewed as the first component of the flash-evoked after-discharge (Bigler, 1977; Schwartzbaum, 1975; Shearer and Creel, 1978). This after-discharge is produced by a thalamic recurrent inhibitory system involving both the dLGN and the thalamic reticular nucleus (see review by Bigler, 1977). The actions of baclofen on N_{150} and P_{242} could therefore result from the actions of baclofen on GABA terminals in the thalamus (Crunelli et al., 1988; Zhu and Lo, 1999) and/or the cortex.

Of interest in this regard is the use of baclofen to decrease the amount of ethanol intake in both laboratory animals and humans (see Colombo et al., 2004 for review). While most authors feel that baclofen achieves these results by reducing dopamine release in the nucleus accumbens portion of the mesolimbic dopamine pathway (Colombo et al., 2004), it has also been suggested that baclofen may attenuate the corticothalamic activity necessary for sustaining behavioral activation states

(Anstrom et al., 2003). As mentioned above, the N_{150}-P_{242} portion of the cortical waveform is most likely generated by a thalamic reverberatory loop, the output of which is transmitted to the VC. Furthermore, the amplitude of N_{150} and the after-discharge is often viewed as an indicator of arousal (Bigler and Fleming, 1974; Dyer, 1986), such that cortical after-discharge bursting is a reflection of minimal sensory information processing in the cerebral cortex (Standage and Fleming, 1979). Thus, the larger N_{150}-P_{242} amplitude observed following baclofen administration could be viewed as indicative of attenuated arousal in comparison to the normal (i.e., more aroused) state, providing some support for the Anstrom et al. (2003) proposal. However, this increase in both N_{150} and P_{242} amplitude was found only at the highest doses of baclofen (5.0 and 10.0 mg/kg) used in the present study, and therefore may not be relevant to other research utilizing lower effective doses (e.g., Colombo et al., 2003a,b; Daoust et al., 1987; Walker and Koob, 2007).

GABA is unevenly distributed in the brain, with the SC being one of the areas with the highest concentration (Okada et al., 1971). In addition to intrinsic GABAergic neurons in the SC (Mize, 1988), there is also an apparent GABAergic projection from the substantia nigra pars reticulata to the intermediate layers of the SC (Araki et al., 1984; Vincent et al., 1978), as well as a possible GABAergic input from the substantia nigra pars lateralis to the superficial layers of the SC (Redgrave et al., 1990). Within the SC, the highest level of GABA is found in the superficial gray layer (Okada, 1992). Likewise, the density of both GABA-A and GABA-B receptor subtypes is highest in the superficial gray layer, although in the rat SC there is a greater density of GABA-B receptors than GABA-A receptors (Mize, 1992).

FEPs recorded from the SC were altered by baclofen in the present study. Baclofen depressed the amplitude of component P_{28} in the early positive complex, as well as depressing all 3 portions of the later negative wave (N_{49}, N_{55}, N_{59}). Only component P_{39} was unaffected. Interestingly, the GABA-A agonist THIP produced different results in earlier work (Hetzler and Zeisset, 1997). In that study, THIP enhanced the amplitude of component P1 (P_{28}), decreased the amplitude of P3 (P_{39}), and altered N4a (N_{49}) and N4b (N_{55}) in a biphasic manner (i.e., increase at lower dose/decrease at higher dose).

However, perhaps most interesting is the observation that nicotine affects SC FEPs in a manner remarkably similar to baclofen, with a reduction in P_{27}, lack of effect on P_{37}, and a reduction in both N_{48} and N_{53} (Hetzler and Theinpeng, 2004). The main cholinergic input to the superficial visual layers of the SC originates in the contralateral parabigeminal nucleus, which, in turn, receives visual input from the ipsilateral SC (Binns, 1999; Sefton and Martin, 1984). Acetylcholine released in the SC from this pathway appears to act on nicotinic receptors that modulate the release of GABA from inhibitory neurons. This is done via an apparent combination of nicotinic receptors located presynaptically on retinal axon terminals (which increase the release of glutamate onto the inhibitory neurons) and receptors located postsynaptically on the inhibitory neurons (which directly increase the release of GABA; Binns, 1999). Secondary GABA release and activation of GABA-B receptors may therefore underlie most of the SC amplitude effects observed in that past study on nicotine.

