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Time course of chronic diazepam effects on the auditory evoked potential of the rat

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Abstract

The time course of chronic diazepam effects on auditory evoked potentials was studied in rats. Auditory evoked potentials were elicited by background and target tones in a passive oddball paradigm. Diazepam was administered by slow release implants to establish constant blood concentrations. Recordings were made during 21 days of treatment and 9 days after treatment ceased. Diazepam increased the amplitude of the P_{40} component and decreased the amplitude of the P_{72}–P_{102} components elicited by background tones. Diazepam increased the amplitude of the P_{40}–P_{48} component and decreased that of the N_{58} component elicited by target tones. These effects remained constant during treatment. Diazepam further decreased the amplitude of the P_{102} component elicited by target tones. This effect became more distinct over time. No group differences were found 9 days after treatment. The constant drug effects on middle-latency components (P_{40}–P_{48}) might reflect diazepam-induced changes in sensory information processing. The decreased long-latency component (P_{102}) might reflect a diminished attention to, or discrimination of, target tones. The time course of this effect might reflect diazepam-enhanced habituation. © 1998 Elsevier Science B.V.

Keywords: Diazepam; Tolerance; Auditory evoked potential; Habituation; Oddball paradigm; (Rat)

1. Introduction

Benzodiazepines have sedating, muscle relaxant, anti-convulsant and anxiolytic effects (for review, see File, 1990). Benzodiazepines are therefore often prescribed for extensive periods of time, as long as several years or even for life (Haafkens, 1997). However, benzodiazepines affect cognitive processes such as attention and memory (for review, see Golombok et al., 1988; Curran, 1991). Tolerance develops to a number of the effects of benzodiazepines, e.g. in rats to the sedating, muscle relaxant, anti-convulsant (for review, see File and Cooper, 1985; Löscher and Schwark, 1985; File, 1990; Hutchinson et al., 1996) and anxiolytic effects (File et al., 1991). It is still unclear however, whether the effects on cognition associated with the chronic use of benzodiazepines are persistent (Lucki et al., 1986), since longitudinal studies of benzodiazepine effects on cognitive processes are rare (Curran, 1991).

Tolerance refers to the process by which the effect of the same dose of a drug decreases with repeated drug administration (Hutchinson et al., 1996). Whether or not signs of tolerance develop during chronic administration of benzodiazepines may depend on both the dose-regimen and the investigated variable (Antelman et al., 1989; Kalynchuk et al., 1994; Hutchinson et al., 1996). Repeated doses of benzodiazepines in rats result in major fluctuations in the blood concentrations of the drug (Gallager et al., 1985) due to the short half-life (± 1 h) in these animals (Friedman et al., 1986). In humans, repeated doses result in more constant blood concentrations due to the long half-life (35–100 h, Wan et al., 1996). Subcutaneously implanted silastic tubes containing diazepam allow for continuous release, resulting in constant blood concentrations in rats (Gallager et al., 1985; Ramsey-Williams et al., 1994; Wu et al., 1994; Van Rijn and Jongsma, 1995). Experiments using these silastic tube implants showed that tolerance developed to the anti-convulsant effect of diazepam (Gallager et al., 1985; Ramsey-Williams et al.,

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1994) and to its anxiolytic effect (Davis and Gallager, 1988). Using this method, we studied the time course of chronic diazepam effects on auditory evoked potentials in the rat.

Evoked potentials provide a sensitive method for studying the effects of drugs on sensory aspects of information processing (Noldy et al., 1990; Ehlers et al., 1991; Meador, 1995). Evoked potentials are discrete and minute electrical potentials that appear in the electroencephalogram (EEG). They are usually produced by, and time-locked to, sensory stimuli (Näätänen, 1990; Coenen, 1995). Middle-latency components of auditory evoked potentials appearing between 10–50 ms after stimulus onset are thought to reflect sensory aspects of auditory information processing (Barth and Di, 1990). The long-latency auditory evoked potentials, occurring later than 50 ms after stimulus onset, only appear in conjunction with cognitive processes in rats (Shaw, 1988). Therefore, the effects of benzodiazepines on the components of the auditory evoked potential appearing >50 ms after stimulus onset might reveal insight into their effects on cognition. The effects of diazepam were studied with respect to middle- and long-latency components of auditory evoked potentials evoked by background and target tones in a passive oddball paradigm (Ehlers et al., 1991). An oddball paradigm is an experimental paradigm that is often used in human cognitive psychology (Polich, 1986). During the oddball task the subject is exposed to two different stimuli, one of which occurs relatively infrequently and is designated as a target (Blackwood and Muir, 1990). Stimulus-change and unpredictability are the main features of this paradigm (Blackwood and Muir, 1990).

