0031-6997/89/4101-0053$02.00/0
PHARMACOLOGICAL REVIEWS
Vol. 41, No. 1
Printed in U.S.A.

Neuropeptide Modulation of Central Vestibular Circuits*

CAREY D. BALABAN, VESNA P. STARČEVIĆ, AND WALTER B. SEVERS

Department of Otolaryngology, The Eye and Ear Institute of Pittsburgh, University of Pittsburgh, Pittsburgh, Pennsylvania 15213, Department of Pharmacology, College of Medicine, The Pennsylvania State University, Hershey, Pennsylvania 17033, and Institute of Physiology, Faculty of Medicine, University of Belgrade, Belgrade, Yugoslavia (V. P. S.)

* Supported by NIH Grants K04 NS00891 (C.D.B.) and TW03743 (V.P.S.)

I. Introduction

The vestibular system mediates postural and ocular adjustments to changes in the position of the head in space. Signals originating in the horizontal, posterior, and anterior semicircular canals provide information about angular acceleration of the head, while the otolith organs (saccule and utricle) convey inputs reflecting linear acceleration due to either gravity or movements in other directions. These inputs are processed in central circuits that include vestibular nuclei and cerebellum to produce compensatory vestibular reflexes (49, 228). These physiological responses maintain gaze and postural stability in darkness when the head is fixed relative to the trunk. Under normal physiological conditions, though, these circuits also receive proprioceptive inputs reflecting the movement of the head on the trunk and visual inputs concerning the movement of the visual surround with respect to the head. These inputs are then used to generate compensatory motor responses to changes of position of the head and body in three-dimensional space. Thus, central vestibular circuits are specialized for motor and sensory functions involved in maintenance of postural and ocular stability.

There is a relative paucity of information about actions of transmitters and neuromodulators in central vestibular circuits. Although direct effects of neuroactive compounds on vestibular nuclear neurons have been reported in the literature (cf., 47, 114, 115, 137), our understanding of the role of these compounds in maintenance of postural and ocular stability is rudimentary. This review approaches the question of the role of neuropeptides in vestibular system performance by focusing initially on central vestibular symptoms that are elicited by direct intracranial injections of neuroactive substances in conscious rats. This approach is essentially a pharmacological perturbation analysis, which investigates the effects of a specific chemical manipulation on spontaneous activity (192, 208). The mechanisms producing effects in these studies of global properties can then be dissected by further experiments and attributed to actions at single or multiple sites in central neural circuits. In the course of studies of the behavioral and neurochemical effects of centrally administered somatostatin (SRIF) (10, 12, 33, 35, 50, 84, 89, 104, 132, 219, 229), arginine-vasopressin (AVP) (1, 26, 37–39, 50, 70, 105, 106, 117, 119, 156, 215, 232–235), lysine-vasopressin (1, 119), oxytocin (117, 119), opioid agonists and antagonists (52, 79, 91, 98, 103, 108, 163, 223), substance P (99, 130), bradykinin antagonists (162), and sulfonated derivatives of cholecystokinin heptapeptide (133), investigators have reported an unusual pattern of spontaneous motor activity: rats display transient attacks of ataxia, head tilt, nystagmus, body sway, and listing of the body in the direction of the head tilt. This progresses in many animals to a characteristic behavior termed *barrel rotation* (50), where the animal repeatedly rolls about its longitudinal axis. Although barrel rotation has been variously interpreted in the recent literature as a pathological effect (119), a

convulsive disorder (1), a dystonia (184), or an effect at the level of the vestibular nuclear complex (34–36), it was well-recognized as a hallmark of unilateral damage to central or peripheral vestibular circuits during the early decades of the twentieth century (65, 74–78, 122, 127, 128, 129, 145, 149–151, 157, 167, 188–190, 221). The response was first described in the literature by Pourfour du Petit in 1710 (167) and Magendie in 1824 (129) after damage to the cerebellar peduncles or vermal regions of cerebellar cortex, and was later shown to be a characteristic response of quadrupeds to asymmetric manipulations of structures processing inputs from *vertical* (i.e., anterior or posterior) semicircular canals (cf., 149–151). This communication examines this earlier literature from the standpoint of actions of neuroactive substances at central sites implicated in the production of barrel rotation. The major goal of this review is to provide a synthesis of findings from these diverse areas of the literature. Such a synthesis is needed to develop hypotheses for sites of action of these peptides and, perhaps more importantly, for identifying their putative roles in vestibular physiology and pathophysiology.

The organization of this review can be summarized as follows. After an initial introduction to motor symptoms elicited by intracerebroventricular (i.c.v.) injections of neuropeptides, a detailed analysis of our previous data is presented to illustrate basic properties displayed by the incidence and onset latency of symptoms after i.c.v. injections of SRIF and AVP. This analysis argues that barrel rotation is not a nonspecific precursor to a convulsive syndrome elicited by the peptides; rather, it represents a specific response to the peptides. Further analyses of the data regarding onset latency to barrel rotation (BR), based upon hazard plotting techniques, suggest a discrete underlying temporal basis for the phenomenon. The ensuing sections of the review, then, integrate information from diverse areas of the neurobiological literature into a cohesive framework for studying these effects within the context of central neurotransmitter regulation of postural and ocular equilibrium.

The problem of relating barrel rotation with actions at specific sites in central vestibular circuits requires a systematic review of both the pharmacology of the phenomenon and a long history of neurobiological studies establishing that barrel rotation is elicited specifically by experimental manipulations of the vestibular nerve, vestibular nuclei, and related central structures in quadrupeds. These topics are reviewed in Sections III and IV. Section V, then, presents a multiple site model for the temporal structure of barrel rotation and a synthetic discussion of the possible correspondence of anatomic sites with sites in the model, based upon the distribution of endogenous peptides and receptors in central structures. This discussion concludes that endogenous neuropeptides can elicit vestibular dysfunction via specific actions at central sites, suggesting that they are important modulators of central vestibular circuits.

II. Incidence and Temporal Dynamics of Motor Dysfunction Elicited by SRIF and AVP: Peptide Actions and Interactions

A. Overview: Neuropeptides, Vestibular Dysfunction and Convulsions

Among neuropeptides that elicit distinct symptoms of vestibular dysfunction, the properties of SRIF and AVP have been documented in greatest detail. Studies of the effects of injections of these peptides into either the cerebral ventricles or central neural structures have revealed specific symptoms of motor dysfunction in rats (1, 10, 12, 26, 33, 35, 37–39, 50, 51, 70, 84, 89, 104–106, 117, 119, 131, 132, 156, 219, 229, 232, 235), which are summarized in table 1. These symptoms can be classified as representing a) a rapidly evolving, transient disequilibrium syndrome, b) an acute convulsive syndrome, and c) long-term symptoms indicative of pathological changes in the central nervous system and/or altered neural function. It is important to note that disequilibrium and convulsive syndromes are mediated by at least partially independent sites, since they are dissociable on the basis of dose (10). After central injections of SRIF and/or AVP, a proportion of the rats display transient attacks of symptoms associated with acute vestibular dysfunction, which include ataxia, head tilt, vertical, horizontal or alternating nystagmus, body sway, and listing of the body in the direction of head tilt. This progresses in most animals to repetitive bouts of BR. The duration of BR bouts is variable; it may appear intermittently for a period ranging from less than 5 min to 24 h. After bouts of symptoms of disequilibrium, some animals display a convulsive syndrome, often signalled by a vigorous scratching with the hindlimbs and pallor of the extremities and pinnae. This usually progresses further to dyspnea, apnea, and clonic-tonic seizures, which may be related to hypoxia. These convulsive syndromes can lead to significant mortality, which is frequently associated with pulmonary edema. These acute syndromes, then, appear to implicate central actions of neuropeptides in vestibular physiology and pathophysiology.

In addition to acute vestibular symptoms, chronic vestibular effects have been observed several days after SRIF or AVP administration. After SRIF administration, some rats display bouts of ataxia and vertiginous symptoms for a 24- to 36-h period. This effect probably reflects death of cerebellar Purkinje cells in lobules I to III and IX to X (10). Administration of AVP, though, has markedly different long-term effects: there is no evidence of toxic effects on cerebellar Purkinje cells after AVP administration (10); rather, the rats are sensitized to the effects of a subsequent dose of AVP (106, 232, 233). A similar sensitization to centrally administered

TABLE 1
Classification of neuropeptide-induced motor dysfunction

Disequilibrium Syndrome	Convulsive Syndrome	Long-Term Effects
1. Ataxia, nystagmus, and postural instability	1. Dyspnea 2. Apnea	1. Ataxia, postural instability and Purkinje cell death with SRIF
2. Barrel rotation	3. Clonic-tonic convulsions 4. Pulmonary edema	2. Sensitization with AVP
Repetitive, intermittent bouts	Lethal	Persistent

AVP has also been reported after manipulations leading to vasopressin release in rats (37).

These documented effects of single doses of SRIF or AVP raised the question of whether the effects are mediated by actions at common central sites. Our initial studies (10) yielded the intriguing finding that the effects of co-administered AVP and SRIF interact in a highly nonlinear manner (10), which motivated a more detailed examination of interactions between i.c.v. bolus injections of these neuropeptides in conscious rats. Thus, we examined interactions between co-administered i.c.v. doses of SRIF and either vasopressin or (1-(β-mercapto-β,β-cyclopentamethylene propionic acid), 2-(O-methyl)-tyrosine)-Arg^8 vasopressin (mcAVP), a vasopressin antagonist with anti-vasopressor activity. These experiments have identified several important features of interactive effects of neuropeptides to induce these syndromes (9, 206). The incidence of barrel rotation and the lethal convulsive syndrome did not reflect a simple linear addition of effects of SRIF and AVP, and their relative dose-response relations suggested that they are independent syndromes elicited by the peptides. When combined with data from our previous work (10, 12, 231–234), these experiments also yielded the unexpected finding that the time course of susceptibility to BR displays several discrete states, characterized by discrete values of the instantaneous rate of occurrence of this symptom (13). These states are not related simply to the incidence of barrel rotation, and are not a simple linear function of the doses of SRIF and AVP applied. In addition, these discrete states of postural destabilization appear to change within discrete "latency windows." This suggests that neuropeptides may be involved in setting or maintaining states of postural stability at central vestibular sites.

This section presents a comprehensive analysis of the cumulative data base from our studies of motor responses after i.c.v. SRIF and AVP. In addition to describing basic dose-response properties, this discussion is intended to document both the nature of the data set and the logic that we have employed in analyses of incidence and latency data. This series of analyses, then, integrated with both the earlier literature and recent data concerning site-specific distribution and actions of these peptides in the central nervous system, forms the basis for the ensuing discussion of potential neural substrates for neuropeptide-induced postural destabilization.

B. Incidence of Barrel Rotation and Mortality: Peptide Effects on Trigger Mechanisms

1. Barrel rotation incidence. Examination of barrel rotation incidence as a function of dose of SRIF and either AVP or mcAVP reveals nonlinear interactions between the peptides. The incidence data from our previous studies (9, 10, 206, 231–233) for different peptide treatment groups are summarized in figs. 1 and 2 (upper panels). The data for the 40 μg of SRIF (SRIF 40) group represents a cumulative data set spanning several studies; the other groups represent results of individual studies. The barrel rotation incidences for 1 and 0.5 μg of AVP (AVP 1 and AVP 0.5) alone are are 50% (232) and 24% (10), respectively; a dose of 1 μg of mcAVP does not produce barrel rotation (231). The results of paired comparisons (χ^2 tests) for these barrel rotation incidence data are summarized in table 2. Two basic findings are worthy of note. First, the SRIF 20-AVP 0.5 and SRIF

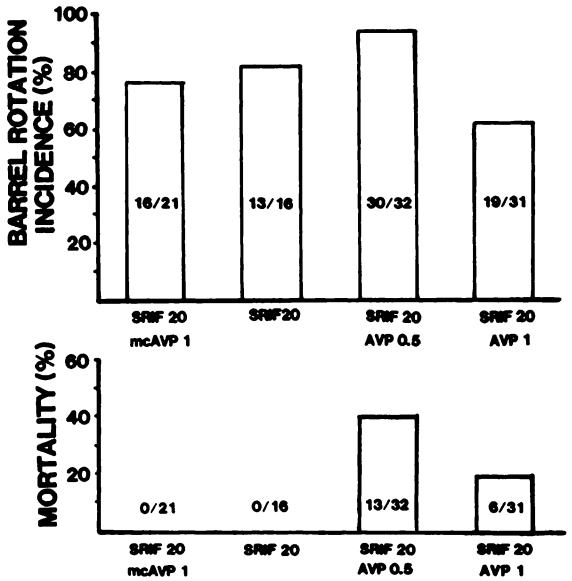

FIG. 1. Incidence of barrel rotation and mortality as a function of intracerebroventricular doses of SRIF alone (20 μg) or with either AVP or mcAVP in conscious rats. The data are taken from references (9, 10, 206, 231–233) and unpublished experiments. The ratio of the number of responsive rats to the number tested is listed for each condition. The results of paired statistical comparisons of barrel rotation incidences are summarized in table 2; paired comparisons for mortality incidences are summarized in table 3.

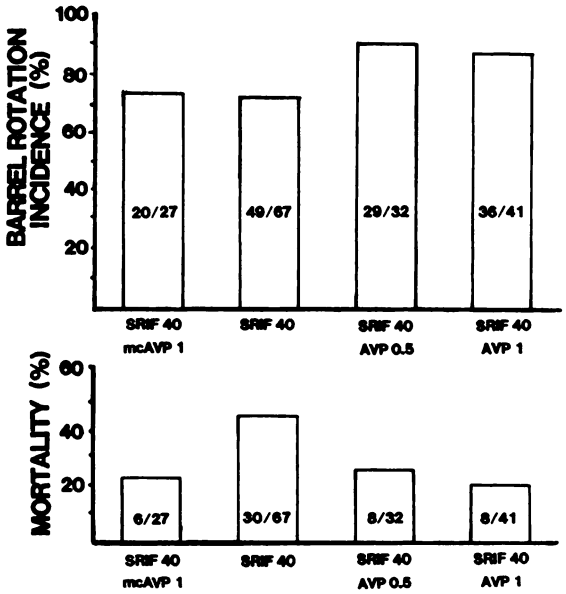

FIG. 2. Incidence of barrel rotation and mortality as a function of intracerebroventricular doses of SRIF alone (40 μg) or with either AVP or mcAVP in conscious rats. The data are summarized from references (9, 10, 206, 231–233) and unpublished experiments. The ratio of the number of responsive rats to the number tested is listed for each condition. The results of paired statistical comparisons of barrel rotation incidences are summarized in table 2; paired comparisons for mortality incidences are summarized in table 3.

40-AVP 0.5 groups displayed higher barrel rotation incidences than either the SRIF 40 or the SRIF 20-AVP 1 groups. Second, the SRIF 20-AVP 1 group had a lower BR incidence than the SRIF 40-AVP 1 group. These findings indicate that the barrel rotation incidence is affected significantly by interactions of SRIF and AVP, but that the interactions are nonlinear. The addition of 0.5 μg of AVP to a 40 μg dose of SRIF increases the incidence of barrel rotation beyond the effects of SRIF alone. However, the addition of 1 μg of AVP or 1 μg of mcAVP does not significantly alter the response to 40 μg of SRIF. By contrast, addition of either 0.5 μg of AVP or 1 μg of mcAVP did not alter the barrel rotation incidence from the level produced by 20 μg of SRIF alone. Paradoxically, the addition of 1 μg of AVP to 20 μg of SRIF significantly depressed barrel rotation incidence to a level less than the response to either SRIF 20-AVP 0.5, SRIF 40-AVP 0.5, or SRIF 40-AVP 1. Thus, actions of AVP on SRIF-induced barrel rotation vary with the dose of SRIF.

2. Direction of barrel rotation as a function of cannula laterally: Emergence of a contralateral bias. One surprising property that emerged from these studies was the finding that two combined peptide doses (40 μg of SRIF and either 1 μg of AVP or 1 μg of mcAVP) produced a significant directional preference for barrel rotation (9). The rats in these groups tended to show barrel rotation in a direction contralateral to the injected lateral ventricle ($p < 0.05$, Fisher's exact test). This preference was absent for groups receiving 40 μg of SRIF and 0.5 μg of AVP, 20 μg of SRIF and 0.5 μg of AVP, and 20 μg of SRIF and 1 μg of AVP. Furthermore, this laterality effect has not appeared in previous studies using doses of either peptide alone (e.g., 1, 10, 12, 33–35, 119, 232). This emergent laterality effect was independent of the barrel rotation incidence in these groups. As discussed in Section IV, the emergence of a laterality effect in vestibular symptoms is of significance because it indicates an underlying lateralization of an effect in central vestibular circuits. Given the injection site in the lateral ventricle, these data suggest that the destabilizing effects of SRIF depend critically upon an AVP concentration window at a telencephalic site. Either a unilateral high AVP concentration or blockade of receptors at this site, then, may bias the response to SRIF in the contralateral direction.

3. Mortality. Mortality was an invariant endpoint of the convulsive syndrome elicited by SRIF and AVP. Thus, analyses of the incidences of these phenomena are equivalent. The incidence of mortality after i.c.v. SRIF, AVP, and combined doses of the peptides is summarized from our previous studies (9, 10, 206, 231–233) in the lower panel of figs. 1 and 2; the results of paired comparisons between treatment groups are summarized in table 3. The SRIF 40 and SRIF 20-AVP 0.5 groups represent a cumulative data set from several studies (9, 10, 12, 206); data for other groups are taken from single studies. Although mortality after either SRIF or AVP alone increased with a dose of either peptide, the effects of combined doses of peptides were not simply additive. For example, a combination of 20 μg of SRIF and 0.5 μg of AVP produced greater mortality than predicted for either peptide alone (Fisher's exact test, $p < 0.01$), while the effects of 40 μg of SRIF were depressed by addition of 1 μg of AVP (χ^2 test, $p < 0.05$). The addition of the AVP antagonist, mcAVP, to 40 μg of SRIF produced only a marginal decrease in mortality compared to the effects

TABLE 2

Statistical differences in barrel rotation incidence as a function of peptide dose[a]

SRIF 20 AVP 0.5	SRIF 40 AVP 0.5	SRIF 40 AVP 1	SRIF 20	SRIF 20 mcAVP 1	SRIF 40 mcAVP 1	SRIF 40	SRIF 20 AVP 1
———	———	———	———	———	———		
		———	———	———	———	———	
			———	———	———	———	———

[a] The peptide treatment groups from the upper panels of figs. 1 and 2 are listed (from left to right) in descending order of barrel rotation incidence. Treatment groups that *do not* differ significantly ($p > 0.05$, χ^2 test, paired comparisons) are indicated by each level of underlining.

of SRIF alone. This indicates that both peptides interact at the level of mechanisms producing lethal convulsive symptoms.

The incidence of mortality after combined doses of SRIF and AVP indicates that *different interactions* between SRIF and AVP produce disequilibrium and the lethal convulsive syndrome. These interactive effects are best appreciated by consideration, first, of the effects of doses of SRIF at fixed doses of AVP and mcAVP and second, of the effects of doses of mcAVP and AVP at fixed doses of SRIF (figs. 1 and 2 and table 3). First, for each dose of AVP or mcAVP, different rules for interactions appear to govern mechanisms mediating convulsions and mortality. For 1 μg of mcAVP, as in the absence of AVP, mortality emerged only in the presence of 40 μg of SRIF, but at a rate lower than for the SRIF dose alone. For 0.5 μg of AVP, mortality was significantly potentiated when the peptide was co-administered with 20 μg of SRIF; the addition of 40 μg of SRIF did not significantly affect mortality beyond the level produced by either 40 μg of SRIF alone or 20 μg of SRIF and 1 μg of AVP. Finally, mortality was unaffected when 1 μg of AVP was combined with either dose of SRIF. Thus, although the 1 μg of AVP appears to be sufficient to saturate mechanisms mediating convulsions, it appears that these mechanisms are sensitive to both SRIF and AVP when lower AVP doses are employed.

This concept of two different operating domains for mechanisms underlying the lethal convulsive syndrome is also apparent from the effects of mcAVP or AVP on responses to fixed SRIF doses. For a 20 μg SRIF dose, the addition of 0.5 μg of AVP resulted in a mortality rate 1 greater than for either peptide alone. By contrast, the response after addition of 1 μg of AVP mirrored the effects of AVP alone. For the 40 μg SRIF dose, though, there was a different pattern of interaction. Addition of either 1 μg of AVP or 1 μg of mcAVP, depressed mortality from the level produced by the SRIF dose alone $p < 0.05$, χ^2 test). The decrease produced by addition of 0.5 μg of AVP was not significant ($p > 0.05$). It is interesting to note that the mortality rate in rats given 40 μg of SRIF and 1 μg of either AVP or mcAVP was equivalent to the level produced by 1 μg of AVP alone in our previous studies (232). This suggests that 1 μg of AVP can occlude the response to 40 μg of SRIF, but that lower doses of AVP interact nonlinearly with SRIF to produce convulsions leading to death. In particular, the equivalent effects of combined doses of SRIF and either AVP or mcAVP suggest that the mechanism(s) producing mortality are sensitive to endogenous AVP.

4. Independence of barrel rotation incidence and mortality: Separate trigger mechanisms for disequilibrium and convulsive symptoms. Comparisons of the incidences of barrel rotation and mortality confirm the previous observation that these effects are dissociable on the basis of dose (e.g., 10). The fact that statistically similar incidences of barrel rotation are associated with markedly different mortality rates is obvious from inspection of figs. 1 and 2; the data are shown as a scatter plot in fig. 3 to illustrate the lack of a relationship. This simple observation, though, also reflects more profound differences in the expression of disequilibrium (dependent variable: barrel rotation) and convulsive (dependent variable: mortality) symptoms as a function of neuropeptide interactions. As discussed above (figs. 1 and 2), the mortality from a 1 μg of AVP dose is not affected by addition of either 20 or 40 μg of SRIF; however, addition of 40 μg of SRIF produced a significant increment in barrel rotation to the level produced by SRIF alone. Similarly, while a combined dose of 40 μg of SRIF and 0.5 μg of AVP produced a marginal, but not significant reduction in mortality from the level expected for SRIF alone, it produced a significant elevation in the incidence of barrel rotation. This suggests that the rules of interaction of i.c.v. SRIF and AVP are distinct at the sites eliciting vertiginous and convulsive symptoms. This feature of the data is consistent with the view that barrel rotation is not a precursor to a convulsive syndrome; rather, barrel rotation and lethal convulsions are independent peptide effects.

C. Barrel Rotation: Changes in Discrete States of Postural Destabilization during "Latency Windows"

1. General configuration of hazard functions for barrel rotation latencies. The latency to barrel rotation is an example of a "waiting time" measurement, which is most appropriately analyzed by statistical methods for lifetime data (58, 113, 122). We have adopted a hazard plotting approach to analysis of barrel rotation data (10, 232, 233), which permits a graphical estimation of the hazard function from plots of the cumulative hazard function for the data set (113). Briefly, the underlying hazard function for peptide-induced barrel rotation is based on a two-parameter exponential model. This distribution is described by two parameters, a threshold latency param-

TABLE 3

Statistical differences in the incidence of mortality as a function of peptide dose[a]

SRIF 40	SRIF 20 AVP 0.5	SRIF 40 AVP 0.5	SRIF 20 AVP 1	SRIF 40 mcAVP 1	SRIF 40 AVP 1	AVP 1	AVP 0.5

[a] The peptide treatment groups from the lower panels of figs. 1 and 2 and other published reports (9, 232) are listed (from left to right) in descending order of incidence. Treatment groups that *do not* differ significantly ($p > 0.05$, χ^2 or Fisher's exact test, paired comparisons) are indicated by each level of underlining. There was no mortality in the SRIF 20, SRIF 20-mcAVP 1 and 1 μg mcAVP groups (206, 231).

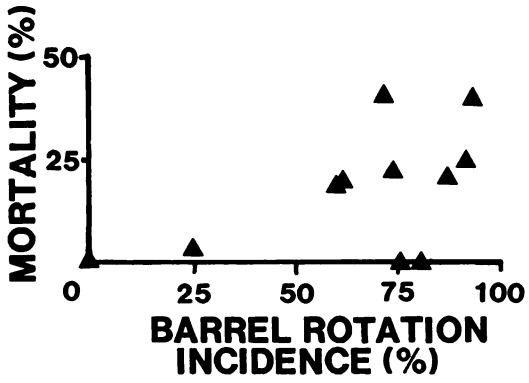

FIG. 3. Scatter plot illustrating the lack of a relationship between the incidence of barrel rotation and mortality in conscious rats after intracerebroventricular injection of SRIF alone, AVP alone, or combined peptide doses. This plot is constructed from the eight conditions in figs. 1 and 2 and data from references (9, 227–229). Each point on the plot represents one experimental condition. No statistically significant pattern is evident.

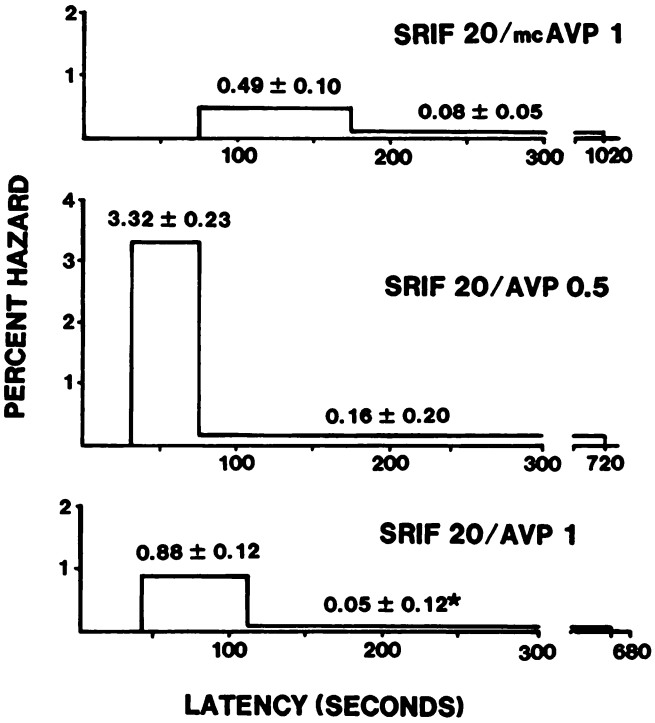

FIG. 4. Hazard functions for the onset of barrel rotation after intracerebroventricular injection of SRIF (20 μg) alone or with either AVP or mcAVP in conscious rats (206). The θ^{-1} parameter is represented on the *y*-axis as a function of time after peptide administration. The value of this parameter $\pm s_b$ is specified separately for the two constant hazard epochs that characterize each condition. The μ parameter represents the time of onset of the first hazard phase; values are listed in table 5.

eter, μ, which expresses the minimum latency to barrel rotation in the population, and a hazard parameter, θ^{-1}, which expresses the instantaneous probability of the onset of barrel rotation as a function of time. Under ambient illumination, either i.c.v. AVP or SRIF produces hazard functions consisting of two constant hazard epochs; after a minimum latency, a high hazard period is followed by an abrupt transition to a low hazard period (10, 232, 233). For other experimental manipulations, though, a single two-parameter exponential function was observed (232, 233).