Given the involvement of central GABAergic systems in thermoregulation (e.g., Jha et al., 2001; Yakimova et al., 1996), baclofen-induced changes in body temperature would be expected. In the present study, high doses (5-10 mg/kg) of baclofen produced a dose-dependent hypothermia. Past studies disagree on the direction and extent in which baclofen alters body temperature in rats, with reports of both baclofen-induced hypothermia (Phillis et al., 2001; Rawls et al., 2004; Zarrindast and Oveissi, 1988) and hyperthermia (Addae et al., 1986; Horton et al., 1988; Sancibrian et al., 1991; Zarrindast and Oveissi, 1988).

These inconsistencies appear to be mainly attributable to two factors: the dose of baclofen, and the method of administration. When baclofen is administered either sc or ip, doses at or slightly below 10 mg/kg typically produce hypothermia (Phillis et al., 2001; Rawls et al., 2004; Zarrindast and Oveissi, 1988), while doses at or above 20 mg/kg ultimately yield hyperthermia (Sancibrian et al., 1991; Zarrindast and Oveissi, 1988). In contrast, centrally administered (e.g., intracerebroventricular) baclofen seems to invariably result in hyperthermia after some threshold level is surpassed (Addae et al., 1986; Horton et al., 1988; Zarrindast and Oveissi, 1988).

Given that a significant hypothermia was observed in the present experiment following administration of both the 5.0 and 10.0 mg/kg doses of baclofen, and that there is a clear relationship between reduced body temperature and increased FEP peak latency (but not alterations in peak amplitude; Hetzler et al., 1988), to what extent were any observed changes in FEP peak latency attributable to hypothermia? Interestingly, since most peak latencies that were affected showed a reduction in peak latency, body temperature is generally not implicated. The latencies of two VC components did increase following baclofen administration: VC components P_{23} and P_{242}. The relationship between VC component P_{242} and body temperature is unknown. However, for VC component P_{23}, the estimated latency increase from a 1.0 °C decrease in body temperature is about 1.4–1.7 ms (Hetzler et al., 1988). The average increase in latency for this component at 25–45 min following administration of the 10.0 mg/kg dose was 2.39 ms, while the average hypothermia was 0.82 °C. This amount of hypothermia could account for most, though not all, of the observed latency increase for this component. The reductions in peak latency observed in some components presumably result from the direct actions of baclofen itself.

The mechanisms by which baclofen can directly alter component latencies include changes in synaptic delay as well as changes in axonal conduction velocity. By acting on both pre- and post-synaptic GABA-B receptor sites, baclofen can modulate both the release and post-synaptic effects of a variety of neurotransmitters (Howe et al., 1987; Pirot et al., 1992; Santiago et al., 1993; Wojcik and Holopainen, 1992), altering the time-course of synaptic temporal and spatial summation, and therefore modifying FEP component latencies. In addition, Sun and Chiu (1999) have reported that neonatal rat optic nerve axons express N-type calcium channels which are regulated by GABA-B receptors, such that calcium influx is inhibited by baclofen. Since axonal Ca^{+2} transients can modify the speed of propogation of action potentials (Lüscher et al., 1996), this provides another mechanism whereby baclofen could alter FEP component latencies.

