throughout the CNS at a rate much slower than can be attained by using either iontophoresis or pressure. Rather, therapeutic application of the drug would be expected to attenuate naturally occurring purine-mediated excitation through cross-desensitization. Another site at which purines and benzodiazepines might interact is the putative purine receptor associated with inhibition of excitability. Therapeutic administration of a benzodiazepine might antagonize these purine-mediated inhibitory events.

Benzodiazepines can modulate the GABA-mediated inhibition of CNS neurons, which suggests that this interaction might account for some of the therapeutic actions of these drugs (*20*). Since GABA does not compete with benzodiazepines for the same receptor site in vitro (*3*), these drugs do not appear to be interacting directly with GABA receptors. The data reported here show that a benzodiazepine can function as an agonist at one putative purine receptor site and as an antagonist at another. These observations, coupled with the fact that specific purines can displace benzodiazepines in binding studies in vivo (*6*) and in culture (*21*), suggest that benzodiazepines interact directly with two classes of purine receptor. The interactions between benzodiazepines and purines, and between benzodiazepines and GABA, and their relationship to the therapeutic actions of the benzodiazepines require further investigation (*22*).

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21. Preliminary studies of benzodiazepine binding to primary cultures have revealed high-affinity, saturable binding sites for benzodiazepines with an affinity constant approaching that reported for CNS sites (P. Skolnick, S. M. Paul, A. Huang, J. L. Barker, J. H. Neale, unpublished observations).
22. The therapeutic efficacy of benzodiazepines in the treatment of Lesch-Nyhan syndrome [W. N. Kelley and J. B. Wyngaarden, in *Metabolic Basis of Inherited Disease*, J. B. Stanbury, J. B. Wyngaarden, D. S. Frederickson, Eds. (McGraw-Hill, New York, 1978), p. 1011] may be related to effects of the drugs on purine receptors since there is a fourfold increase in cerebrospinal fluid purine concentration associated with the syndrome [F. N. Rosenbloom, W. N. Kelley, J. Miller, J. F. Henderson, J. A. Seegmiller, *J. Am. Med. Assoc.* **202**, 175 (1967)].

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Target Velocity Signals of Visual Tracking in Vermal Purkinje Cells of the Monkey

Abstract. *Discharges of Purkinje cells were recorded from the vermis, lobules VI and VII, of a monkey trained to track a visual target. When the monkey tracked a sinusoidally oscillating target, cellular activity changed in phase with the velocity signal of the eye movement. When the monkey fixated a stationary point, almost identical modulation in activity occurred, reflecting the velocity signal of the motion of the retinal image of the target. The data suggest that the vermis participates in the control of smooth pursuit eye movements by providing the oculomotor system with the actual target velocity information which is the sum of eye velocity and retinal image velocity signals.*

The maintenance of images on the fovea is a prerequisite for proper visual function and is the responsibility of the pursuit eye movement system. Images of moving objects of interest, having first been brought into the region of maximal visual acuity by saccadic eye movements, are sustained on the fovea by pursuit eye movements. Of the parameters characterizing target motion, velocity is important for tracking (*1*). Since a smooth pursuit eye movement is the result of an attempt to match the angular velocity of the eye movement to the velocity of the target, information concerning target velocity must be available to the pursuit eye movement system. In the presence of free eye and head movements, however, absolute target velocity is not directly available, and its determination depends on information concerning the relative motions of (i) target

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and eye (retinal image velocity), (ii) eye and head (eye velocity), and (iii) head and ground (head velocity) (*2*). Neural activity reflecting the sum of such velocity signals should, therefore, be observed in some brain structures thought to be constituents of the smooth pursuit system. The demonstration of visual inputs to the lobules VI and VII of the cerebellar vermis (*3*) implicate this structure as a possible site for observing cellular activity related to target velocity. On the basis of experiments on monkeys trained to track a visual target, we report that discharges of some Purkinje cells in the vermal lobules reflect the absolute velocity of target movement.

Extracellular recordings were made in the vermis of three monkeys trained to fixate a small spot of red light and track the spot as it moved. Each animal was seated in a primate chair designed to offer a clear view of the central 30° of the visual field. The head was immobilized by affixing two pairs of bars, which were inserted into transverse tubes on the skull, to the frame that supported the chair. Hydraulically driven stainless steel microelectrodes were positioned in the target structure through an implanted cylinder. Eye positions were recorded by electrooculograms in both horizontal and vertical planes. Eye movements and alertness were monitored also through a closed-circuit infrared television camera. In order to dissociate retinal image velocity from eye velocity, unit activity was studied in two situations: (i) when the animal tracked the spot moving sinusoidally in the horizontal plane and (ii) when the animal fixated a point on a stationary random-dot background while the red spot was moved sinusoidally. Discharges of Purkinje cells were identified by their characteristic complex spikes interspersed within tonic simple spike activity (*4*).

