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The Conditioned Eyeblink Response: A Role for the GABA-B Receptor?

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RAMIREZ, O. A., A. F. NORDHOLM, D. GELLERMAN, J. K. THOMPSON AND R. F. THOMPSON. *The conditioned eyeblink response: A role for the GABA-B receptor?* PHARMACOL BIOCHEM BEHAV **58**(1) 127–132, 1997.—In well-trained animals, infusion of the GABA-B agonist baclofen into the cerebellar interpositus nucleus and overlying cortex abolished the conditioned response (CR) with no effect on the unconditioned response (UR) with doses at or above 5.0 mM. Infusion of the GABA-B antagonist CGP 5584-5A alone had no effect on the CR or UR. However, administration of 5 mM baclofen soon after infusion of CGP 5584-5A (15 min) resulted in no reduction of percent CR and only partial reduction of CR amplitude. Naive animals given interpositus infusions of baclofen during training showed no learning, yet learned normally in postinfusion training. The distribution of (radiolabelled) baclofen was localized and remained within the cerebellum. The results presented here are consistent with a growing body of literature supporting the hypothesis that the memory trace for eyeblink conditioning is formed and stored in the cerebellum and may involve GABAergic mechanisms. © 1997 Elsevier Science Inc.

GABA-B receptors Baclofen Cerebellum Interpositus nucleus Eyeblink conditioning

A FUNDAMENTAL goal in behavioral neuroscience is to elucidate neuronal pathways and structures involved in the regulation of behavior. In the case of learning and memory, once these pathways are established for a given form of memory, then the physical/biological changes that are associated with the behavior can be characterized. To this end, the conditioned eyeblink response has become a widely used behavioral preparation in the study of associative learning and memory; it allows a great deal of experimental control. Evidence is now conclusive that the cerebellum and its associated circuitry form the essential neural system for this form of learning and memory and strongly supports the view that the neuroanatomical locus of storage for the memory is in the cerebellum (10,19).

There are many reports in the literature indicating the disruptive effects of physical/chemical agents on conditioning of the eyeblink response. For example, inactivation of the interpositus nucleus (deep cerebellar nuclei) by reversible cooling (5), muscimol infusion (9), or lidocaine infusion (13) during acquisition training completely prevented acquisition of the eyeblink response, yet in postinactivation training animals learned as if naive.

Given the fact that muscimol, GABA-A receptor agonist, completely blocks learning and expression of the conditioned eyeblink response (9), we sought to determine what role, if any, the GABA-B receptor might play in the classically conditioned eyeblink response. Neuroanatomically, GABA-B receptors can be subclassified according to their signal transduction mechanisms. GABA-B receptors are known to be located presynaptically and postsynaptically and can be identified pharmacologically (2,7,14). Activation of postsynaptic GABA-B receptors can cause an increase in K^+ conductance, thus hyperpolarizing the postsynaptic cell (12, 16). Activation of presynaptic GABA-B receptors is associated with Ca^+ channels and causes a decrease in neurotransmitter release, apparently by several mechanisms (6). We infused the GABA-B agonist baclofen into the region of the cerebellar interpositus nucleus ipsilateral to the side of training in already-trained animals

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and over the course of training during eyeblink conditioning of rabbits.

One possible hypothesis would be that baclofen might reduce the presynaptic release of endogenous GABA in a selective manner and possibly increase the rate of acquisition of the conditioned eyeblink response. Alternatively, baclofen also exerts postsynaptic inhibitory effects, as noted (12,16), and appears to inhibit the release of transmitter at some excitatory synapses (1). We also administered baclofen together with a suitable antagonist (CGP 5584-5A) to determine receptor specificity. In an earlier study, we reported that infusion of GABA-A antagonists (picrotoxin, bicuculline methiodide) into the interpositus abolished the conditioned eyeblink response in a dose-dependent manner in already-trained rabbits (11). We report here that localized cerebellar infusion of baclofen abolished the conditioned eyeblink response in a dose-dependent manner and that this effect is blocked by CGP 5584-5A. Baclofen infused into the cerebellum (interpositus nucleus) during training completely prevented learning of the conditioned response.

