©1987 The Institute of Mind and Behavior, Inc.
The Journal of Mind and Behavior
Autumn 1987, Volume 8, Number 4
Pages 591 [115]–604 [128]
ISSN 0271–0137
ISBN 0–930195–04–3

What Do GABA Neurons Really Do? They Make Possible Variability Generation in Relation to Demand

Eugene Roberts

Beckman Research Institute of the City of Hope

It is proposed that GABA neurons play key roles in maintaining meaningful communications within and among neural units by making possible variability generation in relation to demand. Activities of GABAergic inhibitory projection neurons from command centers and local circuit GABAergic inhibitory interneurons allow adaptive nervous system function to take place in a manner characterized by freedom without license. Through their multiple activities and connections these neurons make possible smooth transitions between modes of nervous system function over a range of increasing demands (neural pressures), enabling organisms to explore full ranges of their options.

Living organisms are programmed to attain certain goals: survival and reproduction. Their functions are aimed at achieving and maintaining maximal behavioral flexibility in reacting to and acting upon the environment, while keeping them prepared to face the unexpected. A key organizing principle of adaptive function is the coupling of variability generation to functional demand. While cycling freely through all their operational modes, healthy living systems use their functional capabilities to an extent which is sufficient to ensure a high probability of achieving solutions to the problems with which they are faced. Disease may be said to occur when there is continued uncoupling, for whatever reason, between environmental pressures on living systems and their abilities to adapt to them.

In the adaptive range, the gamut of mutually shaping interactions among units of any living system, from cell to society, may be epitomized by the following unauthorized emendation of an old socialist dictum: to each according to its needs, from each according to its capabilities, and together for survival and reproduction. In nervous systems, as in all complex systems,

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This work was supported in part by the Mathers Foundation and grants NS-18859 and NS-18858 from the National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health. Valuable discussions with F.E. Dudek, A. Iberall, A. Mandell, S. Matthysse, P.V. Russo, and R.E. Wimer are gratefully acknowledged. This article is reprinted from *Experimental Neurology*, 93, 279–290 (1986), with permission from Academic Press; Copyright © 1986 by Academic Press, Inc. Requests for reprints should be sent to Eugene Roberts, Ph.D., Department of Neurobiochemistry, Beckman Research Institute of the City of Hope, Duarte, California 91010.

dynamic tension exists between influences that maintain the relative freedom of interactions in such a cooperative community and those that tend to synchronize activities of the constituent units or to isolate them from each other functionally. The health of cells, individuals, and nations often is precarious because the respective systems are walking tightropes between states of freedom without license, tyrannical authority, and anarchy. Sometimes it may take but little additional input to tip the balance in catastrophic fashion (Thom, 1975) from one to another of these modes. It is interesting in this light to contemplate some of the easily observable neurotic behavior and psychic consequences of the irremediable tensions in individual human beings between the demands of instinct and the restrictions of civilization, the ready transitions between political tyranny and revolution that have occurred throughout history and are widely evident today, and the fluctuations in affect that occur in manic-depressive disorder.

Variability Generation in Relation to Functional Demand

There is little experimental information on the topic of variability in the nervous system. Indeed, variability seems to have been anathema as a topic because of an undesirability of inequalities in variability for some standard statistics, or because it is intellectually disturbing to those who tend to engage in typological thinking. Unusual circumstances led me to overcome my own resistance to this subject. Experiments designed to determine whether or not the neural connections of the hypophysiotrophic region (HTA) of the hypothalamus are essential for learning (habituation, acquisition, retention, and extinction) showed that learning took place approximately to the same extent whether or not the HTA was isolated neurally from the rest of the brain (Roberts et al., 1982). Thus, if the operation of the HTA is essential at all for learning, the relatively slow humoral communication to and from the isolated region may be sufficient to maintain the required processes at a normal level. In a situation in which rats were learning to press a lever for food while being rewarded at fixed intervals, a curious finding was that variability in response rates among individual animals in a group with hypothalamic islands (HIs) was significantly lower than that among sham-operated controls (S) during acquisition and extinction. In the S animals the relation between the standard deviation (SD) of the group and the mean number of responses was essentially linear until a ceiling effect became apparent. The coefficient of variation (SD/mean) was essentially constant over a wide range of response rates; i.e., differences between the individual members of the S group became accentuated in a regular fashion when greater activity was demanded. Although we cannot know all that went on in the experimental box, it seems plausible that variability in lever pressing occurred as the animals engaged in other activities. Amplification of variability with increased performance did

not take place in the same manner in the HI group, the SD for the HI group increasing much less with increased response than for the S group.