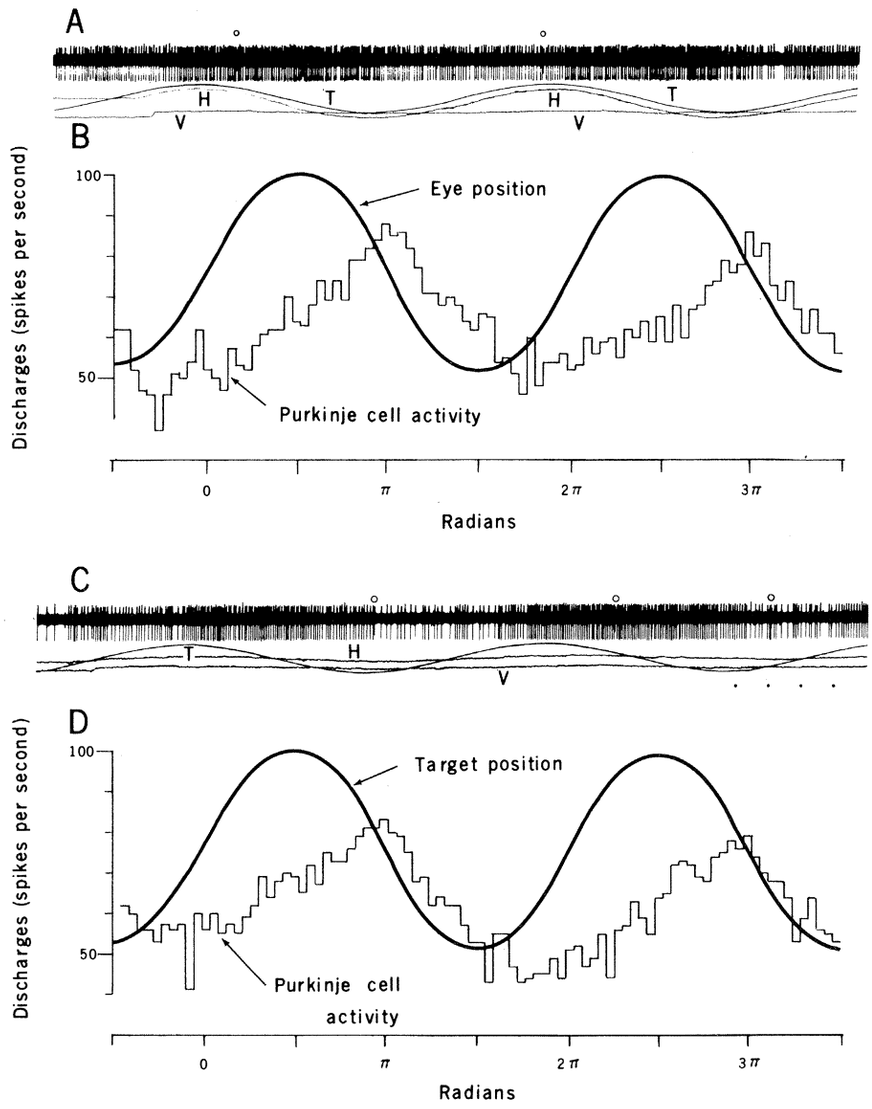

Fig. 1. Discharges of a Purkinje cell during pursuit eye movement (A and B) and during fixation with a sinusoidally moving target (C and D). (A) and (C) are examples of original spike records. (B) and (D) indicate the frequency of Purkinje cell discharges (spikes per second) averaged from 15 cycles. Tracking and target oscillations occurred at 0.4 Hz (± 10°) in the horizontal plane. A peak frequency of 83 spikes per second occurring in phase with eye velocity was observed during pursuit eye movement (B), and a peak of 81 spikes per second corresponded to retinal image velocity during fixation. Small circles (A) and (C) denote complex spikes. Complex spikes were not temporally related to any parameters of target or eye movements. Abbreviations: *T*, target movement; *H*, horizontal electrooculogram; and *V*, vertical electrooculogram.