METHODS

Subjects

Male New Zealand albino rabbits weighing between 2.0 and 3.0 kg were the subjects for the present experiment. A total of 22 animals were used; 15 completed the experiment. The cannula placement was such that drug infusion was ineffective in four animals (see Fig. 6), and in three other animals the cannula implantation damaged the small region of the interpositus essential for learning and memory of the eyeblink conditioned response (9,10,19) and these animals were unable to learn. All animals were individually housed, maintained on a 12 L:12 D cycle, and given food and water ad lib. These conditions meet or exceed the standards for care of laboratory animals as outlined in the *NIH Guide for the Care and Use of Laboratory Animals*.

Surgery

All surgical procedures were performed under aseptic conditions (18). Animals were anesthetized with a cocktail of rompun (6 mg/kg) and ketamine (60 mg/kg) and maintained under halothane gas and oxygen (1.5–2.5%) while cannulae made of 23-gauge steel tubing (23 mm in length) were placed stereotactically in an area near the left anterior interpositus nucleus, approximately 0.5 mm anterior, 5.5 mm lateral, and 14.5 mm ventral to lambda. The cannulae and a head stage (made to accommodate a microtorque potentiometer and air puff delivery nozzle) were cemented into place with dental acrylic. Once cemented, stylets made from 00 insect pins, which fit snugly into the 23-gauge tubing, were placed into the cannulae. Rabbits were allowed to recover for 1 week prior to behavioral training.

Behavioral Training

In expression testing, we trained the rabbits using standard procedures, measuring extension of the left nictitating membrane (NM) with a 1-kHz, 85-dB, 348-ms tone conditioned stimulus (CS) and a 98-ms corneal air puff (2.1 N/cm^2 = 3 psi) unconditioned stimulus (US), with CS and US coterminating (5,9,13). The intertrial interval (ITI) varied randomly from 20 to 40 s, with an average of 30 s. Rabbits were given 100 trials per day, presented in 10 blocks of 10 trials per block. The first trial in each block was a tone-alone trial, the next four trials were paired (tone–air puff trials), then an air puff-alone trial, followed by four paired trials. After asymptotic conditioned response performance was achieved, animals were infused with baclofen or CGP 5584-5A alone or in combination.

The behavioral training for the acquisition phase of this experiment was identical to that described above. However, during the first 3 days of training, animals were infused with baclofen or saline (see Infusion Protocols). This in turn was followed by 3 days of rest (no infusions), then 3 days of no-infusion training.

Infusion Protocols

In the expression phase of this experiment, baclofen (Sigma Chemical Co.; 0.21–20 mM) or saline was administered to well-trained animals. All animals (n = 3) received 1 μl of a specific drug/dose via a 27-gauge, 25-mm-long infusion cannula (infusion rate 0.3 μl/min). Animals were given three blocks of 10 trials at the following time points: prior to infusion, immediately (1 min) after infusion, 1 h postinfusion, and 24 h postinfusion. After a day of rest, the same procedure was repeated with a different drug/dose. Doses were 0 (i. e., saline) and 0.21, 0.43, 0.87, 1.75, 2.5, 5.0, 10.0, and 20.0 μM baclofen; dose sequences were counterbalanced. To establish that the effect of baclofen (abolition of the conditioned response) was due to selective activation of the GABA-B receptors, 3.0 mM CGP 5584-5A (graciously provided by Ciba-Giegy, Basel, Switzerland), a specific antagonist of the GABA-B receptor, was infused 15 min prior to baclofen (5 mM). We also tested CGP 5584-5A alone (0.05 and 3.0 mM) to determine if it had any effect on the conditioned response (CR) or the unconditioned response (UR). Three animals were used in the CGP–baclofen study, and all conditions given to each animal (one animal was used in both the baclofen expression and CGP conditions). Both baclofen and CGP 5584-5A were dissolved in sterile saline. In the acquisition phase of the experiment, animals were infused with 1 μl of 20 mM baclofen (infusion rate 0.3 μl/min) (n = 5) or the same amount of saline (n = 5). Animals were then placed in their home cage for 1 h and brought back for the behavioral training described above. A 1-h time interval was used based on results from the expression–retention testing.