In the hypothalamus the integrated stimulus pattern is brought immediately into interplay with the neuroendocrine system headquartered in the HTA. The neural and endocrine outputs from the hypothalamus, in general, and the HTA in particular, are believed to play important roles in regulating reactions that make neural building blocks of behavioral programs available. The outputs are important also in making the decisions as to which of the behavioral patterns that are at the top of the available hierarchy of options at a particular time will be released (Oomura, 1980; Roberts and Matthysse, 1970). Neural isolation of the HTA probably reduces capacity to analyze the subtleties of environmental patterns, thereby decreasing the versatility of behavioral repertoires that can be organized in response to those patterns. The HTA plays key roles in individual (homeostatic) and group (reproductive) survival. Through its neural and endocrine outputs it also may increase behavioral diversity among individuals of a given species in a manner related to readiness states and environmental demands by producing controlled amplification of inherent and developmentally induced differences. In natural environments, variability amplification may be important in ensuring the survival of a species by unveiling sufficient varieties of behavioral strategies to enable an effective breeding population to exist even under the most stringent circumstances.

In view of the above, it appeared to me that one of the most important principles of function in the nervous system as a whole or in its constituent parts must be the coupling of variability generation to functional demand.

Roles of GABA Neurons

Paradoxical as it may seem initially, facile traverse of the adaptive functional range in the nervous system largely is made possible by diverse activities of inhibitory interneurons. Inhibitory projection and local circuit neurons (most frequently GABAergic) play crucial roles in information processing in the brain. It is inhibition in all its forms that enables a nervous system, and therefore the organism it inhabits, to generate the variability in behavior that allows it to adjust the extents and rates at which it effectively roams its functional terrain to seek adaptive options. The organism pays a price for this essential facilitation; e.g., perhaps as much as one-half of the glucose and oxygen utilized by the brain supports the activites of inhibitory interneuronal elements.

Local circuit inhibitory interneurons. Desynchronizing influences within sectors of the vertebrate central nervous system are mediated largely by local circuit inhibitory interneurons that are interspersed among the output neurons and are synaptically activated by them. These interneurons, in turn,