The hazard functions for barrel rotation after combined injections of SRIF and either mcAVP or AVP show the same configuration as for injections of either peptide alone under ambient illumination conditions (Figs. 4 and 5). These graphs represent the instantaneous probability of the initiation of barrel rotation (hazard in units of %/s) as a function of time after i.c.v. injection of different peptide combinations. The least-squares estimates of the hazard parameter were obtained as the slope of the cumulative hazard plots (10, 113, 232, 233), and are reported with both correlation coefficients and standard deviation estimators (s_b, ref. 95). After a threshold latency (μ), there was an initial high hazard epoch, followed by a second lower hazard epoch that continued up to 1045 s after peptide injection. This indicates that the general properties of mechanisms underlying the temporal development of barrel rotation are not altered by co-administration of SRIF, AVP, and mcAVP. This invariance in the general configuration of the hazard function is consistent with the hypothesis that SRIF and AVP elicit barrel rotation at sites that provide convergent input onto central, postural stabilization mechanisms. The degree of central postural destabilization, then, is reflected in both the magnitude and the location of the hazard function. The magnitude is reflected by the hazard parameter (θ^{-1}); the location is reflected by the minimum latency (μ) and median latency for each dose of peptides.

The analysis that follows will describe effects of SRIF and AVP on the time course of barrel rotation onset, stressing insights gained by hazard analysis. As an overview, salient properties of these hazard functions are summarized as follows:

1. Addition of 1 μg of mcAVP to 20 μg of SRIF did not affect either the minimum latency or the initial or late phase θ^{-1} (206) from findings for 20 μg of SRIF alone (10).
2. Addition of 1 μg of mcAVP to 40 μg of SRIF significantly reduced the initial phase θ^{-1} ($p < 0.05$) from the values from the cumulative 40 μg of SRIF data set, without affecting the minimum latency or late phase θ^{-1} (9).
3. Addition of either 0.5 or 1 μg of AVP to 20 μg of SRIF both increased the initial phase θ^{-1} and decreased the minimum latency (206) from the previously reported values for the SRIF dose alone (10).
4. Addition of either 0.5 or 1 μg of AVP to 40 μg of SRIF did not affect the hazard function (9).

2. Hazard epochs as discrete states: peptides and discrete levels of postural destabilization. Consideration of the cumulative data base from our previous studies revealed a remarkable feature of hazard functions for barrel ro-

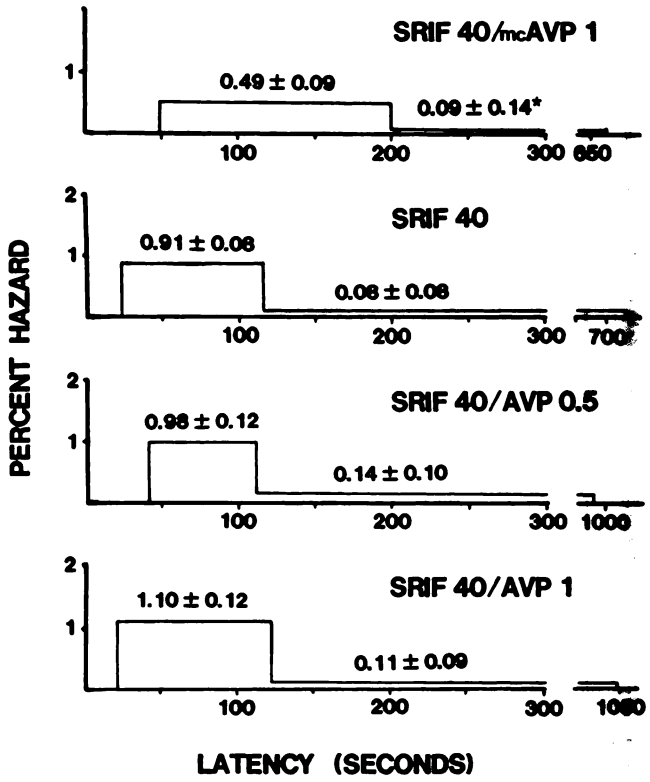

FIG. 5. Hazard functions for the onset of barrel rotation after intracerebroventricular injection of SRIF (40 μg) alone or with either AVP or mcAVP in conscious rats (9). The θ^{-1} parameter is represented on the *y*-axis as a function of time after peptide administration. The value of this parameter $\pm s_\theta$ specified separately for the two constant hazard epochs that characterize each condition. The μ parameter represents the time of onset of the first hazard phase; values are listed in table 4.

tation latency: the probabilities of the onset of barrel rotation during the initial and late hazard phases reflect at least four discrete states of postural destabilization. This is most obvious after consideration of the values of the hazard parameter (θ^{-1}) across experimental groups (table 4). The hazard parameter values can be sorted into four groups, labeled states 1 through 4 in table 4, across 16 different treatments. One-way analysis of variance (with state as a factor with four levels) showed a highly significant difference in θ^{-1} values between states ($p < 0.001$), and Scheffé tests (paired comparisons of states) indicated that the states each are characterized by a distinct θ^{-1} value ($p < 0.05$ for all comparisons). Thus, hazard analysis has revealed a previously unsuspected aspect of the vertiginous symptoms of peptides leading to barrel rotation: there are at least four discrete states of neuropeptide-induced postural destabilization.

The identification of these four underlying states of neuropeptide-induced postural destabilization provides a framework for evuluating the effects of SRIF and AVP mechanisms in the time course of barrel rotation. Since the late phase hazard was not affected by combined peptide treatment, we only consider effects on either the location of the entire hazard distribution or on θ^{-1} during the initial phase. For comparative purposes, the initial phase hazard values are graphed as a function of peptide treatment in fig. 6. Although the initial phase hazard increased with the dose of either AVP or SRIF alone, there is no simple relationship between the dose of co-administered peptides and the initial phase θ^{-1}. The relationship is clearly nonlinear. However, two properties are worthy of note. First, the addition of 1 μg of mcAVP to 40 μg of SRIF significantly depressed the initial phase θ^{-1} produced by the latter peptide alone ($p < 0.05$). The decrease in initial phase θ^{-1} produced by adding 1 μg of mcAVP to 20 μg of SRIF was not significant. In the hazard state terminology, addition of 1 μg of mcAVP to 40 μg of SRIF reduced the initial phase θ^{-1} from state 3 to state 2, while the initial phase θ^{-1} values of the response to 20 μg of SRIF and 1 μg of mcAVP-20 μg of SRIF were both state 2. This implies that endogenous AVP contributes to the increment from a state 2 to a state 3 initial phase θ^{-1} when the SRIF dose is increased from 20 to 40 μg. The second point of interest is that the effects of AVP on initial phase θ^{-1} varied with the dose of SRIF (fig 6, left panel). The initial phase θ^{-1} state for a 40-μg SRIF dose was not affected by either AVP dose employed. However, the initial phase θ^{-1} state for a 20 μg dose was markedly potentiated ($p < 0.05$) from state 2 to state 4 by addition of 0.5 μg of AVP, while the state 3 initial phase response produced by 20 μg of SRIF and 1 μg of AVP was significantly lower than the response to 20 μg of SRIF-0.5 μg of AVP and significantly higher than the response to 20 μg of SRIF alone. This indicates that the state of postural destabilization after i.c.v. SRIF and AVP is sensitive to interactions between the peptides. In particular, the initial phase θ^{-1} appears to be stable for higher doses of both peptides, suggesting that interactions are most potent at subsaturating doses.

3. Nonparametric analyses: further support for discrete destabilization states in barrel rotation. Hazard analysis has the advantage of providing a parametric method for analyzing barrel rotation latency data. Since all the latency data sets are non-Gaussian but identically distributed, an alternative approach is to test for shifts in the location of the barrel rotation latency distribution with nonparametric methods. Application of this approach to the collective data set revealed that there were significant differences in barrel rotation latency data from different treatment groups (Kruskal-Wallis test, $p < 0.001$), and the significant differences from paired comparisons by Mann-Whitney *U* tests are summarized in table 5. As predicted by the hazard analysis, these nonparametric analyses revealed three different classes of barrel rotation latency responses to i.c.v. neuropeptides. The distribution with the shortest latency corresponded to the groups with a state 4 initial hazard phase, consistent with a greater risk per second of barrel rotation initiation. The intermediate class had a longer median barrel rotation latency after peptide exposure, and

TABLE 4
Hazard Epochs as States of Destabilization[a]

State	$\theta^{-1} \pm s_\theta$	Treatment	Phase	Onset latency	N
4	3.32 ± 0.23	SRIF 20-AVP 0.5, light, naive	Initial	41 s	24
4	2.79 ± 0.68	AVP 1, light, naive	Initial	48 s	>30
4	2.40 ± 0.38	AVP 0.5, light, sensitized	Initial	30 s	>30
4	3.05 ± 0.18	AVP 0.5, dark, sensitized	Only	30 s	26
4	3.44 ± 0.40	AVP 0.5, labyrin, light, sensitized	Only	28 s	20
4	4.47 ± 0.94	AVP 0.5, labyrin, dark, sensitized	Only	32 s	21
4	3.42 ± 0.40	AVP 0.5, 3-AP, light, sensitized	Only	80 s	19
4	3.39 ± 0.40	AVP 0.5, 3-AP, dark, sensitized	Only	29 s	18
3	0.91 ± 0.08	SRIF 40, light, naive	Initial	23 s	34
3	0.98 ± 0.12	SRIF 40-AVP 0.5, light, naive	Initial	40 s	18
3	1.10 ± 0.12	SRIF 40-AVP 1, light, naive	Initial	20 s	24
3	0.88 ± 0.12	SRIF 20-AVP 1, light, naive	Initial	40 s	15
2	0.62 ± 0.11	SRIF 20, light, naive	Initial	78 s	9
2	0.47 ± 0.11	AVP 0.5, light, naive	Initial	46 s	6
2	0.49 ± 0.10	SRIF 20-mcAVP 1, light naive	Initial	75 s	9
2	0.49 ± 0.09	SRIF 40-mcAVP 1, light, naive	Initial	49 s	16
2	0.46 ± 0.14	AVP 0.5, light, sensitized	Late	73 s	>10
1	0.08 ± 0.08	SRIF 40, light, naive	Late	115 s	15
1	0.11 ± 0.18	SRIF 20, light, naive	Late	205 s	4
1	0.08 ± 0.05	SRIF 20-mcAVP 1, light, naive	Late	175 s	7
1	0.16 ± 0.20	SRIF 20-AVP 0.5, light, naive	Late	74 s	6
1	0.05 ± 0.12	SRIF 20-AVP 1, light, naive	Late	115 s	4
1	0.09 ± 0.14	SRIF 40-mcAVP 1, light, naive	Late	199 s	4
1	0.14 ± 0.10	SRIF 40-AVP 0.5, light, naive	Late	110 s	11
1	0.11 ± 0.09	SRIF 40-AVP 1, light, naive	Late	120 s	12
?	0.81 ± 0.31	AVP 1, light, naive	Late	73 s	>10
		Drug pretreatment groups			
		Data from AVP 0.5, light, sensitized condition			
4	3.85 ± 0.81	Atropine (5 mg/kg) day 1	Only	35 s	13
4	2.78 ± 0.13	Atropine (5 mg/kg) day 3	Only	42 s	20
4	1.95 ± 0.10	Atropine (5 mg/kg) days 1 and 3	Only	34 s	20
4	2.00 ± 0.10	Diazepam (5 mg/kg) day 3	Only	88 s	17
4	3.50 ± 0.52	Phenobarbital (50 mg/kg) day 3	Only	55 s	15
4	2.37 ± 0.01	Phenytoin (100 mg/kg) day 3	Only	55 s	15
4	2.69 ± 0.11	Phenytoin (200 mg/kg) day 3	Only	141 s	18
4	2.19 ± 0.05	Valproic acid (125 mg/kg) day 3	Only	136 s	19
4	2.49 ± 0.03	Valproic acid (250 mg/kg) day 3	Only	40 s	15

[a] Abbreviations: This table summarizes the parameters of the hazard functions for barrel rotation onset in different peptide groups from our previous studies (9, 10, 206, 232, 233) and unpublished results. The onset latency designates μ for initial high hazard phase and μ_1 for the late, low hazard phase of biphasic hazard functions. For hazard functions with only a single, high hazard phase, μ is listed. The number of animals in each phase (N) is listed in the last column. All numbers after peptides refer to doses in μg. *Naive* rats received no prior peptide treatment. *Sensitized* rats received 1 μg of AVP 2 days prior to testing; the test date is termed *day 3*. *Light* indicates that testing was done under normal ambient illumination; *dark* indicates testing in darkness. Groups of animals with inferior olivary ablation by 3-acetylpyridine intoxication are designated by 3-*AP*; labyrinthectomy is abbreviated *labyrin*. For drug-pretreated animals, the day of drug treatment is also listed.

comprised treatment groups displaying a state 3 initial hazard phase. Finally, the treatments in the response class displaying the longest median latencies corresponded to the groups with the lowest initial hazard phase for barrel rotation (state 2) and with longer minimum barrel rotation latencies, reflecting both a longer threshold time for triggering the response and a lower risk of barrel rotation initiation per second after peptide administration. These analyses, then, provide further evidence that i.c.v. injections of SRIF and AVP can produce discrete states of postural destabilization, culminating in barrel rotation.

4. Evidence for discrete "latency windows" for hazard state changes. The observation that SRIF and AVP can induce four discrete hazard states for BR initiation leads to the obvious question of whether the latencies of state changes are also discrete. Fig. 7 shows a histogram of the minimum BR latencies (black bars), transition latencies from initial to late θ^{-1} BR epochs (white bars), and maximum BR latencies (shaded bars) for the treatment conditions listed in table 4. These latencies are not distributed either uniformly (Kolmogorov-Smirnov D or Kuiper's V statistic, $p > 0.15$) or continuously; rather, they appear to be grouped in a series of discrete "latency

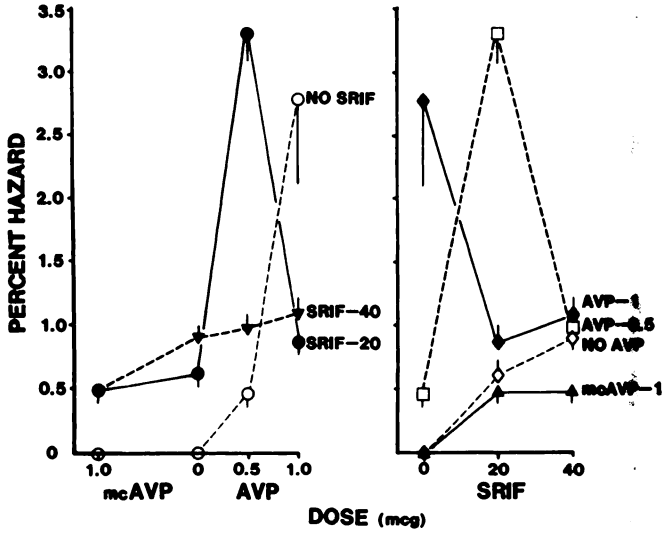

FIG. 6. The relationship of the initial phase hazard parameter (θ^{-1}) to applied intracerebroventricular doses of SRIF and AVP to conscious rats. The effects of adding AVP or mcAVP to fixed SRIF doses are shown in the left panel; the effects of adding SRIF to fixed AVP or mcAVP doses are illustrated on the right. Note the nonlinear interaction between the peptides.

windows." The earliest window, designated T_1, consists exclusively of values for the initial (or the only) epoch of BR initiation. The T_1 latencies range from 20 to 56 s, with a mean latency of 37.2 ± 2.3 (SEM) s. The second latency window, termed T_2, consists of both transition latencies to the late hazard epoch for BR (μ_1) and minimum BR latencies (μ) for different treatment groups. These latencies range from 73 to 88 s, with a mean latency of 77.3 ± 2.0 s. A third window, termed T_3, begins at 105 s and extends until at least 128 s after peptide injection. Although the paucity of observations in this range does not permit reliable discrimination of either the upper bound of T_3 or the boundaries of other components. the clustering of observations in the 138 to 154 s, 170 to 180 s, 660 to 720 s and 991 to 1045 s ranges suggests the potential existence of other latency windows. The possibility of these longer latency time windows for changes in hazard states should be clarified when effects of these neuropeptides are observed over other experimental conditions.

A single latency window is not characteristic for a particular hazard state (fig. 8A). For example, state 4 epochs may begin in the periods designated T_1, T_2, or a longer component (possibly T_3) in the limited conditions in the literature, while state 2 may begin in either T_1 or T_2. Similarly, the onset of state 1 occurs across several latency windows. These data suggest, then, that the latency windows for state transitions reflect temporal dynamics of trigger mechanisms. These dynamics appear to be partially independent of the value of θ^{-1} during the ensuing hazard epoch. This partial independence forms the basis for a hypothesis (see section V A) that θ^{-1} states are determined by perturbations of neuronal activity at single or multiple sites in central vestibular circuits. By contrast, the latency windows for state transition would represent temporal characteristics of central circuits attempting to compensate for this central functional imbalance.

5. Hazard epoch durations: a discrete distribution? The existence of discrete BR hazard states and discrete latency windows for state changes raises the possibility that the durations of individual hazard states will be discrete. This issue is important because it reveals information about the the temporal stability of neural circuits producing postural destabilation. Fig. 8B shows a histogram of hazard state durations. As expected, the distribution is not uniform; rather, it appears that there are discrete durations that are possible for each state, prior to either the last rat beginning BR or a drop to a lower hazard state. Although these data are suggestive of characteristic temporal properties of hazard states, more data are needed to demarcate duration groups robustly.

D. Relationship between Barrel Rotation Latency and Susceptibility to Lethal Convulsions: Intersecting Dose Domains for Independent Events.

The incidence data in figs. 1 through 3 clearly demonstrated that the vertiginous and convulsive effects are dissociable on the basis of dose, suggesting a lower dose threshold for barrel rotation than convulsive disorders culminating in death. However, as noted in a previous publication (10), the hazard plot for barrel rotation latencies predicted the mortality for both 40 μg of SRIF

TABLE 5

Barrel rotation latency as an index of states of postural destabilization[a]

SRIF 20 AVP 0.5	SRIF 40 AVP 1	SRIF 40 AVP 0.5	SRIF 40	SRIF 20 AVP 1	SRIF 40 mcAVP 1	SRIF 20	SRIF 20 mcAVP 1
49 s	63 s	*69 s*	63 s	68 s	94 s	135 s	101 s
31 s	*20 s*	*40 s*	*23 s*	*40 s*	*49 s*	*78 s*	*75 s*
STATE 4		STATE 3				STATE 2	

INITIAL PHASE HAZARD

[a] The different experimental treatment groups are listed with median and minimum barrel rotation latencies; the minimum latencies are italicized. Treatment groups that are not signifcantly different by Mann-Whitney *U* tests ($p > 0.05$) are underlined.

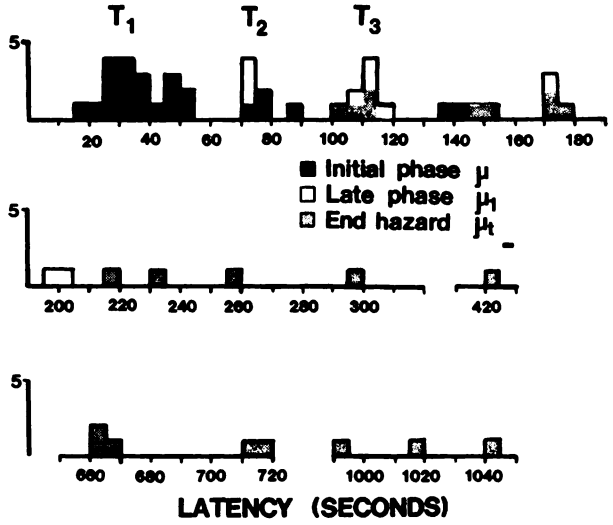

FIG. 7. Frequency histogram displaying the distribution of the parameters of hazard functions for barrel rotation as a function of time after peptide administration to conscious rats (13). This figure is a composite of the 25 conditions summarized in table 4. The parameters are illustrated separately for the onset of the initial phase (μ), the transition to the late phase (μ_1), and the end of risk of barrel rotation onset (μ_t) These hazard phase transitions are not distributed uniformly ($p > 0.15$, Kolmogorov-Smirnov D and Kuiper's V tests). Rather, they are clustered in latency windows. The most distinct of these windows are labeled T_1 through T_3.

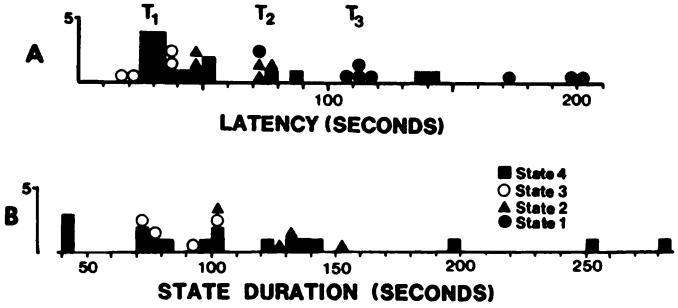

FIG. 8. Histograms of onset latencies (A) and durations (B) of hazard states defined in table 4. The frequency of occurrence of onset latencies of states 1 to 4 across 25 intracerebroventricular peptide conditions is illustrated in the upper histogram (A). The time windows (T_1–T_3) are identical to fig. 7. The lower histogram (B) illustrates the frequency of occurrence of different state durations for states 2 to 4; state 1 durations are omitted because they are much greater than other state durations listed. Note the nonuniform distribution in both histograms.

and 20 μg of SRIF-0.5 μg of AVP treated rats; this relationship did not hold for rats given AVP alone. The previous result was striking: 97% of the rats that died in the two groups showed barrel rotation during the initial, high hazard phase, and 80% of the rats in the initial hazard phase died after displaying barrel rotation. These data suggested that both the location and duration of the initial hazard phase for barrel rotation predicted sensitivity to the convulsive effects of SRIF.

A predictive relationship between barrel rotation incidence during the initial, high hazard phase and subsequent convulsions and death of the animal is supported by results from SRIF-treated groups. However, this relationship is not a simple function of peptide treatment, barrel rotation incidence, or the barrel rotation hazard function. First, mortality was only observed in conditions where the minimum latency for barrel rotation was less than about 50 s; the two conditions with minimum latencies greater than 70 s (20 μg of SRIF and 20 μg of SRIF-1 μg of AVP) did not produce mortality. Second, as shown in fig. 9, animals displaying barrel rotation during the initial, high hazard phase were highly susceptible to the convulsive syndrome leading to death. Across all dose conditions producing mortality, 65 of 70 (93%) of the rats that displayed lethal convulsions had previously displayed barrel rotation during the initial, high θ^{-1} phase of the hazard function. These first two factors were reflected in significantly shorter barrel rotation latencies in animals that died versus animals that survived across groups (Mann-Whitney U test, $p < 0.001$). However, the probability of mortality of rats displaying initial phase barrel rotation varied with the condition and was not simply a function of the minimum latency or the value of θ^{-1} in the initial phase. The incidence of mortality of rats displaying initial phase barrel rotation was significantly higher for the 40 μg of SRIF group than for any other group (χ^2-square test, $p < 0.05$); there were no other significant intergroup differences. This indicates that the dose of SRIF determines whether addition of AVP will potentiate or depress the probability that rats

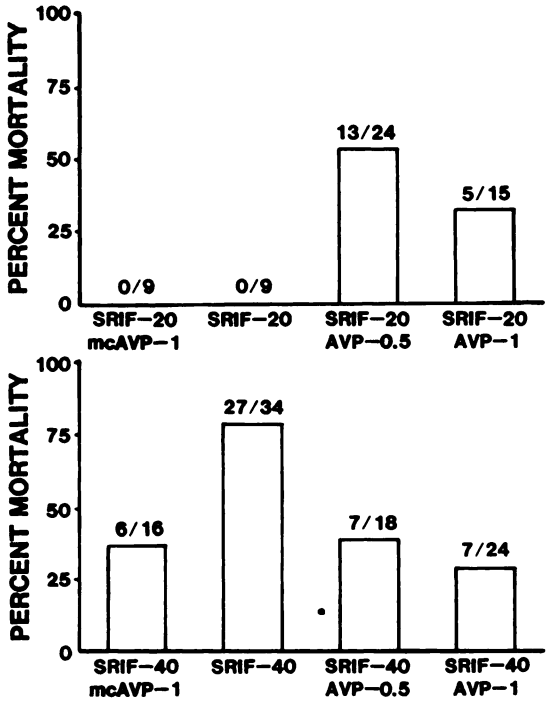

FIG. 9. Incidence of mortality in conscious rats that showed barrel rotation during the initial phase of the hazard function. These data are based upon a subset of the data presented in figs. 1 and 2. The proportion of rats that displayed lethal convulsions after displaying barrel rotation in the initial hazard epoch is listed for each peptide dose condition. Statistical analyses are presented in the text. Note that the incidence of lethal convulsions in these rats is not a simple function of peptide doses applied.

displaying initial phase barrel rotation will undergo lethal convulsions. For the lower (20 μg) SRIF dose, addition of AVP shifted the hazard function to the left (see previous section) and increased the probability that rats undergoing initial phase barrel rotation will display convulsive symptoms resulting in death. However, addition of either AVP or mcAVP to the higher dose of SRIF (40 μg) significantly depressed the incidence of mortality in the animals displaying initial phase barrel rotation. It is critical to note, though, that the hazard function was not affected significantly by addition of AVP to 40 μg of SRIF, implying that the apparent linkage between barrel rotation latency and mortality reflects interactions of the peptides is at independent sites mediating vertiginous and convulsive syndromes.

The implication that peptide interactions in two separate mechanisms underlie the apparent correlation between barrel rotation latency and mortality is also supported by comparisons of the barrel rotation latencies of rats which died versus those which survived in the different groups. Mann-Whitney *U* test comparisons between barrel rotation latencies of surviving or dying rats in each group revealed significantly shorter barrel rotation latencies for rats that died versus those that survived after receiving either 40 μg of SRIF alone or 40 μg of SRIF and 1 μg of mcAVP; there were no significant barrel rotation latency differences as a function of subsequent mortality in any other treatment groups. This suggests that endogenous AVP is an important factor in the intersecting dose domains for postural destabilization and susceptibility to lethal convulsions.

An important effect of AVP on the strength of barrel rotation latency as a predictor of the occurrence of subsequent lethal convulsions is indicated by results of multiple regression analysis. These analyses examined the percent mortality in each group as a linear function of AVP dose, mcAVP dose, SRIF dose, initial phase hazard (θ^{-1}) or initial phase hazard state (see tables 4 and 5), minimum barrel rotation latency, and median barrel rotation latency. The incidence of mortality was predicted as a linear function of three variables: minimum barrel rotation latency, initial phase hazard state and dose of AVP (adjusted $r^2 = 0.82$, $p < 0.005$, table 6).

TABLE 6

Multiple regression analysis of incidence of mortality as a function of AVP dose and the minimum barrel rotation latency and initial phase θ^{-1} state for barrel rotation[a]

Equation 1:

Incidence of mortality = $b_1 [D_{AVP}] + b_2 \mu + b_3 [\theta_s] + c$

$b_1 \pm SE = -0.243 \pm 0.064$
$b_2 \pm SE = -0.006 \pm 0.002$
$b_3 \pm SE = 0.093 \pm 0.041$
constant = 0.308

Multiple correlation: 0.938 $F(3,6) = 14.672$ $p < 0.005$
Adjusted r^2: 0.820

Equation 2:

Incidence of mortality = $b_1 [D_{AVP}] + b_2 \mu + c$

$b_1 \pm SE = -0.193 \pm 0.076$
$b_2 \pm SE = -0.008 \pm 0.002$
$c = 0.634$

Multiple correlation: 0.882 $F(3,6) = 12.212$ $p < 0.01$
Adjusted r^2: 0.713

[a] The initial phase θ^{-1} states for each dose protocol are summarized in Table 4. The dose protocols used in the regression analysis were SRIF, AVP, SRIF + AVP, and SRIF + mcAVP from the experiments on naive rats summarized in Table 4. In these equations, D_{AVP} represents the dose of AVP (in μg) or mcAVP (in $-\mu g$), μ represents the minimum barrel rotation latency for treatment group, and Θ_s represents the discrete value of the state (2–4) of the value of θ^{-1} during the initial phase of the barrel rotaion hazard function. The regression estimates of the coefficients b_1, b_2, b_3 and c are also listed. These models provided the best fit to the data set.