The objective of this study was to investigate the effects of chronic administration of diazepam on the rat auditory evoked potential in order to determine whether or not tolerance would develop to these effects over a period of 21 days. Diazepam was administered by subcutaneous slow-release implants for 21 days (Van Rijn and Jongsma, 1995). Auditory evoked potentials were elicited by frequently occurring background tones and infrequently occurring target tones.

2. Materials and methods

This study was performed in accordance with the guidelines of the European Community for the use of experimental animals. Approval of the local ethics committee for animal studies was obtained.

2.1. Animals

Sixteen male WAG/Rij rats (age 10 months, weight 350 ± 16 g (mean $\pm$ S.D.)) were maintained on a 12–12 h light–dark cycle with lights off at 9.00 a.m., and were singly housed with food and water ad libitum.

2.2. Surgical procedures

Hypnorm anesthesia (0.315 mg/ml fentanyl citrate and 10 mg/ml fluanisone, 0.8 ml/kg i.m.) combined with Nembutal anesthesia (60 mg/ml sodium pentobarbital, 0.35 ml/kg i.p.) was used for implanting tri-polar electrodes (Plastics One, MS 333/2a) which were fixed on the skull with dental acrylic cement. Coordinates related to bregma were: A 2.0, L 2.0; and: A -3.7, L 9.0, respectively. The ground electrode was placed above the cerebellum. Animals were allowed to recover for four weeks before silastic tubes were implanted. The tubes were implanted, in pairs, under the skin of the back of the animals. For each experimental animal we used 8 silastic tubes of 8 cm length (Dow Corning, 0.062 inch inner diameter; 0.095 inch outer diameter), each containing 100 mg of solid diazepam without any vehicle (Roche Nederland). The diazepam output from the implanted silastic tubes was 17.6 ± 1.6 (mean $\pm$ S.D.) mg per animal per day (i.e. ± 2 mg/kg per h). Control animals received 8 empty silastic tubes of the same length. Implantation and removal of the silastic tubes took place under ether anesthesia.

2.3. Recording procedures

EEG signals were measured between 1 and 100 Hz and recorded digitally with a sample frequency of 512 Hz. EEGs were recorded during treatment on day 1, 3, 8, 14 and 21 from 14.00 h till 15.30 h in the afternoon. After removal of the silastic tubes all animals had two more stimulation sessions without recording on day 1 and day 4 after removal of the silastic tubes. A final recording was made 9 days after removal of the silastic tubes.

Auditory evoked potentials were evoked by two pure tone pip stimuli with a stimulus duration of 20 ms and were presented with random inter-stimulus intervals between 2.5–3.5 s. Frequently occurring background tones (90% of the trials, 8 kHz, 96 dB), interspersed with infrequently occurring target tones (10% of the trials, 12 kHz, 102 dB), were presented. Per recording session a total of 1500 stimuli were presented. White background noise of 85 dB was present.

2.4. Data analysis

Auditory evoked potentials were determined by averaging EEG fragments recorded 100 ms before stimulus onset until 900 ms after stimulus onset. A rejection program was utilized to eliminate individual trials in which the EEG exceeded 600 μV, thereby excluding trials with high EEG amplitudes due to e.g. motor artefacts.

2.5. Statistical analysis

Two outliers were excluded because no clear components could be detected in the auditory evoked potential recorded 9 days after removal of the silastic tubes. Compo-

nent latencies were selected on the basis of the maximum peak amplitude of the total grand average auditory evoked potential determined on the last recording day. Individual amplitudes at selected latencies were included in the analysis. Auditory evoked potentials elicited by background tones and target tones were analyzed separately.