Histology

At the end of training, each animal was sacrificed by injecting sodium pentobarbital into the marginal ear vein. After the injection, a direct current marking lesion (1.0 mA for 10 s) was passed through an electrode made to the exact length of the infusion cannula. Each rabbit was then perfused intracardially with normal saline, which was followed by 10% formalin. The brain was removed and fixed in 30% sucrose–formalin solution. After fixation, brains were embedded in albumin and 80-μm serial sections were taken and stained with Prussian Blue; cresyl violet was used as a counterstain. In a total of four animals, the baclofen infusion was ineffective, as noted above. In all these cases, the cannula tip missed the anterior interpositus nucleus. Locations of these missed cannulae are shown in Fig. 6.

Some animals in the acquisition study were infused with [^{3}H] baclofen in a volume equivalent to that received during training (e.g., 1 μl), allowed to rest for 1 h, and then sacrificed, just as was the case during prior baclofen-infusion training. The total amount of baclofen given in the 1-μl infusion (radiolabelled plus unlabelled) was 20 mM (as in the acquisition procedure), with a specific activity of 1 μCi/μg, infused at a

rate of 0.3 μl/min. After 1 h, the animals were anesthetized with halothane and decapitated. Their brains were removed and rapidly frozen, then sectioned and exposed to autoradiographic film (Hyperfilm, Amersham) for 6 weeks to maximize the visualization of the diffusion pattern. Film was developed for 3–5 min at room temperature with Kodak GBX developer and fixed for 5 min. The sections were then stained with cresyl violet to visualize brain structures, and the stained sections and autoradiographs were superimposed to determine the extent of diffusion.

Data Analysis

The following data were collected for each session: percent CRs, amplitude of the CRs, onset latency of the CRs, and amplitude of the URs. We report here on the effects of these GABA-B agents on percent CRs, amplitude of the CRs and amplitude of the URs. In the retention experiments, a two-way analysis of variance (ANOVA) was used to determine if there was any difference in the time of testing with respect to drug infusion (e.g., preinfusion, postinfusion, etc.—referred to as *test time*) and dose of drug [e.g., 0 (saline), 0.21 μM, etc.—referred to as *dose*] with a post hoc Bonferroni method ($p < 0.05$). In the acquisition experiments, a Student's *t*-test was used to determine if there was a significant difference in trials to criterion (eight conditioned responses out of nine trials) between the saline and baclofen groups (i.e., trials to criterion of the saline group on days 1–3 and trials to criterion in the baclofen group on days 4–6).

RESULTS

Figure 1 shows the effects of baclofen on percent CRs in well-trained animals. Baclofen produces a highly significant dose-dependent decrease in percent CRs both immediately and 1 h postinfusion [test time: $F(3, 95) = 29.18$, $p < 0.0001$; dose: $F(8, 19) = 6.15$, $p < 0.001$]. Indeed, percent CRs is close to zero at and above 5 mM baclofen. The effect of baclofen is absent at all doses 24 h after infusion.

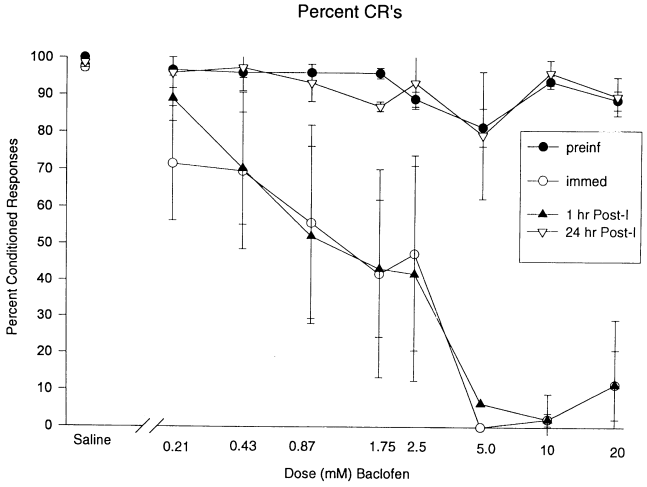

FIG. 1. Dose–response functions for percent eyeblink CRs (left eye) as a function of dose of baclofen infused into the vicinity of the left cerebellar interpositus nucleus in well-trained animals. Key (Figs. 1–4): preinf, response level before infusion; immed, 1 min postinfusion; 1 hr Post-I, 1 h postinfusion; 24 hr Post-I, 24 h postinfusion. Error bars on this and all subsequent graphs correspond to SEM.