E. Neurotoxicity

All protocols employing i.c.v. SRIF have produced degenerating Purkinje cells in the cerebellar cortex (fig. 10). As reported previously (10, 12), degenerating axons could be traced through the cerebellar white matter to terminal fields in the fastigial and vestibular nuclei. A detailed analysis of the patterns of degeneration will be the subject of a separate communication. There is no evidence that mcAVP or AVP either potentiated or inhibited cerebellar neurotoxicity (9, 206). Since i.c.v. AVP does not appear to be toxic in the cerebellar cortex at doses employed, Purkinje cell degeneration may be a specific effect of SRIF on cerebellar circuits.

III. Pharmacology of Barrel Rotation

A. Lethal Convulsions and Barrel Rotation as Independent Events

Studies of the effects of i.c.v. AVP and SRIF suggest that mechanisms producing barrel rotation and lethal convulsions are independent. One consistent finding is that the incidences of these phenomena are dissociable on the basis of dose. Although both responses display reasonably flat dose-response relations, the threshold dose is lower for barrel rotation than mortality for i.c.v. administration of either peptide alone (1, 10, 119). As a result, lethal convulsions with attendent pulmonary edema were not observed in a number of studies employing i.c.v. doses of somatostatin in a range up to 25 μg (1, 10, 33, 35, 50, 84, 89, 104, 132, 219, 229). Furthermore, barrel rotation is not an obligatory prelude to the onset of the convulsive syndrome; some rats die from convulsive sequelae without previous barrel rotation (10). A dissociation between the incidence of these two syndromes was also apparent for the combined doses of the peptides in our studies (fig. 3). This implies that at least partially independent sites and mechanisms are involved in the generation of the two syndromes.

Despite the evidence for independent mechanisms for neuropeptide-induced barrel rotation and lethal convulsions, there is some evidence that susceptibility to these

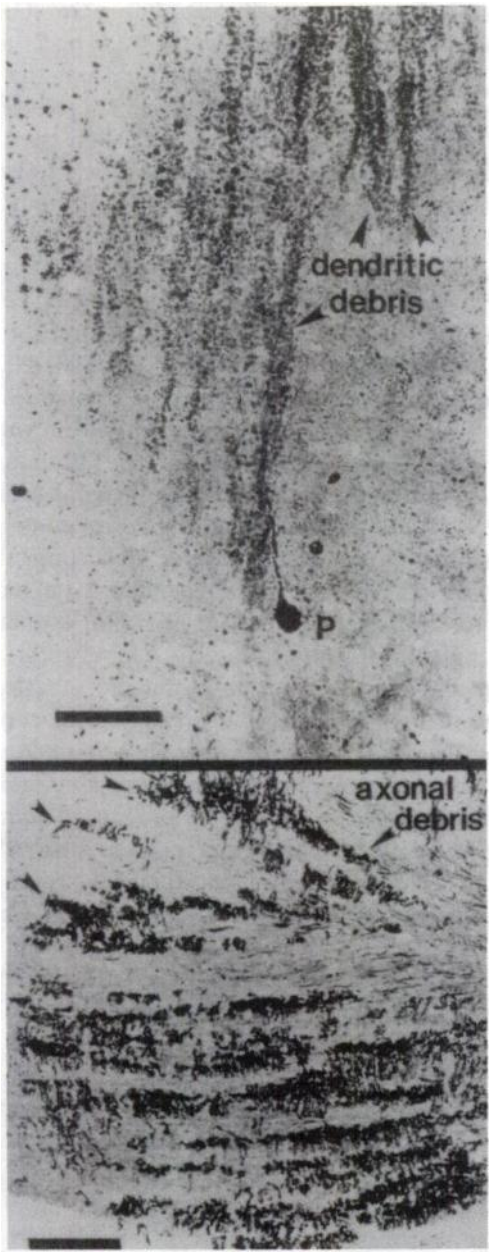

FIG. 10. Photomicrographs displaying degenerating cerebellar Purkinje cell somata (P) and dendrites (upper panel) and axons (lower panel) in a rat given 40 μg of SRIF. The selective silver degeneration stain (cupric-silver method) yields a dense black precipitate in degenerating neural processes. The appearance of degenerating Purkinje cells is characteristic of all SRIF-treated groups of rats. The calibration bars represent 100 μm in the upper panel and 50 μm in the lower panel.

events may be correlated under certain dose conditions. The barrel rotation latency during the early phase of the hazard function has been shown to be a predictor of mortality for animals given 40 μg of SRIF, but not AVP (10). This increased risk of mortality for animals with early hazard phase barrel rotation latencies has been consistent across treatment conditions in our studies. However, the probability of mortality of rats displaying early hazard phase barrel rotation varied markedly and nonlinearly with the combined dose conditions. Multiple regression analysis indicated that the best linear model for predicting mortality is a function of the dose of AVP, the minimum barrel rotation latency for the group (μ) and the initial phase θ^{-1} value. The regression coefficient for the AVP dose is negative, indicating that increasing doses of AVP can reduce the probability of convulsions in animals displaying the same barrel rotation latencies. The net result is a mortality rate at the highest combined doses that are comparable to the effects of 1 μg of AVP alone. These analyses indicate that, for higher doses of SRIF, rats are susceptible to both sequelae. However, a selective effect of AVP at convulsive sites can occlude the effects of SRIF, which gives the appearance of uncoupling the association between barrel rotation latency and convulsions by reducing the mortality to a level produced by the higher dose of AVP alone.

The identity of central sites mediating the lethal convulsive effects of these peptides is unclear. However, it is of interest to note that mortality after central administration of SRIF and/or AVP is often associated with pulmonary edema. Neurogenic pulmonary edema has been well-documented as a consequence of either bilateral lesions of nucleus tractus solitarius (27, 66, 194, 211) or high cervical transection (27). Since nucleus tractus solitarius displays moderate to high levels of specific binding sites for AVP (25, 31, 60, 215) and SRIF (218), it is an obvious candidate for a site involved in generation of the lethal syndrome after neuropeptide administration. This anatomic site is clearly distinct from the sites that are likely to produce vestibular aberrations that will be reviewed in the succeeding sections.

B. Barrel Rotation Incidence and Peptide Dose

1. Dose-response relation for AVP. In any discussion of the dose-response relationship for AVP-induced barrel rotation, it is important to differentiate between results in naive versus sensitized rats. Sensitization to the effects of i.c.v. AVP has been observed reproducibly in studies employing a variety of multiple dosing protocols (26, 37, 105, 232). This consistent finding indicates that the i.c.v. AVP treatment history affects responsiveness to the peptide. Thus, this discussion is restricted to observations on naive rats (i.e., animals receiving their first injection of AVP).

A caveat in the interpretation of dose-response data regards the hydration state or postsurgical status of the animals. Sensitization to effects of i.c.v. AVP has been reported 2 days after a hemorrhage of 15% of total blood volume or an intraperitoneal injection of hypertonic saline (37). This implies that *endogenous* vasopressin may affect sensitivity of the central nervous system to *exogenously applied* peptide. Although cerebrospinal fluid (CSF) levels of AVP show a circadian rhythm in rats (139), we have not observed consistent differences in responses as a function of the time of peptide administration. However, these factors are potential confounded

variables when results from different laboratories are compared.

Barrel rotation after i.c.v. AVP has been described as an all-or-none response with a relatively flat dose-response function (232). However, since most previous studies utilized relatively small numbers of rats at each dose, the shape of the dose-response relationship is not clear. This problem is complicated by the consistent finding that, for sample sizes of at least 10 rats, there are no reports of a dose of AVP that produces barrel rotation in 100% of naive rats tested. For example, Kruse et al. (119) reported barrel rotation in 4 of 12 rats at an 8 ng bolus dose, 4 of 12 rats at a 40 ng dose, 6 of 12 rats at a 200 ng dose, 5 of 10 rats at a 1 μg dose, and 9 of 10 rats at a 5 μg dose. This indicates a fairly flat relationship over a wide dose range, since the proportion of responsive rats did not differ significantly for doses between 8 ng and 1 μg. A similar dose-response relation was shown for intracisternal injections ranging from 1 to 100 ng of AVP, with relatively small numbers of rats in each group (26). Although we previously confirmed a relatively flat dose-response relationship for doses ranging from 250 ng to 1 μg of i.c.v. AVP (232), our subsequent examination (10) of the effects of a 500 ng dose in a larger population of rats ($n = 25$) suggest that a monotonically increasing relationship may exist for bolus i.c.v. injections. In our two conditions with relatively large sample sizes, 500 ng of AVP produced barrel rotation in 6 of 25 rats [compared with 4 of 8 in an independent sample in our initial study, (232)], while 1 μg of AVP produced barrel rotation in 110 of 207 rats (232). Thus, the effects of lower doses of AVP must be examined in larger numbers of animals to characterize the dose-response relationship.

The minimum dose of i.c.v. AVP that reportedly elicits barrel rotation ranges from 8 to 250 ng in studies employing bolus injection protocols (1, 26, 119, 232); a minimum dose of 3.5 ng was reported in continuous infusion experiments (232). A dose of 1 ng in the fourth ventricle was reported to produce barrel rotation in one study (26); BR was also reported after a 25 ng intrathecal dose in another study (215). These doses were lower than the 100 pmol (i.e., 108 ng) dose reported to produce barrel rotation after bilateral infusion into either ventral septal area or anterior hypothalamic area in either naive or sensitized rats (156), but were in the same range as the doses that produced BR after intracerebellar injection (131). However, these threshold doses are about 3 orders of magnitude greater than normal CSF levels of AVP, which have been reported to be approximately 20 pg/ml in both rats (16, 121, 139, 140, 148, 172, 173, 180) and dogs (210). Other analyses of CSF from quadrupeds, reviewed by Sorensen (200), report baseline concentrations ranging from 3.8 to 25 pg/ml. However, these concentrations are increased 4-fold by physiological manipulations as diverse as dehydration (e.g., 146, 207) or retention testing for passive avoidance learning (120). Assuming a CSF volume of 250 μl in a rat (123), the threshold dose for barrel rotation of 3.5 ng is approximately 3 orders of magnitude greater than the resting CSF concentration. The 500 ng dose, then, is approximately 5 orders of magnitude greater than the baseline concentration in bulk CSF. It is interesting to note that studies of the effects of AVP on neurons in hippocampal slice preparations have employed 1 μM doses of the peptide (e.g., 2), which is consistent with the expected CSF concentration of AVP that produces BR. Given the small number and inhomogeneous distribution of neurons secreting AVP (32, 90, 118, 195, 196, 209), it is plausible to achieve such high local concentrations near the secretory sites during neuronal activation within the physiological domain. Furthermore, the inhomogeneous distribution of high affinity binding sites for AVP in the brain (25, 31, 60, 216), particularly in areas containing AVP terminals, argues that locally high concentrations of AVP at central release sites should be extremely efficacious in triggering specific neuronal events. Thus, even though the threshold dose for barrel rotation after i.c.v. peptides is plausible for a local concentration under dehydration or other extreme physiological conditions, issues of drug distribution argue that it overestimates the sensitivity of underlying neuronal mechanisms. Local injection experiments are needed, though, to address this question explicitly. Similar increases in CSF AVP also appear as a consequence of pathological processes. For example, marked (3- to 5-fold) elevations of CSF AVP were demonstrated in cats during anesthesia and brain surgery (170) and in rats after i.c.v. infusion of hypertonic artificial CSF (16). However, the former elevation was transient, resolving within 6 h. By contrast, chronic 1.5- to 2-fold mean increases in baseline AVP concentrations have been reported in CSF from populations of patients with high pressure hydrocephalus, intracranial tumors, benign intracranial hypertension, intracranial hemorrhage, craniocerebral trauma, and mania (198–200). Again, the strict localization of AVP in a small subset of neurons and the localization of high affinity binding sites in specific brain regions suggest the likelihood that locally high concentrations of AVP may be present at sites of high sensitivity to the peptide in these pathological states.

2. Dose-response relation for SRIF. A flat dose-response relation for the incidence of SRIF-induced barrel rotation was first reported by Cohn and Cohn (50). Barrel rotation has been reported after i.c.v. SRIF over a dose range of 10 to 150 μg (1, 10, 33, 35, 50, 84, 89, 104, 132, 219, 229). Burke and Fahn (34) also reported that barrel rotation was produced by a 2.5-μg bolus in the fourth ventricle in 2 of 4 rats tested. Although the barrel rotation incidence has not been determined with appropriate numbers of rats across the dose range in a single study, the data suggest that the dose-response relationship is relatively discrete and flat, changing from a very low

incidence to complete expression (70–80% incidence) over the 10 to 20 μg range. Unfortunately, there is a lack of quantitative data in most reports. For example, Garcia-Sevilla et al. (84) reported no barrel rotation after a 10 μg i.c.v. dose (in an unspecified sample size), but "strong barrel rotation" after a 20-μg dose, while Vijayan and McCann (219) reported the emergence of barrel rotation in an unspecified proportion of rats given 10 μg of SRIF i.c.v. More recently, Burnard et al. (39) reported barrel rotation in 1 of 18 rats given a 2.5 μg dose i.c.v. and a 2 of 10 incidence at a 5 μg dose. Interstitial injections of 10 μg of SRIF in the hippocampus reportedly produced barrel rotation in one of an unspecified sample size of rats (175), while the same dose in the striatum (178) was also reported to produce gradual rolling to one side in an unspecified proportion of rats. Barrel rotation has also been reported after a 2.5 μg injection in the vestibular nuclei (35). Lower doses (e.g., 1 μg of SRIF) have failed to produce barrel rotation at any site (e.g., 35, 89, 132, 174–178, 219). Experiments with larger sample sizes indicate that the incidence of barrel rotation is identical at 20 and 40 μg i.c.v. doses of SRIF, which produce an incidence of 70 to 80% (10). Thus, the dose-response relationship for appears to be extremely steep between 10 and 20 μg doses, reaching a relative plateau above 20 μg. More detailed dose-response studies in the range of 1 to 20 μg should resolve whether the relationship is continuous or discrete.

The i.c.v. dose threshold for eliciting SRIF-induced barrel rotation has been reported to be approximately 10 μg (6 nmol) by several studies (35, 89, 219). Although minimum doses ranging from 10 to 15 nmol have been reported by other investigators (1, 84, 132, 229), Burnard et al. (39) reported a low incidence of barrel rotation after a 2.5 μg dose. As in the case of AVP, these doses would be expected to produce a concentration on the micromolar order in the 250 μl volume of CSF in the rat, which is consistent with the doses applied in hippocampal slice preparations to observe physiological effects of SRIF (225). In contrast, the mean SRIF concentration reported in normal rat CSF is 37.7 fmol/ml (165). Like AVP in CSF, the SRIF concentration can be altered several-fold by experimental manipulations. For example, after pentylenetetrazole treatment, the postictal level of SRIF increases 2- to 3-fold in naive rats and 5-fold in kindled rats (165). This SRIF is apparently of neuronal origin, since the increase in CSF SRIF after pentylenetetrazole treatment is associated with a significant, transient decrease in striatal SRIF levels (166). Thus, it is plausible that highly elevated local levels of SRIF are present at least transiently, implying that elevated CSF SRIF concentrations represent a spillover of elevated secretion from release sites.

Clinical studies indicate that CSF concentrations of SRIF-like immunoreactivity vary as a function of pathological conditions. Control concentrations in studies from different laboratories are fairly consistent; for example, control CSF SRIF concentrations of 54.7 ± 1.9 pg/ml in adults under 55 years old and 56.2 ± 2.2 pg/ml for older adults (19), 53.12 ± 11.09 pg/ml (207), and 12.5 ± 0.7 fmol/ml (approximately 20 pg/ml) (101) have been reported in recent studies. It is possible that a component of the variation in these estimates reflects molecular heterogeneity of somatostatin-like immunoreactivity, because some antibodies recognize both somatostatin and several higher molecular weight peptides in human CSF (54). However, Cramer et al. (54) have also reported that the ratio of SRIF to higher molecular weight molecular forms increases in pathological states, indicating that a component of the immunoreactivity represents release of SRIF into CSF.

The consistent theme developing from these studies is that CSF SRIF concentrations are elevated significantly during acute pathology (19, 116, 161). By contrast, they are reduced significantly with the progression of some degenerative disorders such as Alzheimer's disease (19, 159, 168, 197, 230), Parkinson's disease (55, 69, 101), multiple sclerosis (19, 201), Huntington's disease (53), and in patients with long-standing residual cortical pathology (19). The acute changes may reflect either the release of SRIF from dying neurons, neuronal release of SRIF from undamaged regions, or a combination of these factors. Reduced levels in chronic degenerative diseases, though, may reflect either a net loss of SRIF-containing neurons with progression of the disease (e.g., 59, 182) or a down-regulation of secretion of the peptide. These results have led to the suggestion that an elevated CSF SRIF concentration may be a marker for acute central neural pathology. For example, Beal et al. (18) documented up to 7-fold elevations of SRIF-like immunoreactivity in CSF of patients with acute spinal cord pathology, central nervous system tumors, and acute cortical pathology; one of the latter patients showed a 20-fold increase in SRIF-like immunoreactivity in association with a left frontal lobe abscess and meningitis. More modest, but significant, increases were observed in febrile infants. Stepien et al. (207) noted similar increases in CSF SRIF-like immunoreactivity in patients with central tumors and increased CSF pressure, but noted that immunoreactivity did not differ significantly from that in control subjects in patients with tumors but normal intracranial pressure. This does not contradict the inference that CSF SRIF may reflect acute pathology; rather, it implies that increased intracranial pressure may contribute to the increased CSF concentrations of the peptide in some pathological states. In any case, given the small population of neurons producing SRIF (100, 220) and the restricted distribution of SRIF binding sites in the brain (218), it seems likely that high local concentrations of the peptide are developed during pathological states.

3. Dose-response relation for other peptides and anti-

cholinergic agents. a. LYSINE VASOPRESSIN, OXYTOCIN, VASOTOCIN, AND OXYPRESSIN. Lysine vasopressin, oxytocin, vasotocin, and oxypressin are four peptides related to AVP that also produce barrel rotation when administered i.c.v. to rats (1, 117, 119). The dose ranges, though, are similar to those reported for AVP. Barrel rotation has been reported for lysine vasopressin over an i.c.v. dose range of 1.5 to 200 ng (1, 119), for vasotocin over a dose range of 200 ng to 5 μg (119), for oxytocin over a 500 ng to 5 μg dose range (117, 119), and for oxypressin at a 5 μg dose (119). The dose-response relations for both lysine vasopressin (an unnatural form in rats) and vasotocin, like the relation for AVP, are flat, developing full responsiveness over a narrow dose range (119). However, the relatively limited number of doses and the numbers of rats given the other peptides do not permit assessment of the configuration of the dose-response relation or the threshold dose for triggering barrel rotation. Oxypressin, though, seemed to be the least potent, and neither ring nor tail fragments of AVP were effective in eliciting BR (119). Given the similarities of these dose-response relations to the properties of the naturally occurring form of vasopressin in rats, AVP, it seems likely that these structurally similar peptides act at a common site to trigger barrel rotation.

Unlike lysine vasopressin and oxypressin, oxytocin is a normal endogenous neuropeptide in rats with regulated release into CSF. Estimates of the CSF concentration of oxytocin in rats vary widely, ranging from 4.5 to about 75 pg/ml (16, 102, 139, 140, 173, 180). Levels of the same order of magnitude have been reported in guinea pigs, cats, and monkeys (172, 173, 180). Oxytocin release into CSF is at least partially independent of release into plasma (102, 180), and there is a prominent circadian modulation of CSF oxytocin in experimental animals (139, 172, 173). Release of oxytocin in the central nervous system may also be evoked by experimental manipulations. For example, an almost 6-fold increase in CSF oxytocin was reported after i.c.v. infusion of hypertonic artificial CSF in rats (16) and a marked increase in CSF oxytocin was demonstrated after electrical stimulation of the medial hypothalamus (102). Since oxytocin, like AVP, is expressed selectively by restricted populations of neurons in the brain, the oxytocin release underlying these increased CSF levels is likely to produce local concentrations of the neuropeptide that are orders of magnitude higher than the spillover effects in CSF.

b. OPIOID PEPTIDE AGONISTS AND ANTAGONISTS. The first published report of opiate-induced BR was Iwamoto and Way's observation after interstitial injections of morphine into substantia nigra in rats (98); similar effects have been reported subsequently for large intrathecal or caudal intramedullary doses of morphine but not methadone (79, 158, 223). Given the discrete distributions of endogenous opioid peptides and receptors in the central nervous system (135, 136), the observation that specific somatostatin analogues are potent μ opioid antagonists (109) and the fact that dynorphin (a naturally occurring opioid peptide) is co-localized with AVP in magnocellular neurons in the hypothalamus (224), these observations with a xenobiotic opiate raise the question of whether endogenous opioids produce vestibular dysfunction, either by direct actions or via interactions with central SRIF and AVP mechanisms.

A number of studies indicate that BR can be elicited by perturbation of central opioid systems. Intracerebroventricular administration of the 13-amino acid terminal fragment of dynorphin [dynorphin(1–13)] elicits barrel rotation, with i.c.v. doses ranging from 32 to 164 μg (20–100 nmol) in both rats (91, 163) and mice (108); a 138 μg dose of D-Ala^2-dynorphin (1–11) was also reported to produce barrel rotation (91). The response to 32 μg of dynorphin(1–13) was blocked by premedication with naloxone (163). Barrel rotation also appears after intrathird ventricle but not intrathecal injections of dynorphin(1–13) (103), indicating that it is a central effect mediated by opiate receptors. Furthermore, barrel rotation appears after i.c.v. administration of either 10 μg of a 6-opioid antagonist, ICI 174864 (52), 125 μg of the 6-opioid agonist D-Pen^{2,5}-enkephalin (52) or microgram order doses of a selective κ-opioid antagonist (Dr. Sheldon Sparber, personal communication). Neither β-endorphin (89) nor leucine-enkephalin (1), though, elicit barrel rotation. None of these studies adequately documents the dose-response relationship for opioid neurochemicals. However, they suggest that barrel rotation may result from disruption of a dynamic equilibrium of central opioid mechanisms, either by direct activation or by blockade of at least central δ- and/or κ-opiate receptors. It is interesting to note the parallel between this common effect of opiate agonists and antagonists for eliciting barrel rotation and the fact that both morphine and naloxone increase the susceptibility of cats to motion sickness (56). The implied hypothesis is clear: central opioid receptors are important for maintenance of normal operating characteristics in circuits governing equilibrium and postural stability.

c. CHOLECYSTOKININ, SUBSTANCE P, AND BRADYKININ ANTAGONISTS. Barrel rotation has not been observed after either central administration of cholecystokinin octapeptide (CCK-8) or ceruletide (240) or i.c.v. injections of 30 nmol (28 μg)/10 μl of cholecystokinin heptapeptide (CCK-7) (133). However, both the sulfonated form of CCK-7 (CCK-7S) and the *t*-butyl-oxycarbonyl deriviate of CCK-7S (Boc-CCK-7S) produced barrel rotation at i.c.v. doses of 40 and 30 nmol/10 μl, respectively (133). The description was identical to SRIF- or AVP-induced effects: head tilt was reported to develop within 2 min of CCK-7S or Boc-CCK-7S administration, with the initiation of barrel rotation bouts 1 to 3 min later. Barrel rotation persisted up to 30 min. The failure of an equimolar dose of CCK-7 to elicit barrel rotation suggests

that this is a specific effect. Similarly, barrel rotation was reported after both intraventricular and intracisternal injections of substance P; Magnusson et al. (130) reported that contralateral horizontal circling progressed to contralateral BR in rats given a 25 to 60 μg/5 to 12 μl i.c.v. bolus, while James and Starr (99) observed BR in 24 of 31 rats given an intracisternal bolus of 10 μg/10 μl of this peptide. However, since data were reported over a limited dose range for CCK-7S, Boc-CCK-7S and substance P, the nature of their dose-response relations is unknown.

More detailed dose-response information is available for the effects of bradykinin analogs. Perry (162) reported that barrel rotation appeared at an i.c.v. dose of 20 nmol/5 μl for bradykinin analogs with a D-Phe^7 substitution. The analog B4162 produced barrel rotation at a 5 nmol (approximately 6 μg) dose. The dose-response relation for B4162 was also similar to that for SRIF and AVP, developing from low (approximately 20%) to maximal (approximately 80%) responsiveness over the 10 to 20 nmol dose range. Thus, dose-response relationships for the incidence of i.c.v. neuropeptide-induced barrel rotation have the common feature of a steep development of a maximum responsiveness, which does not increase for large increments in dose.

d. CHLORPROMAZINE METHIODIDE AND ANTICHOLINERGIC AGENTS. Chlorpromazine methiodide is a quaternary chlorpromazine derivative that, unlike the parent molecule, is a potent ligand at muscarinic cholinergic receptors (36). The lowest i.c.v. doses reported to produce barrel rotation in rats were 3.6 μg/10 μl (184) and 5 μg/10 μl (36); barrel rotation has also been reported after a 5 μg/10 μl dose in the fourth ventricle (34). Unfortunately, the small numbers of animals used at each dose do not permit rigorous characterization of the dose-response relationship. For example, Burke et al. (36) used groups of 6 to 10 rats to study barrel rotation incidence after 5, 10, 15 and 20 μg/10 μl i.c.v. injections of chlorpromazine methiodide, but statistical comparisons of their published incidence data reveal no significant differences between the 5, 10, and 15 μg doses. Thus, studies with larger sample sizes are needed to clarify the configuration of these relations.

The observations of barrel rotation after i.c.v. injections of antimuscarinic agents and the potent muscarinic ligand properties of chlorpromazine methiodide suggest that the latter compound acts via an anticholingeric mechanism (34, 36). Barrel rotation has been reported after i.c.v. injections of propantheline bromide (10 and 15 μg/10 μl), atropine sulfate (100 and 250 μg/10 μl), scopolamine HCl (300 and 600 μg/10 μl), and benztropine mesylate (800 μg/10 μl) and 10 μl doses of 3 mM methantheline bromide and homatropine bromide (36). Neither carbachol (6 μg/10 μl, $n = 3$ rats) nor succinylcholine (11 μg/10 μl, $n = 2$ rats) was reported to induce barrel rotation in the same study (36), but these data are inconclusive because they reflect both a small sample size and single dose. However, it does seem clear that blockade of endogeous muscarinic cholinergic neurotransmission can produce symptoms of central vestibular dysfunction in rats.