For each component group differences in amplitude were determined as:

$$\text{difference} = \text{mean}_{\text{experimentals}} - \text{mean}_{\text{controls}}, \text{and S.E.M.} = \sqrt{\left((\text{S.E.M.}_{\text{controls}})^2 + (\text{S.E.M.}_{\text{experimentals}})^2\right)}.$$

Non-linear regression analysis, using the program GraphPad Prism 2.0, was performed on the data as this analysis takes into account the ratio scale of the time axis. *F*-tests were used to determine:

– Whether an exponential association described group differences in time significantly better than a linear regression, if not:

– Whether the linear regression differed significantly from a linear regression with slope = 0 (no time-dependent effect), and if not:

– Whether the linear regression with slope = 0 differed significantly from a linear regression with a slope = 0 and intercept = 0 (no time-dependent effect and no drug effect).

The component amplitudes measured 9 days after the end of treatment were tested by using a Student's *t*-test.

3. Results

Grand average auditory evoked potentials over 21 treatment days and 9 days after the end of treatment for both experimental ($n = 6$) and control animals ($n = 8$) are shown in Fig. 1a and b. Fig. 1a shows the grand average auditory evoked potentials evoked by background tones. Fig. 1b shows the grand average auditory evoked potentials evoked by target tones.

After determination of maximal peak values of the total grand average auditory evoked potentials recorded 9 days