Even when sinusoidal oscillations of a visual target were limited to the horizontal plane, a substantial number of Purkinje cells (14 of 89) in the vermis showed cyclic modulation in their simple spike activity. In Fig. 1 are shown the modulations in the activity of a Purkinje cell during smooth pursuit eye movements (A and B) and during sinusoidal movement of the target spot while the monkey fixated a point in the stationary random-dot background (C and D). The activity of the Purkinje cell changed cyclically with a phase shift of approximately 1/2 π radians from the eye position curve (Fig. 1B). The peak activity appeared synchronously with the peak velocity of smooth pursuit eye movements in the preferred direction. As retinal image velocity was minimal during this period, the modulation in activity was primarily a reflection of eye velocity signals arising in the oculomotor system. An almost identical modulation was observed in the second situation, during which there were no measurable eye movements when the red spot was oscillated sinusoidally in the horizontal plane (Fig. 1D). In this situation, eye velocity was minimal and the modulation in activity reflected retinal image velocity arising in the visual system. The observed cellular activity, which reflects both eye and retinal image velocities, exhibits the requisite functional properties associated with a neural correlate of target velocity.

When the frequency of sinusoidal oscillation of the spot was varied without changing the amplitude, the peak firing rate of the resultant modulations in Purkinje cell activity linearly increased. Changes in the peak activity of the Purkinje cell in Fig. 1 were evaluated from 64 cycles of spot movement when the eyes were relatively steady. Peak firing rates of 77.5, 82.5, 103.4, and 122.9 spikes per second were observed in association with peak target velocities of 18.8, 25.0, 31.4, and 44.0 deg/sec, respectively. The relationship between firing rate and target velocity was fairly linear up to velocities associated with the

limits of normal smooth pursuit eye movements (*2*). The activity of the Purkinje cell, therefore, reflected the velocity component of the target movement.

Mossy-fiber activity was recorded in order to determine whether eye and retinal image velocity signals were converging on vermal Purkinje cells via separate channels. Target velocity signals appear to be formed prior to the input stage of the vermis, since mossy-fiber activity also reflected target velocity. Figure 2 shows the behavior of a mossy-fiber unit recorded from the vermis in the same experimental situation as for Purkinje cells. The modulation in activity during pursuit eye movements (Fig. 2, A and B), during which eye velocity signals were dominant, was almost identical with that recorded during sinusoidal target movement (C and D), during which retinal image velocity was the primary determinant of activity changes. The appearance of peak firing rates in phase with the peak velocity of either eye movement or retinal image motion indicates that actual target velocity signals were already present at the input stage of the vermis. This modulation of mossy-fiber discharges exhibited maximal firing rates of 89, 100, and 110 spikes per second in association with peak target velocities of 18.8, 31.4, and 44.0 deg/sec, respectively. Peak firing rate was again linearly related to actual target velocity. The actual target velocity signal, therefore, arises in brainstem oculomotor centers and is transmitted to vermal Purkinje cells by mossy fibers.

The cerebellar vermis, lobules VI and VII, takes part in oculomotor function (*5*) and receives visual inputs via both climbing and mossy-fiber systems (*6*). The conveyance of proprioceptive information from the extraocular muscles to this region of the vermis also indicates a role in eye movement control (*7*). The exact nature of this role has not been clarified, but saccadic eye movements have been observed when the vermis was stimulated (*8*). Single-unit studies on alert cats and monkeys have shown that vermal Purkinje cells exhibit saccade-related bursts and pauses in activity (*9*). We also detected such Purkinje cells along the same electrode tracks from which visually related activity was recorded. Involvement with saccadic eye movement control is also indicated by vermal lesion studies (*10*). The vermis may not be essential to initiate pursuit eye movements, since tracking could not be elicited with normally effective moving stimuli in hemicerebellectomized monkeys with sparing of the vermis (*11*). A role for the vermis in the fine control of smooth eye movements cannot, however, be ruled out, since detailed tests of tracking normalcy have not been conducted in monkeys with exclusive vermal lesions.

The observation of unit activity reflecting target velocity information in the vermis suggests that this region takes part in the control of pursuit eye movements. Purkinje cell activity reflecting eye and head velocity has been discovered in the flocculus (*12, 13*), but Lisberger and Fuchs (*12*) have shown that target velocity may not be involved, since signals reflecting retinal image velocity contributed little to the modulation of activity in floccular Purkinje cells (*14*). Head velocity signals, though necessary for a complete description of target velocity, did not arise in our study. We felt that testing visual responsiveness directly was most important, and using a moving spot during fixation isolated the retinal image velocity, which has been the elusive component in the search for neural correlates of target velocity. Previous studies of vermal lobules VI and VII implicate a role only in saccadic eye movement control. Our study indicates that the same vermal region also participates