4. Dose-response relation for combined doses of SRIF and AVP. The incidence data for barrel rotation after combined i.c.v. doses of SRIF and AVP imply that the sites of action for each peptide are at least partially independent. Consistent with the results of Burnard et al. (39) over a lower SRIF dose range (2.5–10 μg), co-administration of 1 μg of mcAVP and SRIF resulted in the same incidence of barrel rotation as the dose of SRIF alone. This indicates that actions of endogenous AVP are not necessary for triggering SRIF barrel rotation. The effects of co-administered AVP and SRIF, though, are complex and nonlinear. For example, co-administration of 0.5 μg of AVP and 40 μg of SRIF resulted in a barrel rotation incidence greater than that for either peptide alone, while a dose of 1 μg of AVP and either 20 or 40 μg of SRIF produced the same barrel rotation incidence as the SRIF dose alone. Since no dose protocol produced a 100% response rate in large samples of rats, one possible implication is that a small percentage of rats is refractory to barrel rotation after SRIF or AVP. Furthermore, the response rate is near maximal for the doses of SRIF employed. Thus, the additive effects of these peptides should be investigated in detail at a lower SRIF dose to assess interactions between circuits sensitive to each peptide.

In virtually every study employing sample sizes greater than 10, the direction of AVP- or SRIF-induced BR was not related to the location of the injection in the left or right lateral ventricle (e.g., 10, 26, 132, 232). Thus, the emergence of a contralateral directional bias for BR after i.c.v. doses of 40 μg of SRIF and 1 μg of either AVP or mcAVP was an unexpected finding in the recent experiments (9) discussed in section II.. The production of the same directional bias by co-administration of either AVP or its antagonist with SRIF provides further evidence that the peptides interact nonlinearly in central circuits that maintain stability in the plane of vertical semicircular canals. Since the injection was made in the lateral ventricle, this interactive effect is probably mediated by a site or sites proximal to the ventricular wall; i.e., a telencephalic locus. Candidates for these sites of interaction include the bed nucleus of the stria terminalis and the basal ganglia (see section V). However, since the occurrence of directional bias was independent of both the incidence of BR and the hazard function, it is not clear whether the directional bias reflects a direct additive effect of peptides at common sites or complex interactions of partially independent circuits.

C. Effects of Systemic Drugs on AVP- and SRIF-Induced Barrel Rotation: Evidence for Interactions with Other Transmitter Systems

1. Cholinergic mechanisms. Antimuscarinic agents have been reported to have differential efficacy against

SRIF- and AVP-induced barrel rotation. Peripheral administration of atropine either completely (50) or transiently (132) blocked SRIF-induced barrel rotation, while the antimuscarinic agent trihexyphenidyl completely inhibited the response (132). By contrast, atropine produced only a 50% depression in the incidence of AVP-induced barrel rotation in naive rats (233), and did not affect lysine-vasopressin-induced barrel rotation in a smaller sample of rats (119). Since i.c.v. antimuscarinic agents also elicit barrel rotation (36), possibly through the vestibular nuclei (34), the reports that SRIF exerts anti-M1 muscarinic effects in brain membrane preparations (146, 147) and the finding that i.c.v. SRIF produces a selective increase in acetylcholine turnover in the diencephalon and brainstem (132) implicate cholinergic mechanisms in the development of SRIF-induced barrel rotation. Although a cholinergic contribution does not appear to be as profound for AVP barrel rotation, a role of cholinergic mechanisms in interactions between coadministered neuropeptides is worthy of investigation.

2. Catecholaminergic mechanisms. Catecholaminergic mechanisms do not appear to be involved appreciably in triggering SRIF-induced barrel rotation. Garcia-Sevilla et al. (84) reported that whole brain dopamine and serotonin levels were decreased and 5-hydroxyindoleacetic acid levels were elevated 60 min after SRIF injections (20 μg followed by 8 μg, i.c.v.), indicating increased activity in both pathways at a dose that produces BR. However, Cohn and Cohn (50) reported that reserpine or haloperidol pretreatment did not affect the incidence of SRIF-induced barrel rotation, which appears to preclude a significant dopaminergic contribution to the onset of motor disturbances. Noradrenergic involvement is also unlikely, since systemic phenoxybenzamine did not affect the incidence. However, the possibility of a serotonergic contribution or a more subtle effect on the hazard function for development of barrel rotation has not been investigated.

The evidence regarding catecholaminergic involvement in AVP-induced barrel rotation is suggestive but not conclusive. Kruse et al. (119) reported that pretreatment with haloperidol (0.5 mg/kg s.c.), propranolol (2.5 mg/kg s.c.), phentolamine (7.5 mg/kg s.c.), or methysergide (5 mg/kg s.c.) did not affect barrel rotation incidence in response to lysine-vasopressin, but that the incidence was depressed by chlorpromazine (5 mg/kg s.c.). By contrast, Yamada and Furukawa (235) reported enhanced barrel rotation responses to a subthreshold dose of a vasopressin analog (10 μg of i.c.v. aminosuberyl^{1,6}-arginine^{8}-vasopressin) after either systemic pretreatment with haloperidol (1 mg/kg), fluphenazine (9 mg/kg) or α-methyl-*p*-tyrosine or i.c.v. pretreatment with 6-hydroxydopamine, suggesting that dopaminergic mechanisms inhibit the generation of BR by this analog. Paradoxically, the incidence of AVP-induced barrel rotation is attenuated by bilateral destruction of substantia nigra with the neurotoxin 6-hydroxydopamine (234). A similar depression in incidence was obtained after bilateral kainic acid lesions of the basal ganglia, and neither nigral nor caudate-putamen lesions were found to affect sensitization to a subsequent dose of AVP (234). Given the lack of characterization of the properties of aminosuberyl^{1,6}-arginine^{8}-vasopressin at AVP receptors and its low potency for eliciting BR (30 μg threshold versus 10 ng for AVP), it is not possible to reconcile this discrepancy in effects. Although these data suggest the possibility of a nigrostriatal dopaminergic component in the trigger for AVP-induced barrel rotation, more rigorous and complete experimental investigations are required to characterize the role of dopaminergic mechanisms in BR.

3. Effects of diazepam and GABAergic agents. Since diazepam is an efficacious medication for patients with acute vertigo (14), it is an obvious drug to test for ability to depress barrel rotation. Diazepam (5 mg/kg i.p.) has been reported to inhibit significantly the incidence of barrel rotation elicited by i.c.v. injections of AVP (233), SRIF (12), and bradykinin antagonists (162). In the case of AVP barrel rotation, the decreased incidence in sensitized rats was accompanied by a significant rightward shift of the hazard function, which reflected a significantly longer latency for barrel rotation onset (233). The profound depression of responsiveness to SRIF by diazepam precluded hazard analysis because few rats displayed BR (12). Since muscimol (0.5 mg i.c.v.) also attenuated barrel rotation incidence (162), it is likely that sites involved in generation of barrel rotation are sensitive to effects of benzodiazepines and/or γ-aminobutyric acid (GABA). A poential role of GABAergic circuits is also consistent with reports that barrel rotation appears after i.c.v. picrotoxin (0.5 μg/5 μl) (231), after single interstitial doses of picrotoxin in the vestibular nuclear complex (34) or the caudal pole of the parafascicular nucleus near the interstitial nucleus of Cajal (236), or after multiple injections of bicuculline methiodide in substantia nigra (110). Finally, an interaction between GABAergic and AVP mechanisms in sensitization to AVP BR is indicated by the finding that prior exposure to i.c.v. picrotoxin (1 μg/5 μl on day 1) sensitized rats to effects of a subsequent dose of AVP (0.5 μg/5 μl on day 3) (231). Thus, picrotoxin pretreatment mimicked the effects of prior AVP exposure.

4. Antiseizure medications. Reports of the efficacy of antiseizure medications in preventing neuropeptide-induced BR are limited. Phenytoin (100–200 mg/kg i.p.) attenuated AVP-induced BR in either naive or sensitized rats (1, 233); however, it did not affect BR incidence after administration of a bradykinin antagonist (162). By contrast, a 50 mg/kg dose of phenobarbital reduced the incidence of both AVP and bradykinin antagonist-induced BR (162, 233). Valproic acid (125 or 250 mg/kg i.p.) also reduces the incidence of AVP-induced BR in

sensitized rats (233). Unfortunately, the limited data base makes it difficult to infer mechanisms or sites of action from these studies. However, the differential efficacy of phenytoin suggests that BR responses to AVP and bradykinin antagonists are elicited by independent mechanisms.

IV. Barrel Rotation as an Index of Central Vestibular Dysfunction: Historical Review of Sites Producing Disequilibrium

Previous studies suggest that neuropeptide- or neurotransmitter-induced barrel rotation is a specific, integrated response involving motor circuits distributed across multiple levels of the neuraxis. As reviewed above, barrel rotation has been reported after injections of several distinct neuropeptides or their structural analogs into cerebrospinal fluid. Barrel rotation has been reported after microinjections of antimuscarinic agents, chlorpromazine methiodide, or SRIF into the vestibular nuclei (34, 35), kainic acid into the fastigial nucleus (96), and picrotoxin into the the caudal pole of the thalamic parafascicular complex near the interstitial nucleus of Cajal (236), suggesting that multiple sites have the capability to trigger the response. This participation of multiple sites in the triggering process is also indicated by the effects of chemical lesions of substantia nigra or the basal ganglia and mechanical lesions of the cerebellar vermis and hemispheres, which depress the incidence of AVP-induced barrel rotation in naive rats (231). The incidence was also depressed when rats were given AVP under ambient illumination after 3-acetylpyridine (3-AP) ablation of the inferior olive; however, the response incidence was normal when 3-AP-treated rats were given i.c.v. AVP in darkness (233). Furthermore, although vestibular or visual inputs are not necessary for the expression of barrel rotation, the time course for initiation of AVP-induced barrel rotation is affected by both vestibular and visual inputs (233). These data suggest that the experimental identification of mechanisms underlying neuropeptide- and anticholinergic-induced barrel rotation require an understanding of the role of the vestibular nuclei, cerebellum, substantia nigra, and basal ganglia in postural stability. This section reviews literature regarding the ability of each structure, both in isolation and in combination with other structures, to produce barrel rotation after experimental manipulation. The contributions of peptidergic and cholinergic neurotransmission can then be assessed within the context of these circuits to understand the implications for normal and pathological function.

A. Barrel Rotation as a Symptom of Central and Peripheral Vestibular Dysfunction

Barrel rotation and circling behaviors ("circus movement") were well-documented as results of central lesions of the vestibular nerve, vestibular nuclei, and central vestibular pathways by the early twentieth century (e.g., 65, 78, 122, 127, 128, 129, 145, 149–151, 167, 188–190, 221). Barrel rotation was historically one of the first motor symptoms described after lesions of the central nervous system in experimental animals. It was first reported by Pourfour du Petit in 1710 (167); this observation cited later by both Longet (127) and Vulpian (221). In studies published between 1824 and 1843, BR was recognized as an acute manifestation of vestibular nerve and middle cerebellar peduncular section (e.g., 127, 129). The descriptions presented by Magendie in 1824 (129) and Vulpian in 1866 (221) are particularly lucid, leaving little doubt regarding the identity of their rotation syndrome with BR. The phenomenon was so well-established that Vulpian apparently used barrel rotation after a deep lesion of the middle cerebellar peduncle of rabbits and rats as a demonstration experiment in his lectures. Vulpian (221) also noted the significance of the tonic eye deviation accompanying BR, arguing that it indicated a state of vertigo that was linked to the rotational movement. Furthermore, he suggested that the most plausible hypothesis explaining BR was that the unilateral lesion removed one component of a circuit in dynamic balance, producing central disequilibrium. Other nineteenth century and early twentieth century investigators reported this "forced movement" in quadrupeds and primates (65, 78, 122, 127, 145, 149–151, 188, 189) and BR after cerebellar peduncular section were attributed to damage to the restiform (and probably the juxtarestiform) body (188, 189). The results of unilateral labyrinthectomy in mammals have been reviewed in detail by Schaeffer and Meyer (190); a subsequent study confirmed acute barrel rotation in rats after unilateral labyrinthectomy (125). However, the literature demonstrating barrel rotation and circling behaviors after documented central lesions has not been reviewed systematically. As a result, this section will first review the basic postural symptoms of disequilibrium after central lesions to establish a context for interpreting neuropeptide-induced postural destabilization. The evidence that barrel rotation after asymmetric lesions or pharmacological interventions in the vestibular nuclei, cerebellar cortex, nucleus interstitialis (Cajal), or nucleus Darkschewitch, substantia nigra and basal ganglia may influence vestibular stabilization will then be reviewed within the context of these symptoms. Finally, we will discuss evidence that these sites may influence the incidence and time course of SRIF- and AVP-induced barrel rotation.

Studies of effects of unilateral lesions on peripheral and central vestibular circuits have emphasized a distinction between acute and chronic symptoms of damage. One hallmark of these circuits is central compensation: the extreme symptoms expressed during the acute phase typically resolve over a variable period of time, depending upon lesion site and species (e.g., 76, 134, 149–151). Since

neuropeptide-induced barrel rotation is an acute symptom, produced in the first 20 min after peptide injection, the acute signs of unilateral manipulations of vestibular circuits are of greatest interest. However, uncompensated effects will also be reviewed.

B. Definition of Symptoms of Unilateral Vestibular Damage across Species: Rolling and Circling Syndromes

A systematic description of the effects of central vestibular damage was published by Muskens between 1904 and 1922 (149–151), in a series of studies which correlated histologically verified anatomic damage with forced movements (BR, circling, and nystagmus) indicative of posture asymmetry and disequilibium. These investigations of the effects of lesions of the vestibular root, vestibular nuclei, medial longitudinal fasciculus (his nomenclature: "posterior longitudinal bundle"), and the area of nucleus interstitialis and nucleus Darkschewitch in rabbits and cats were particularly useful because they used the Marchi technique to correlate symptoms with damage to specific vestibular output pathways, either as fibers-of-passage or at their origin (149–151). However, it is the insightful categorization of forced movements that is particularly germane to establishing a clinical context for barrel rotation and neuropeptide-induced disequilibrium.

Muskens described two basic classes of sequelae of central and peripheral vestibular damage:

1. Rolling movements around the long axis of the animal (barrel rotation), accompanied by head and eye rotation. These persistent rolling movements were "characterized by their vehement nature"; this is typified by the term "rotational fits" that was used by Russell in 1896 (189). Muskens regarded falling toward or lying on one side as a milder manifestation of rolling movements, especially when accompanied by head and eye deviation or by nystagmus.
2. Horizontal circling, or circus movements, accompanied by ocular nystagmus and conjugate, tonic deviation of the eyes and head. A tonic leftward or rightward deviation of the head and eyes was viewed as a milder manifestation of this symptom. These movements were characterized as "quieter and more deliberate" than rolling movements.

These involuntary movements were regarded as manifestations of selective, unilateral disruption of central pathways originating in the horizontal and anterior semicircular canals. In particular, Muskens' description of rolling movements is virtually identical to neuropeptide-induced disequilibrium in our studies, suggesting mediation by similar neural substrates.

It is particularly important to note that these forced movement syndromes are defined as continua, proceeding from postural and ocular deviations to rotation or circus movements. This point is evident in the two gradients in severity of expression of these symptoms described by Muskens (150, 151), a rostrocaudal gradient within the neuraxis of a single species and a species gradient between quadruped mammals, primates, and human patients. Within quadrupeds, the symptoms decline in severity as lesions ascend the neuraxis. In primates, the circling and rotation disorders are very rarely expressed; the animals show only postural destabilization, nystagmus, and tonic head or eye deviation during the acute phases after vestibular nerve or nuclear lesions (see below for review). These observations, though, support the view that barrel rotation is an acute, extreme manifestation of vestibular dysfunction in rodents, functionally equivalent to the vertigo, postural, and ocular symptoms displayed acutely in patients with vestibular dysfunction.

C. Symptoms of Lesions of the Vestibular Nerve and Nuclei

A major contribution of Muskens' work was the demonstration that symptoms associated with BR and circling behaviors in either direction can be attributed to lesions at particular central sites in ascending vestibular pathways. In all of these cases, BR or circus movements may be interpreted as a consequence of unilateral removal of a tonic vestibular input, with results predictable from basic vestibular physiology. This asymmetry in tonic drive will produce a vertiginous sensation of spinning in the plane of the affected canal inputs and will also result in asymmetric activation of vestibulo-spinal and vestibulo-ocular reflexes to oppose this perceived rotation. This unopposed activation then will produce circling or barrel rotation contralateral to the direction of perceived rotation. Lesions of the vestibular root, as reported by many investigators (e.g., 125, 127, 149, 190), produced BR toward the injured side, often accompanied by skew deviation and rotation of the eyes about an anteroposterior axis. Rolling movements and eye and head rotation in the direction of the lesion were also observed after lesions of the lateral vestibular nucleus proper and the lateral horn of the medial longitudinal fasciculus (ascending tract of Deiters). By contrast, rolling movements (BR) in a direction contralateral to the lesion were observed after damage to the inferior vestibular nucleus. Damage to the medial vestibular nucleus, though, produced ipsilateral circus movements, while contralateral eye deviation and circus movements were produced by lesions of the superior vestibular nucleus. These early studies, then, demonstrate that unilateral disruption of different components of the vestibular nuclei (or fibers of passage in these regions) can selectively produce ipsilateral or contralateral barrel rotation in rabbits and cats.

There are prominent species differences in the severity and duration of postural and ocular responses to unilateral vestibular nerve and vestibular nuclear lesions in quadrupeds and primates. Quadruped mammals (e.g., cat, rabbit, guinea pig, and rat) typically display long-axis rotation or circling behavior in addition to ataxia, tonic

head torsion, and tonic eye deviation toward the injured side, nystagmus beating toward the normal side and contralateral extensor activation during the acute phase after unilateral lesion (e.g., 125, 150, 151, 190). Primates and humans, by contrast, are usually reported to display only head torsion, spontaneous nystagmus, and a tendency to fall toward or lay on the lesioned side during the acute period (67, 68, 75–77, 157, 190, 193, 217). This suggests that barrel rotation or circus movements are extreme expressions of vestibular dysfunction in quadrupeds, with primates and man displaying less severe endpoints to these syndromes. This concept, advanced by Muskens (149–151), is supported by Dow's (68) striking description of the behavior of rhesus monkeys after unilateral labyrinthectomy:

> As soon as the animal was able to sit up or stand, in addition to the abnormal head posture . . . the extremities on the operated side were flexed and adducted, and on the normal side extended and abducted. First attempts at walking and running were characterized by falling, deviation and circling to the operated side. *Spiralling about the longitudinal axis of the body in jumping, swimming and climbing a vertical bar was consistently present. This was always in the same direction as the head rotation, that is, the back rotated toward the side of the labyrinthectomy.* All these symptoms were accentuated and detectable longer postoperatively if the examination was made with the animal blindfolded. . . . *Repeated rolling movements, as seen in lower animals, did not occur.* (pp. 393–395, italics added for emphasis)

,This observation of long axis rotation (spiralling motion) during climbing, swimming, or jumping of hemilabyrithectomized rhesus monkeys confirmed previous observations of Northington and Barrera (157) and was summarized in tabular form as a hallmark of unilateral damage to the vestibular nerve or vestibular nuclei in 1938 by Ferraro and Barrera (76). These observations, then, suggest that long axis rotation after unilateral vestibular insult in monkeys may be masked by proprioceptive and visual mechanisms when limbs are in contact with a horizontal surface under ambient illumination. The symptoms are exacerbated when either of these sensory inputs is absent or attenuated.

To our knowledge, there are only two published reports of spontaneous, "forced" rolling in rhesus monkeys after unilateral vestibular nuclear lesions. Ferraro and Barrera (75) reported that electrolytic lesions damaging the lateral and inferior vestibular nuclei (and sometimes, the dorsomedial tip of the restiform body) in monkeys resulted in "symptoms of the forced type, (with) marked rolling movements manifested toward the side of the lesion." These symptoms appeared in the absence of damage to the eighth nerve trunk. However, subsequent anatomic studies indicate that, in addition to direct neuronal damage, these lesions probably interrupted both primary vestibular afferents to the rostral third of the medial vestibular nucleus (41) and the ipsilateral and contralateral descending projections of the fastigial nucleus (17). A contribution of fibers-of-passage to the symptoms after these lateral lesions is plausible, given the 1940 report by Ferraro, Pacella, and Barrera (77) that discrete lesions in the medial vestibular nucleus of rhesus monkeys produced "*[i]n severer cases, rolling movements on the floor around the animal's longitidinal axis and toward the side of the lesion . . . for a period of several days postoperatively.*" They concluded: "*These rolling movements might be an exaggeration of the tendency to fall over of rotate toward the side of the lesion and probably hold the same significance as do the spiraling movements in space.*" One additional report is equivocal: Cranmer (57) reported that "*[o]n recovery from anesthesia (after a right superior vestibular nucleus lesion) the monkey crawled in a circular movement to the left, occasionally falling and rolling over to the right.*" The observations after vestibular nuclear lesions in monkeys, then, support Muskens'conclusion that forced rotation (barrel rotation) and circling are extreme manifestations of central vestibular dysfunction in mammals.

D. Effects of Cerebellar Lesions

1. Cerebellar peduncular lesions. Barrel rotation was first described in the literature as a cerebellar phenomenon in 1710 (167). In 1824, Magendie reported that barrel rotation appeared acutely in rabbits (and other unspecified mammals) after lesions of the cerebellar peduncles or sagittal cuts through the cerebellum bisecting the distance between the midline and the right or left margin of the cerebellar hemisphere (129). He also abolished this behavior by subsequent ablation of the contralateral cerebellum or cerebellar peduncle, and concluded that postural equilibrium requires balanced output of both sides of the cerebellum. Although these experiments demonstrated that barrel rotation can be triggered acutely by a unilateral cerebellar lesion, the damage clearly involved interruption 1) of direct cerebellar inhibition to the vestibular nuclei, 2) of cerebellar nuclear outputs to the vestibular nuclei, reticular formation, red nucleus, and thalamus, and 3) afferents to the cerebellar cortex.

The "forced movements" observed after unilateral cerebellar peduncular lesions in quadrupeds were specifically attributed to damage to the inferior cerebellar peduncle by the first decade of the twentieth century (149, 150, 188, 189). Ferrier and Turner (78) presented the first detailed reports of long axis rotation (barrel rotation) after unilateral inferior cerebellar peduncle lesions in monkeys. However, the effects of lesions in these studies prior to 1910 did not distinguish between differential involvement of the restiform and juxtarestiform bodies. Ferraro and Barrera (75) placed small electrolytic lesions in the juxtarestiform body, dorsal to the vestibular nuclei, in rhesus monkeys and observed occasional falling toward the side of the lesion, a slight torsion of the chin toward the lesioned side, spontaneous nystagmus, and spiraling contralateral to the lesion during

jumping or climbing. Rolling movements, though, were not observed. These symptoms were absent in monkeys with lesions of either the restiform body or the dorsal spinocerebellar tract (74), but were observed with combined lesions of the restiform body and vestibular nuclei (76). Since the forced movements after cerebellar peduncular section are in the direction opposite those after vestibular nerve or nucleus lesions, they probably reflect interruption of direct Purkinje cell inhibition of vestibular nuclear neurons. These direct projections originate in the vermis of the anterior and posterior lobes and in the flocculonodular lobe (97).

2. Cerebellar cortical stimulation and lesions. Postural destabilization is less profound after lesions or stimulation of cerebellar cortex than after peduncular or vestibular lesions. Characteristic postural effects have been observed after lesions or stimulation of vermal regions of the anterior and posterior lobes and of the nodulus (see below), which are probably related to differential outputs of these regions to the fastigial nucleus and vestibular nuclei.

Unilateral manipulations of the cerebellar anterior lobe produced postural asymmetry but not barrel rotation or forced circling in mammals. For example, Sprague and Chambers (204, 205) reported that electrical stimulation of sites in the cerebellar anterior lobe in intact cats typically produced ipsilateral inhibition and contralateral facilitation of flexor tonus in limbs and axial musculature. Unilateral anterior vermal stimulation has also been reported to produce head rotation in the direction of the electrode, such that the chin pointed contralaterally (48, 138); these sites were located in dorsal folia of the nodulus. The opposite effects were reported after unilateral anterior lobe ablations (204, 205); cats displayed extension and abduction of the ipsilateral limbs, partial flexion and adduction of the contralateral limbs, difficulty righting until the second postoperative day, and a tendency to fall to the side opposite the lesion. It is important to note that these postural effects were seen in only limb and axial musculature, reflecting the direct inhibitory projections of the anterior lobe to vestibulospinal tract neurons or fastigial nucleus neurons (97). This is expected, since the connections of the anterior lobe are consistent with the absence of nystagmus, a component of both neuropeptide-induced disequilibrium and forced movement syndromes after vestibular nerve or nucleus lesions. Thus, a unilateral effect at the level of the anterior lobe can only account for truncal components of neuropeptide-induced disequilibrium.

By contrast to anterior lobe manipulations, unilateral stimulation or ablation of the posterior vermis or nodulus usually produced positional and/or transient spontaneous nystagmus; head or postural deviations were also reported in some studies (57, 67, 72, 73, 83, 87, 152–155, 181, 202, 203). These central vestibular effects can be attributed to direct connections of these regions with vestibular and fastigial nuclei. For example, Ron and Robinson (181) reported that stimulation of the ventral uvula and dorsal nodulus evoked nystagmus with downward slow phases in rhesus monkeys, while dorsal uvula and ventral nodulus sites evoked nystagmus with upward slow phases. They did not observe any systematic relationship for horizontal components of nystagmus. Aschan et al. (6), though, reported that positional nystagmus (with contralateral slow phases) was elicited by electrical stimulation of the lateral, but not medial, aspect of the nodulus of rabbits. Since positional nystagmus has been reported after lesions of these regions is blocked by bilateral labyrinthectomy (72, 203), the symptom can be attributed to a central asymmetry in vestibular circuits. Finally, asymmetric lesions of the nodulus-uvula produced symptoms opposite vestibular lesions in rhesus monkeys: transient nystagmus appeared with fast phases in the direction of the lesion, the occiput was rotated contralaterally, the animals fell and deviated to the contralateral side in running and jumping, and the animals spiraled toward the contralateral side when climbing and jumping (67). These findings suggest that a unilateral effect at the level of the nodulus and/or uvula may contribute to the evolution of forced movements culminating in barrel rotation. However, it is not clear whether asymmetric activation or inhibition of this cortical region is sufficient to produce barrel rotation in quadrupeds.

3. Cerebellar nuclear effects. The interpretation of lesion or stimulation studies of the fastigial nucleus is complicated by a serious fibers-of-passage problem. In addition to being embedded in cerebellar white matter, the fibers entering the hook bundle cross through contralateral fastigial nucleus en route to the brain stem and reticular formation (e.g., 17). This latter anatomic feature argues that even unilateral electrolytic lesions or electrical stimulation may have bilateral effects. However, recent studies employing the excitatory neurotoxin, kainic acid, have selectively ablated fastigial nucleus neurons without appreciable damage to fibers-of-passage. Unilateral lesions of the fastigial nucleus, with variable cerebellar damage and no vestibular nuclear damage, were reported to produce a disequilibrium syndrome leading acutely to barrel rotation in rats (96). These symptoms were not produced by cerebellar cortical lesions alone or lesions of other nuclei. Imperato et al. (96) also reported that unilateral fastigial injections of the GABA agonist, muscimol, and antagonist, bicuculline methiodide, produced the same postural syndrome without barrel rotation. Both kainate injections and muscimol produced contralateral limb extension and abduction and head tilt toward the injected side, suggesting a disfacilitation of the vestibular nuclei. The opposite effects were obtained with bicuculline. These data, then, are consistent with a possible role of asymmetric activation or inhibition of fastigial neurons in the generation of

neuropeptide-induced postural destabilization. These effects do not appear after manipulations of cerebellar interposed or dentate nuclei (e.g., 179).