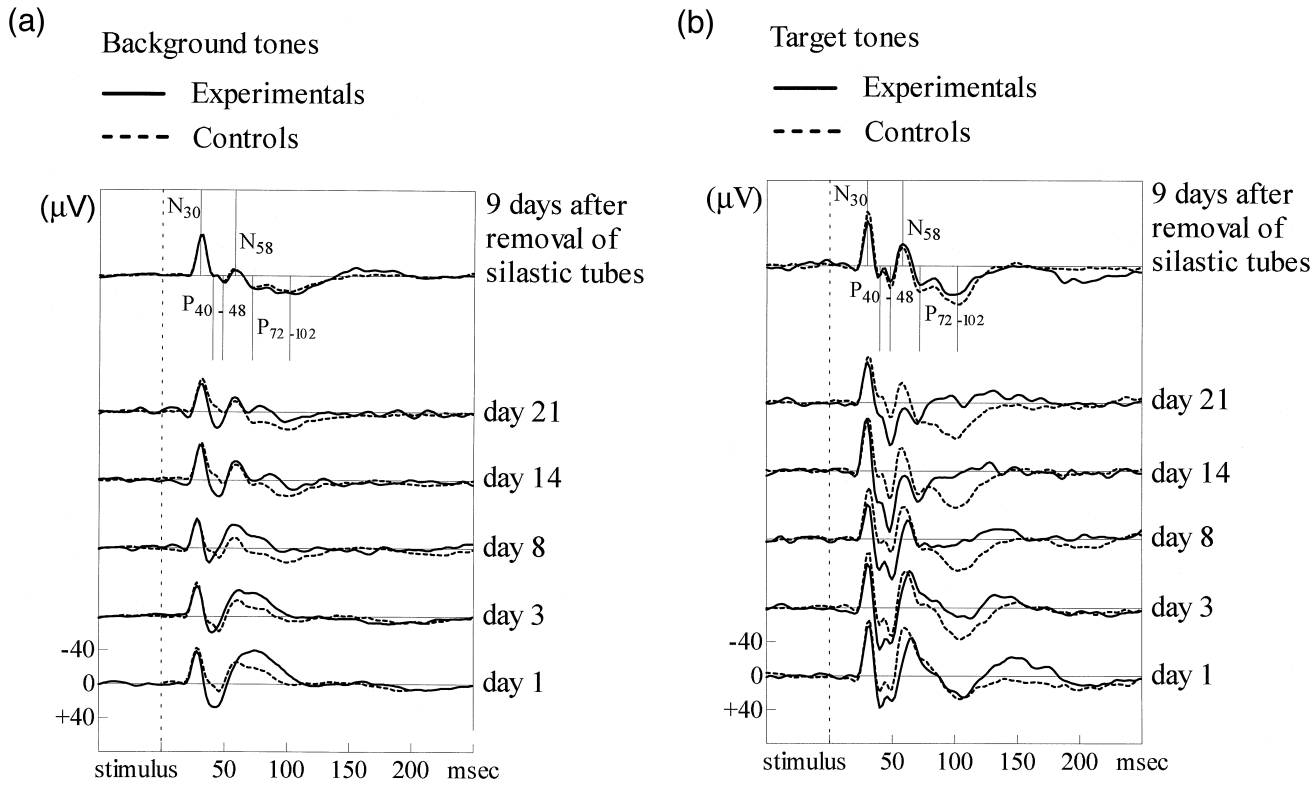

Fig. 1. (a) Grand average auditory evoked potentials evoked by background tones for experimental (solid lines) and control animals (dotted lines) on days 1, 3, 8, 14 and 21 during treatment and 9 days after removal of the silastic tubes. Amplitudes are given in μV (*y*-axes) and latencies are given in milliseconds after stimulus onset (*x*-axes). The N_{30}, P_{40}, P_{48}, N_{58}, P_{72} and P_{102} components are marked in the grand average auditory evoked potentials measured 9 days after removal of silastic tubes. In experimental animals the P_{40} component increased and the P_{72} and P_{102} components decreased during the 21 days of treatment. No differences between experimental and control animals were found 9 days after removal of the silastic tubes. (b) Grand average auditory evoked potentials evoked by target tones for experimental (solid lines) and control animals (dotted lines) on days 1, 3, 8, 14 and 21 during treatment and 9 days after removal of the silastic tubes. Amplitudes are given in μV (*y*-axes) and latencies are given in milliseconds after stimulus onset (*x*-axes). The N_{30}, P_{40}, P_{48}, N_{58}, P_{72} and P_{102} components are marked in the grand average auditory evoked potentials measured 9 days after removal of silastic tubes. In experimental animals the P_{40}–P_{48} components increased and the N_{58} component decreased. The P_{102} component decreased during the 21 days of treatment. This latter effect became more distinct over time. No differences between experimental and control animals were found 9 days after removal of the silastic tubes.

after tube removal, N_{30}, P_{40}, P_{48}, N_{58}, P_{72} and P_{102} components could be identified.

The difference scores for the amplitudes of the N_{30}, P_{40}, P_{48}, N_{58}, P_{72} and P_{102} components are shown in Fig. 2a and b for background tones and target tones, respectively. For each component of auditory evoked potentials, best fits are depicted. Parameter estimates and *P*-values are given for components for which the best fit over time differed significantly from no effect ($y = ax + b,\ a = 0,\ b = 0$).

3.1. Diazepam effects on auditory evoked potentials evoked by background tones

The P_{40} component evoked by background tones (see Fig. 2a) had a higher amplitude (i.e. a more positive deflection) for experimental than for control animals during the 21 days of treatment. The P_{72} and P_{102} components for experimental animals showed a decrease in amplitude (i.e. a less positive deflection) for background tones. The