During the FEP collection period, the 10.0 mg/kg dose of baclofen significantly decreased photocell beam interruptions, while behavioral observations of open field behavior indicated that the 10.0 mg/kg baclofen dose depressed rearing and restricted hind limb movements, producing ataxia and apparent disorientation. In line with these findings, past studies have indicated that baclofen produces a dose-dependent depression of behavior in the rat. Thus, most studies employing very low doses of baclofen (0.5–4.0 mg/kg) report no changes in spontaneous behaviors in an open field (Car and Wisniewski 1998; Colombo et al., 2003a,b; Hotsenpiller and Wolf, 2003) or locomotion in an elevated plus-maze (Zarrindast et al., 2001). In drug discrimination studies (Grech and Balster, 1993; Munzar et al., 2000), baclofen produces a dose-dependent decrease in response rate, with one study (Grech and Balster, 1993) reporting an ED_{50} of 5.0 mg/kg, and no responding at 20 mg/kg. Similarly, an early study (Mehta and Ticku, 1987) reported that a 20 mg/kg dose of baclofen produced total catatonia in rats, with a 10 mg/kg dose resulting in a much lesser degree of catalepsy, and 7.5 mg/kg having no obvious effect.

In conclusion, the present study demonstrates that activation of GABA-B receptors modifies FEPs recorded from both the VC and SC. However, the mechanism(s) by which baclofen alters FEPs are not clear since activation of GABA-B receptors decreases the release of several neurotransmitters, including dopamine, serotonin, norepinephrine, glutamate, and GABA (Howe et al., 1987; Pirot et al., 1992; Santiago et al., 1993; Wojcik and Holopainen, 1992). Thus, baclofen can simultaneously affect the activity of many types of neurons, making it difficult to localize the origin of the effects reported here.

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References

Addae JI, Rothwell NJ, Stock MJ, Stone TW. Activation of thermogenesis of brown fat in rats by baclofen. Neuropharmacology 1986;25:627–31.

Addolorato G, Caputo F, Capristo E, Colombo G, Gessa GL, Gasbarrini G. Ability of baclofen in reducing alcohol craving and intake: II-Preliminary clinical evidence. Alcohol Clin Exp Res 2000;24:67–71.

Addolorato G, Caputo F, Capristo E, Domenicali M, Bernardi M, Janiri L, et al. Baclofen efficacy in reducing alcohol craving and intake: a preliminary double-blind randomized controlled study. Alcohol Alcohol 2002;37:504–8.

Anstrom KK, Cromwell HC, Markowski T, Woodward DJ. Effect of baclofen on alcohol and sucrose self-administration in rats. Alcohol Clin Exp Res 2003;27:900–8.

Araki M, McGeer GL, McGeer EG. Presumptive gamma-aminobutyric acid pathways from the midbrain to the superior colliculus studied by a combined horseradish peroxidase-gamma-aminobutyric acid transaminase pharmacohistochemical method. Neuroscience 1984;13:433–9.

Beaulieu C, Kisvarday Z, Somogyi P, Cynader M, Cowey A. Quantitative distribution of GABA immunopositive and immunonegative neurons and synapses in the monkey visual cortex (area 17). Cereb Cortex 1992;2:295–309.

Bigler ED. Neurophysiology, neuropharmacology and behavioral relationships of visual system evoked after-discharges: a review. Biobehav Rev 1977;1:95–112.

Bigler ED, Fleming DE. Habituation and the occurrence of photically evoked after-discharges in the albino rat. Bull Psychon Soc 1974;4:275–7.

Binns KE. The synaptic pharmacology underlying sensory processing in the superior colliculus. Prog Neurobiol 1999;59:129–59.

Borbély AA. Pharmacological Modifications of Evoked Brain Potentials. Berne: Hans Huber; 1973.

Bowery NG. $GABA_B$ receptors and their significance in mammalian pharmacology. Trends Pharmacol Sci 1989;10:401–7.

Bowery NG, Enna SJ. γ-Aminobutyric acid-B receptors: first of the functional metabotropic heterodimers. J Pharmacol Exp Ther 2000;292:2–7.

Car H, Wisniewski K. The effect of baclofen and AP-7 on selected behavior in rats. Pharmacol Biochem Behav 1998;59:685–9.

Colombo G, Serra S, Brunetti G, Vacca G, Carai MAM, Gessa GL. Suppression by baclofen of alcohol deprivation effect in Sardinian alcohol-preferring (sP) rats. Drug Alcohol Depend 2003a;70:105–8.