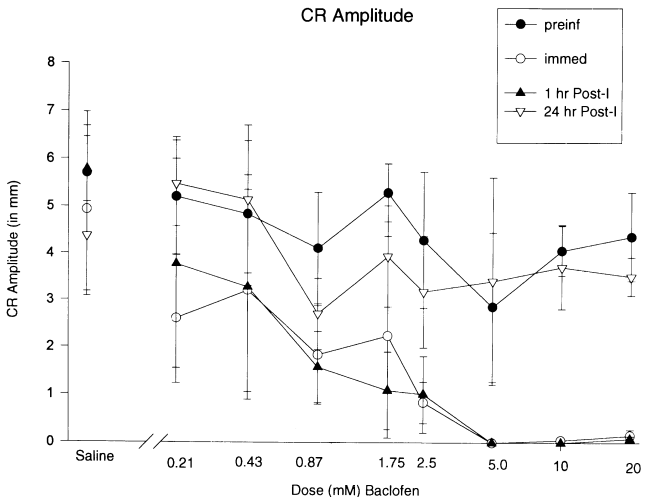

FIG. 2. Exactly as Fig. 1, except conditioned eyeblink amplitude is displayed.

Figure 2 shows the effects of baclofen on CR amplitude for the same animals as in Fig. 1. Again, baclofen causes a highly significant dose-dependent decrease in CR amplitude, both immediately and 1 h postinfusion [test time: $F(3, 95) = 10.31$, $p < 0.0001$; dose: $F(8, 95) = 4.31$, $p < 0.001$]. Conditioned response amplitudes are virtually zero at and above 5 mM. The effect of baclofen is absent at all doses 24 h after infusion. There is no evidence that baclofen increases CR amplitude; indeed there is a numerical, albeit nonsignificant, decrease in CR amplitude even at the lowest dose (0.21 mM).

There was no significant effect of baclofen on UR amplitude in US-alone trials either immediately or at 1 h postinfusion at any dose [test time: $F(3, 95) = 1.49$, $p > 0.05$, NS; dose: $F(8, 95) = 1.78$, $p > 0.05$, NS]. Consequently, the profound dose-dependent actions of baclofen on CR percent and amplitude (Figs. 1, 2) cannot be due to effects of baclofen on the UR.

Figure 3 illustrates the effects on percent CRs in well-trained animals of 0.5 and 3.0 mM CGP 5585-5A alone, baclofen

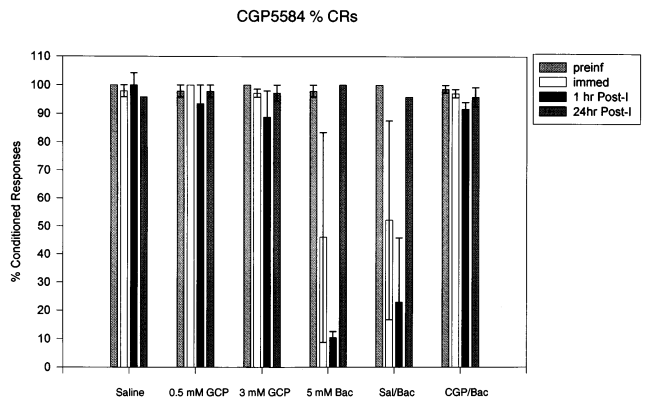

FIG. 3. Percent CRs in a group of animals receiving infusions into the interpositus nucleus of CGP 5584-5A alone (0.5 or 3 mM), 5 mM baclofen (see Fig. 1), saline plus 5 mM baclofen, or 3 mM CGP plus 5 mM baclofen. Note that the massive baclofen (5 mM) impairment of the CR 1 h after administration is completely blocked by prior (15 min) infusion of the GABA-B antagonist CGP 5584-5A. See legend of Fig. 1 for explanation of notation.