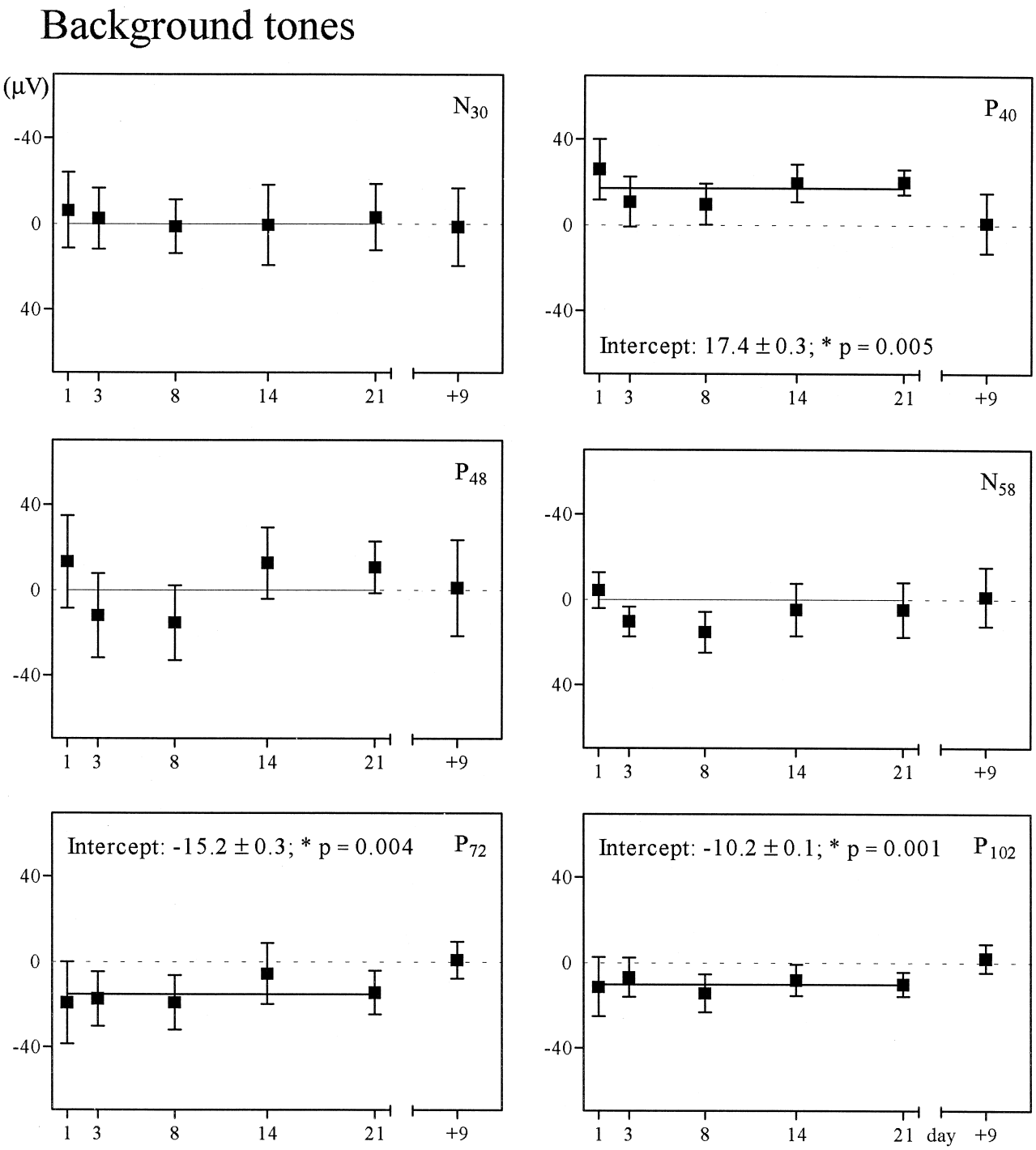

Fig. 2.