E. Midbrain Sites and Forced Movements: Interstitial Nucleus of Cajal, Rostral Interstitial Nucleus of the Medial Longitudinal Fasciculus and Nucleus of Darkschewitch

An additional group of sites that may contribute to neuropeptide-induced barrel rotation is located near the rostral extent of the medial longitudinal fasciculus. This region encompasses several distinct nuclei, the interstitial nucleus of Cajal, the rostral interstitial nucleus of the medial longitudinal fasciculus, and the nucleus of Darkschewitch, which are involved in the control of vertical gaze (40, 45) and dynamic aspects of vertical vestibulo-ocular reflexes (4, 160). This region directly influences vestibular nuclear neurons receiving vertical canal inputs (80) and affects head posture (81). Muskens (151) observed barrel rotation ("rolling movements") and tonic eye deviation acutely in rabbits and cats after midbrain lesions involving the posterior commissure, the interstitial nucleus of Cajal, and nucleus of Darkschewitch. The rotation was toward the normal side and diminished "after a few days." Hassler and Hess (88), though, reported that unilateral stimulation of the rostral pole of the interstitial nucleus produced long axis rotation (BR) in alert cats. Subsequent studies employing electrolytic lesions observed head tilt toward the normal side after recovery from surgery in cats and monkeys (45, 81, 88), which also appears reversibly after unilateral procaine microinjections into the interstitial nucleus in cats (81). Interactions between unilateral labyrinthectomy and interstitial nucleus lesions suggest that the interstitial nucleus interacts with afferent vestibular inputs to control head posture (81), possibly at the level of vertical vestibulo-ocular reflex relay neurons in the vestibular nuclei (80). Although these recent studies suggest a contributory role of these midbrain regions to the forced movement syndromes reported by Muskens (149–151), they did not report barrel rotation during the acute recovery period. However, it seems likely that this region is responsible for the barrel rotation reported after injections of picrotoxin into the "parafascicular nucleus" in rats (236), since the illustrated injection site is at the level of the posterior commissure, in close proximity to the interstitial nucleus of Cajal and nucleus of Darkschewitch (see Figure 3 of reference 236). Thus, this midbrain region is another likely site for eliciting barrel rotation or circus movements.

F. Basal Ganglia, Substantia Nigra, and Equilibrium

The concept that the basal ganglia serve as a supravestibular center was first introduced by Muskens (151). This hypothesis was based upon the emergence of circus and rolling movements after lesions which included the globus pallidus, the lack of movements after control lesions of the midbrain, diencephalon and telencephalon, and the observation of both striopetal projections (with the Marchi method) and retrograde degeneration in the globus pallidus after midbrain lesions producing rotation movements. While these anatomic findings may reflect mechanical damage to fiber tracts such as the pallidopedunculopontine pathway (111), subsequent studies provide several lines of evidence that the basal ganglia and substantia nigra may modulate the performance of central vestibular circuits.

The first experimental evidence that the basal ganglia may influence responsiveness of the vestibular system emerged from a series of experimental studies based upon Muskens' hypothesis. During the mid-1930s, a series of studies by Delmas-Marsalet (62, 63) and Bergouignan and Verger (24) reported that the circling behaviors elicited by unilateral ablation of the caudate or lentiform nucleus in dogs were accentuated after ipsilateral rotation and abolished after contralateral rotation of the animal in a modified Barány chair. Although they did not measure the slow phase velocity of post-rotatory nystagmus, it was reported to be subjectively normal. They also analyzed the responses of the dogs to transtympanic instillation of 1.5 ml of a 5% cocaine solution, which produces symptoms of an ipsilateral hemilabyrinthectomy (61). They reported that the ipsilateral circling behaviors produced by unilateral caudate lesions were potentiated by applying cocaine to either the ipsilateral or contralateral labyrinth and that nystagmus due to vestibular anesthesia was in the appropriate direction for normal dogs. After lentiform nucleus lesions, though, they obtained the same results for ipsilateral cocaine application, but noted that contralateral cocaine injections abolished motor symptoms of unilateral lentiform nucleus ablation. Nystagmus, though, was elicited in the appropriate direction. Several years later, Mettler and Mettler (144) reported reduced reflex responses to rotation after bilateral caudate ablation in cats and that bilateral caudate lesions after bilateral labyrinthectomy resulted in only symptoms of caudate damage. This led to a conclusion that the effects of caudate ablation are not dependent upon labyrinthine influences; rather, the basal ganglia lesions were said to produce "labyrinthine disregard" (142–144). The concept that vestibular circuits are involved in the generation of circling disorders elicited by manipulations of caudate nucleus cholinesterase activity was also suggested by Essig et al. (71). However, these behavioral observations could be interpreted to indicate that the circling behavior elicited by unilateral basal ganglia (or substantia nigra) ablation represents an asymmetric release of vestibular circuits from descending control. Alternatively, the data are consistent with a summation of independent effects of vestibular and basal ganglia circuits at a common site. Thus, these studies do not provide direct evidence of

either sites or the nature of basal ganglia interactions with central vestibular circuitry.

A second line of evidence consistent with Muskens' hypothesis has emerged from more recent studies of patients with Parkinson's disease, which is one chronic condition when the CSF concentration of SRIF is reduced significantly with progress of the disorder (69, 101). Although Mettler (142) stated in 1940 that "it is easy enough to forecast the side of greatest injury (in basal ganglia) by the post-rotatory action of the patient. . . .," quantitative physiological studies of vestibular responses in patients with basal ganglia disease have only been reported during the previous decade. Reichert et al. (171) reported that a significantly greater proportion of patients with Parkinson's disease had decreased to absent responses to bithermal caloric vestibular stimulation (versus age-matched controls), that the degree of vestibular impairment was associated significantly with postural instability, and that the severity of both postural instability and abnormal results of caloric testing seemed to be related to the progress of the disease. White et al. (226), in a more rigorous physiological study of horizontal vestibulo-ocular reflex performance, also reported increased impairment of reflexes with progress of the disease. All patients with Parkinson's disease showed deficits in their ability to suppress the vestibulo-ocular reflex by fixating a visible target, corroborating a previous report of a small deficit in 3 of 8 patients (214). However, only patients with advanced disease showed a depressed vestibulo-ocular reflex gain in darkness; these patients also had deficits in their abilities to enhance the vestibulo-ocular reflex by fixating either a visible stationary target or an imagined stationary target. In a companion study, White et al. (227) found that saccadic and smooth pursuit eye movement deficits also progress with the course of Parkinson's disease. Of particular interest is their observation that the closed loop smooth pursuit gain was reduced uniformly at all target frequencies, which they noted is also found in patients with cerebellar degeneration (239) and after cerebellar flocculus ablation in monkeys (238). Taken together, these data are consistent with a hypothesis that substantia nigra and/or basal ganglia can influence vestibular or cerebello-vestibular integration in relation to compensatory motor activity.

There is a paucity of recent experimental investigations of interactions between the substantia nigra-basal ganglia axis and vestibular reflex function. However, there is direct evidence that unilateral manipulations of substantia nigra or basal ganglia can produce barrel rotation in rats. Kelly et al. (110) reported that a two-dose protocol of intranigral microinjections of the potent GABA antagonist, bicuculline methiodide (100 ng/1 μl) produced continuous barrel rotation in four rats tested with a second dose given after an interval of 6 days. In addition, Iwamoto and Way (98) reported a progression of symptoms from horizontal rotation (circling) to barrel rotation with increasing unilateral intranigral doses of morphine (2 to 64 nmol/1 μl), while James and Starr (99) observed barrel rotation in rats after intranigral injections of bacitracin, picrotoxin or kainic acid. Similarly, Taylor et al. (212) reported dose-dependent circling and BR in rats after unilateral injections of kainic acid in the rostral caudate-putamen; BR was also reported after relatively large intra-amygdaloid injections of this neurotoxin (22). These reports, then, indicate that neural events in nigral and basal ganglia circuits have the potential to affect postural stability in the plane of horizontal or vertical semicircular canals.

Other studies support a nigral or basal ganglia effect on vestibular behavior in both primates and quadruped mammals, but the neural substrates and nature of these interactions have not been characterized adequately. Although monkeys with unilateral 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) lesions of substantia nigra reportedly show either ipsilateral circling spontaneously or begin to circle contralaterally after L-DOPA-carbidopa treatment (15), their postural and ocular responses to vestibular and optokinetic stimulation have not been examined. Similarly, monkeys with bilateral MPTP lesions have been reported to demonstrate a loss of vestibular righting reflexes, a failure of upgaze, and abnormal smooth pursuit eye movements (191), but their vestibular and optokinetic responses have not been characterized. However, Boussaoud and Joseph (28) have shown that unilateral microinjections of muscimol in pars reticulata of substantia nigra of cats produced contralateral head turning and a decreased gain of the vestibulo-ocular reflex for ipsilateral but not contralateral rotation. Optokinetic responses, though, were symmetric. By contrast, bilateral muscimol injections resulted in bilateral neck hypertonia without affecting the vestibulo-ocular reflex gain. Although these data are consistent with the concept that an asymmetry in nigral or basal ganglia output may result in asymmetric vestibular function, they also are not sufficient to explain the bidirectional vestibulo-ocular reflex gain deficit reported in Parkinson's disease. However, it is clear that the substrates for basal ganglia-vestibular interactions can be identified with current experimental methods.

G. Summary: Barrel Rotation and Disequilibrium Syndromes

An experimental literature, extending from 1710 to the present, indicates that barrel rotation is an extreme, severe manifestation of asymmetric activity in structures in the central nervous system that process vestibular information and mediate postural stability. As such, it represents the endpoint of a syndrome of dysfunction in circuits processing information from at least the vertical semicircular canals in quadrupeds. Less severe components of this syndrome include unstable gait, bouts of tonic unilateral hindlimb and forelimb extension and

contralateral flexion with falling toward the latter side, head torsion toward the flexed side, and ocular nystagmus. Circus movements (head-to-tail circling) after central vestibular lesions in quadrupeds, on the other hand, may reflect asymmetric activation of circuits processing horizontal canal inputs.

Lesion studies indicate that barrel rotation is a specific symptom of unilateral damage to a connected network of structures regulating postural stability. These studies implicate the vestibular nuclei, midline cerebellar cortex or fastigial nucleus, midbrain structures in the vicinity of the interstitial nucleus of Cajal, and, possibly, the basal ganglia or substantia nigra, as sites where functional asymmetry may result in disequilibrium and barrel rotation. This raises the hypothesis, then, that discrete hazard states for initiation of SRIF- or AVP-induced barrel rotation represent different degrees of asymmetric activation of these circuits. The direct implication is intriguing: these endogenous neuropeptides may modulate states of sensitivity and/or balance of central vestibular circuits.

V. Possible Sites and Mechanisms for Barrel Rotation

A. Barrel Rotation and States of Destabilization: A Model for Central Mechanisms Producing Hazard Functions

1. General considerations: Properties of hazard functions for barrel rotation onset. Hazard plotting analyses of BR latency data have revealed discrete temporal properties of the susceptability to BR onset after i.c.v. injections of SRIF, AVP, or combined doses of peptides in rats under a variety of experimental conditions. The hazard functions, estimated by least-squares analyses of hazard plots, are shown schematically in fig. 11. After a threshold latency, μ, naive rats given i.c.v. SRIF, AVP, or combined doses under normal ambient illumination enter an initial epoch with a relatively high instantaneous risk of BR onset ($\theta^{-1}{}_1$ in %/s). At a second latency, μ_1, the instantaneous probability of BR initiation drops abruptly to a lower value ($\theta^{-1}{}_2$), which terminates at time μ_t. Our empirical studies (9, 10, 206, 231–233) suggest the existence of constraints on "permissible" values of both the θ^{-1} parameter to four states and the μ parameter to distinct temporal windows (section II A). Furthermore, as summarized in fig. 11, the $\theta^{-1}{}_1$ to $\theta^{-1}{}_2$ transition was abolished by administering AVP in darkness and after labyrinthectomy or inferior olivary lesions with 3-acetylpyridine; the value of μ was also shifted significantly to the left by acute removal of visual inputs in animals with olivary lesions. Since these properties appear to be independent of the absolute incidence of BR in the population, they represent a discrete, highly ordered response of the central vestibular system to pharmacological perturbation. This section uses these hazard functions to develop a heuristic model for the actions of SRIF and AVP that lead to the severe vestibular dysfunction represented by BR. The following section relates this model to the distribution and actions of neuropeptides in central vestibular circuitry. This leads to a series of hypotheses concerning the relationship of the model derived from hazard analyses to physiological actions of peptides at specific central sites.

The discussion in *Section II* illustrated a series of important properties of the hazard functions for BR onset. First, as shown in Table 4, there are four discrete states of postural destabilization, represented explicitly as ranges of θ^{-1}. Second, there are temporal windows which constrain the appearance of μ, μ_1, and μ_t. Third, θ^{-1} reflects both the dose of SRIF or AVP and interactions between peptides; it can also be sensitized for AVP-induced BR. Fourth, μ can reflect increasing doses of either SRIF or AVP and sensitization to AVP BR; however, it is insensitive to combined doses of peptides. Fifth, the θ^{-1} state for the initial (or only phase) is insensitive to deprivation of visual or vestibular inputs, inferior olive ablation, atropine, and antiseizure medications. Sixth, μ_1 is eliminated by deprivation of visual or vestibular inputs, inferior olivary ablation, atropine, and antiseizure medications. Seventh, for AVP, BR can be shortened by deprivation of visual input to rats after inferior olive ablation and can be lengthened by diazepam, phenytoin (200 mg/kg), or valproic acid (125 mg/kg); the θ^{-1} state

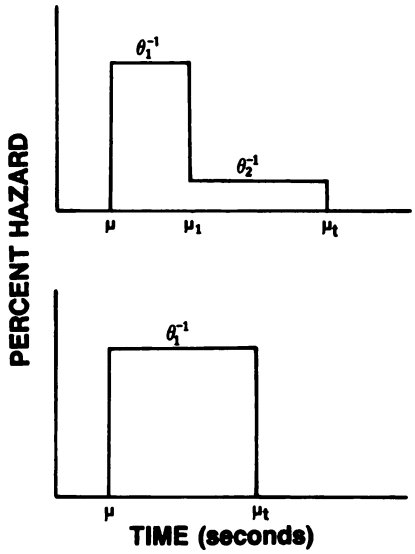

FIG. 11. The general structure of empirical hazard functions for barrel rotation onset in conscious rats. Under normal ambient illumination, the hazard functions obtained with SRIF and/or AVP in drug-free rats display two characteristic phases (upper panel). After a minimum latency, there is an initial phase of high instantaneous probability of onset of barrel rotation. This instantaneous probability is characterized by the hazard parameter ($\theta^{-1}{}_1$). There is a sharp transition in the hazard parameter at latency μ_1 to a lower instantaneous probability of the onset of motor symptoms ($\theta^{-1}{}_2$). This late hazard phase terminates at time μ_t. The lower panel shows the configuration of hazard functions for drug-free animals tested in darkness or after lesions of the central nervous system; the same configuration is observed after various drug regimens. Note that the late phase of the hazard function is absent.

is not affected by these manipulations. Finally, these properties argue that the mechanisms generating θ^{-1} and the μ parameters are at least partially independent.

2. Biological interpetation of barrel rotation hazard functions. A review of the literature indicated that barrel rotation in quadrupeds is an acute, extreme symptom of vestibular dysfunction, which is elicited by an asymmetric perturbation of vestibular circuitry by lesions or pharmacological manipulations (section IV). A component of the mechanisms mediating BR, then, clearly must include the responses of central vestibular circuits to asymmetric perturbations. In a quadruped, BR seems to indicate a asymmetry in signals related to vertical semicircular canals, which are roughly perpendicular to the axis of self-rotation. Furthermore, the effects of AVP are probably central because they are not blocked by bilateral labyrinthectomy. In this context, peptide-induced BR is simply the failure of central vestibular circuitry to compensate for a peptide-elicited destabilization. This leads directly to an intuitive description of the application of the hazard functions to neuropeptide-induced BR. After a minimum period for drug distribution, the peptide produces an effect at receptors in central vestibular structures that lead to a physiological asymmetry in the circuit. However, central circuits initiate a compensatory process to counteract this perturbation. The rate of failure of this compensation process over time is described explicitly by the hazard function. Thus, this mode of analysis provides a quantitative description of the time course of failure of postural stability after a known experimental manipulation.

This intuitive description can be replaced by a more formal statement of the relationship of parameters of the hazard function to the phenomenon of BR. The latency to BR onset after i.c.v. neuropeptides reflects at least three processes that are potentially influenced by peptide dose and time. The influences of 1) peptide delivery, distribution and pharmacokinetics, 2) the primary action of peptides leading to an asymmetry in vestibular circuits, and 3) the engagement or failure of circuits to compensate for the asymmetry are reflected in the parameters of the hazard function. As a consequence, each feature of the hazard function has an explicit biological interpretation:

1. The minimum latency (μ) is the minimum time for the occurrence of all three processes. For a given dose of a peptide or combination of peptides, it is assumed that the minimum value of μ approximates the system response when compensatory mechanisms either failed instantaneously or were never engaged. Since μ decreased with increased doses of SRIF or AVP (and the resultant increment in $\theta^{-1}{}_1$ state), it appears to be a function of peptide delivery, the severity of the physiological destabilization of central vestibular circuits, and/or failure of engagement of compensatory processes.
2. The $\theta^{-1}{}_1$ parameter directly reflects the severity of the perturbation of central vestibular circuits. It is a function of the sensitivity of animals to a given peptide dose; i.e., for AVP, the parameter can be altered by prior exposure to the peptide.
3. The transitions from $\theta^{-1}{}_1$ to $\theta^{-1}{}_2$ at μ_1 reflect engagement of central compensatory mechanisms which counter the destabilization introduced by the pharmacological perturbation. The initial, high hazard phase represents the uncompensated state, i.e., the system's failure rate prior to engagement of compensatory mechanisms. In this sense, μ_1 represents the latency between peptide injection and engagement of compensatory mechanisms that require both visual and vestibular inputs in normal rats. Thus, the duration of the initial phase (duration = $\mu_1 - \mu$ in normal rats under ambient illumination) provides an estimate of the integrative latency for these compensatory mechanisms.
4. The mechanisms that reduce either $\theta^{-1}{}_1$ or $\theta^{-1}{}_2$ to zero hazard at μ_i have not been affected profoundly by experimental manipulations. They are slower for SRIF than for AVP and may reflect a decay of the effect at the primary site(s) of action. These features summarize the conceptual basis for modeling the BR hazard function.

3. Model for SRIF- and AVP-Induced Barrel Rotation. A model for the hazard functions for BR onset latencies is shown in fig. 12. This model consists of two basic parts: 1) a four-stage, peptide-sensitive compartment and 2) a peptide-insensitive component that constantly sets values of μ and θ^{-1} and that inactivates stages A and B of the peptide-sensitive component. The actions of this peptide-insensitive component, then, generate the inflections in θ^{-1} at μ_1. In terms of the preceding discussion, the former stages reflect direct actions of peptides on central vestibular circuits, while the latter component represents destabilization dynamics and engagement of compensatory mechanisms.

The four underlying stages of the peptide-sensitive component are derived from the discrete behavior of the θ^{-1} parameter documented in Section II An exponential regression model was used for these constant hazard state data because it is an appropriate approach for determining the dependence of constant hazard functions on concomitant variables (121). Since the hazard parameter θ^{-1} displays four levels or states, a model of the form

$$\theta^{-1}(n) = \begin{cases} \exp(1.087n - 3.261) & \text{for } n = 1,2,3,4 \\ 0 & \text{for } n = 0 \end{cases}$$

was fitted to the data, where n = the state number and θ^{-1} = the empirically observed value for that experimental condition. The least squares regression for data from states 1 to 4 were highly significant ($r^2 = 0.96$). This indicates, then, that the behavior of the θ^{-1} parameter

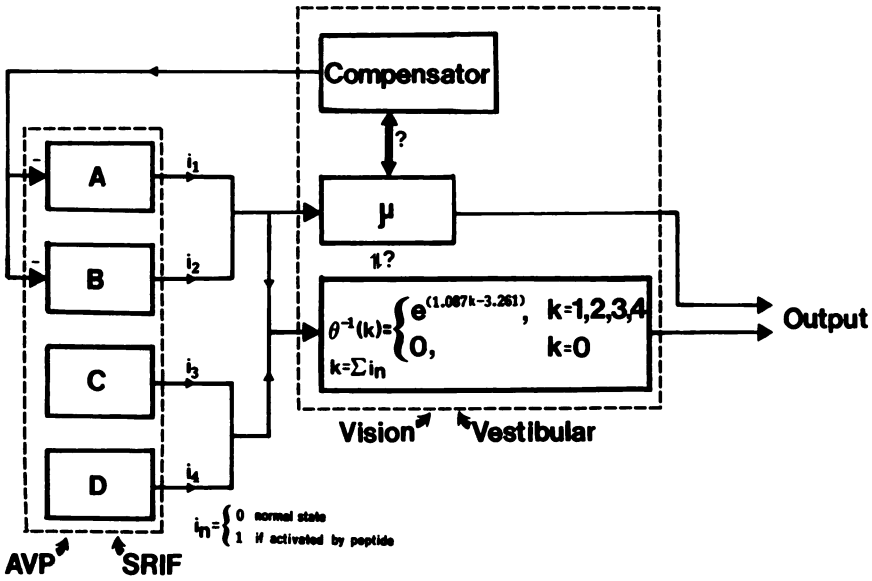

FIG. 12. Proposed model for generation of hazard functions for barrel rotation onset in conscious rats. The model has both peptide-sensitive and peptide-insensitive components. The peptide-sensitive component contains four sensitive stages that determine values of both μ and θ^{-1}. Transitions in hazard states are mediated by a peptide-insensitive compensator that is sensitive to visual and vestibular information. See text for further description.

can be modeled as exponential process for transforming activation of four discrete stages or sites into levels of postural instability. In the model (fig. 12), activation of each site (labeled A-D) by a neuropeptide results in a change in state of an indicator variable (i_n) from the stable value of 0 to a value of 1. The hazard state is then expressed as the current value of $\Sigma(i_n)$, which generates the current value of the θ^{-1} parameter in the peptide-insensitive component of the model. This model, then, explains the discrete behavior of θ^{-1} in terms of activation of different combinations of four sensitive sites or stages.

The criterion for selecting the properties for activation of each of these stages was the reproduction of the empirical hazard functions after application of different doses of SRIF and/or AVP. The properties of these stages are summarized as follows:

Stage A requires the presence of basal [AVP] and has a relatively high sensitivity to [AVP]. It has relatively low sensitivity to [SRIF]. Its maximum duration, in the absence of systemic drug treatment, was 142 s (for sensitized rats given 0.5 μg of AVP in darkness).

Stage B has a relatively low sensitivity to [AVP], but its sensitivity can be increased by prior exposure to this peptide. However, this site has relatively high [SRIF] sensitivity. Its maximum duration, in the absence of systemic drug treatment, was 150 s (for naive rats given 40 μg of SRIF and 1 μg of mcAVP).

Stage C has relatively high sensitivity to [AVP]. It has a nonlinear sensitivity to [SRIF] which can block activation at higher doses. Its maximum duration, in the absence of systemic drug treatment, was 142 s (for sensitized rats given 0.5 μg of AVP in darkness).

Stage D has relatively low [AVP] sensitivity, which can be increased by prior exposure to the peptide, It has relatively high [SRIF] sensitivity. Its maximum duration, in the absence of systemic drug treatment, was 142 s for rats given AVP and 925 s for SRIF.

The activation of these peptide-sensitive stages also sets the value of the minimum latency parameter of the hazard function. Since the permissible time windows for the μ parameter are independent of the specific peptide injected, the process that updates this parameter is located in the peptide-insensitive compartment of the model. The minimum latency (μ) is a discrete function of the activation state of stages A and B. Activation of stage A is sufficient to produce a μ value in the range of 20 to 55 s (T_1). Activation of stage B alone has emerged in only three experimental conditions to date (table 7). Two of these conditions yielded a value in the range of 73 to 88 s (T_2); the remaining condition (SRIF 40-mcAVP 1) showed a of 49 s (T_1). Further studies yielding stage B activation are needed to define further its relationship to values of the μ parameter.

The compensator in the peptide-insensitive compartment of the model (fig. 12) has several noteworthy properties. First, it is sensitive to the identity and number of activated stages in the peptide-sensitive compartment. Second, its dynamic behavior is affected by at least visual and vestibular inputs. Third, its operations are independent of the individual peptide(s) employed. Fourth, it only inactivates stages A and B. Finally, it requires a minimum integration time on the order of 40 s before it can inactivate these stages. The patterns of activation of these stages for different treatment conditions are summarized in table 7.

The components of the model have been derived di-

TABLE 7

Summary of generation of hazard functions by the model in fig. 12[a]

Peptide/ dose	Stage	T_1	T_2	T_3	T_4	Long
SRIF 20	A					
	B		XXXXXX	XXXXXX		
	C					
	D		XXXXXX	XXXXXX	XXXXXX	
SRIF 40	A	XXXXXX	XXXXXX			
	B	XXXXXX	XXXXXX			
	C					
	D	XXXXXX	XXXXXX	XXXXXX	XXXXXX	
SRIF 40	A					
mcAVP 1	B	XXXXXX	XXXXXX			
	C					
	D	XXXXXX	XXXXXX	XXXXXX	XXXXXX	
SRIF 40	A	XXXXXX	XXXXXX			
AVP 0.5	B	XXXXXX	XXXXXX			
or	C					
AVP 1	D	XXXXXX	XXXXXX	XXXXXX	XXXXXX	
SRIF 20	A					
mcAVP 1	B		XXXXXX	XXXXXX		
	C					
	D		XXXXXX	XXXXXX	XXXXXX	
SRIF 20	A	XXXXXX				
AVP 0.5	B	XXXXXX				
	C	XXXXXX				
	D	XXXXXX	XXXXXX	XXXXXX	XXXXXX	
AVP 0.5	A	XXXXXX	XXXXXX			
naive	B					
	C	XXXXXX	XXXXXX	?		
	D					
AVP 1	A	XXXXXX				
naive	B	XXXXXX				
	C	XXXXXX	XXXXXX	XXXXXX		
	D	XXXXXX	XXXXXX	XXXXXX		
AVP 0.5	A	XXXXXX				
sensit	B	XXXXXX				
light	C	XXXXXX	XXXXXX	XXXXXX		
	D	XXXXXX	XXXXXX	XXXXXX		
AVP 0.5	A	XXXXXX	XXXXXX	XXXXXX		
sensit	B	XXXXXX	XXXXXX	XXXXXX		
dark	C	XXXXXX	XXXXXX	XXXXXX		
	D	XXXXXX	XXXXXX	XXXXXX		
AVP 0.5	A	XXXXXX	XXXXXX			
sensit	B	XXXXXX	XXXXXX			
labyr	C	XXXXXX	XXXXXX			
light	D	XXXXXX	XXXXXX			
AVP 0.5	A	XXXXXX	XXXXXX			
sensit	B	XXXXXX	XXXXXX			
labyr	C	XXXXXX	XXXXXX			
dark	D	XXXXXX	XXXXXX			

[a] The pattern of activation of peptide-sensitive stages (A–D) is shown for each peptide condition in drug-free rats. The abbreviations for treatment groups are identical to Table 4. The time epochs T_1 (20–85 sec), T_2 (73–88 sec), T_3 (105–≈130 sec), T_4 (≈140–200 sec) and Long (>250 s) represent the hazard state transition windows derived from fig. 8. Abbreviations: *sensit*, sensitized; *labyr*, labyrithectomized; *light*, peptide given under normal laboratory illumination; *dark*, peptide given in darkness.

rectly from empirically determined properties of barrel rotation latency data from drug-free rats. The existence of four peptide-sensitive stages, of separate peptide-insensitive integrative operations for determining θ^{-1} and μ, and of a peptide-insensitive compensator are inferred from presently available data. However, it is premature to speculate on the nature of interactions between the peptide-dependent and -independent compartments or between processes within individual compartments. For example, the data do not yet permit resolution of the source or nature of the central signals that activate the compensator. Potential sources include one or more of the following possibilities: a direct output from peptide-sensitive stages (e.g., stages A and B), a direct output from mechanisms generating μ and/or θ^{-1}, a direct feedback of motor output signals (corollary discharge) or sensory signals reflecting a mismatch between the abnormal motor output and the actual orientation of the animal in three-dimensional space. Similarly, the data base does not yet clarify whether the mechanism μ determining is 1) an independent element or 2) a component of the compensator. However, identification of the sites in the central nervous system that mediate these properties will permit experimental resolution of these issues.