Colombo G, Vacca G, Serra S, Brunetti G, Carai MAM, Gessa GL. Baclofen suppresses motivation to consume alcohol in rats. Psychopharmacology (Berl) 2003b;167:221–4.

Colombo G, Addolorato G, Agabio R, Carai MAM, Pibiri F, Serra S, et al. Role of GABAB receptor in alcohol dependence: reducing effect of baclofen on alcohol intake and alcohol motivational properties in rats and amelioration of alcohol withdrawal syndrome and alcohol craving in human alcoholics. Neurotox Res 2004;6:403–14.

Corrigall WA, Coen KM, Adamson KL, Chow BLC, Zhang J. Response of nicotine self-administration in the rat to manipulations of mu-opioid and γ-aminobutyric acid receptors in the ventral tegmental area. Psychopharmacology 2000;149:107–14.

Creel D, Dustman RE, Beck EC. Intensity of flash illumination and the visually evoked potential of rats, guinea pigs and cats. Vision Res 1974;14:725–9.

Crunelli V, Haby M, Jassik-Gerschenfeld D, Leresche N, Pirchio M. Cl^-- and K^+-dependent inhibitory post-synaptic potentials evoked by interneurones of the rat lateral geniculate nucleus. J Physiol 1988;399:153–76.

Czachowski CL, Legg BH, Stansfield KH. Ethanol and sucrose seeking and consumption following repeated administration of the $GABA_B$ agonist baclofen in rats. Alcohol Clin Exp Res 2006;30:812–8.

Daoust M, Saligaut C, Lhuintre JP, Moore N, Flipo JL, Boismare F. GABA transmission, but not benzodiazepine receptor stimulation, modulates ethanol intake by rats. Alcohol 1987;4:469–72.

Dressnandt J, Conrad B. N. medianus somatosensory-evoked potentials before and after intrathecal baclofen. Electroencephalogr Clin Neurophysiol 1996;99:355.

Dyer RS. The use of sensory evoked potentials in toxicology. Fundam Appl Toxicol 1985;5:24–40.

Dyer RS. The interactions of behavior and neurophysiology. In: Annau Z, editor. Neuro-Behavioral Toxicology. Baltimore: Johns Hopkins University Press; 1986. p. 193–213.

Dyer RS, Annau Z. Flash evoked potentials from rat superior colliculus. Pharmacol Biochem Behav 1977;6:453–9.

Faingold CL, N'Gouemo P, Riaz A. Ethanol and neurotransmitter interactions — from molecular to integrative effects. Prog Neurobiol 1998;55:509–35.

Flannery BA, Garbutt JC, Cody MW, Renn W, Grace K, Osborne M, et al. Baclofen for alcohol dependence: a preliminary open-label study. Alcohol Clin Exp Res 2004;28:1517–23.

Fox SS, Rosenfeld JP. Recording evoked potentials. In: Myers RD, editor. Methods in Psychobiology. Specialized Laboratory Techniques in Neuropsychology and Neurobiology. New York: Academic Press; 1972. p. 345–69.

Gelatt KN, editor. Textbook of Veterinary Ophthalmology. Philadelphia: Lea & Febiger; 1981.

Gil Z, Connors BW, Amitai Y. Differential regulation of neocortical synapses by neuromodulators and activity. Neuron 1997;19:679–86.

Goldberg ME, Robinson DL. Visual system: superior colliculus. In: Masterton RB, editor. Handbook of Behavioral Neurobiology, vol. 1. New York: Plenum Press; 1978. p. 119–64.

Grech DM, Balster RL. Pentobarbital-like discriminative stimulus effects of direct GABA agonists in rats. Psychopharmacology 1993;110:295–301.

Harrison NL, Lange GD, Barker JL. (−)-Baclofen activates presynaptic GABA-B receptors on GABAergic inhibitory neurons from embryonic rat hippocampus. Neurosci Lett 1988;85:105–9.