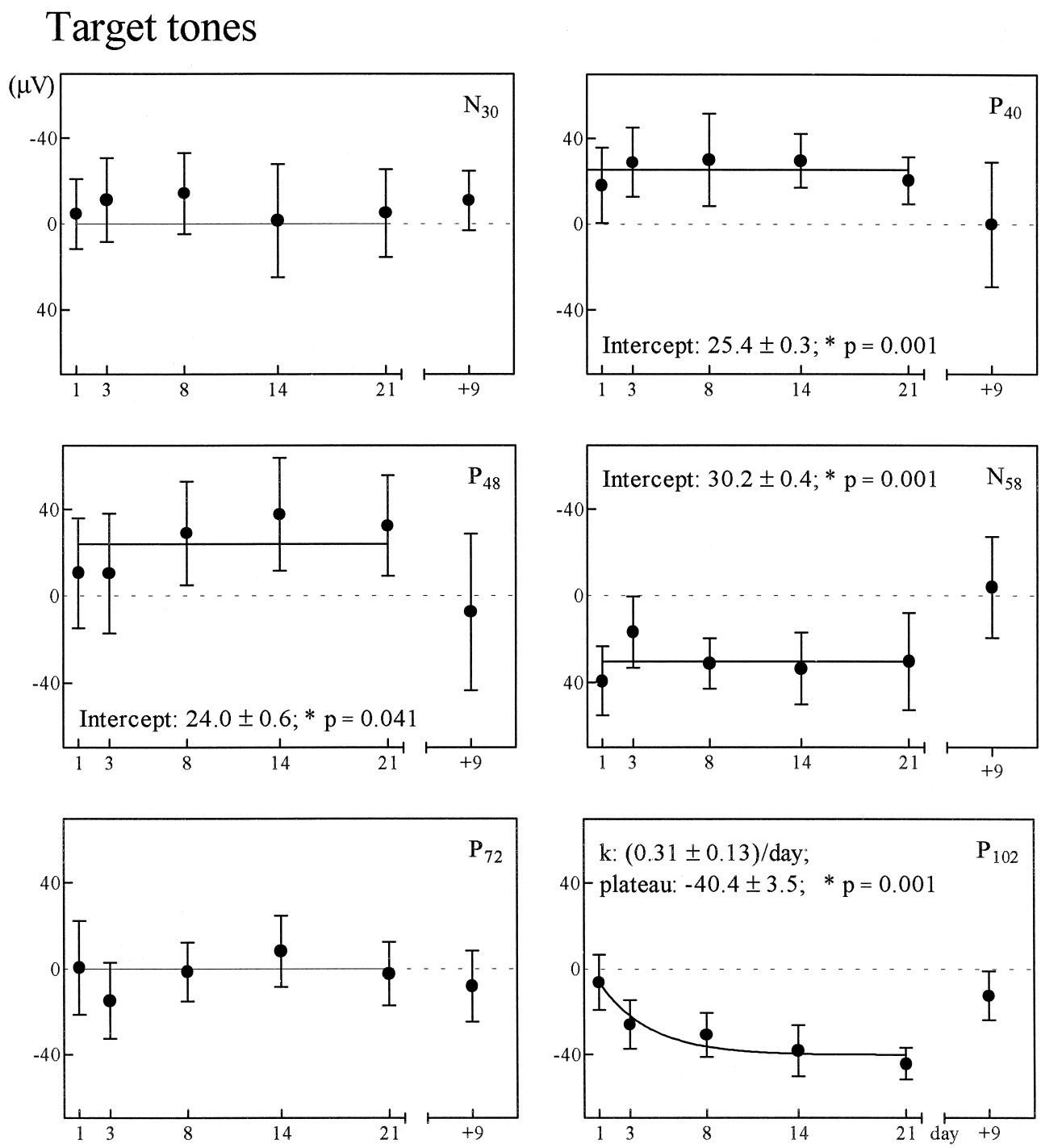

Fig. 2. (a) Difference scores (on *y*-axes in μV) between experimental and control animals for components of auditory evoked potentials evoked by background tones. Used fits over 21 treatment days (*x*-axes) show the time course of the diazepam effect. The P_{40} component had a higher amplitude (i.e. a more positive deflection) in experimental animals than in control animals. The P_{72} and P_{102} components had a lower amplitude (i.e. a less positive deflection) in experimental animals than in control animals. The time course of these drug effects was best described by straight, horizontal lines and differed significantly from a constant zero effect. Intercepts and *P*-values are given in the panels. Differences were no longer found 9 days after removal of the silastic tubes. (b) Difference scores (on *y*-axes in μV) between experimental and control animals for components of auditory evoked potentials evoked by target tones. Used fits over 21 treatment days (*x*-axes) show the time course of the diazepam effect. The P_{40} and P_{48} components had a higher amplitude (i.e. a more positive deflection) in experimental animals than in control animals. The N_{58} component in experimental animals had a decreased amplitude (i.e. a less negative deflection). The time course of these drug effects was best described by straight, horizontal lines and differed significantly from a constant zero effect. Intercepts and *P*-values are given in the panels. The P_{102} amplitude was decreased in experimental animals. The time course of this decrease was best described by an exponential decay model. Plateau, *k* and *P*-value are given in the panel. Differences were no longer found 9 days after removal of the silastic tubes.

time course of these drug effects were best described by straight, horizontal lines (*F*-tests: constant drug effect ($y = bx + a;\ b = 0$) differed significantly from a constant zero effect ($y = bx + a;\ a = 0,\ b = 0$). For *P*-values see Fig. 2a). No differences between experimental and control animals were found 9 days after removal of the silastic tubes.