B. Potential Sites of Action of i.c.v. SRIF and AVP

Analysis of hazard functions for BR predicts a model with four stages that are sensitive to neuropeptides and a compensatory mechanism that is sensitive to visual and vestibular inputs and central vestibular stability. An obvious question arises: "Where are these mechanisms in the brain?" Our knowledge of central vestibular pharmacology is insufficient to answer this question at present. However, a comparison of the properties of the stages in the model with properties of central structures that can elicit BR in lesion studies (section IV C) can identify potential sites for involvement in the different compartments of the model. The explicit assumption in this section is that sensitive sites for AVP and SRIF will display both specific binding and immunoreactive terminals for the peptide in question. This simplifying assumption is made for inferential purposes only; it is obvious that a high density of specific binding sites or immunoreactive processes is not necessary for the appearance of a specific, physiologically significant effect. The incorporation of multiple sites of action of AVP and SRIF in the model is supported by results of previous studies. Boakes et al. (26) reported that the fourth ventricle was a highly sensitive site for inducing AVP BR, citing a 50% incidence for a 1 ng dose. This was confirmed subsequently by Maiti et al. (131), who presented evidence that the sensitive site may involve the cerebellar nodulus and/or uvula, although a cerebellar nuclear effect cannot be excluded. By contrast, Naylor et al. (156) reported a site that could be sensitized to AVP administration in the basal forebrain, near the bed nucleus of the stria terminalis. The simplest, comprehensive explanation of these results is that there are two distinct sites for AVP action in BR. One is located in the basal forebrain or rostral hypothalamus; the second is found in the vicinity of the medulla or cerebellum. Similarly, the vestibular nuclei are a sensitive site for SRIF-induced BR (35), while the sensitive forebrain site for AVP can be sensitized by prior exposure to SRIF (38). In the absence of hazard functions, their correspondence to stages in the model cannot be ascertained. However, they confirm the existence of multiple sites of action at different levels of the nervous system that affect vestibular function.

A discussion of the potential sites of action mediating SRIF and AVP BR requires an initial consideration of the mode of application of the drug and conditions for stability for vestibular circuits. This is illustrated by the example of effects of antimuscarinic cholinergic agents and opioid peptide analogs. When viewed outside the context of BR as a form of central vestibular dysfunction, the fact that antimuscarinic agents can both produce barrel rotation (36, 231) when given i.c.v. and block neuropeptide-induced barrel rotation when give peripherally (50, 229) may seem contradictory. The same principle applies to reports that both dynorphin (91, 103, 108, 163) and selective δ opiate agonists (52) produce barrel rotation when given i.c.v. However, the lesion experiments imply that neuropeptide-induced barrel rotation in quadrupeds is a hallmark of an imbalance between left and right vertical semicircular canal signals at central sites. Clearly, there are several ways to achieve such an imbalance. First, asymmetric delivery of either an agonist or antagonist can produce an imbalance, either by direct excitation or inhibition or by disfacilitation or disinhibition with different time courses or potencies at left versus right sites. For example, normal anatomic asymmetry in the configuration of the brain stem or cerebellum could produce asymmetric delivery to sites surrounding the ventricular system. A second possibility is that the transfer function of neurons in the central circuits is altered such that the ability to compensate for fluctuations in tonic inputs originating in the left and right vestibular endorgans is compromised. As a result, normal physiological asymmetry could cascade to simulate a severe central imbalance. A third possibility is that receptors for these compounds are distributed asymmetrically in central vestibular structures. A fourth possibility is that the central vestibular system is normally in a compensated state, which corrects for congenital asymmetries in physiological properties of left and right vestibular endorgans or central circuits. From this perspective, BR may represent a form of decompensation due to a transient perturbation by the neuroactive compounds. The critical concept is that postural and ocular stability depends upon a dynamic equilibrium between signals originating in the left and right vestibular endor-

gans: this equilibrium can be disrupted by either agonists or antagonists of the same neurotransmitter or neuromodulator, resulting in the same vestibular dysfunction syndrome. Each of these mechanisms has distinct implications for possible roles of neuroactive substances in vestibular physiology. Tests of these hypotheses regarding site-specific mechanisms of action, though, require identification of the potential sites of action. This section considers the evidence for each site that has been implicated in BR in either lesion, stimulation, or pharmacological experiments.

1. Vestibular nuclei and fastigial nucleus. Several lines of evidence implicate the vestibular and fastigial nuclei as major sites of action of i.c.v. SRIF and antimuscarinic agents in the production of BR. First, direct microinjections of SRIF (35) and antimuscarinic cholinergic drugs (34, 231) into the vestibular nuclei produce BR. Second, the vestibular nuclei and fastigial nucleus display intermediate to high concentrations of high affinity SRIF binding sites (218); binding is greatest in the medial vestibular and fastigial nuclei, with slightly lower binding in the superior, lateral, and inferior vestibular nuclei. Third, SRIF-like immunoreactive cell bodies and axons are found in these regions: there is a relatively sparse distribution of cells and axons displaying SRIF-like immunoreactivity in these nuclear groups, with slightly higher densities of fibers reported in periventricular regions of the medial and superior vestibular nuclei, the ventrolateral quadrant of the lateral vestibular nucleus, and the medial aspect of the fastigial nucleus (100, 220). This suggests that SRIF may be released in these regions as a consequence of neural activity. Fourth, muscarinic cholinergic binding is high in the medial vestibular nucleus, with intermediate binding in the lateral and inferior vestibular nuclear groups (186, 222); fastigial nucleus binding was not significant in one study (186) and not described in the other (222). Fifth, there is a sparse distribution of choline acetyltransferase-positive neurons in these regions (5, 112). Sixth, direct application of these substances produces postsynaptic effects on at least vestibular nuclear neurons. For example, Chan-Palay et al. (47) reported that SRIF depresses spontaneous responses of lateral vestibulospinal tract neurons in the rat lateral vestibular nucleus and that the effect summates with GABA inhibition. Similarly, neuropharmacological studies demonstrated that neurons in medial and lateral vestibular nuclei show opposite responses to iontophoretically applied cholinergic agonists (acetylcholine and nicotine) and to systemically applied cholinergic antagonists (114, 115, 137); the most common responses were enhancement of firing rate by iontophoretic acetylcholine or systemic physostigmine administration and depression by scopolamine or mecamylamine. These earlier findings are consistent with the recent report that medial vestibular nucleus neurons are depolarized by both muscarinic and nicotinic agonists in slice preparations and that these actions are blocked by selective antagonists (164). Since both SRIF and antimuscarinic cholinergic agents can produce BR, while systemic antimuscarinic agents antagonize the effects of SRIF (reviewed above), the most parsimonious explanation is that the actions of SRIF depend upon background cholinergic activity. This implies that the actions of SRIF either modulate or are modulated by muscarinic activity at these sites.

The present experimental record does not permit assessment of possible differential roles of the vestibular nuclei or fastigial nucleus in initiation of SRIF or antimuscarinic-induced BR or in determining the hazard function for BR onset. The best evidence for an effect of these structures is provided by the studies of Burke and Fahn (34, 35), who placed 0.5 μl injections of either antimuscarinic agents, chlorpromazine methiodide, or SRIF in the vestibular nuclei of rats. Inspection of their figures, though, clearly shows that the injection cannulae passed directly through the fastigial nucleus. This immediately raises the question of diffusion of the injection to the latter structure and/or a confounded effects of a simultaneous, partial lesion of the fastigial nucleus. The same criticism applies to a subsequent study using anticholinergic agents (231). As a result, these data must be interpreted conservatively as being consistent with a role of the both regions in BR evoked by SRIF or antimuscarinic agents.

Experimental evidence suggests that the vestibular nuclei and/or fastigial nucleus may not be not a primary site of action in AVP-induced BR. Although Boakes et al. (26) reported a significant leftward shift of the dose-response relation for BR after AVP injections in the fourth ventricle, Wurpel (231) found that microinjections of AVP into the vestibular nuclear complex did not alter the incidence from the value produced by lateral ventricular injections. This is consistent with the apparent lack of prominent AVP binding (25, 31, 216) or immunoreactive fibers in these regions (32, 195, 196, 209). However, Maiti et al. (131) reported a low threshold site for AVP BR in the nodulus-uvula. Since they could not exclude the possibility that the fastigial nucleus was involved in the injection sites, the possibility of a contributory role for these sites to AVP BR or to the interactions of AVP and SRIF cannot be excluded.

The possible role of these structures in BR induced by opioid agonists and antagonists is also worthy of note. The medial and lateral vestibular nuclei show low-intermediate levels of dynorphin-like immunoreactivity (237). Proenkephalin-positive neurons have been identified both in a fiber plexus extending within the medial and inferior vestibular nuclei and in neurons within the fastigial nucleus (141). Furthermore, exogenously applied [Leu]- or [Met]enkephalin depresses the spontaneous firing rate of lateral vestibular nucleus neurons in a dose-dependent manner (47). Like the depressive effects of

SRIF, the responses to [Met]enkephalin peptides summated with effects of GABA. While [Leu]enkephalin elicited the same behavior from some cells, it antagonized the effects of GABA at other cells. Although there are no direct studies of microinjections of opioid peptides in the vestibular or fastigial nuclei to examine vestibular disturbances, these reports imply that these regions are a likely site for opiate effects on central circuits processing vestibular information.

2. Cerebellar cortex. Experimental data implicate the cerebellar cortex in the generation of BR after i.c.v. SRIF or AVP injections. Maiti et al. (131) reported that BR was elicited in a dose-dependent manner by 1 μl infusions of 20 to 200 pmol (approximately 20 to 200 ng) AVP into the region of the cerebellar nodulus (and, possibly the underlying cerebellar nuclei) in rats. Prior exposure to AVP at this site sensitized rats to subsequent application of the peptide, and these effects were blocked by kainic acid lesions of the cerebellar site. These data suggest a primary role of the cerebellar cortex in the generation of AVP BR. However, it is not the sole trigger site, because cerebellectomy depressed but did not eliminate BR incidence after i.c.v. AVP (229). Cerebellectomy abolished the phenomenon of sensitization to i.c.v. AVP, though, indicating that the cerebellum is essential for adjusting the sensitivity of central vestibular circuits to the peptide. By contrast, SRIF (but not AVP) injection results in a characteristic pattern of Purkinje cell death in the cerebellar anterior lobe in rats that display barrel rotation (10, 12). It is significant to note that the degenerated Purkinje cells project directly to the lateral vestibular nucleus, which gives rise to vestibulospinal projections. Although it has not been determined if Purkinje cell toxicity is a direct or indirect effect of SRIF administration, these data are suggestive of a cerebellar role in SRIF BR.

The distribution of endogenous neuropeptides and receptors in the cerebellar cortex is consistent with a primary role in BR. Both SRIF- (100, 220) and AVP-like (32, 90) immunoreactivities are present in the cerebellar cortex. In particular, SRIF-like immunoreactivity was reported in at least a subset of Purkinje cells and Golgi cells (47, 100, 220) and in climbing fibers in the rat flocculus (220). However, the distribution of high affinity binding sites for either peptide is modest, at best, and not associated densely with any particular regions (e.g., vestibulocerebellum) or cellular elements (e.g., 25, 31, 216, 218). Clearly, explicit investigations of the effects of direct application of these peptides to discrete cell populations and regions of cerebellar cortex are needed to clarify the nature of the cerebellar contribution to SRIF- and AVP-evoked postural destabilization.

The cerebellum displays a dense distribution of high affinity binding sites for two other classes of peptides that elicit BR. A dense, homogeneous distribution of κ-opioid receptors has been described in cerebellar cortex, with neglible levels of δ- or μ-receptors in the same regions (213). By contrast, substance P shows an exquisitely discrete pattern of high affinity binding in the cerebellar cortex (20, 183), which is restricted to a series of sagittal bands in the molecular layer of lobule X and the most ventral folium of lobule IX. A similar banding pattern has been reported for muscarinic binding in lobules IX to X and sagittal bands of pseudocholinesterase-positive Purkinje cells (86) are also restricted to this region. These binding patterns are similar to sagittal patterns of climbing fiber innervation and Purkinje cell output projections to different vestibular nuclei (7, 11, 107), suggesting a relationship to specific cerebellar output circuits. The selective distribution of pseudocholinesterase is also compelling, because, in addition to its cholinesterase activity, this enzyme can hydrolyze substance P (126). In light of the observation of James and Starr (99) of BR after intracisternal injections of substance P, these data raise the hypothesis that this peptide elicits BR via a direct effect on nodulus Purkinje cells. They also suggest a possible contribution of this region to BR after i.c.v. anticholinergic injections.

Perturbation of physiological properties of cerebellar afferents is another possible substrate for cerebellar influences on the incidence and sensitization of rats to AVP BR. The climbing fibers are of particular concern in this regard. These afferents originate in the inferior olive (97), and the axons contribute collateralized projections to cerebellar and vestibular nuclei. The inferior olive has high concentrations of specific AVP binding sites (216). Olivary subdivisions also show appreciable concentrations of SRIF-like immunoreactive axons and cell bodies (100, 220) and intermediate levels of muscarinic binding (222). Since the inferior olive degenerates retrogradely after mechanical ablation of the cerebellar cortex (97), olivary disruption is a possible confounded variable in cerebellar ablation experiments. This is an important problem in studies of the stability of central vestibular circuits, given the demonstration by Llinas et al. (125) that compensation for a hemilabyrinthectomy disappears after inferior olivary lesions in rats.

Chemical ablation experiments support a role of the inferior olive in AVP BR. After destruction of the inferior olive by 3-acetylpyridine intoxication (8, 125), the initial incidence of BR was depressed significantly when AVP was administered under normal ambient illumination (233). Although the rats were sensitized to the effects of a subsequent dose of AVP, the μ parameter of the hazard function was delayed significantly without affecting θ^{-1}. This finding suggests the emergence of an extraolivary inhibitory or compensatory mechanism. A strikingly different response pattern was observed when 3-acetylpyridine-treated rats were given AVP in darkness: the initial incidence of BR was identical to control rats given the peptide in either light or darkness and sensitization did not occur. Furthermore, the BR hazard function after

the second AVP dose was identical to a control population given AVP in darkness. While these experiments demonstrated that the effects of cerebellectomy cannot be attributed purely to secondary degeneration of the inferior olive, they yield some interesting insights into properties of cerebellar circuits in AVP BR. Since the incidence of AVP BR is reduced and the sensitization phenomenon abolished by after cerebellectomy, these findings imply 1) *that an extraolivary (and possibly extracerebellar) visual compensatory mechanism inhibits the incidence of BR* and 2) *that both visual input via extraolivary pathways and intact climbing fibers projections to the cerebellum are necessary for sensitization to AVP BR.* In terms of the model, they implicate olivo-cerebellar circuits as one component of the compensatory process. Although this role is consistent with the effects of ablating these circuits on vestibular compensation after hemilabyrinthectomy (127), it does not adequately explain the delay in the parameter for 3-acetylpyridine-treated rats in an illuminated laboratory. In the absence of further experimental data, possible explanations in terms of the model range from unmasking of a tonic, inhibitory drive to sites sensitive to the peptide to an abnormal operating characteristic for compensatory circuits.

3. Substantia nigra and basal ganglia. Examination of the literature clearly indicates that asymmetric pharmacological manipulations of substantia nigra can result in horizontal circling that progresses to BR. For example, intranigral microinjections of a single dose of morphine (98), bacitracin, picrotoxin, or kainic acid (99), and a two-dose protocol with bicuculline methiodide (110) have all been reported to elicit BR in rats. However, intranigral injections of 1 to 10 μg of substance P (99) produced only a contraversive circling that was blocked by haloperidol, while intranigral dynorphin injections produced a dose-dependent contraversive circling that was blocked by naloxone (92). Finally, 100 pmol (100 ng) of AVP (156) failed to produce motor disturbances in six rats tested. This latter finding suggests, then, that the AVP-like immunoreactive fiber plexus (196) and pattern of AVP binding (25) in substantia nigra do not reflect a primary site of action of AVP in triggering BR. However, other lines of evidence suggest a role of nigrostriatal circuits in generation of the response to i.c.v. AVP. Chemical ablation of substantia nigra and the neighboring ventral tegmental area with 6-hydroxydopamine depressed the incidence of BR in response to AVP, but sensitization to a second dose of the peptide was unaffected (234). The same effects were observed after bilateral kainic acid lesions of the striatum (234). These data indicate that an intact nigrostriatal system and/or ventral tegmental area is not necessary for either triggering AVP BR in naive animals or for the sensitization process. However, they suggest that these circuits are involved in complete expression of the response. Since the incidence of BR was too low to determine the hazard function, these effects cannot be related explicitly to the schema in fig. 12.

The caudate-putamen contains peptidergic and cholinergic cells, axons, and high affinity binding sites, which make it an obvious candidate for sites of action of neuropeptides in the induction of motor disturbances. For example, somata and axon plexuses displaying SRIF-like (100, 220), proenkephalin, and prodynorphin (135; 136, 141), substance P-like (124) and choline acetyltransferase immunoreactivity (5, 93, 112) have all been reported in the striatum. These regions also show moderate levels of SRIF binding (218), moderate to high levels of substance P binding (20, 183), and dense to very dense distributions of δ, κ, and μ opiate binding (135, 136). However, unlike substantia nigra, unilateral manipulations of the striatum do not appear to consistently elicit BR. For example, to our knowledge, there is only a single report that unilateral kainic acid injections in the rostral caudate-putamen produces barrel rotation (212). Furthermore, intrastriatal injections of up to 10 μg of SRIF did not elicit BR in another report (178). Thus, the depression of AVP BR incidence after bilateral caudate-putamen lesions (221) does not appear to reflect ablation of a primary site of initiation; rather, this finding suggests that intact nigrostriatal circuitry is necessary for complete expression of the response.

4. Other potential sites. a. BASAL FOREBRAIN: BED NUCLEUS OF THE STRIA TERMINALIS. Naylor et al. (156) presented convincing evidence of a sensitive forebrain site that displays sensitization to AVP-induced motor disturbances and BR. Injections of 100 pmol (approximately 100 ng)/0.5 μl into a region between the anterior commissure and and the anterior hypothalamus elicited a low incidence of BR after an initial exposure. This dose is higher than doses which produce BR in the fourth ventricle or cerebellar nodulus (26, 131) and the incidence did not differ appreciably from the effects of an equivalent i.c.v. dose in other studies (e.g., 1, 26). However, administration of the same dose after 1 to 2 days revealed a potent sensitization to effects of the peptide. Inspection of their illustration revealed that effective injection sites were clustered within and in the immediate proximity of the bed nucleus of the stria terminalis; the relatively large injection cannulae (20 gauge; approximately 900 μm outside diameter) preclude resolution to the level of subnuclear regions. The distribution of immunoreactive neuropeptides and high affinity binding sites and the connections of this basal telencephalic region are consistent with a role in BR. The bed nucleus of the stria terminalis contains a high concentration of high affinity AVP binding sites (216), a light density of AVP immunoreactive fibers (195, 196), a heavy density of SRIF-like immunoreactive processes (100, 220), and a moderate to high density of SRIF receptors (218). This nucleus also has significant distributions both of high affinity muscarinic (185) and μ-, δ- and κ-opioid receptors

(135, 136) and of immunocytochemically identified choline acetyltransferase- (112), pro-opiomelanocortin-, pro-enkephalin-, and pro-dynorphin-containing neurons (136). These data, then, are consistent with the demonstration that this site can be sensitized by prior AVP exposure to elicit a high incidence of BR and suggest that it may form one substrate for interactions between the AVP and other peptides. Finally, since injections of SRIF in this region can sensitize rats to subsequent injections of AVP (38), the bed nucleus of the stria terminalis may be partially responsible for the contralateral bias in the direction of barrel rotation in the SRIF 40-AVP 1 and SRIF 40-mcAVP 1 groups.

The connections of the bed nucleus of the stria terminalis imply that it may provide a descending input to midbrain dopaminergic neurons. This pathway, then, would provide inputs that can be sensitized by prior exposure to AVP. As reviewed by de Olmos et al. (64), the lateral division of the bed nucleus of the stria terminalis, like the central amygdaloid nucleus, contributes descending projections to two midbrain dopaminergic cell groups (pars compacta of substantia nigra, the ventral tegmental area), to a major noradrenergic cell group (locus coeruleus), and to three central autonomic regions (parabrachial nucleus, dorsal motor nucleus of the vagus nerve, and nucleus tractus solitarius). Since other divisions of the bed nucleus of the stria terminalis project to both the lateral division of the nucleus and to the central amygdaloid nucleus, these direct and indirect descending pathways are likely to mediate the responses elicited by AVP. However, connections that are likely to mediate interactions between this sensitive site and more caudal sensitive regions are unclear.

b. INTERSTITIAL NUCLEUS OF CAJAL.The interstitial nucleus of Cajal and adjacent regions were suggested by previous studies as sites at the mesodiencephalic junction that are involved in BR generation (see section IV). However, the apparent lack of detectable peptidergic and cholinergic receptors and SRIF, AVP, substance P, or choline acetyltransferase immunoreactivity argue against a direct peptidergic action in the interstitial nucleus as a mediator of BR. This does not imply, though, that the interstitial nucleus of Cajal can be excluded as a modulator of sites affected directly by the peptides. The model derived from the hazard functions contains both 1) a peptide-insensitive compensatory component that is sensitive to both vestibular and visual influences and 2) a site that adds the effects of activation of the peptide-sensitive stages to produce the hazard function. Furthermore, the literature discussed above has suggested that potential peptide-sensitive sites for BR initiation are organized around two neuronal networks, one located in cerebellum and the brain stem (i.e., a vestibular-fastigial-cerebellar axis) and the other in the subthalamus and ventral forebrain (i.e., a substantia nigra-ventral tegmental area-basal ganglia-bed nucleus of the stria terminalis-amygdala axis). Thus, candidates for peptide-insensitive compensatory or summation mechanisms should also be connected with these spatially distinct peptide-sensitive regions.

The connections of the interstitial nucleus of Cajal suggest that it is a strong candidate for a structure involved in these peptide-insensitive processes. First, the efferent connections of the interstitial nucleus of Cajal are consistent with neuropeptide-induced BR as a symptom of vestibular dysfunction in the plane of the vertical semicircular canals. Neurons in the interstitial nucleus project directly to vertical canal-recipient neurons in the vestibular nuclei (80) and the structure is important for maintaining vertical gaze stability (e.g., 4, 40, 45). The nucleus also projects to both the inferior olive and spinal cord (e.g., 3, 45), which provide other pathways for influencing vestibular nuclear or motor function. Second, neurons in the interstitial nucleus receive both vestibular and visual inputs. Neurons in this region receive direct vestibular nuclear afferents that are driven by vertical and horizontal canal signals (e.g., 80–82); visual inputs from both the pretectum (23) and the superior colliculus (94) have also been documented. Finally, the interstitial nucleus of Cajal appears to receive inputs from both the brain stem and the subthalamic-ventral forebrain circuits that are potential sites of peptide action in BR initiation. Although the projections from the vestibular and fastigial nuclei and group y to the interstitial nucleus are well-established (e.g., 82), the evidence for nigral or ventral tegmental inputs to this structure has not been addressed explicitly in the literature. One potential indirect nigral input, via the nigrotectal pathway, has already been described. In addition, anatomic studies raise the possibility that the interstitial nucleus of Cajal receives a direct input from substantia nigra [compare chartings in refs. 21 and 85 with the description of the interstitial nucleus of Cajal (187)]. Given that BR can be produced by unilateral stimulation of this region (88), these data support a role of the interstitial nucleus of Cajal in compensatory or summation processes underlying the hazard function.

5. Global perspective: simultaneous actions at multiple sites. Empirical results concerning a) the incidence of BR as a function of SRIF and AVP doses, b) hazard functions for BR onset, c) the distribution of sites that produce BR after lesions or local pharmacological manipulations, and d) the distribution of SRIF and AVP binding in the brain all imply that BR reflects simultaneous and specific actions of the peptides at multiple sites. In particular, the behavior of the hazard functions suggests that there are four stages (or mechanisms) that are sensitive to SRIF and AVP and that at least one peptide-insensitive site compensates for the peptide-induced perturbation and may summate the effects of the peptide-sensitive mechanisms. The formulation of this model has now raised the question of the location of

neuronal populations that underlie these stages. Although it is tempting to associate a single site with a single stage, it is premature to exclude the possibility that a given anatomic structure may be involved in more than one stage of the hazard-based model. Furthermore, these stages may correspond, not to single structures, but to multineuronal networks spanning several structures (e.g., cerebello-corticonuclear circuits). These important caveats must be considered in future studies of sites producing BR.

The current literature allows a tentative association of some central vestibular structures with components of the model in fig. 12. The fastigial and vestibular nuclei are two candidates for sites involved in stages B and/or D on the basis of high SRIF sensitivity. The bed nucleus of the stria terminalis is another candidate for involvement in stages B and/or D, since it shows both AVP and SRIF binding and can be sensitized to effects of AVP by prior exposure to the peptide. By contrast, potential sites involved in stages A and/or C include the inferior olive, cerebellar cortex, and, possibly, a basal forebrain region such as the bed nucleus of the stria terminalis. The interstitial nucleus of Cajal is a candidate for a peptide-insensitive compensatory site. These hypothetical sites of action are amenable to direct experimental verification by observing hazard functions after local peptide injections.

VI. Concluding Remarks

This review has presented evidence that multiple endogenous neuropeptides and antimuscarinic cholinergic agents can elicit symptoms of vestibular dysfunction via specific actions in central vestibular circuits. These central sites are characterized by the presence of these neuropeptides and their high affinity receptors. Since experimental evidence indicates that multiple, interactive sites of neuropeptide action are present in vestibular circuits, changes in the functional status at one or more sites are likely to have an impact on the responses of the vestibular system to regulate postural and ocular stability. Furthermore, since central vestibular circuits are involved in generation of autonomic symptoms associated with motion sickness (169) and vertigo, it is reasonable to posit that alterations of neuropeptide functions at these central sites are of pathophysiological significance. Finally, the documented efficacy of some clinically useful antiseizure medications against neuropeptide-induced vestibular dysfunction raises the issue of a linkage between central actions of these peptides and vestibular epilepsy (29, 30).