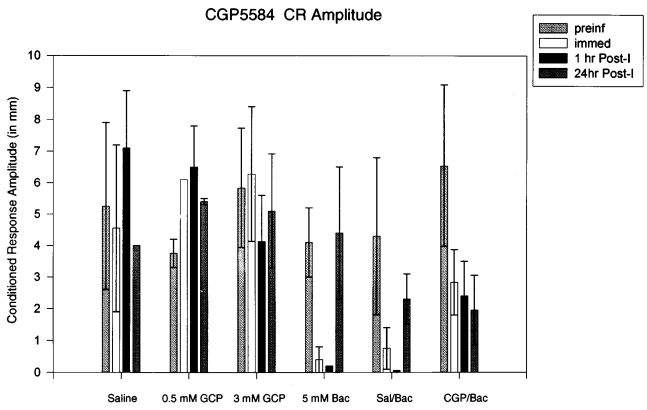

FIG. 4. Exactly as Fig. 3, except conditioned eyeblink amplitude is displayed. Note here that CGP only partially antagonized the effect of baclofen on CR amplitude, whereas it completely antagonized the effect of baclofen on percent CRs (Fig. 3).

alone (5 mM), and saline in combination with 5 mM baclofen and 3.0 mM CGP 5585-5A given as a pretreatment 15 min before 5.0 mM baclofen. Saline controls 1 h after infusion show 98% CRs. Neither dose of CGP 5584-5A had any effect on percent CRs. Baclofen alone markedly impaired percent CRs, as in Fig. 1. However, prior administration of 3.0 mM CGP completely blocked the effect of 5 mM baclofen on percent CRs.

The same basic results were found for the CR amplitude measure: namely, CGP alone had no effect, baclofen massively reduced CR amplitude [$F(5, 63) = 3.73$, $p < 0.05$], and CGP partially reversed the effects of baclofen (see Fig. 4). Numerically, CGP pretreatment only partially restored CR amplitude, whereas it completely restored percent CR (Fig. 3). There were no drug effects at all with CGP alone, baclofen alone, or both together on UR amplitude (US-alone trials) for the animals described above (e.g., Figs. 3, 4) [$F(5, 63) = 1.50$, $p > 0.05$, NS].

Figure 5 shows the effects of infusion of baclofen (1 μl of 20 mM baclofen) or the same amount of saline 1 h prior to training on the acquisition of the conditioned eyeblink response. The graph demonstrates that animals infused with baclofen show no evidence of learning during days 1–3 (infusion), whereas saline control animals show normal acquisition. In postinactivation training (days 3–6), baclofen animals show an increase in conditioned responding across training days similar to that of the saline control animals. As can be seen, the acquisition curve on days 1–3 for the saline infusion animals superimposes onto the acquisition curve for post-baclofen inactivation days 3–6. Training on days 1–3 with baclofen resulted in no savings at all in subsequent learning relative to controls. Thus, the numbers of trials to criterion (eight CRs in nine consecutive trials) are 138 for the saline control group (days