3.2. Diazepam effects on auditory evoked potentials evoked by target tones

With respect to the P_{40} and P_{48} components evoked by target tones (see Fig. 2b), the amplitudes were higher (i.e. a more positive deflection) in experimental than in control animals during the 21 days of treatment. For the N_{58} component experimental animals showed a decrease in amplitude (i.e. a less negative deflection) for target tones. The time course of these drug effects were best described by straight, horizontal lines (for *P*-values, see Fig. 2b). With respect to the P_{102} component, a decreased amplitude (i.e. a less positive deflection) in experimental animals was found. This effect became more distinct over time. The time course of this decrease was best described by an exponential decay model: $y = y(1) - y(\text{plateau}) * (\exp(-kx))$; with $y(1)$ is the difference on day 1, $y(\text{plateau})$ and k are the parameter estimates, see Fig. 1b. No differences between experimental and control animals were found 9 days after removal of the silastic tubes.

4. Discussion

The objective of this study was to investigate the effects of chronic administration of diazepam on the rat auditory evoked potential in order to determine whether or not tolerance would develop to these effects over a period of 21 days. In this study tolerance to diazepam did not develop for any of the changes in the rat auditory evoked potential. All diazepam effects were reversible as there were no differences between experimental and control animals 9 days after removal of the silastic tubes.

4.1. Diazepam effects on middle-latency components of auditory evoked potentials

An increase in the P_{40} amplitude evoked by background tones and P_{40}–P_{48} amplitude evoked by target tones was found. This effect remained stable during the 21 days of treatment. As middle-latency components of auditory evoked potentials are supposed to express aspects of sensory information processing, diazepam might have a constant effect on aspects of auditory information processing. Most studies report that diazepam decreases the amplitude of auditory evoked potentials (Noldy et al., 1990; Allen et al., 1991). Contradictory findings however, are not uncommon, as benzodiazepine's effects on the amplitude of auditory evoked potentials appear to be dose-related (Böker and Heinze, 1984; Bartel et al., 1988). Bringmann and Klingberg (1995) reported an increased middle-latency negative peak in the rat evoked potential in states of low arousal. Increased amplitude of auditory evoked potentials due to a decrease in arousal is in agreement with the, in general, depressant effects of diazepam (File, 1990).

Furthermore, a correlation between background EEG and evoked potentials might be expected since an evoked potential is a sensory driven segment of EEG activity (Bringmann and Klingberg, 1995). Background EEG activity and evoked potentials have been related by several authors (Van Dijk et al., 1992; Makeig, 1993; Brandt et al., 1994). Benzodiazepines are known to increase activity in the beta-band (12–40 Hz) of the EEG (Van Rijn and Jongsma, 1995). Increased beta-activity however, is in conflict with a decreased arousal, because the former is normally seen under enhanced levels of arousal. Since it is known that diazepam causes both lowered arousal and increased beta-activity, this effect has been described as pharmacological dissociation (Coenen and Van Luijtelaar, 1991). Hence, both an increase in EEG beta-activity and a decrease in arousal might additionally account for the increase in the amplitude of the middle-latency components of auditory evoked potentials. Our previous study showed that the enhancement of beta-power was stable during the 21 days of treatment (Van Rijn and Jongsma, 1995). In the present study, the diazepam-induced increase in the middle-latency components of auditory evoked potentials was stable during treatment and could be related to an increase in activity in the beta-band, since both these diazepam effects remain stable over time.

