activity by ANP. A role for this domain in signal transduction is consistent with its high degree of conservation in all membrane guanylate cyclases sequenced thus far from sea urchins and mammals (*3, 4, 12, 13*).

We have noted the similarity in overall topology between the guanylate cyclase–ANP receptor and protein tyrosine kinase–growth factor receptors (*3*). Like the ANP receptor, these receptors contain an extracellular binding domain, a single transmembrane domain, a protein kinase domain adjacent to the membrane, and a COOH-terminal domain. A model has been proposed in which the protein kinase activity of the epidermal growth factor (EGF) receptor is sterically inhibited by interaction of the kinase domain with the COOH-terminal domain; this interaction is disrupted after EGF binding and the subsequent autophosphorylation of the COOH-terminal domain (*14*). In the case of the ANP receptor, the situation could be reversed: the kinase-like domain may be a negative regulator of the COOH-terminal, guanylate cyclase domain.

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8. To delete kinase-like sequences, we cloned a Hind III fragment, comprising nucleotides 1376 to 2722, of the ANP receptor cDNA into the Hind III site of the plasmid pSP72 (Promega), which had first been modified by insertion of an Nhe I linker into its Pvu II site. The Pvu II fragment, comprising nucleotides 1709 to 2549, of the ANP receptor cDNA (corresponding to amino acids 468 to 747) was then excised, the plasmid was religated, and the sequence of the truncated insert was determined [F. Sanger, S. Miklen, A. R. Coulson, *Proc. Natl. Acad. Sci. U.S.A.* **74**, 5463 (1977)] with a Sequenase kit (U.S. Biochemical Corporation). The truncated Hind III fragment was inserted in place of the wild-type Hind III fragment in the previously described ANP receptor construct in Bluescript (*3*). To delete COOH-terminal sequences, we excised the ANP receptor cDNA from Bluescript with Sal I and Sma I and subcloned the fragment into Sal I–Sma I–digested pSP72. After Kpn I and Sma I digestion, unidirectional exonuclease III digestion and S1 nuclease treatment [S. Henikoff, *Gene* **28**, 351 (1984)] was performed with the Promega Erase-a-Base kit; a termination codon was introduced by linker tailing [R. Lathe, M. P. Kieny, S. Skory, J. P. Lecocq, *DNA* **3**, 173 (1984); F. Cobianchi and S. H. Wilson, *Methods Enzymol.* **152**, 94 (1987)] with an Nhe I linker containing termination codons in all reading frames (New England Biolabs). Sequence analysis indicated that the clone terminates at nucleotide 2915, corresponding to Leu^{868}. The kinase deletion mutant was subcloned into pSVL as described (*3*), and the COOH-terminal deletion mutant was excised from pSP72 as a Sal I–Bgl II fragment and cloned into Xho I–Bam HI–digested pSVL.
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14 June 1989; accepted 2 August 1989

Ocular Responses to Linear Motion Are Inversely Proportional to Viewing Distance

U. SCHWARZ, C. BUSETTINI, F. A. MILES

Eye movements exist to improve vision, in part by preventing excessive retinal image slip. A major threat to the stability of the retinal image comes from the observer's own movement, and there are visual and vestibular reflexes that operate to meet this challenge by generating compensatory eye movements. The ocular responses to translational disturbances of the observer and of the scene were recorded from monkeys. The associated vestibular and visual responses were both linearly dependent on the inverse of the viewing distance. Such dependence on proximity is appropriate for the vestibular reflex, which must transform signals from Cartesian to polar coordinates, but not for the visual reflex, which operates entirely in polar coordinates. However, such shared proximity effects in the visual reflex could compensate for known intrinsic limitations that would otherwise compromise performance at near viewing.