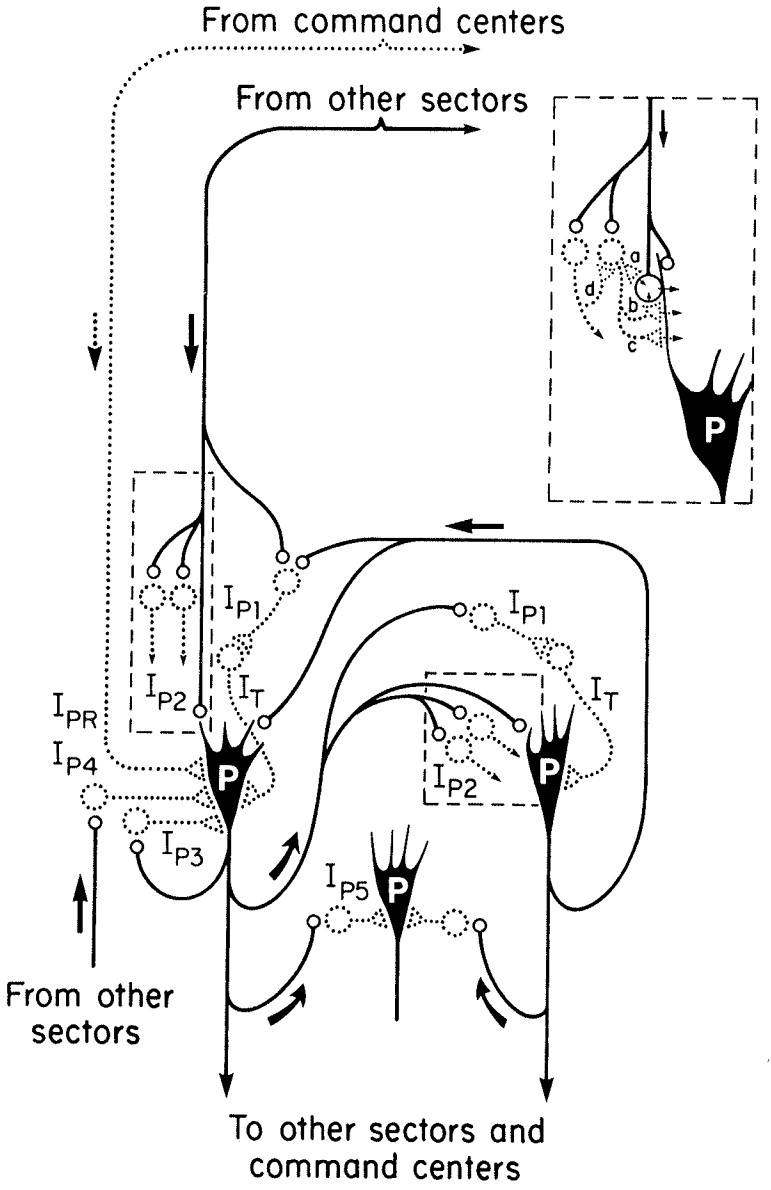

Figure 1: A composite scheme illustrating some types of relationships in which GABA neurons participate in a given neural sector. Excitatory neurons are dark and their processes are shown as solid lines; the dotted ones are inhibitory. P are the principal, often pyramidal, neurons that integrate incoming signals from dendritic endings to initial axonal segments, and through their activities express frequency-dependent aspects of coded neural programs that are communicated to the neurons onto which they synapse. P neurons are shown to be under the restraint of tonically active local circuit (I_T) and

synapse extensively upon the output neurons and upon each other (see Figure 1). Output neurons of throughput neural circuitry usually communicate by liberating excitatory transmitters, e.g., glutamatergic neurons of entorhinal cortex that project to the hippocampus. Those from command centers usually release inhibitory transmitters, e.g., GABAergic cerebellar Purkinje cells that project to deep cerebellar and Deiters's nuclei.

Projection neurons from one neural sector to another, excitatory or inhibitory, often are distributed in a laminar fashion, appearing in essentially parallel arrays on tissue sections. Wherever one looks, the relative regularity in arrangement of either inhibitory or excitatory projection (often pyramidal) neurons contrasts markedly with the irregularity of the disposition of local circuit inhibitory interneurons and of their terminals. Release of activity in a neural unit results in activation of its components, interneurons and output neurons, in such a manner as to facilitate the processing of information coming to it from other neural units and the communication of the processed results to other such units or to effector cells in muscles, glands, etc. Tonically active inhibitory neurons create a barrier to the passage of information through a neural unit, offering resistance against which the firing tendencies can interact