Herr DW, Boyes WK. Electrophysiological analyses of complex brain systems: sensory-evoked potentials and their generators. In: Chang LW, Slikker W,

editors. Neurotoxicology approaches and methods. New York: Academic Press; 1995. p. 205–21.
Hetzler BE, Dyer RS. Contribution of hypothermia to effects of chloral hydrate on flash evoked potentials of hooded rats. Pharmacol Biochem Behav 1984;21:599–607.
Hetzler BE, Theinpeng M. Nicotine alters flash-evoked potentials in Long–Evans rats. Pharmacol Biochem Behav 2004;77:717–29.
Hetzler BE, Zeisset HL. THIP, a selective gamma-aminobutyric acid receptor agonist, alters flash-evoked potentials in rats. Pharmacol Biochem Behav 1997;58:923–32.
Hetzler BE, Heilbronner RL, Griffin J, Griffin G. Acute effects of alcohol on evoked potentials in visual cortex and superior colliculus of the rat. Electroencephalogr Clin Neurophysiol 1981;51:69–79.
Hetzler BE, Boyes WK, Creason JP, Dyer RS. Temperature-dependent changes in visual evoked potentials of rats. Electroencephalogr Clin Neurophysiol 1988;70:137–54.
Horton RW, LeFeuvre RA, Rothwell NJ, Stock MJ. Opposing effects of activation of central $GABA_A$ and $GABA_B$ receptors on brown fat thermogenesis in the rat. Neuropharmacology 1988;27:363–6.
Hotsenpiller G, Wolf ME. Baclofen attenuates conditioned locomotion to cues associated with cocaine administration and stabilizes extracellular glutamate levels in rat nucleus accumbens. Neuroscience 2003;118:123–34.
Howe JR, Sutor B, Zieglgänsberger W. Baclofen reduces post-synaptic potentials of rat cortical neurons by an action other than its hyperpolarizing action. J Physiol (London) 1987;384:539–69.
Jha SK, Islam F, Mallick BN. GABA exerts opposite influence on warm and cold sensitive neurons in medial preoptic area in rats. J Neurobiol 2001;48:291–300.
Kamatchi GL, Ticku MK. Functional coupling of presynaptic GABA-B receptors with voltage-gated $Ca2^+$ channel: regulation by protein kinases A and C in cultured spinal cord neurons. Mol Pharmacol 1990;38:342–7.
Kasamatsu T, Mizobe K, Sutter EE. Muscimol and baclofen differentially suppress retinotopic and nonretinotopic responses in visual cortex. Vis Neurosci 2005;22:839–58.
Kofler M, Donovan WH, Loubser PG, Beric A. Effects of intrathecal baclofen on lumbosacral and cortical somatosensory evoked potentials. Neurology 1992a;42:864–8.
Kofler M, Saltuari L, Schmutzhard E, Berek K, Baumgartner H, Russegger L, et al. Electrophysiological findings in a case of severe intrathecal baclofen overdose. Electroencephalogr Clin Neurophysiol 1992b;83:83–6.
König JFR, Klippel RA. The Rat Brain, A Stereotaxic Atlas of the Forebrain and Lower Parts of the Brain Stem. New York: Krieger; 1963.
Lüscher C, Lipp P, Lüscher HR, Niggli E. Control of action potential propagation by intracellular Ca^{2+} in cultured rat dorsal root ganglion cells. J Physiol (London) 1996;490:319–24.
Meeren HKM, Van Luijtelaar ELJM, Coenen AML. Cortical and thalamic visual evoked potentials during sleep-wake states and spike-wave discharges in the rat. Electroencephalogr Clin Neurophysiol 1998;108:306–19.
Mehta AK, Ticku MK. Baclofen induces catatonia in rats. Neuropharmacology 1987;26:1419–23.
Mize RR. Immunocytochemical localization of gamma-aminobutyric acid (GABA) in the cat superior colliculus. J Comp Neurol 1988;276:169–87.
Mize RR. The organization of GABAergic neurons in the mammalian superior colliculus. In: Mize RR, Marc RE, Sillito AM, editors. GABA in the retina and central visual system. Progress in Brain Research, Vol 90. Amsterdam: Elsevier; 1992. p. 219–48.
Moller A, Eysteinsson T. Modulation of the components of the rat dark-adapted electroretinogram by the three subtypes of GABA receptors. Vis Neurosci 2003;20:535–42.
Munzar P, Kutkat SW, Miller CR, Goldberg SR. Failure of baclofen to modulate discriminative-stimulus effects of cocaine or methamphetamine in rats. Eur J Pharmacol 2000;408:169–74.
Murakoshi T, Guo JZ, Ichinose T. Electrophysiological identification of horizontal synaptic connections in rat visual cortex in vitro. Neurosci Lett 1993;163:211–4.
Okada Y. The distribution and function of gamma-aminobutyric acid (GABA) in the superior colliculus. In: Mize RR, Marc RE, Sillito AM, editors. GABA in the retina and central visual system. Progress in Brain Research, Vol 90. Amsterdam: Elsevier; 1992. p. 249–62.