WHEN LOOKING OUT FROM A speeding train or bus, nearby objects are seen to rush by while more distant ones seem relatively stable. The motion of an image across the retina is determined by the angular velocity of the object with respect to the observer, and when the observer's motion is purely translational, as in the case of the passenger, simple geometry indicates that this velocity must depend on the proximity of the object (*1*). In order to scrutinize any given object in this passing scene, the observer must track it with his eyes, thereby compensating for his own bodily motion and, the nearer the object, the more vigorously the observer must track. Visual tracking, mediated by the ocular following reflex (OFR), is important in this (*2*), but during many natural activities such as walking some of the ocular compensaton is provided by the translational vestibulo-ocular reflex (TVOR), which senses linear accelerations of the head through the otolith organs embedded in the base of the skull (*3*). To be optimally effective, the output of the TVOR should accord with the proximity of the object of interest. Earlier reports did not specify proximal viewing and suggested that the TVOR was rather weak in humans (*4*). However, better responses are obtained if the subject attempts to fixate an imagined nearby target (*5*), and TVOR responses have been linked to the vergence angle of the two eyes (*6*). We now describe experiments on monkeys which indicate that the TVOR responses to lateral translation are linearly related to the inverse of the viewing distance (*1*). We also report that this dependence on proximity is shared by the OFR, which we suggest provides a visual back-up to the TVOR.

The TVOR was investigated in four rhesus monkeys seated on a sled that moved on a linear track and that accelerated the animals along the interaural axis (*7*). The movements of the sled were gentle and brief, consisting of one cycle of sinusoidal jerk in either direction (period, 200 ms; amplitude, 630 cm/s^2 per second), after which the sled cruised at the acquired speed for 200 ms before gradually slowing to a halt. Sled acceleration commenced only after the animal had satisfactorily fixated one of five randomly selected targets (light-emitting diodes at viewing distances of 16, 25, 50, 100, 150 cm) for randomly varied time periods ranging from 250 to 500 ms. The target was extinguished immediately before the onset of acceleration, leaving the room dark throughout the period of sled motion. A total of 60 responses was obtained for each stimulus at each viewing distance. To preclude learning, animals never experienced sled motion in the light.

Sled motion evoked consistent compensatory eye movements and, as Fig. 1A shows

Laboratory of Sensorimotor Research, National Eye Institute, National Institutes of Health, Bethesda, MD 20892.

for one animal, the response varied inversely with the viewing distance of the previously fixated target. When the maximum compensatory eye speed achieved within 250 ms of the onset of sled motion was used as the response measure and plotted against the prior viewing distance in reciprocal meters (diopters), it was evident that the relationship was linear (Fig. 1B). Similar data were obtained from all four animals, and regression lines had a mean slope of 1.4 degrees/s per diopter (range, 1.0 to 2.1 degrees/s per diopter) with a mean intercept of 1.4 degrees/s (range, 0.1 to 3.6 degrees/s). Full compensation for the sled motion would require a slope of 2.3 degrees/s per diopter with an intercept of zero. Based on this, the gain of the TVOR (measured response/required response) always exceeded unity with the most distant target (mean, 1.5) and fell short of unity with the nearest (mean, 0.7). Thus, TVOR responses were robust and showed the desired dependence on proximity but compensated appropriately only at one particular viewing distance.

In a separate series of experiments with the same four monkeys, we studied the effect of viewing distance on the OFR responses elicited by brief linear motion of the visual scene (*2*). Visual stimuli were random dot patterns subtending 40 degrees and back-projected onto a tangent screen facing the animal. The pattern was moved either leftward or rightward at 80 degrees/s for 100 ms. Six viewing distances were used (20, 25, 33, 50, 100, and 150 cm), the visual stimulus being adjusted for each so as to have constant size and speed for the animal; that is, the retinal stimulus was the same at all viewing distances. Data were collected in blocks of trials at each distance, each block involving six presentations of each stimulus in a randomized order. The sequence of distances was varied randomly and a total of 60 responses was obtained for each stimulus at each distance. Animals were neither trained to track the moving scene nor reinforced for doing so (*8*).