Figure 1 continued

projection (I_{PR}) inhibitory interneurons. Phasically active inhibitory neurons (I_{P1}) inhibit I_T neurons when activated by neurons from the same or other sectors. Excitatory nerves synapse directly on dendrites of P neurons and also send branches to GABAergic inhibitory interneurons (I_{P2}), which through their terminals modify the activity generated by direct excitatory input (Figure 1, inset). Terminals from such interneurons may form axoaxonic synapses (a) with the excitatory terminals, producing presynaptic inhibition. They may form axodendritic synapses (c) with dendrites in close proximity to the excitatory synapses, giving feed-forward postsynaptic inhibition. In some instances, particularly potent inhibition might be exerted by individual inhibitory terminals that form both axoaxonic and axodendritic synapses (b). There can be synaptic inhibition of one I_{P2} interneuron by another (d), decreasing the above-described types of inhibition and resulting in presynaptic faciliation. Phasically active inhibitory neurons (I_{P3}) are activated by excitatory recurrent collaterals of P neurons and exert recurrent hyperpolarizing postsynaptic inhibition on the same P neurons by which they are activated, allowing the inhibitory phasing by a neuron of its own activity. Inhibitory interneurons also may be activated by collaterals coming from neurons in other sectors (I_{P4}), furnishing the links for feedback inhibition, and by collaterals from neurons in the same sector giving lateral inhibition of competing or redundant neurons (I_{P5}). In most instances direct excitation probably is not sufficient, by itself, to release the P neurons for activity during normal nervous system function. The permissive element in the activity of P neurons is postulated to be release from the inhibitions exerted by tonically active projection (I_{PR}) and local circuit (I_T) neurons (Roberts, 1980, 1984, 1986). As the intensity of a particular input pattern to an organism is increased from some low basal level, there would be corresponding increases in excitatory influences directly on P neurons and on disinhibitory (I_{P1}) neurons in given neural sectors. Mutual inputs from excitatory axon collaterals of P neurons would add to excitatory and disinhibitory influences in the same sector. Together, increasing direct excitation and disinhibition would result in corresponding releases of greater and more varied activites in and among the P neurons, some of which would be selected for continuing participation in information processing by decreases in the inhibition exerted by projection neurons from inhibitory command centers (see Figure 3).

in Yin-Yang fashion, resulting in variable levels of nerve activity. This has desynchronizing effects on the activities of the output neurons because connectivities and local conditions in the vicinities of even closely lying neurons differ significantly. However, the major desynchronizing influences at the local level probably are exerted by ubiquitously occurring phasically active inhibitory interneurons which, through terminals of their multiple branches, participate in many diverse activity-structuring processes, such as pre- and postsynaptic inhibition, disinhibition, and presynaptic facilitation (Figure 1).

When information is being processed most effectively, I posit that increases in activity elicited in a particular neural unit are accompanied by increases both in the extent of the output and in its variability. The interposition of inhibitory interneurons in neural circuitry enables the nervous system, at all levels, to be its own variability generator, i.e., the presence of inhibitory interneurons endows neural units with an expansible capacity for processing information in relation to demand. Because of the spotty activities of these interneurons and their metabolic and structural plasticity, neural units in which they participate possess local creativity, enabling the achievement of unpredicable solutions to the problems with which they constantly are faced and the retention of "memories" of these solutions. In a neural system from which inhibitory neurons are removed or in which they become dysfunctional (see Figure 2), excitatory projection neurons (hippocampal pyramidal cells, for example) can co-opt each other into synchronous oscillatory activity by mutually exchanged collaterals acting through excitatory chemical synapses and gap junctions and by the electrical fields that are created. Information processing capacity becomes negligible within neural units during such paroxysmal activity (Dudek, Andrew, MacVicar, Snow, and Taylor, 1983; Jeffereys and Haas, 1982; Johnston and Brown, 1981; MacVicar and Dudek, 1980).

Inhibitory projection neurons from command-control centers. Local neural units must receive permission (disinhibition) from command centers before they can begin to function at all or to increase their activity above a certain basal level; and complete autonomy never is granted them. Only in disease do individual neural units and individual neurons within the units become free-running. Nervous systems do not operate in a linear fashion. Minimally, a bifurcation of the flow of neural information from a particular sector takes place into direct throughput channels and also into those leading to coordinative command centers, such as the cerebellar cortex and the basal ganglia (see Figure 3). In the latter specialized regions, information arriving from several sources is integrated. The output reflecting this analysis, with variable time delays, then plays upon neural elements in the direct channels to adjust the activity therein, giving it permission to occur and sculpting it, as well, so that it becomes compatible temporally and spatially with activity elsewhere in the central nervous system. Command centers are presumed to