4.2. Diazepam effect on long-latency components of auditory evoked potentials evoked by background tones

We found a decrease in the P_{72} and P_{102} components elicited by background tones. A decreased amplitude of late auditory evoked potentials after acute diazepam treatment has previously been reported (Bartel et al., 1988; Noldy et al., 1990; Allen et al., 1991; Martin et al., 1992), and may be interpreted as a decrease in the excitability of the central nervous system (Noldy et al., 1990).

4.3. Diazepam effect on long-latency components of auditory evoked potentials evoked by target tones

The dominant component of the auditory evoked potential elicited by a target tone is a large late positivity: the P_{300} component (Polich, 1986; Ehlers and Chaplin, 1992). Although some studies reported a P_{300} component in the rat auditory evoked potential using a passive oddball paradigm (Hurlbut et al., 1987; Ehlers and Chaplin, 1992), others could not detect a P_{300} component using this paradigm (Ehlers et al., 1991). In the present study, no P_{300} component in the auditory evoked potential elicited by the

target tone was found. This could have been due to the number of trails in each session. It has been reported that the P_{300} component diminishes, and eventually disappears, in a passive oddball paradigm after more than 100 presentations of the target tone (O'Brien, 1982). In our study about 150 target tones were presented in each session. Besides a P_{300} component, increased amplitudes at 60–80 and 120–180 ms after stimulus onset have also been found with target tones (Ehlers et al., 1991), and are thought to reflect cognitive processes like attention to, and discrimination of, target tones.

We found a decreased amplitude of the N_{58} component elicited by target tones after diazepam. This effect was stable over time. In addition, we found a reduction of the P_{102} component specifically with the target tones. This effect became more distinct over the 21 days of treatment such that the P_{102} component had disappeared at day 21, as can be seen in Fig. 1b. To our knowledge, time-dependent effects of benzodiazepines on evoked potentials have been described only in humans. Allen et al. (1991) found that alprazolam, given over 10 days, constantly decreased the amplitude of auditory evoked potentials. Higgitt et al. (1988) also found that ketazolam and lorazepam decreased the amplitude of auditory evoked potentials. They also reported signs of tolerance in the last session, but only with respect to lorazepam (Higgitt et al., 1988). A closer look at their results however, shows that the amplitude of auditory evoked potentials in the placebo group decreased over time, whereas the lorazepam effect remained relatively stable and the ketazolam effect became more distinct over time. This last observation is in agreement with our diazepam effect with respect to the P_{102} component evoked by target tones. The different effects of alprazolam (Allen et al., 1991), ketazolam and lorazepam (Higgitt et al., 1988) with time suggest that differences in drug effects over time might be attributed to the different benzodiazepines used.

In general, a decrease in a reaction to a stimulus with time reflects habituation (Herr et al., 1994). Böker and Heinze (1984) found a decrease in the P1 and N2 components of a visually evoked potential in humans. Moreover, these decreases became more distinct over trials within the session. In addition, Widgiz and Beck (1990) reported that diazepam enhanced habituation of exploratory behavior in rats over sessions. In the present study, the time course of the diazepam effect with respect to the amplitude of the P_{102} component evoked by target tones can be interpreted as an enhanced habituation elicited by diazepam.

In summary, diazepam has a constant effect on sensory aspects of information processing, as expressed in the altered amplitudes of the middle-latency components of auditory evoked potentials elicited by both the background and target tones. No tolerance developed over 21 days of treatment with respect to these effects.

Diazepam further seems to affect cognitive processes as expressed by the effect of the drug on the P_{102} component evoked specifically by target tones. It is hypothesized that during the 21 days of treatment diazepam diminished attention to, and discrimination of, target tones, as seen by a gradually disappearing P_{102} component. This effect might be related to an enhanced habituation evoked by diazepam.

The effects of benzodiazepines are reported to be either constant over time (Van Rijn and Jongsma, 1995) or to decrease over time (Hutchinson et al., 1996). The time-dependency of the diazepam effect on the P_{102} component of the rat auditory evoked potential evoked by target tones adds an additional time-dependent effect, namely a more pronounced drug effect over time.

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