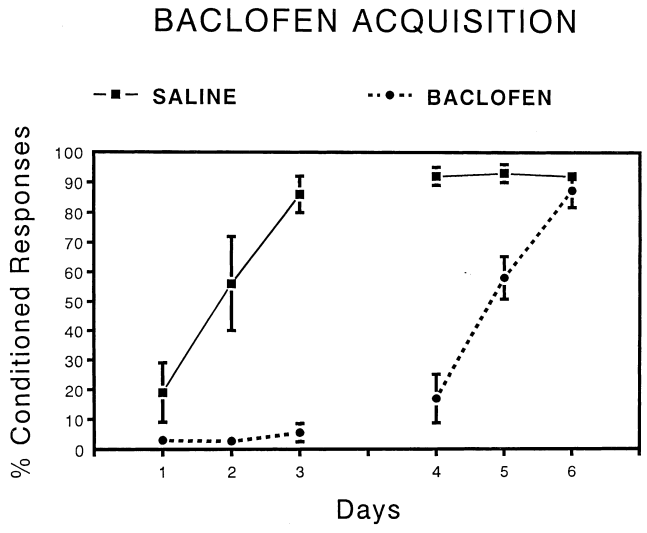

FIG. 5. Effects of infusion of baclofen ($n = 5$) or saline ($n = 5$) into the left cerebellar interpositus nucleus on acquisition of the classically conditioned eyeblink response. Days 1–3 represent days of infusion of baclofen or saline; days 4–6 represent no-infusion days. Animals given saline infusions show clear evidence of conditioning on days 1–3, whereas the animals given infusions of baclofen do not. On days 4–6, saline-infused animals are at asymptotic levels of performance, whereas the animals previously infused with baclofen show conditioning similar to that seen on days 1–3 for the saline group.

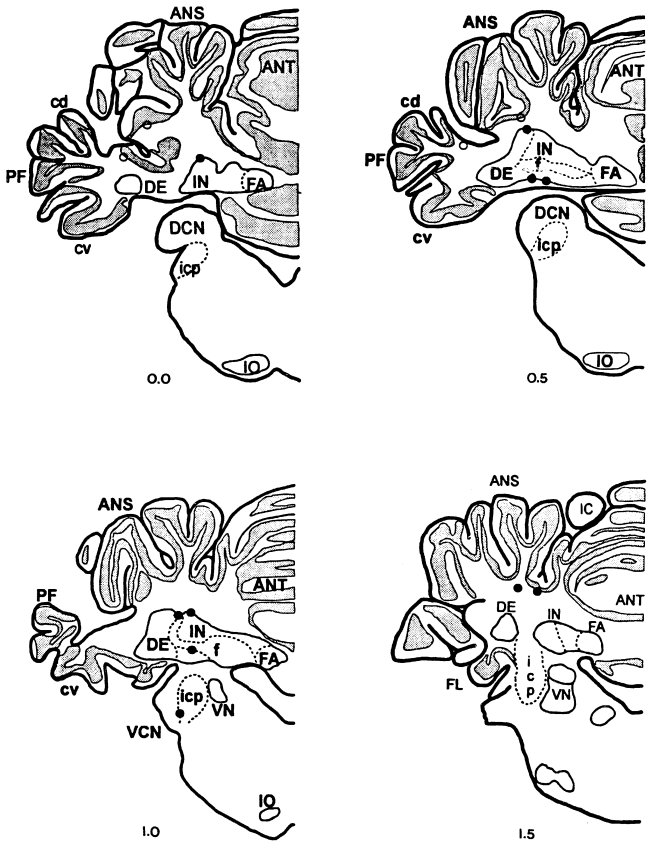

FIG. 6. A diagram of standard sections of the cerebellum showing the effective (filled circles) and ineffective (open circles) cannula placements for the animals given baclofen during retention testing and acquisition training. ANS, ansiform lobe; ANT, anterior lobe; cd, crus dorsal; cv, crus ventral; DE, dentate nucleus; DCN, dorsal cochlear nucleus; FA, fastigial nucleus; f, fibers; FL, flocculus; icp, inferior cerebellar peduncle; IO, inferior olive; IN, interpositus nucleus; PF, paraflocculus; VCN, ventral cochlear nucleus; VN, vestibular nucleus.

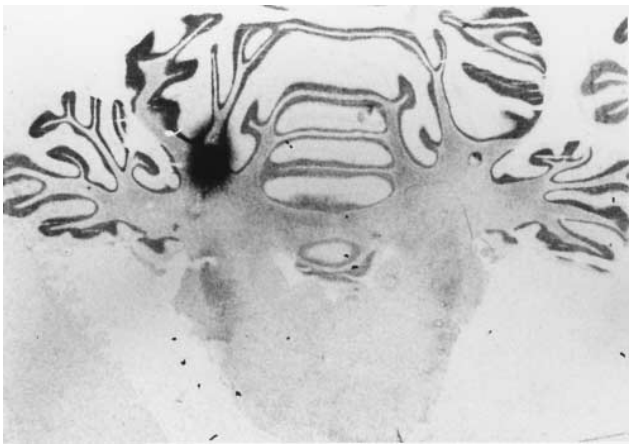

FIG. 7. Photomicrograph of [^{3}H]baclofen infused into the cerebellum. The distribution of radiolabel is rather localized and clearly shows that the amount of baclofen infused (1 μl) during this experiment did not diffuse out of the cerebellum (see text for details).