Note added in proof: A recent paper (cited below) has documented the efficacy of multiple anticonvulsant drugs against barrel rotation that was induced by intrastriatal quinolinic acid injections in rats.

MARRANNES, R. AND WAUQUAIR, A.: Episodic barrel rotation induced by intrastriatal injection of quinolinic acid in rats: inhibition by anticonvulsants. Pharmacol. Biochem. Behav., **31:** 153–162, 1988.

REFERENCES

1. ABOOD, L. G., KNAPP, R., MITCHELL, T., BOOTH, H., AND SCHWAB, L.: Chemical requirements of vasopressins for barrel rotation convulsions and reversal by oxytocin. J. Neurosci. Res. **5:** 191–199, 1980.
2. ALBECK, D., AND SMOCK, T.: A mechanism for vasopressin action in the hippocampus. Brain Res. **463:** 394–397, 1988.
3. ALDES, L. D., AND BOONE, T. B.: Does the interstitial nucleus of Cajal project to the hypoglossal nucleus in the rat? J. Neurosci. Res. **12:** 553–561, 1984.
4. ANDERSON, J. A., PRECHT, W., AND PAPPAS, C.: Changes in the vertical vestibulo-ocular reflex due to kainic acid lesions of the interstitial nucleus of Cajal. Neurosci. Lett. **14:** 259–264, 1979.
5. ARMSTRONG, D. M., SAPER, C. S., LEVEY, A. I., WAINER, S. H., AND TERRY, R. D.: Distribution of cholinergic neurons in rat brain: demonstrated by the immunochemical localization of choline acetyltransferase. J. Comp. Neurol. **216:** 53–68, 1983.
6. ASCHAN, G., EKVALL, L., AND GRANT, G.: Nystagmus following stimulation in the central vestibular pathways using permanently implanted electrodes. Acta Oto-laryngol. (suppl.) **192:** 63–77, 1964.
7. BALABAN, C. D.: Olivovestibular and cerebellovestibular connections in albino rabbits. Neuroscience **12:** 129–149, 1984.
8. BALABAN, C. D.: Central neurotoxic effects of intraperitoneally administered 3-acetylpyridine, harmaline and niacinamide in Sprague-Dawley and Long-Evans rats: a critical review of central 3-acetylpyridine neurotoxicity. Brain Res. Rev. **9:** 21–42, 1985.
9. BALABAN, C. D., FREDERICKS, D. A., LIN, H., STARCEVIC, V. P., AND SEVERS, W. B.: Role of arginine-vasopressin in somatostatin-induced barrel rotation and convulsions in rats. FASEB J. **2:** A1153, 1988.
10. BALABAN, C. D., FREDERICKS, D. A., WURPEL, J. N. D., AND SEVERS, W. B.: Motor disturbances and neurotoxicity induced by centrally administered somatostatin and vasopressin in conscious rats: interactive effects of two peptides. Brain Res. **445:** 117–129, 1988.
11. BALABAN, C. D., AND HENRY, R. T.: Zonal organization of olivo-nodulus projections in albino rabbits. Neurosci. Res. **5:** 409–423, 1988.
12. BALABAN, C. D., ROSKAMS, A.-J., AND SEVERS, W. B.: Diazepam attenuation of somatostatin-induced motor disturbances and neurotoxicity. Brain Res. **458:** 91–96, 1988.
13. BALABAN, C. D., STARCEVIC, V. P., AND SEVERS, W. B.: Neuropeptide-induced postural destabilization: a potential state variable for rate of onset of barrel rotation. Soc. Neurosci. Abstr. **14:** 267, 1988.
14. BALOH, R. W.: Vertigo. *In* Current Therapy in Neurologic Disease-2, ed. by R. T. Johnson, pp. 7–10, Dekker, Toronto, 1987.
15. BANKIEWICZ, K. S., OLDFIELD, E. H., CHIUEH, C. C., DOPPMAN, J. L., JACOBOWITZ, D. M., AND KOPIN, I. J.: Hemiparkinsonism in monkeys after unilateral internal carotid artery infusion of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Life Sci. **39:** 7–16, 1986.
16. BARNARD, R. R., JR., AND MORRIS, M.: Cerebrospinal fluid vasopressin and oxytocin: evidence for an osmotic response. Neurosci. Lett. **29:** 275–269, 1982.
17. BATTON, R. R., JAYARAMAN, A., RUGGIERO, D., AND CARPENTER, M. B.: Fastigial efferent projections in the monkey: an autoradiographic study. J. Comp. Neurol. **174:** 281–306, 1976.
18. BEAL, M. F., GROWDON, J. H., MAZUREK, M. F., MCENTEE, W. J., AND MARTIN, J. B.: CSF somatostatin in dementia. Neurology **34** (suppl. 1): 120, 1984.
19. BEAL, M. F., MAZUREK, M. F., BLACK, P. MCL., AND MARTIN, J. B.: Human cerebrospinal fluid somatostatin in neurological disease. J. Neurol. Sci. **71:** 91–104, 1985.
20. BEAUJOUAN, J. C., TORRENS, Y., SAFFROY, M., AND GLOWINSKI, J.: Quantitative autoradiographic analysis of the distribution of binding sites for [^{125}I]Bolton-Hunter derivatives of eledoisin and substance P in the rat brain. Neuroscience **18:** 857–875, 1986.
21. BECKSTEAD, R. M., DOMESICK, V. S., AND NAUTA, W. J. H.: Efferent connections of the substantia nigra and ventral tegmental area in the rat. Brain Res. **175:** 191–217, 1979.
22. BEN-ARI, Y., TREMBLAY, E., AND OTTERSON, P.: Injections of kainic acid into the amygdaloid complex of the rat: an electrographic, clinical and histological study. Neuroscience **5:** 515–528, 1980.
23. BENEVENTO, L. A., REZAK, M., AND SANTOS-ANDERSON, R.: An autoradiographic study of the projections of the pretectum in the rhesus monkey (Macaca mulatta): evidence for sensorimotor links to the thalamus and oculomotor nuclei. Brain Res. **127:** 197–218, 1977.
24. BERGOUIGNAN, M., AND VERGER, P.: Les réactions labyrinthiques chez le chien apres lesion d'un noyau caudé. C. R. Soc. Biol. Paris **118:** 1539–1541, 1935.
25. BIEGON, A., TERLOU, M., VOORHUIS, TH. D., AND DE KLOET, E. R.: Arginine-vasopressin binding sites in rat brain: a quantitative autoradiographic study. Neurosci. Lett. **44:** 229–234, 1984.
26. BOAKES, R. J., EDNIE, J. M., EDWARDSON, J. A., KEITH, A. B., SAHGAL,

A., AND WRIGHT, C.: Abnormal behavioural changes associated with vasopressin induced barrel rotations. Brain Res. **326:** 65–70, 1985.
27. BORISON, H. L., AND KOVACS, B. A.: Central mechanism in pulmonary edema of nervous origin in guinea pigs. J. Physiol. (Lond.) **145:** 374–383, 1959.
28. BOUSSAOUD, D., AND JOSEPH, J. P.: Role of the cat substantia nigra pars reticulata in eye and head movements. II. Effects of local pharmacological injections. Exp. Brain Res. **57:** 297–304, 1985.
29. BRANDT, TH.: Vertigo and dizziness. *In* Diseases of the Nervous System, ed. by A. K. Asbury, G. M. McKhann, and W. I. Donald, vol. 1, pp. 561–576, W. B. Saunders, Philadelphia, 1986.
30. Brandt, Th., and Daroff, R. B.: The multisensory physiological and pathological vertigo syndromes. Ann. Neurol. **7:** 195–203, 1980.
31. BRINTON, R. E., GEE, K. W., WALMSLEY, J. K., DAVIS, T. P., AND YAMAMURA, H.I.: Regional distribution of putative vasopressin receptors in rat Brain and pituitary by quantitative autoradiography. Proc. Natl. Acad. Sci. U.S.A. **81:** 7248–7252, 1984.
32. BULJS, R. M., DEVRIES, G. J., VAN LEEWEN, F. W., AND SWAAB, D. F.: Vasopressin and oxytocin: distribution and putative functions in the brain. Prog. Brain Res. **60:** 115–122, 1983.
33. BURKE, R. E., AND FAHN, S.: Electroencephalographic studies of chlorpromazine methiodide and somatostatin-induced barrel rotation in rats. Exp. Neurol. **79:** 704–713, 1983.
34. BURKE, R. E., AND FAHN, S.: Chlorpromazine methiodide acts at the vestibular nuclear complex to induce barrel rotation in the rat. Brain Res. **288:** 273–281, 1983.
35. BURKE, R. E., AND FAHN, S.: Studies of somatostatin-induced barrel rotation in rats. Regul. Peptides **7:** 207–220, 1983.
36. BURKE, R. E., FAHN, S., WAGNER, H. R., AND SMEAL, M.: Chlorpromazine methiodide-induced barrel rotation: an antimuscarinic effect. Brain Res. **250:** 133–142, 1982.
37. BURNARD, D. M., PITTMAN, Q. P., AND VEALE, W. L.: Increased motor disturbances in response to arginine vasopressin following hemorrhage or hypertonic saline: evidence for central AVP release in rats. Brain Res. **273:** 59–65, 1983.
38. BURNARD, D. M., PITTMAN, Q. P., AND VEALE, W. L.: Potentiation of arginine-vasopressin's convulsant-like actions by somatostatin (SS): potential mechanisms of action. Soc. Neurosci. Abstr. **11:** 709, 1985.
39. BURNARD, D. M., VEALE, W. L., AND PITTMAN, Q. J.: Prevention of arginine-vasopressin-induced motor disturbances by a potent vasopressor antagonist. Brain Res. **362:** 40–46, 1986.
40. BÜTTNER-ENNEVER, J. A., AND BÜTTNER, U.: A cell group associated with vertical eye movements in the rostral mesencephalic reticular formation of the monkey. Brain Res. **151:** 31–47, 1978.
41. CARLSEN, J., AND DEOLMOS, J. S.: A modified cupric-silver technique for the impregnation of degenerating neurons and their processes. Brain Res. **208:** 426–431, 1981.
42. CARLETON, S. C., AND CARPENTER, M. S.: Distribution of primary vestibular fibers in the brainstem and cerebellum of the monkey. Brain Res. **294:** 281–298, 1984.
43. CARPENTER, M. B.: Lesions of the fastigial nuclei in the rhesus monkey. Am. J. Anat. **104:** 1–32, 1959.
44. CARPENTER, M. B., FABREGA, H., AND GLINSMANN, W.: Physiological deficits occurring with lesions of labyrinth and fastigial nuclei. J. Neurophysiol. **22:** 222–234, 1959.
45. CARPENTER, M. B., HARBISON, J. W., AND PETER, P.: Accessory oculomotor nuclei in the monkey: projections and effects of discrete lesions. J. Comp. Neurol. **140:** 131–154, 1970.
46. CARREA, R. M. E., AND METTLER, F. A.: Physiologic consequences following extensive removals of the cerebellar cortex and deep cerebellar nuclei and effect of secondary cerebral ablations in the primate. J. Comp. Neurol. **87:** 169–288, 1947.
47. CHAN-PALAY, V., ITO, M., TONGROACH, P., SAKURAI, M., AND PALAY, S.: Inhibitory effects of motilin, somatostatin, [Leu]enkephalin, [Met]enkephalin and taurine on neurons of the lateral vestibular nucleus: interactions with γ-aminobutyric acid. Proc. Natl. Acad. Sci. U.S.A. **79:** 3355–3359, 1982.
48. CLARK, S. L.: Responses following electrical stimulation of the cerebellar cortex in the normal cat. J. Neurophysiol. **2:** 19–35, 1939.
49. COHEN, S.: The vestibulo-ocular reflex arc. *In* Handbook of Sensory Physiology Vestibular System, ed. by H. H. Kornhuber et al., vol. VI/I, pp.477–549. Springer, New York.
50. COHN, M. L., AND COHN, M.: Barrel rotation induced by somatostatin in the non-lesioned rat. Brain Res. **96:** 138–141, 1975.
51. CORCORAN, M. E., CAIN, D. P., FINLAY, J. M., AND GILLIS, B. J.: Vasopressin and kindling of seizures. Life Sci. **35:** 947–952, 1984.
52. COWAN, A., ZHU, X. Z., AND PORRECA, F.: Studies in vivo with ICI 174864 and [D-Pen^{2}DD-Pen^5]enkephalin. Neuropeptides **5:** 311–314, 1985.
53. CRAMER, H., KOHLER, J., OEPEN, G., SCHONBERG, G., AND SCHROTER E: Huntington's chorea—measurements of somatostatin, substance P and cyclic nucleotides in the cerebrospinal fluid. J. Neurol. **225:** 183–187, 1981.
54. CRAMER, H., SCHAUDT, D., RISSLER, K., STRUBEL, D., WARTER, J. M., AND KUNTZMANN, F.: Somatostatin-like immunoreactivity and substance P-like immunoreactivity in the CSF of patients with senile dementia of Alzheimer type, multi-infarct syndrome and communicating hydrocephalus. J. Neurol. **232:** 346–351, 1985.
55. CRAMER, H., WOLF, A., RISSLER, K., WEIGEL, K., AND OSTERTAG, C.: Ventricular somatostatin-like immunoreactivity in patients with basal ganglia disease. J. Neurol. **232:** 219–222, 1985.
56. CRAMPTON, G. H., AND DAUNTON, N. G.: Systemic naloxone increases the incidence of motion sickness in the cat. Pharmacol. Biochem. Behav. **19:** 827–829, 1983.
57. CRANMER, R.: Nystagmus related to lesions of the central vestibular apparatus and the cerebellum. Ann. Otol. Rhinol. Laryngol. **60:** 186–196, 1951.
58. DAVID, H. A.: Order Statistics, pp. 120–124, John Wiley, New York, 1970.
59. DAVIES, P., KATZMAN, R., AND TERRY, R. D.: Reduced somatostatin-like immunoreactivity in cerebral cortex from cases of Alzheimer's disease and Alzheimer senile dementia. Nature (Lond.) **288:** 279–280, 1980.
60. DE KLOET, E. R., ROTTEVEEL, F., VOORHUIS, TH. A. M., AND TERLOU, M.: Topography of binding sites for neurohypophyseal hormones in rat brain. Eur. J. Pharmacol. **110:** 113–119, 1985.
61. DELMAS-MARSALET, P.: La cocaïnisation des labyrinthes du chien et ses effets experimentaux. C. R. Soc. Biol. Paris **116:** 56–57, 1934.
62. DELMAS-MARSALET, P.: Asymétrie des paralysies labyrinthes droit et gauche chez le chien dont un lobe préfrontale est lésé. C. R. Soc. Biol. Paris **116:** 58–60, 1934.
63. DELMAS-MARSALET, P., BERGOUIGNAN, M., AND VERGER, P.: Réactions chez le chien dont un noyau lenticulaire est détruit. C. R. Soc. Biol. Paris **119:** 1219–1221, 1935.
64. DE OLMOS, J. S., ALHEID, G. F., AND BELTRAMINO, C. A.: Amygdala. *In* The Rat Nervous System, vol. 1, Forebrain and Midbrain, ed. by G. Paxinos, pp. 223–334. Academic Press, Sydney, Australia, 1985.
65. DICKINSON, W. H.: On the functions of the cerebellum. Br. For. Med.-Chirur. Rev. **36:** 455–480, 1865.
66. DOBA, N., AND REIS, D. J.: Acute fulminating hypertension produced by brainstem lesions in the rat. Circ. Res. **32:** 584–593, 1973.
67. DOW, R. S.: Effect of lesions in the vestibular part of the cerebellum in primates. Arch. Neurol. Psychiatry **40:** 502–520, 1938.
68. DOW, R. S.: The effects of unilateral and bilateral labyrinthectomy in monkey, baboon and chimpanzee. Am. J. Physiol. **121:** 392–399, 1938.
69. DUPONT, E., CHRISTENSEN, S. E., HANSEN, A. P., OLIVERIAS, B. F., AND ORSKOV, H.: low cerebrospinal fluid somatostatin in Parkinson's disease—an irreversible abnormality. Neurology **32:** 312–314, 1982.
70. EHLERS, C., REED, T. K., WANG, M., LEBRUN, C. J., AND KOOB, J.F.: EEG effects of subcutaneous and intracerebroventricular injections of arginine-vasopressin in the rat. Psychopharmacology (Berlin) **87:** 430–433, 1985.
71. ESSIG, C. F., HAMPSON, J., MCCAULEY, A., AND HIMWICH, H. E.: An experimental analysis of biochemically induced circling behavior. J. Neurophysiol. **13:** 269–275, 1950.
72. FERNANDEZ, C., ALZATE, R., AND LINDSAY, J. R.: Experimental observations on postural nystagmus. II. Lesions of the nodulus. Ann. Otol. Rhinol. Laryngol. **69:** 94–114, 1960.
73. FERNANDEZ, C., AND FREDERICKSON, J. M.: Experimental cerebellar lesions and their effect on cerebellar function. Acta Oto-laryngol. (suppl.) **192:** 52–62, 1964.
74. FERRARO, A., AND BARRERA, S. E.: The effects of lesions of the dorsal spinocerebellar tract and corpus restiforme in the Macacus rhesus monkey. Brain **58:** 174–202, 1935.
75. FERRARO, A., AND BARRERA, S. E.: Effects of lesions of the juxtarestiform body (I.A.K. bundle) in Macacus rhesus monkeys. Arch. Neurol. Psychiatry **35:** 13–29, 1936.
76. FERRARO, A., AND BARRERA, S. E.: Differential features of "cerebellar" and "vestibular" phenomena in Macacus rhesus. Arch. Neurol. Psychiatry **39:** 902–918, 1938.
77. FERRARO, A., PACELLA, B. L., AND BARRERA, S. E.: Effects of lesions of the medial vestibular nucleus. J. Comp. Neurol. **73:** 7–36, 1940.
78. FERRIER, D., AND TURNER, W. A.: A record of experiments illustrative of the symptomatology and degenerations following lesions of the cerebellum and its peduncles and related structures in monkeys. Phil. Trans. R. Soc. London Ser. B 185: 719–779, 1894.
79. FRENK, H., WATKINS, L. R., AND MAYER, D. J.: Differential behavioral effects induced by intrathecal microinjection of opiates: comparison of convulsive and cataleptic effects produced by morphine, methadone and D-Ala^2-methionine-enkephalinamide. Brain Res. **299:** 31–42, 1984.
80. FUKUSHIMA, K., TAKAHASHI, K., FUKUSHIMA, J., OHNO, M., KIMURA, T., AND KATO, M.: Effects of lesion of the interstitial nucleus of Cajal on vestibular nuclear neurons activated by vertical vestibular stimulation. Exp. Brain Res. **64:** 496–504, 1986.
81. FUKUSHIMA, K., TAKAHASHI, K., KUDO, J., AND KATO, M.: Interstitial-vestibular interaction in the control of head posture. Exp. Brain Res. **57:** 264–270, 1985.
82. FUKUSHIMA, K., TERASHIMA, T., KUDO, J., INOUE, Y., AND KATO, M.: Projections of the group y of the vestibular nuclei and the dentate and fastigial nuclei of the cerebellum to the interstitial nucleus of Cajal. Neurosci. Res. **3:** 285–299, 1986.
83. FULTON, J. F., AND DOW, R. S.: The cerebellum: a summary of functional localization. Yale J. Med. Biol. **10:** 89–119, 1937.
84. GARCIA-SEVILLA, J. A., MAGNUSSON, T., AND CARLSSON, A.: Effect of

intracerebroventricularly administered somatostatin on brain monoamine turnover. Brain Res. 155: 159–164, 1978.
85. GERFEN, C. R., STAINES, W. A., ARBUTHNOTT, G. A., AND FIBIGER, H. C.: Crossed connections of the substantia nigra in the rat. J. Comp. Neurol. 207: 283–303, 1982.
86. GORENSTEIN, C., BUNDMAN, M. C., BRUCE, J. L., AND ROTTER, A.: Neuronal localization of pseudocholinesterase in the rat cerebellum: sagittal bands of Purkinje cells in the rat nodulus and uvula. Brain Res. 418: 68–75, 1987.
87. GRANT, G., ASCHAN, G., AND EKVALL, L.: Nystagmus produced by localised cerebellar lesions. Acta Oto-laryngol. (suppl.) 192: 78–84, 1964.
88. HASSLER, R., AND HESS, W. R.: Experimentelle und anatomische Befunde über die Drehbewegungen und ihre nervösen Apparate. Arch. Psychiatr. Z. Neurol. 192: 488–526, 1954.
89. HAVLICEK, V., AND FRIESEN, H. G.: Comparison of behavioral effects of somatostatin and beta-endorphin in animals. *In* Central Nervous System Effects of Hypothalamic Hormones and Other Peptides, ed. by R. Collu, pp. 381–402, Raven Press, New York, 1979.
90. HAWTHORN, J., ANG, V. T. Y., AND JENKINS, J. S.: Localization of vasopressin in the rat brain. Brain Res. 197: 75–81, 1980.
91. HERMAN, B. H., LESLIE, H. F., AND GOLDSTEIN, A.: Behavioral effects and in vivo degradation of incerebroventricularly administered dynorphin(1–13) and D-ala²-dynorphin(1–11) in rats. Life Sci. 27: 883–892, 1980.
92. HERRERA-MARSCHITZ, M., HÖKFELT, T., UNGERSTEDT, U., AND TERENIUS, L.: Functional studies with the opiate peptide dynorphin: acute effects of injections into substantia nigra reticulata of naive rats. Life Sci. 33 (suppl. I): 555–558, 1983.
93. HOUSER, C. R., CRAWFORD, G. D., BARBER, R. P., SALVATERRA, P. M., AND VAUGHN, J. E.: Organization and morphological characteristics of cholinergic neurons: an immunocytochemical study with a monoclonal antibody to choline acetyltransferase. Brain Res. 266: 97–119, 1983.
94. HUERTA, M. F., AND HARTING, J. K.: Tectal control of spinal activity: neuroanatomical demonstration of pathways connecting the superior colliculus with the cervical spinal cord grey. Prog. Brain Res. 57: 293–328, 1982.
95. HUNTSBERGER, D. V., AND BILLINGSLEY, P.: Elements of Statistical Inference, 4th ed., Allyn and Bacon, Boston, 1977.
96. IMPERATO, A., NICOLETTI, F., DIANA, M., SCAPAGNINI, U., AND DI CHIARA, G.: Fastigial influences on postural tonus as studied by kainate lesions and by local infusion of GABAergic drugs in the rat. Brain Res. 295: 51–63, 1984.
97. ITO, M.: The Cerebellum and Motor Control, Raven Press, New York, 1984.
98. IWAMOTO, E. T., AND WAY, E. L.: Circling behavior and stereotypy induced by intranigral opiate injections. J. Pharmacol. Exp. Ther. 203: 347–359, 1977.
99. JAMES, T. A., AND STARR, M. S.: Effects of substance P injected into the substantia nigra. Br. J. Pharmacol. 65: 423–429, 1979.
100. JOHANSSON, O., HÖKFELT, T., AND ELDE, R. P.: Immunohistochemical distribution of somatostatin-like immunoreactivity in the central nervous system of the adult rat. Neuroscience 13: 265–339, 1984.
101. JOLKKONEN, J., SOININEN, H., HALONEN, T., YLINEN, A., LAULUMAA, V., LAAKSO, M., AND RIEKKINEN, P.: Somatostatin-like immunoreactivity in the cerebrospinal fluid of patients with Parkinson's disease and its relation to dementia. J. Neurol. Neurosurg. Psychiatry 49: 1374–1377, 1986.
102. JONES, P. M., ROBINSON, I. C., AND HARRIS, M. C.: Release of oxytocin into blood by electrical stimulation of hypothalamus or neural lobe in the rat. Neuroendocrinology 37: 454–458, 1983.
103. KANEKO, T., NAKAZAWA, T., IKEDA, M., YAMATSU, K., IWAMA, T., WADA, T., SATOH, M., AND TAKAGI, H.: Sites of analgesic action of dynorphin. Life Sci. 33 (suppl. I): 661–664, 1983.
104. KASTIN, A., COY, D. H., JACQUET, Y., SCHALLY, A. V., AND PLOTNIKOFF, N. P.: CNS effects of somatostatin. Metabolism 27 (suppl. 1): 1247–1252, 1978.
105. KASTING, N. W., VEALE, W. L., AND COOPER, K. E.: Convulsive and hypothermic effects of vasopressin in the brain of the rat. Can. J. Physiol. Pharmacol. 58: 316–319, 1980.
106. KASTING, N. W., VEALE, W. L., COOPER, K. E., AND LEDERIS, K.: Vasopressin may mediate febrile convulsions. Brain Res. 213: 327–333, 1981.
107. KATAYAMA, S., AND NISIMARU, N.: Parasagittal zonal pattern of olivonodular projections in rabbit cerebellum. Neurosci. Res. 5: 424–438, 1988.
108. KATZ, R. J.: Behavioral effects of dynorphin—a novel opiate peptide. Neuropharmacology 19: 801–803, 1980.
109. KAZMIERSKI, W., WIRE, W. S., LUI, G. K., KNAPP, R. J., SHOOK, J. E., BURKS, T. F., YAMAMURA, H. I., AND HRUBY, V. J.: Design and synthesis of somatostatin analogues with topographic properties that lead to highly potent and specific μ-opioid receptor antagonists with greatly reduced binding at somatostatin receptors. J. Med. Chem. 131: 2170–2177, 1988.
110. KELLY, J., ALHEID, G. F., NEWBERG, A., AND GROSSMAN, S. P.: GABA stimulation and blockade in the hypothalamus and midbrain: effects on feeding and locomotor activity. Pharmacol. Biochem. Behav. 7: 537–541, 1977.
111. KIM, R., NAKANO, K., JAYARAMAN, A., AND CARPENTER, M. B.: Projections of the globus pallidus and adjacent structures: an autoradiographic study in the monkey. J. Comp. Neurol. 169: 263–289, 1976.
112. KIMURA, H., MCGEER, P. L., PENG, J. H., AND MCGEER, E. G.: The central cholinergic system studied by choline acetyltransferase immunohistochemistry in the cat. J. Comp. Neurol. 200: 151–200, 1981.
113. KING, J. R.: Probability Charts for Decision Making, pp. 177–202, Industrial Press, New York, 1971.
114. KIRSTEN, E. B., AND SCHOENER, E. P.: Action of anticholinergic and related agents on single vestibular neurons. Neuropharmacology 12: 1167–1177, 1973.
115. KIRSTEN, E. B., AND SHARMA, J. N.: Characteristics and response differences to iontophoretically applied norepinephrine, D-amphetamine and acetylcholine on neurons in the medial and lateral vestibular nuclei of the cat. Brain Res. 112: 77–90, 1976.
116. KOHLER, J., SCHROTER, E., AND CRAMER, H.: Somatostatin-like immunoreactivity in the cerebrospinal fluid of neurological patients. Arch. Psychiat. Nervenkr. 231: 503–508, 1982.
117. KORDOWER, J. H., AND BODNAR, R. J.: Vasopressin analgesia: specificity of action and non-opioid effects. Peptides 5: 747–756, 1984.
118. KOZLOWSKI, G. P., NILAVER, G., AND ZIMMERMAN, E. A.: Distribution of neurohypophyseal hormones in the brain. Pharmacol. Ther. 21: 325–349, 1983.
119. KRUSE, H., WIMERSMA-GREIDANUS, TJ. B., AND DEWIED, D.: Barrel rotation induced by vasopressin and related peptides in rats. Pharmacol. Biochem. Behav. 7: 311–313, 1977.
120. LACZI, F., GAFFORI, O., FEKETE, M., DE KLOET, E. R., AND DE WIED, D.: Levels of arginine-vasopressin in cerebrospinal fluid during passive avoidance behavior in rats. Life Sci. 34: 2385–2391, 1984.
121. LAWLESS, J. F.: Statistical Models and Methods for Lifetime Data, 580 pp., John Wiley and Sons, New York, 1982.
122. LEVEN, M., AND OLLIVIER, A.: Recherches sur la physiologie et la pathologie du cervelet. Arch. Gen. Med. 5 S. 20: 513–525, 1862.
123. LEVINGER, I.: The cerebral ventricles of the rat. J. Anat. 108: 447–451, 1971.
124. LJUNGDAHL, A., HÖKFELT, T., AND NILSSON, G.: Distribution of substance p-like immunoreactivity in the central nervous system of the rat. I. Cell bodies and nerve terminals. Neuroscience 3: 861–943, 1978.
125. LLINAS, R., WALTON, K., HILLMAN, D. E., AND SOTELO, C.: Inferior olive: its role in cerebellar learning. Science 190: 1230–1231, 1975.
126. LOCKRIDGE, O.: Substance P hydrolysis by human serum cholinesterase. J. Neurochem. 39: 106–110, 1982.
127. LONGET, F. A.: Anatomie et Physiologie du Système Nerveux de l'Homme et des Animaux Vertébrés, Masson, Paris, 1842.
128. LUCIANI, L.: Il cervelletto: Nuovi studi di fisiologia normale et pathologica, Le Monnier, Florence, 1891.
129. MAGENDIE, M.: Mémoire sur les fonctions de quelques parties du système nerveux. J. Physiol. Exp. Pathol. Paris 4: 399–407, 1824.
130. MAGNUSSON, T., CARLSSON, A., FISHER, G. H., CHANG, D., AND FOLKERS, K.: Effect of synthetic substance P on monoaminergic mechanisms in brain. J. Neural Transm. 38: 89–93, 1976.
131. MAITI, A., SHAHID SALLES, K., GRASSI, S., AND ABOOD, L. G.: Barrel rotation and prostration by vasopressin and nicotine in the vestibular cerebellum. Pharmacol. Biochem. Behav. 25: 583–588, 1986.
132. MALTHE-SORENSSON, D., WOOD, P. L., CHENEY, D. L., AND COSTA, E.: Modulation of the turnover rate of acetylcholine by intraventricular injections of thyrotropin-releasing hormone, somatostatin, neurotensin and angiotensin II. J. Neurochem. 31: 685–691, 1978.
133. MANN, J. F. E., BOUCHER, R., AND SCHILLER, P. W.: Rotational syndrome after central injection of C-terminal 7-peptide of cholecystokinin. Pharmacol. Biochem. Behav. 13: 125–127, 1980.
134. MANNI, E., AND DOW, R.: Some observations on the effects of cerebellectomy in the rat. J. Comp. Neurol. 121: 189–194, 1963.
135. MANSOUR, A., KHATCHATURIAN, H., LEWIS, M. E., AKIL, H., AND WATSON, S. J.: Autoradiographic differentiation of mu, delta and kappa opioid receptors in rat forebrain and midbrain. J. Neurosci. 7: 2445–2464, 1987.
136. MANSOUR, A., KHATCHATURIAN, H., LEWIS, M. E., AKIL, H., AND WATSON, S. J.: Anatomy of CNS opioid receptors. TINS Trends Neurosci. 11: 308–314, 1988.
137. MATSUOKA, I., AND DOMINO, E. F.: Cholinergic mechanisms in the cat vestibular system. Neuropharmacology 14: 201–210, 1975.
138. MCDONALD, J. V.: Responses following electrical stimulation of anterior lobe of cerebellum in cat. J. Neurophysiol. 16: 69–84, 1953.
139. MENS, W. B. J., ANDRINGA-BAKKER, E. A. D., AND VAN WIMERSMA GREIDANUS, TJ. B.: Changes in cerebrospinal fluid level of vasopressin and oxytocin of the rat during various light-dark regimes. Neurosci. Lett. 34: 51–56, 1982.
140. MENS, W. B. J., LACZI, F., TONNAER, J. A. D. M., DE KLOET, E. R., AND VAN WIMERSMA GREIDANUS, TJ. B.: Vasopressin and oxytocin content in cerebrospinal fluid and in various brain areas after administration of histamine and pentylenetetrazole. Pharmacol. Biochem. Behav. 19: 587–591, 1983.
141. MERCHENTHALER, I., MADERDRUT, J. L., ALTSCHULER, R. A., AND PETRUSZ, P.: Immunocytochemical localization of proenkephalin-derived peptides in the central nervous system of the rat. Neuroscience 17: 325–348, 1986.
142. METTLER, F. A.: Relation between pyramidal and extrapyramidal function. Proc. Assoc. Res. Nerv. Ment. Dis. 21: 150–227, 1942.