Brief linear motion of the visual scene

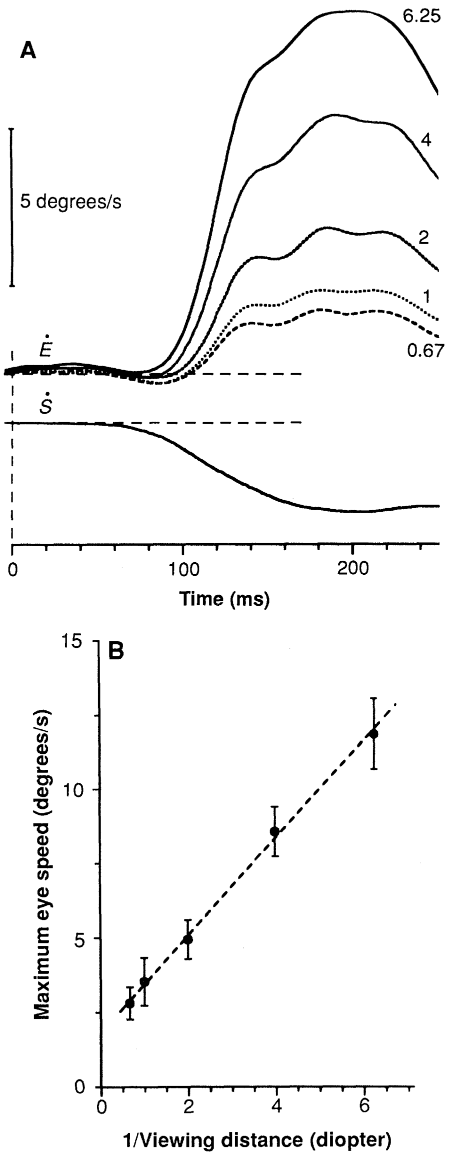

Fig. 1. Dependence of TVOR responses on viewing distance. (**A**) $\dot{E}$, averaged eye speed profiles ($n = 60$ for each trace) for monkey Pu in response to leftward sled motion; numbers at side of each trace indicate prior viewing distance in diopters. $\dot{S}$, sled speed (maximum, 40 mm/s). Calibration bar applies to eye speed only. Upward deflections represent rightward motion. (**B**) Plot of maximum eye speed (achieved within 250 ms of onset of sled motion) against the reciprocal of the viewing distance [for data shown in (A)]. Dashed line is the linear regression (slope, 1.6 degrees/s per diopter; intercept, 1.8 degrees/s). Error bars, ±SD.

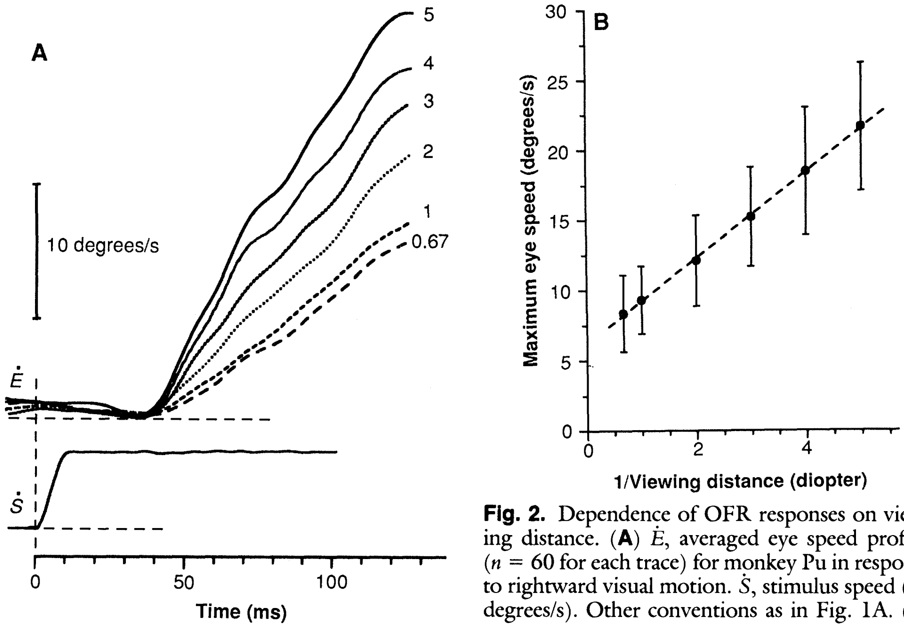

Fig. 2. Dependence of OFR responses on viewing distance. (**A**) $\dot{E}$, averaged eye speed profiles ($n = 60$ for each trace) for monkey Pu in response to rightward visual motion. $\dot{S}$, stimulus speed (80 degrees/s). Other conventions as in Fig. 1A. (**B**) Plot of maximum eye speed (achieved within 100 ms of onset of stimulus motion) against the reciprocal of the viewing distance [for data shown in (A)]. Dashed line is the linear regression (slope, 3.20 degrees/s per diopter; intercept, 6.47 degrees/s). Error bars, ±SD.