Okada Y, Nitsch-Hassler C, Kim JS, Bak IJ, Hassler R. Role of gamma-aminobutyric acid (GABA) in the extrapyramidal motor system. 1. Regional distribution of GABA in rabbit, rat, guinea pig and baboon CNS. Exp Brain Res 1971;13:514–8.
Paul SM. GABA and Glycine. In: Bloom FE, Kupfer DJ, editors. Psychopharmacology: The Fourth Generation of Progress. New York: Raven Press, Ltd.; 1995. p. 87–94.
Penn RD, Kroin JS. Long-term intrathecal baclofen infusion for treatment of spasticity. J Neurosurg 1987;66:181–5.
Petry NM. Benzodiazepine-GABA modulation of concurrent ethanol and sucrose reinforcement in the rat. Exp Clin Psychopharmacol 1997;5:183–94.
Phillis BD, Ong J, White JM, Bonnielle C. Modification of d-amphetamine-induced responses by baclofen in rats. Psychopharmacology 2001;153:277–84.
Pirot S, Godbout R, Tassin JP, Glowinski J, Thierry AM. Inhibitory effects of ventral tegmental area stimulation on the activity of prefrontal cortical neurons: evidence for the involvement of both dopaminergic and GABAergic components. Neuroscience 1992;49:857–65.
Porter JT, Nieves D. Presynaptic $GABA_B$ receptors modulate thalamic excitation of inhibitory and excitatory neurons in the mouse barrel cortex. J Neurophysiol 2004;92:2762–70.
Rawls SM, Tallarida RJ, Kon DA, Geller EB, Adler MW. $GABA_A$ receptors modulate cannabinoid-evoked hypothermia. Pharmacol Biochem Behav 2004;78:83–91.
Redgrave P, Marrow LP, Dean P. Topographical organization of the nigrotectal projection in the rat: Evidence for segregated channels. Eur J Neurosci 1990 (Suppl 3):4253.
Sancibrian M, Serrano JS, Miñano FJ. Opioid and prostaglandin mechanisms involved in the effects of GABAergic drugs on body temperature. Gen Pharmac 1991;22:259–62.
Santiago M, Machado A, Cano J. In vivo release of dopamine from rat striatum, substantia nigra and prefrontal cortex: differential modulation by baclofen. Br J Pharmacol 1993;109:814–8.
Schwartzbaum JS. Interrelationship among multiunit activity of the midbrain reticular formation, and lateral geniculate nucleus, thalamocortical arousal and behavior in rats. J Comp Physiol Psychol 1975;83:131–57.
Sefton A, Martin P. Relation of the parabigeminal nucleus to the superior colliculus and dorsal lateral geniculate nucleus in the hooded rat. Exp Brain Res 1984;56:144–8.
Shao Z, Burkhalter A. Role of $GABA_B$ receptor-mediated inhibition in reciprocal interareal pathways of rat visual cortex. J Neurophysiol 1999;81:1014–24.
Shah AS, Bressler SL, Knuth KH, Ding M, Mehta AD, Ulbert I, et al. Neural dynamics and the fundamental mechanisms of event-related brain potentials. Cereb Cortex 2004;14:476–83.
Shearer DE, Creel D. The photically evoked afterdischarge: Current concepts and potential applications. Physiol Psychol 1978;6:369–76.
Siegel J, Sisson DF. Evoked field potentials — beyond correlates of behavior: an approach to determining the neural mechanism of behavior. In: Haschke W, Roitbak AI, Speckmann E-J, editors. Slow potential changes in the brain. Boston: Birkhauser; 1993. p. 151–65.
Sisson DF, Siegel J. Chloral hydrate anesthesia: EEG power spectrum analysis and effects on VEPs in the rat. Neurotoxicol Teratol 1989;11:51–6.
Smith BR, Boyle AEL, Amit Z. The effects of the $GABA_B$ agonist baclofen on the temporal and structural characteristics of ethanol intake. Alcohol 1999;17:231–40.
Somogyi P. Synaptic organization of GABAergic neurons and GABAA receptors in the lateral geniculate nucleus and visual cortex. In: Man-Kit Lam D, Gilbert CD, editors. Neural Mechanisms of Visual Perception. The Second Retina Research Foundation Symposium. Houston: Portfolio Pub. Co.; 1989. p. 35–62.
Standage GP, Fleming DE. Visual cortical hypersynchronous bursting as an index of shifts in behavioral state. Physiol Behav 1979;23:35–8.
Sun BB, Chiu SY. N-type calcium channels and their regulation by $GABA_B$ receptors in axons of neonatal rat optic nerve. J Neurosci 1999;19:5185–94.
Szczepaniak WS, Møller AR. Effects of L-baclofen and D-baclofen on the auditory system: a study of click-evoked potentials from the inferior colliculus in the rat. Ann Otol Rhinol Laryngol 1995;104:399–404.
Szczepaniak WS, Møller AR. Effects of (−)-baclofen, clonazepam, and diazepam on tone exposure-induced hyperexcitability of the inferior