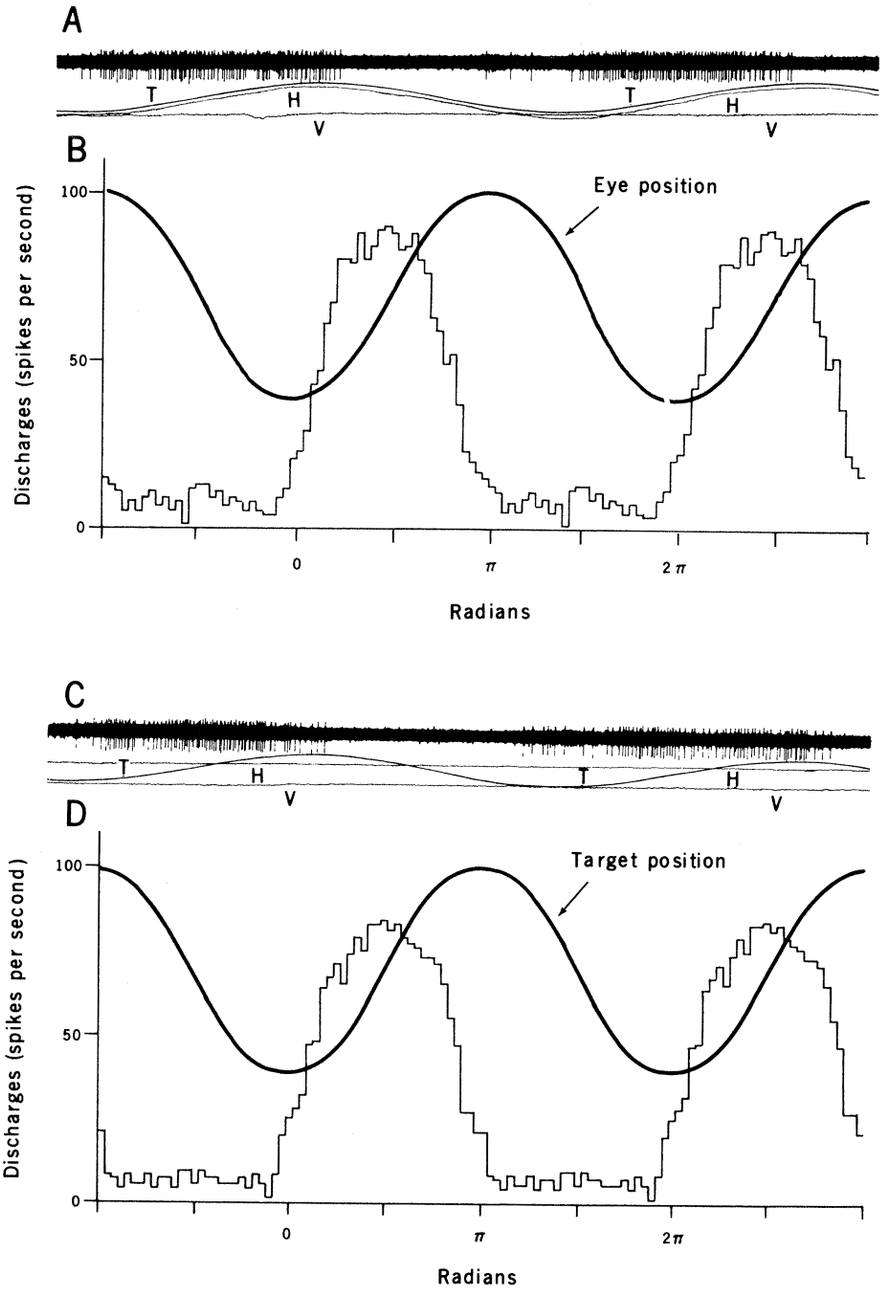

Fig. 2. Discharges of a mossy fiber during pursuit eye movement (A and B) and during fixation with a sinusoidally moving target (C and D). Target oscillations occurred at 0.3 Hz (± 10°), and peak frequencies of 89 and 87 spikes per second were observed during pursuit eye movements and fixation, respectively.

in the control of smooth pursuit eye movements by providing the oculomotor system with target velocity information.