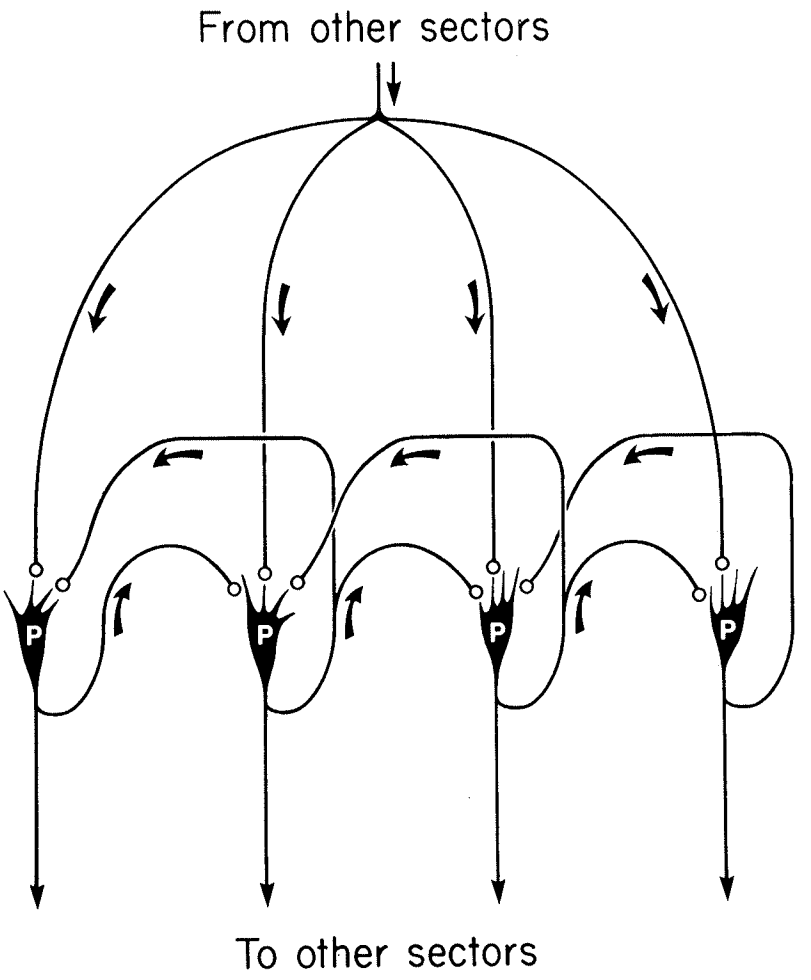

Figure 2: Schematization of basic neural circuitry, such as that shown in Figure 1, without inhibition. Inhibitory neurons may become ineffective in ways indicated in the text. When the resistance offered by inhibitory circuitry is absent or inadequate, activity in some P neurons easily can evoke activity in others. This process can continue until virtually all interconnected P neurons in a given sector become involved in activity that oscillates between the synchronic bursts and inactivity characteristic of seizures.

exert high-frequency tonic inhibition onto their projection sites. When activity occurs in command centers as a result of inputs to the organism, there is selectively decreased inhibition from them (Hikosaka and Wurtz, 1983).

Malfunction. When incoordinations occur, for whatever reason, among the activities of local circuit and projection inhibitory GABAergic neurons and/or neurons that liberate other neurotransmitters and modulators, the