143. METTLER, F. A.: Effects of bilateral simultaneous subcortical lesions in the primate. J. Neuropathol. Exp. Neurol. **4:** 99–122, 1945.
144. METTLER, F. A., AND METTLER, C. C.: Labyrinthine disregard after removal of the caudate. Proc. Soc. Exp. Biol. Med. **45:** 473–475, 1940.
145. MITCHELL, S. W.: Researches on the physiology of the cerebellum. Am. J. Med. Sci. **57:** 320–338, 1869.
146. MIYOSHI, R., KITO, S., MIZUNO, K., AND MATSUBAYASHI, H.: Is the effect of somatostatin on muscarinic receptors selective to M1 type? Brain Res. 377: 348–350, 1986.
147. MIYOSHI, R., KITO, S., MIZUNO, K., AND MATSUBAYASHI, H.: Effects of somatostatin on muscarinic acetylcholine receptor binding in the rat hippocampus. Jpn. J. Pharmacol. **40:** 291–296, 1986.
148. MORRIS, M., BARNARD, R. R., JR., AND SAIN, L. E.: Osmotic mechanisms regulating cerebrospinal fluid vasopressin and oxytocin in the conscious rat. Neuroendocrinology **39:** 377–383, 1984.
149. MUSKENS, L. J. J.: Studies on the maintenance of the equilibrium of motion and its disturbances, so-called "forced movements." J. Physiol. (Lond.) **31:** 204–221, 1904.
150. MUSKENS, L. J. J.: An anatomico-physiological study of the posterior longitudinal bundle in its relation to forced movements. Brain **36:** 352–426, 1914.
151. MUSKENS, L. J. J.: The central connections of the vestibular nuclei with the corpus striatum, and their significance for ocular movements and for locomotion. Brain **45:** 454–478, 1922.
152. MUSSEN, A. T.: Experimental investigations on the cerebellum. Brain **50:** 313–348, 1927.
153. MUSSEN, A. T.: The cerebellum. The method of stimulation and the influence of the localized reactions in determining the course of disputed fissures, the grouping of the lobes, and the exact homology that exists between the lobes and fissures of the cerebella of the cat, monkey and man. J. Nerv. Ment. Dis. **71:** 185–193, 1930.
154. MUSSEN, A. T.: The cerebellum. Comparison of symptoms resulting from lesions of individual lobes with reactions of the same lobes to stimulation: a preliminary report. Arch. Neurol. Psychiatry **25:** 702–722, 1931.
155. MUSSEN, A. T.: Cerebellum and red nucleus. A preliminary report on a new method of physiologic investigation. Arch. Neurol. Psychiatry **31:** 110–126, 1934.
156. NAYLOR, A. M., RUWE, W. D., BURNARD, D. M., MCNEELY, P. D., TURNER, S. L., PITTMAN, Q. J., AND VEALE, W. L.: Vasopressin-induced motor disturbances: localization of a sensitive forebrain site in the rat. Brain Res. **361:** 242–246, 1985.
157. NORTHINGTON, P., AND BARRERA, S. E.: Effects of unilateral and bilateral labyrinthectomy and intracranial section of eighth nerve. Experiments on monkeys. Arch. Neurol. Psychiatry **32:** 51–71, 1934.
158. OLEY, N., CORDOVA, C., KELLY, M. L., AND BRONZINO, J. D.: Morphine adiminstration to the region of the solitary nucleus produces analgesia in rats. Brain Res. **236:** 511–515, 1982.
159. ORAM, J. J., EDWARDSON, J., AND MILLARD, P. H.: Investigation of cerebrospinal fluid neuropeptides in idiopathic senile dementia. Gerontology **27:** 216–223, 1981.
160. PASIK, T., PASIK, P., AND BENDER, M. B.: The pretectal syndrome in monkeys. II. Spontaneous and induced nystagmus, and "lightning" eye movements. Brain **92:** 871–884, 1969.
161. PATEL, Y. C., RAO, K., AND REICHLIN, S.: Somatostatin in human cerebrospinal fluid. N. Engl. J. Med. **296:** 529–533, 1977.
162. PERRY, D. C.: Barrel rotation in rats induced by intracerebroventricular bradykinin antagonists. Pharmacol. Biochem. Behav. **28:** 15–20, 1987.
163. PETRIE, E. C., TIFFANY, B. T., BAKER, T. S., AND DAHL, J. L.: Dynorphin[1–13]: Analgesia, hypothermia, cross-tolerance with morphine and beta-endorphin. Peptides **3:** 41–47, 1982.
164. PHELAN, K. D., AND GALLAGHER, J. P.: The effects of cholinergic agonists on the passive membrane properties of rat medial vestibular nucleus neurons in vitro. Soc. Neurosci. Abstr. **14:** 331, 1988.
165. PITKANEN, A., JOLKKONEN, J., AND RIEKKINEN, P.: Effect of pentylenetetrazol-induced convulsions on somatostatin-like immunoreactivity in rat cerebrospinal fluid. Neuropeptides **9:** 19–24, 1987.
166. PITKANEN, A., SIRVIO, J., JOLKKONEN, J., AND RIEKKINEN, P.: Somatostatin-like immunoreactivity and somatostatin receptor binding in rat brain before and after pentylenetetrazol-induced convulsion. Neuropeptides **7:** 63–71, 1986.
167. POURFOUR DU PETIT, F.: Lettres d'un Medicin des Hôpitaux du Roy à un autre Medicin de ses Amis, pp. 19–20, Charles Gerard Albert, 1710.
168. RASKIND, M. A., PESKIND, E. R., LAMPE, T. H., RISSE, S. C., TABORSKY, G. J., JR., AND DORSA, D.: Cerebrospinal fluid vasopressin, oxytocin, somatostatin and beta endorphin in AIzheimer's disease. Arch. Gen. Psychiatry **43:** 382–388, 1986.
169. REASON, J. T., AND BRAND, J.: Motion Sickness, Academic Press, London,1975.
170. REEDER, R. E., NATTIE, E. E., AND NORTH, W. G.: Effect of vasopressin on cold-induced brain edema in cats. J. Neurosurg. **64:** 941–950, 1986.
171. REICHERT, W. H., DOOLITTLE, J., AND MCDOWELL, F. H.: Vestibular dysfunction in Parkinson disease. Neurology **32:** 1133–1138, 1982.
172. REPPERT, S. M., ARTMAN, H. G., SWANINATHAN, S., AND FISHER, D. A.: Vasopressin exhibits a rhythmic daily pattern in cerebrospinal fluid but not in blood. Science **213:** 1256–1257, 1981.
173. REPPERT, S. M., SCHWARTZ, W. J., ARTMAN, H. G., AND FISHER, D. A.: Comparison of the temporal profiles of vasopressin and oxytocin in the cerebrospinal fluid of the cat, monkey and rat. Brain Res. **261:** 341–345, 1983.
174. REZEK, M., HAVLICEK, V., HUGHES, K. R., AND FRIESEN, H.: Cortical administration of somatostatin (SRIF): effect on sleep and motor behavior. Pharmacol. Biochem. Behav. **5:** 73–77, 1976.
175. REZEK, M., HAVLICEK, V., HUGHES, K. R., AND FRIESEN, H.: Central site of actions of somatostatin: role of hippocampus. Neuropharmacology **15:** 499–504, 1976.
176. REZEK, M., HAVLICEK, V., HUGHES, K. R., AND FRIESEN, H.: Behavioral and motor excitation and inhibition induced by the administration of small and large doses of somatostatin into the amygdala. Neuropharmacology **16:** 157–162, 1977.
177. REZEK, M., HAVLICEK, V., LEYBIN, L., LABELLA, F. S., AND FRIESEN, H.: Opiate-like naloxone-reversible actions of somatostatin given intracerebrally. Can. J. Physiol. Pharmacol. **56:** 227–231, 1978.
178. REZEK, M., HAVLICEK, V., LEYBIN, L., PINSKY, C., KROEGER, E. A., HUGHES, K. R., AND FRIESEN, H.: Neostriatal administration of somatostatin: differential effect of small and large doses on behavior and motor control. Can. J. Physiol. Pharmacol. **55:** 234–242, 1977.
179. RISPAL-PADEL, L., CICIRATA, F., AND PONS, C.: Cerebellar nuclear topography of simple, and synergistic movements in the alert baboon (Papio papio). Exp. Brain Res. **47:** 365–380, 1982.
180. ROBINSON, I. C.: Neurohypophyseal peptides in cerebrospinal fluid. Prog. Brain Res. **60:** 129–145, 1983.
181. RON, S., AND ROBINSON, D. A.: Eye movements evoked by cerebellar stimulation in the alert monkey. J. Neurophysiol. **36:** 1004–1022, 1973.
182. ROSSOR, M. N., EMSON, P. C., MOUNTJOY, C. Q., ROTH, M., AND IVERSON, L. L.: Reduced amounts of immunoreactive somatostatin in the temporal cortex in senile dementia of the AIzheimer type. Neurosci. Lett. **20:** 373–377, 1980.
183. ROTHMAN, R. B., HERKENHAM, M., PERT, C. B., LIANG, T., AND CASCIERI, M. A.: Visualization of rat brain receptors for the neuropeptide, substance P. Brain Res. **309:** 47–54, 1984.
184. ROTROSEN, J., STANLEY, M., KUHN, C., WAZER, D., AND GERSHON, S.: Experimental dystonia induced by quaternary chlorpromazine. Neurology **30:** 878–881, 1980.
185. ROTTER, A., BIRDSALL, N. J. M., BURGEN, A. S. V., HULME, E. C., AND RAISMAN, G.: Muscarinic receptor in the central nervous system of the rat. I. Autoradiographic localization of the binding of ^{3}H-propylbenzilylcholine mustard and its distribution in the forebrain. Brain Res. Rev. **1:** 141–165, 1979.
186. ROTTER, A., BIRDSALL, N. J. M., FIELD, P. M., AND RAISMAN, G.: Muscarinic receptor in the central nervous system of the rat. I. Distribution of the binding of ^{3}H-propylbenzilylcholine mustard in the midbrain and hindbrain. Brain Res. Rev. **1:** 167–183, 1979.
187. RUTHERFORD, J. G., AND GWYN, D. G.: A light and electron microscopic study of the interstitial nucleus of Cajal in the rat. J. Comp. Neurol. **205:** 327–340, 1982.
188. RUSSELL, J. S. R.: Experimental researches into functions of the cerebellum. Phil. Trans. R. Soc. London Ser. B. **185:** 819–862, 1894.
189. RUSSELL, J. S. R. : The effects of interrupting afferent and efferent tracts of the cerebellum. Brit. Med. J. **2:** 914–915, 1896.
190. SCHAEFFER, K. P., AND MEYER, D. L.: Compensation of vestibular lesions. *In* Handbook of Sensory Physiology, ed. by H. H. Kornhuber, vol. VI/2, pp. 461–490, Springer-Verlag, Berlin, 1974.
191. SCHWARTZMAN, R. J., AND ALEXANDER, G. M.: Changes in the local cerbral metabolic rate for glucose in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) primate model of Parkinson's disease. Brain Res. **358:** 137–143, 1985.
192. SEVERS, W. B., SUMMY-LONG, J. Y., TAYLOR, J. S., AND CONNOR, J. D.: A central effect of angiotensin: release of pituitary pressor material. J. Pharmacol. Exp. Ther. **174:** 27–34, 1970.
193. SHANZER, S., AND BENDER, M.: Oculomotor responses on vestibular stimulation of monkeys with lesions of the brain-stem. Brain **82:** 669–682, 1959.
194. SNYDER, D. W., NATHAN, M. A., AND REIS, D. J.: Chronic liability of arterial pressure produced by selective destruction of the catecholamine innervation of the nucleus tractus solitarii. Circ. Res. **43:** 662–671, 1978.
195. SOFRONIEW, M. V.: Morphology of vasopressin and oxytocin neurons and their central processes. Prog. Brain Res. **60:** 101–114, 1983.
196. SOFRONIEW, M. V.: Vasopressin and oxytocin in the mammalian brain and spinal cord. TINS 6: 467–472, 1983.
197. SOININEN, H. S., JOLKKONEN, J. T., REINIKAINEN, K. J., HALONEN, T. O., AND REIKKINEN, P. J.: Reduced cholinesterase activity and somatostatin-like immunoreactivity in the cerebrospinal fluid of patients with dementia of the Alzheimer type. J. Neurol. Sci. **63:** 167–172, 1984.
198. SORENSEN, P. S., GJERRIS, F., AND HAMMER, M.: Cerebrospinal fluid vasopressin and increased intracranial pressure. Ann. Neurol. **15:** 435–440, 1984.
199. SORENSEN, P. S., GJERRIS, F., AND HAMMER, M.: Cerebrospinal fluid vasopressin in neurological and psychiatric disorders. J. Neurol. Neurosurg. Psychiatry **48:** 50–57, 1985.

200. SORENSEN, P. S.: Studies of vasopressin the the human cerebrospinal fluid. Acta Neurol. Scand. **74:** 81–102, 1986.
201. SORENSON, K. V., CHRISTENSEM, S. E., DUPONT, E., HANSEN, A. P., PEDERSON, E., AND OSKOV, A.: Low somatostatin content in cerebrospinal fluid in multiple sclerosis. Acta Neurol. Scand. **61:** 186–191, 1980.
202. SPIEGEL, E. A., AND SCALA, N. P.: Vertical nystagmus following lesions of the cerebellar vermis. Arch. Ophthalmol. **26:** 661–669, 1941.
203. SPIEGEL, E. A., AND SCALA, N. P.: Positional nystagmus in cerebellar lesions. J. Neurophysiol. **5:** 248–260, 1942.
204. SPRAGUE, J. M., AND CHAMBERS, W. W.: Regulation of posture in intact and decerebrate cat. I. Cerebellum, reticular formation and vestibular nuclei. J. Neurophysiol. **16:** 451–463, 1953.
205. SPRAGUE, J. M., AND CHAMBERS, W. W.: Control of posture by reticular formation and cerebellum in the intact, anesthetized and unanesthetized and in the decerebrated cat. Am. J. Physiol. **176:** 52–64, 1954.
206. STARCEVIC, V. P., BALABAN, C. D., AND SEVERS, W. B.: Effects of arginine-vasopressin on somatostatin-induced barrel rotation, and convulsions in rats. Soc. Neurosci. Abstr. **14:** 267, 1988.
207. STEPIEN, H., STAWOWY, A., CIESLAK, D., BRZEZINSKI, J., AND PAWLIKOWSKI, M.: Increased CSF levels of somatostatin in patients with brain tumours, and intracranial hypertension. Horm. Metabol. Res. **18:** 555–557, 1986.
208. SUMMY-LONG, J. Y., KEIL, L. C., SELLS, G., KIRBY, A., CHEE, O., AND SEVERS, W. B.: Cerebroventricular sites for enkephalin inhibition of the central actions of angiotensin. Am. J.Physiol. **244:** R522–R529, 1983.
209. SWAAB, D. F.: Neuropeptides: their distribution and function in the brain. Prog. Brain Res. **55:** 97–122, 1981.
210. SZCZEPANSKA-SADOWSKA, E., SIMON-OPPERMANN, C., GRAY, D. A., AND SIMON, E.: Plasma and cerebrospinal fluid vasopressin in relation to thirst. Pflügers Arch. **400:** 294–299, 1984.
211. TALMAN, W. T., PERRONE, M. H., AND REIS, D. J.: Acute hypertension after local injection of kainic acid into nucleus tractus solitarii of rats. Circ. Res. **48:** 292–298, 1981.
212. TAYLOR, R. J., REAVILL, C., JENNER, P., AND MARSDEN, C. P.: Circling behavior following unilateral kainic acid injections into rat striatum. Eur. J. Pharmacol. **76:** 211–222, 1981.
213. TEMPEL, A., AND ZUKIN, R. S.: Neuroanatomical patterns of the μ, δ, and κ opioid receptors of rat brain as determined by quantitative in vitro autoradiography. Proc. Natl. acad. Sci. U.S.A. **54:** 4308–4312, 1987.
214. TERÄVÄINEN, H., AND CALNE, D. B.: Studies of parkinsonian movement. 2. Initiation of fast voluntary eye movement during postural disturbance. Acta Neurol. Scand. **62:** 149–157, 1980.
215. THURSTON, C. L., CULHANE, E. S., SUBERG, S. N., CARSTENS, E., AND WATKINS, L. R.: Antinociception vs. motor effects of intrathecal vasopressin as measured by four pain tests. Brain Res. **463:** 1–11, 1988.
216. TRIBOLLET, E., BARBERIS, C., JARD, S., DUBOIS-DAUPHIN, M., AND DREIFUSS, J. J.: Localization and pharmacological characterization of high affinity binding sites for vasopressin and oxytocin in the rat brain by light microscopic autoradiography. Brain Res. **442:** 105–118, 1988.
217. UEMURA, T., AND COHEN, S.: Vestibulo-ocular reflexes: effects of vestibular nuclear lesions. Prog. Brain Res. **37:** 515–528, 1972.
218. UHL, G. R., TRAN, V., SNYDER, S. H., AND MARTIN, J. S.: Somatostatin receptors: distribution in rat central nervous system and human frontal cortex. J. Comp. Neurol. **240:** 288–304, 1985.
219. VIJAYAN, E., AND MCCANN, S. M.: Suppression of feeding and drinking activity in rats following intraventricular injection of thyrotropin releasing hormone. Endocrinology **100:** 1727–1730, 1977.
220. VINCENT, S. R., MCINTOSH, C. H. S., BUCHAN, A. M. J., AND BROWN, J. C.: Central somatostatin systems revealed with monoclonal antibodies. J. Comp. Neurol. **238:** 169–186, 1985.
221. VULPIAN, A.: Leçons sur la Physiologie Générale et Comparée du Système Nerveux faites au Muséum d'Histoire Naturelle, pp. 583–602, G. Baillière, Paris, 1866.
222. WALMSLEY, J. K., LEWIS, M. S., YOUNG, W. S., III, AND KUHAR, M. J.: Autoradiographic localization of muscarinic cholinergic receptors in rat brainstem. J. Neurosci. **1:** 176–191, 1981.
223. WATKINS, L. R., FRENK, H., MILLER, J., AND MAYER, D. J.: Cataleptic effects of opiates following intrathecal administration. Brain Res. **299:** 43–49, 1984.
224. WATSON, S. J., AKIL, H., FISCHLI, W., GOLDSTEIN, A., ZIMMERMAN, E., NILAVER, G., AND VAN WIMERSMA GREIDANUS, TJ. B.: Dynorphin and vasopressin: common localization in magnocellular neurons. Science **216:** 85–87, 1982.
225. WATSON, T. W. J., AND PITTMAN, Q. J.: Pharmacological evidence that somatostatin activates the m-current in hippocampal pyramidal neurons. Neurosci. Lett. **91:** 172–176, 1988.
226. WHITE, O. S., SAINT-CYR, J. A., AND SHARPE, J. A.: Ocular motor deficits in Parkinson's disease. I. The horizontal vestibulo-ocular reflex and its regulation. Brain **106:** 555–570, 1983.
227. WHITE, O. S., SAINT-CYR, J. A., TOMLINSON, R. D., AND SHARPE, J. A.: Ocular motor deficits in Parkinson's disease: II. Control of the saccadic and smooth pursuit systems. Brain **106:** 571–587, 1983.
228. WILSON, V. J., AND MELVILL JONES, G.: Mammalian Vestibular Physiology, Plenum Press, New York, 1979.
229. WOOD, P. L., CHENEY, D. L., AND COSTA, E.: Modulation of the turnover rate of hippocampal acetylcholine by neuropeptides: possible site of action of alphamelanocytestimulating hormone, adrenocorticotrophic hormone and somatostatin. J. Pharmacol. Exp. Ther. **209:** 97–103, 1979.
230. WOOD, P. L., ETIENNE, P., LAL, S., GAUTIER, S., CAJAL, S., AND NAIR N. P. V.: Reduced lumbar CSF somatostatin levels in Alzheimer's disease. Life Sci. **31:** 2073–2079, 1982.
231. WURPEL, J. N. D.: Barrel Rotation Evoked by Central Administration of Arginine Vasopressin: Neurobiological and Pharmacological Effects in Conscious Rats. Ph.D. Disseration, The Pennsylvania State University, 1986.
232. WURPEL, J. N. D., DUNDORE, R. L., BARBELLA, Y. R., BALABAN, C. D., KEIL, L. C., AND SEVERS, W. B.: Seizures evoked by intracerebroventricular vasopressin injections in conscious rats: description and general pharmacology. Brain Res. **365:** 21–29, 1986.
233. WURPEL, J. N. D., DUNDORE, R. L., BARBELLA, Y. R., BALABAN, C. D., KEIL, L. C., AND SEVERS, W. B.: Seizures evoked by intracerebroventricular vasopressin injections in conscious rats: visual/vestibular interactions and efficacy of anti-seizure drugs. Brain Res. **365:** 30–41, 1986.
234. WURPEL, J. N. D., DUNDORE, R. L., BALABAN, C. D., KEIL, L. C., AND SEVERS, W. B.: Vasopressin-induced seizures (barrel rotation) after lesions of substantia nigra and basal ganglia. Fed. Proc. **44:** 1389, 1985.
235. YAMADA, K., AND FURUKAWA, T.: Barrel rotation induced by vasopressin and involvement of dopaminergic and cholinergic functions in rats. Arch. Int. Pharmacodyn. Ther. **251:** 88–94, 1984.
236. ZAINOS, A., DEANDA, R., CHAVEZ, L., AND GARCIA-MUNOZ, M.: Turning behavior, barrel rolling and sensory neglect induced by picrotoxin in the thalamus. Exp. Neurol. **83:** 534–547, 1984.
237. ZAMIR, N., PALKOVITS, M., AND BROWNSTEIN, M. J.: Distribution of immunoreactive dynorphin in the central nervous system of the rat. Brain Res. **280:** 81–93, 1983.
238. ZEE, D. S., YAMAZAKI, A., BUTLER, P. H., AND GÜCER, G.: Effects of ablation of flocculus and parafloccullus on eye movements in primate. J. Neurophysiol. **46:** 878–899, 1981.
239. ZEE, D. S., YEE, R. D., COGAN, D. G., AND KING ENGEL, W.: Ocular motor abnormalities in hereditary cerebellar ataxia. Brain **99:** 207–234, 1976.
240. ZETLER, G.: Neuropharmacological profile of cholecystokinin-like peptides. Ann. N.Y. Acad. Sci. **448:** 448–469, 1985.