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14. Activity reflecting target velocity has been reported for Purkinje cells of the flocculus (*13*), but the experimental situation employed was not sufficient to allow the conclusion that a visual component was dissociated from vestibular and oculomotor components.
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Drug Discrimination Training with Progressively Lowered Doses

Abstract. *Rats were trained to discriminate drug from no-drug conditions in a two-lever operant task. Moderately high dosages were used initially. Whenever the discrimination was learned, training was continued with progressively reduced dosages. Eventually the rats discriminated extremely low doses of phenobarbital, chlordiazepoxide, cyclazocine, and fentanyl.*

Drug discrimination (DD) procedures are used as tools for investigating the actions of psychoactive drugs. In most DD studies, rats are trained to discriminate between the presence and the absence of a particular drug and dosage. The utility of the resulting discriminations is influenced by a variety of factors including the duration of training required to establish the discriminations, the stability and accuracy of the discriminations, and the dosage used during training.

The earliest DD studies used highly intoxicating doses (*1*). The development of more sensitive procedures permitted training doses to be somewhat lower (*2, 3*). However, these procedures required 30 to 40 sessions of training before DD's were learned, and the duration of training increased if dosage was decreased. These drawbacks discouraged investigators from using low training doses. Recently we identified further methodological improvements that allowed DD's to be learned with moderate doses in 10 to 15 training sessions (*4*). As it appeared that these methods should make it feasible to establish DD's with lower training doses than had been used previously, we have now attempted to find the lowest dose at which each of several drugs could be discriminated. To determine this "threshold" dose, we started training with a moderately high dose and then reduced the dosage whenever performance indicated that a DD had been learned (*5*).

Rats were deprived of water for 24 hours and trained to bar press in a compartment that contained two bars (*6*). Reinforcement was 0.1 ml of 1 percent saccharin solution. In order to obtain reinforcement, the rats were required to press bar 2 on days when they were drugged and to press bar 1 when undrugged (*7*). An interlocking fixed ratio–fixed interval (FR-10–FI-90 seconds) schedule of reinforcement was used (*8*). After initial shaping was completed, training consisted of daily 15-minute sessions (*9*).

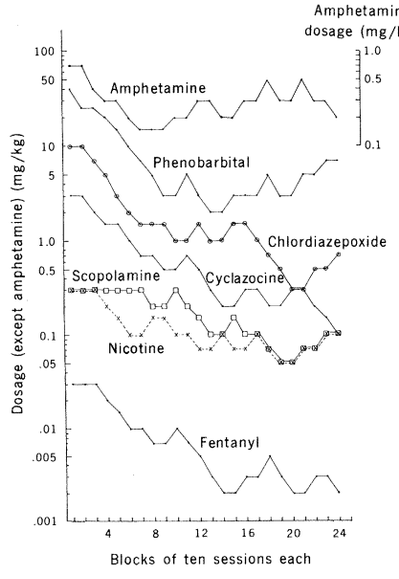

Fig. 1. Rats were required to press bar 1 when drugged and bar 2 when not drugged. Training dosage was decreased whenever this discrimination was learned and increased whenever the discrimination was not learned for 20 consecutive sessions. The plots show training dosages for seven individual rats during successive blocks of ten sessions. Note the displaced ordinate for amphetamine.

At the beginning of each training session, no reinforcement was delivered until the rat had accumulated ten presses on one bar or the other. Presses on both bars before the first reinforcement of each session were used to indicate the accuracy with which the rat could select the currently correct bar on the basis of the imposed drug state (that is, the degree to which the drug and no-drug conditions had acquired discriminative control). Criterion performance was five or fewer presses on the incorrect bar prior to completion of ten presses on the correct bar during eight out of ten consecutive sessions.

The drugs used for training were all known to be discriminable. Initial training dosages, selected on the basis of pilot experiments, ranged from 60 to 90 percent of the maximum doses that could be used without severely disrupting bar pressing. As training proceeded, performance was reviewed every ten sessions, and the training dosage of each drug was altered according to the following rules: (i) If performance was at criterion level during the ten sessions, the dosage was reduced by about 30 percent. (ii) If criterion was not achieved, the dosage was not changed. (iii) Whenever criterion was not achieved during 20 consecutive sessions of training with a particular dosage, the dosage was raised by 30 percent. To avoid behaviorally toxic effects, doses were never raised above the original training dosages.

During successive 10-day blocks of training sessions, all drugs were discriminated, and these discriminations were maintained during reductions in dosage ranging from 60 to 95 percent (Fig. 1). With some drugs, dosage reductions occurred as rapidly as the procedure allowed (30 percent every ten sessions), whereas with other drugs, dosage was reduced more slowly. The number of training sessions before the beginning of criterion performance with the initial training dosages ranged from one with phenobarbital (40 mg per kilogram of body weight) to 51 with scopolamine (0.3 mg/kg); this index of the discriminability of the initial training dose was not highly correlated with the amount of reduction

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