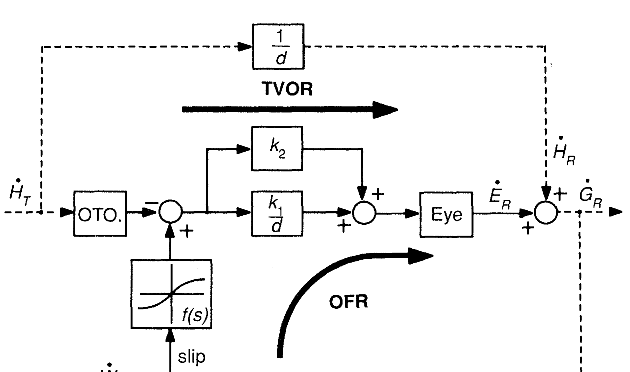

Fig. 3. A block diagram showing the proposed relation between the TVOR and the OFR. Translational head movements affect gaze (position of the eyes with respect to the surroundings) in inverse proportion to the viewing distance, and the TVOR generates compensatory eye movements to cancel this effect. The OFR operates as a negative feedback system, reducing any retinal slip due to residual shifts of gaze. The variable gain element, k_1/d, gives the TVOR its dependence on proximity and tends to offset velocity saturation in the OFR, represented here by the nonlinearity, $f(s)$. Dashed lines represent physical links: $\dot{H}_T$, head velocity in linear coordinates; $\dot{H}_R$, $\dot{E}_R$, $\dot{G}_R$, and $\dot{W}_R$, velocity of head, eyes (in head), gaze, and visual surroundings, respectively, in angular coordinates. OTO, otolith organs.

evoked consistent ocular following and, as Fig. 2A shows for one animal, once again the response varied inversely with the viewing distance. The maximum compensatory eye speeds achieved within 100 ms of the onset of stimulus motion are plotted in Fig. 2B, from which it is evident that OFR responses were a linear function of the inverse of the viewing distance. Similar data were obtained from all four animals. When the data from each animal were expressed as a percentage of that same animal's highest mean response and plotted against the inverse of the viewing distance, there was surprisingly little variation: the range of slopes was only 14% to 16% per diopter (mean, 15% per diopter), and the range of intercepts was 22% to 34% (mean, 28%).

That the OFR shares the TVOR's dependence on proximity leads us to suggest that the two reflexes share a pathway whose efficacy is modulated by absolute distance cues (*9*). Further, we suggest that these two systems are synergistic, functioning to compensate selectively for translational disturbances of the observer (*10*). In our proposed scheme (see Fig. 3), the TVOR and OFR share two gain elements: a variable one (k_1/d, where k_1 is a constant and d is the target distance), which gives the dependence on proximity, and a fixed one (k_2), which accounts for the offset in our data. The variable gain element allows the TVOR to receive inputs encoded in Cartesian coordinates [translational velocity of the head ($\dot{H}_T$)] and to respond with outputs coded in polar coordinates [rotational velocity of the eyes ($\dot{E}_R$)]. That the visual contribution enters the system upstream of the variable gain element might seem less than optimal since negative feedback systems such as this function best when their gain is fixed at some maximum limited only by stability considerations. However, we suggest that the variable element helps to offset velocity saturation, which is known to be present in the OFR (*2*) and has been incorporated into Fig. 3. Retinal slip speeds experienced by the moving observer will tend to vary inversely with viewing distance; hence ocular following will tend to show increasing saturation with near viewing, an effect that the gain element, k_1/d, will counteract. Thus, the observed dependence on proximity meets the geometric needs of the TVOR and offsets the intrinsic limitations of the OFR.