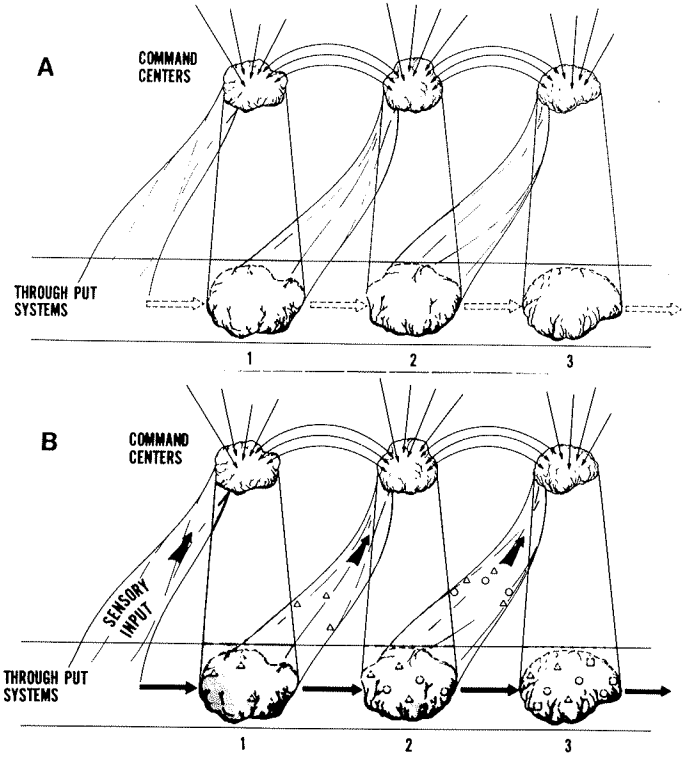

Figure 3: A model for relationships between throughput systems and command centers. Minimally, a bifurcation of the flow of neural information from a particular sector takes place into direct throughput channels and also into those leading to command centers. A—inactive state of command system, in which output cells from the command centers exert maximal inhibition onto their projection sites. Even though spontaneous or evoked neural activities might be released at these projection sites, as described in Figure 1, they would be operating against maximal resistance and quickly would cease functioning under these conditions. B—active state of system, in which selective disinhibition of neural activity in the throughput systems is achieved by decreases in tonic inhibition exerted by the output cells of the command centers. Analysis of the inputs to the command centers is reflected, with variable time delays, in decreased frequencies of firing of appropriate combinations of their inhibitory projection neurons, facilitating release of neural activity at sites to which they project in such a manner that it becomes optimally compatible temporally and spatially with activity elsewhere in the central nervous system. The latter principle has been illustrated convincingly in the monkey for the GABAergic projection neurons from the substantia nigra pars reticulata that relay information from striatal command centers to the intermediate layers of the superior colliculus. The results were consistent with the idea that the substantia nigra cells discharge rapidly and inhibit superior colliculus cells tonically. A release of the tonic inhibition resulting from a decrease in substantia nigra cell activity would contribute to the generation of the burst of activity in the colliculus cells and, consequently, would contribute to the initiation of saccadic eye movements (Hikosaka and Wurtz, 1983).

functional defects that arise might involve a local brain region, several brain regions, or the entire central nervous system. A critically placed local incoordination may have drastic reverberations in the entire nervous system, as found in *grand mal* seizures arising from focal cortical lesions. Under relatively simple environmental conditions in individuals with such incoordinations, the nervous system could function in an apparently adequately adaptive manner, which might appear to be in the normal range. As the complexities and intensities of environmental inputs are increased, there would be correlated increases in extents of uncoupling between increases in activities in neural units and the degrees of asynchrony of activity within them and among them; and synchronous oscillatory activity would begin to occur.

Enchanced synchrony of neuronal firing in a particular neural sector receiving a given input may arise in several ways—increased rate of release of synaptic excitatory transmitters, blockade of inhibitory transmitter receptor mechanisms, desensitization of receptors to inhibitory transmitters, decreased availability of inhibitory transmitter, decreased activity and/or destruction of inhibitory neurons, increased formation or activation of electrotonic junctions, or an excess of disinhibition. There now are many experimental observations relevant to one or another of the above mechanisms. During excessive and prolonged excitatory input to a neural sector, eventually there may be failure of GABAergic function for one of the above reasons, or combinations of them. Inputs from axon collaterals of excitatory neurons to each other would add to the excitatory and disinhibitory influences of neurons in the same neural module, eventually recruiting them into synchronized discharge patterns (Figure 2). For example, there is recurrent excitation between hippocampal pyramidal cells. Spikes in one pyramidal cell can evoke spikes in another pyramidal cell (MacVicar and Dudek, 1980). Were it not for the spotty inhibition furnished by the inhibitory interneurons, this could continue until virtually all available neurons in the modules of a given neural sector would be involved in responding synchronically to the input to that sector. The giant excitatory postsynaptic potentials of seizures can result from the synchronous activity of normal neurons (Johnston and Brown, 1981).

Thus, the very essence of nervous system function depends on the health and welfare of GABAergic neurons, which comprise the major class of inhibitory neuron in the mammalian CNS. These neurons, as well as inhibitory glycinergic ones, appear to be particularly vulnerable to anoxia and to toxic insults of various types. The numbers of GABAergic neurons and/or their ability to make and release GABA may decrease with aging in various brain regions. Both in disease and aging it would be important to determine the nature of this special metabolic vulnerability and to learn how to attenuate it or to prevent it (see Roberts, 1980, 1984, 1986 for more detailed discussion).