colliculus in the rat: possible therapeutic implications for pharmacological management of tinnitus and hyperacusis. Hearing Res 1996;97:46–53.
Tan U. Entropy concept in relation to brain waves and evoked potentials: critique of a physical approach. Int J Neurosci 1985;28:249–60.
Toldi J, Fehér O. The role of the γ-aminobutyrate system in the interactions of cortical evoked potentials. Neuroscience 1985;15:977–81.
Vincent SR, Hattori T, McGeer EG. The nigrotectal projection: a biochemical and ultrastructural characterization. Brain Res 1978;151:159–64.
Walker BM, Koob GF. The γ-aminobutyric acid-B receptor agonist baclofen attenuates responding for ethanol in ethanol-dependent rats. Alcohol Clin Exp Res 2007;31:11–8.
Wojcik WJ, Holopainen I. Role of central $GABA_B$ receptors in physiology and pathology. Neuropsychopharmacol 1992;6:201–14.
Xi Z-X, Stein EA. Baclofen inhibits heroin self-administration behavior and mesolimbic dopamine release. J Pharmacol Exp Ther 1999;290:1369–74.
Yakimova K, Sann H, Schmid HA, Pierau FK. Effects of GABA agonists and antagonists on temperature-sensitive neurons in the rat hypothalamus. J Physiol 1996;494:217–30.
Zarrindast M-R, Oveissi Y. $GABA_A$ and $GABA_B$ receptor sites involvement in rat thermoregulation. Gen Pharmacol 1988;19:223–6.
Zarrindast M-R, Rostami P, Sadeghi-Hariri M. $GABA_A$ but not $GABA_B$ receptor stimulation induces antianxiety profile in rats. Pharmacol Biochem Behav 2001;69:9–15.
Zhu JJ, Lo F-S. Three GABA receptor-mediated postsynaptic potentials in interneurons in the rat lateral geniculate nucleus. J Neurosci 1999;19:5721–30.