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1. The compensatory eye rotation, θ, required to keep the eyes aligned on an object at distance, *d*, when the observer is moved sideways in a straight line ("lateral translation" along the interaural axis) over a distance, *M*, is arctan (*M*/*d*). Taking derivatives, the velocity of the compensatory eye rotation, θ, is given by the expression:

$$\left[\frac{1}{1+\left(\frac{M}{d}\right)^2}\right]\left(\frac{\dot{M}}{d}\right)$$

In our experiments and most comparable everyday situations, the time scale of interest is brief and $d >> M$, so that the first term approaches 1, hence the required compensatory eye movement effectively becomes $\dot{M}/d$.
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8. Our previous studies had shown that ocular following responses are transiently augmented by a prior saccade across a textured scene (*2*), and we made use of this in the present study by having the animal make a 10-degree rightward saccade into the center of the pattern 30 ms before the stimulus motion began. This was achieved by reinforcing the animals for transferring fixation between appropriately positioned target spots projected onto the scene.
9. Additional experiments indicated that the linear dependence of both reflexes on the inverse of the viewing distance was preserved over a range of stimulus motion parameters: sled jerk amplitude was varied from 305 to 940 cm/s^2 per second, and the velocity of the visual scene was varied from 10 to 160 degrees/s. Further data from three of the monkeys indicated that the TVOR responses could be increased by selectively increasing either vergence (by means of base-out prisms with the most distant target) or accommodation (by means of base-in prisms with the nearest target) and these increases in response were similar in the two cases. These findings indicate that the TVOR uses some internal measure of both the vergence and the accommodative states to modulate its gain in accordance with the viewing distance.
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1 June 1989; accepted 10 August 1989

Sequence-Specific Isotope Effects on the Cleavage of DNA by Bleomycin

JOHN W. KOZARICH,* LEROY WORTH, JR., BRUCE L. FRANK, DONNA F. CHRISTNER, DANA E. VANDERWALL, JOANNE STUBBE*

Bleomycin is a metal- and oxygen-dependent DNA cleaver. The chemistry of DNA damage has been proposed to involve rate-limiting abstraction of the 4′-hydrogen. A DNA fragment has been prepared that contains [4′-^{2}H]thymidine residues of high isotopic content. Primary kinetic isotope effects have been directly observed at individual thymidine residues with DNA sequencing technology.

THE ELUCIDATION OF THE MECHANISMS of DNA cleavage by bleomycin (BLM) (*1*), the neocarzinostatin cofactor (*2*), calicheamicin (*3*), esperamicin (*4*), and related compounds (*5*) has been extensively investigated. High sensitivity and precision are required to evaluate the mechanistic changes that may accompany alterations in local DNA conformation or modifications in drug structure or both. We report a new technique that makes use of specifically deuteriated ^{32}P end-labeled DNAs in combination with gel electrophoresis to detect and quantitate potentially rate-limiting carbon-hydrogen bond cleavages by DNA-cleaving drugs at individual sequence sites. We use BLM as an example.

The activity of BLM in vitro depends on Fe(II) and O_2 or Fe(III) and H_2O_2 (*6*). The initial BLM·Fe(II)·O_2 complex (Fig. 1) undergoes one-electron reduction to ultimately yield "activated BLM," which can initiate DNA damage (*7*). Two types of DNA damage are observed with "activated BLM" (Fig. 2, A and B). Pathway A results in the formation of nucleic acid base propenal and a DNA strand scission that yields 3′-phosphoglycolate and 5′-phosphate termini. Pathway B results in the liberation of nucleic acid base plus an alkali-labile site that cleaves at *p*H 12 with piperidine to afford a 3′-phosphate and a 5′-phosphate terminus. On the basis of the identification of the propenal (*7*, *8*), Giloni *et al.* (*8*) inferred that

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J. W. Kozarich, L. Worth, Jr., B. L. Frank, D. F. Christner, D. E. Vanderwall, Department of Chemistry and Biochemistry and Center for Agricultural Biotechnology, University of Maryland, College Park, MD 20742.

J. Stubbe, Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139.

*To whom correspondence should be addressed.