1–3) and 121 for the baclofen group in postinfusion training (days 3–6), not statistically different [$t = 0.65$, $p > 0.05$, NS].

The locations of the lesions marking the position of the cannula tip for baclofen infusion are shown in standardized drawings of cerebellar sections in Fig. 6. The effective cannula tip locations for animals used in both the CR expression and acquisition studies are indicated by solid circles. Ineffective cannula placements, where baclofen infusion had no effect on performance of the CR, are shown as open circles. All effective cannula locations for the acquisition animals are in or closely adjacent to the anterior interpositus nucleus; in one animal in the expression group, the marking lesion was ventral to the interpositus nucleus (Fig. 6). However, examination of the sections for this animal (#94-011) showed that the baclofen infusion extended dorsally up around the cannula shaft to include the entire ventral to dorsal extent of the anterior interpositus nucleus at the medial-lateral area of the cannula. Autoradiographs of [^{3}H]baclofen infusions in animals in which baclofen abolished the CR indicate that the distribution of significant radiolabel included dorsal tissue of the anterior interpositus nucleus and some overlying cortex of lobule HVI (see Fig. 7). Note, however, that lateral cortical placements were negative. The radiolabeled baclofen remained within a relatively localized region of the cerebellum.

CONCLUSION

Many studies have examined the effects of peripherally administered baclofen on memory performance. Baclofen administration has been reported to significantly reduce the number of correct choices in a radial arm maze task (17). In a visual conditional discrimination task (15), baclofen disrupted performance. Posttraining administration of baclofen dose-dependently impaired retention of inhibitory avoidance in mice (4). Administration of baclofen intracerebroventricularly increased food consumption in nonfasted rats, and this effect was reversed with the GABA-B antagonist phaclofen (8). Posttraining infusion of baclofen into the amygdala impaired retention in rats in an inhibitory avoidance task (3).

The GABA-B agonist baclofen infused into the vicinity of the cerebellar interpositus nucleus consistently impaired and abolished performance of the conditioned eyeblink response, with no effect on the reflex response, in a dose-dependent manner, and this effect was blocked by prior infusion of the GABA-B antagonist CGP 5584-5A. Thus, this action of baclofen would seem to be specific to GABA-B receptors (CGP effect). It is of interest that the specific GABA-B antagonist CGP 5584-5A itself has no effect on performance of the CR. Although it is possible that a dose of 3 mM is too low to have an effect, this dose does effectively antagonize an otherwise completely effective dose of baclofen. Both GABA-A agonists (muscimol) and antagonists (picrotoxin, bicuculline) infused into the interpositus nucleus abolish expression of the CR. This would seem to argue that under normal conditions, GABA-A receptors play a more important role in *performance* of the CR than do GABA-B receptors. Because appropriate cerebellar infusions of both GABA-A and GABA-B agonists completely prevent *acquisition* of the CR, it will be of interest to determine the effects of GABA-A and GABA-B antagonists on acquisition of the classically conditioned eyeblink response.

The effects of local infusion of baclofen into the cerebellum are consistent with other reversible lesioning techniques [cold probe, muscimol, and lidocaine; see (5,9,13)] in that inactivation of a critical region of the cerebellum completely prevents acquisition and blocks expression of the eyeblink response. The dose used in the acquisition study, 20 mM, was well beyond the amount (5 mM) necessary to abolish performance of the CR (Figs. 1, 2). Interestingly, even this high dose of baclofen had no effect on the reflex UR. Although it is conceivable that a much lower dose might facilitate learning, even very low doses always reduced CR amplitude (Fig. 2). Consequently, we suggest that at least under the conditions of our experiments, the inhibitory actions of baclofen on neural activity predominate in the cerebellum, resulting in impairing effects on learning and performance of the eyeblink CR, much as occurs with similar administration of muscimol.

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