A common approach in attempting to improve function in a poorly operational system is to keep the components "talking to each other."

Experience shows that the self-organizing properties of biological systems, in general, often enable them to begin to function adaptively at all levels, from intercellular to international, once effective interactions are reinstituted. While characterizing them separately in the laboratory down to the last molecular detail, I believe that it is in such an interactional context that we must begin to think anew about the different specialized regions of the nervous system, and about the structural elements (neurons, glia, blood vessels, extracellular fluid, etc.), the chemical messengers operational within it (neurotransmitters, modulators, hormones, etc.), and the low-energy switches (synapses and gap junctions) that participate in directing the flows of information (see Iberall, 1985; Iberall and McCulloch, 1969; Llinas and Iberall, 1977; Soodak and Iberall, 1978). In all such considerations, GABAergic neural inhibition must play a major role.

Are Pertinent Experiments Possible?

For a given neural sector (viz., model in Figure 1) to be a meaningful component of an information-processing community, total excitation occurring within it must exceed total inhibition. Differences between the two become the forcing function for the system. In the absence of relevant quantitative data and from recent work in biological systems, I surmise that increases in activities with increases in forcing function in neural tissue will occur according to principles of nonlinear dynamics (Lorenz, 1963; Mandell, 1983; Rossler, 1976). From individual neuron to whole brain it would be expected according to the latter concept that with progressively increasing force parameter, each unit would show three characteristic behaviors: smooth, periodic (oscillatory), and turbulent (chaotic). I envision that with full participation of local circuit and projection inhibitory neurons (Figures 1 and 3) the region of smooth flow would extend over a much greater range of force parameter before attaining oscillation than in its absence (Figure 2). In a given neural sector receiving a given input, progressive decreases of efficacy of inhibitory neurons lead to progressively earlier occurrence of oscillatory activity. Relevant experiments were performed with convulsant hydrazides, substances which are known to decrease the rates of formation of GABA in terminals of inhibitory neurons by partially inhibiting the GABA synthesizing enzyme, L-glutamic acid decarboxylase, by reacting with pyridoxal phosphate, the coenzyme (Grafstein, 1963). When such substances were applied topically to segments of neuronally isolated cat cortex, in which neuronal activity did not occur spontaneously but could be elicited by electrical stimulation, there was a long latent period (10 to 30 min) during which time the responses to stimulation remained normal regardless of the frequency of stimulation. After this period, convulsive spikes of rather large amplitude appeared during stimulation. When stimulation of such preparations ceased for 10 min, the

responses to stimulation returned to normal. After a period of stimulation, the spikes reappeared, the time required for their return being proportional to the rate of stimulation. When intervals as long as 15 to 40 s were allowed between stimuli, the spikes did not reappear. It is likely that when the rate of stimulation was low and, therefore, the rate of GABA release from terminals of GABAergic neurons was slow, production of GABA in the terminals was maintained sufficiently to prevent seizures. Increases in rates of nerve activity outstripped the availability of GABA to be released in the presence of substances that inhibit its synthesis, and eventually seizures (synchronization; oscillatory behavior) occurred.

The experiments above, and many other similar ones, support the idea that GABAergic neurons extend the range of force parameter over which smooth functional flow can occur in a neural system, preventing seizures from occurring by acting like reins restraining a team of lively horses. However, the question of crucial interest in the present context is whether the various activities of GABA neurons enable individual output neurons in a particular functional unit (P neurons in Figure 1) increasingly to diverge in their activities as the force parameter is increased in the range within which smooth functional flow exists; i.e., do increases in variability occur in a manner coupled to neural pressures? A positive answer to the latter would lend support to the notion that manifold functions of inhibitory neurons enable increases in information-processing capacity to occur as demand increases. To perform meaningful tests of this hypothesis, it would be necessary to record simultaneously from a number of identified individual neurons within defined neural units, employing conditions as close as possible to those under which normal activity takes place in the system under study. Cross-correlation analyses then could be performed by established techniques (Perkel, Gerstein, and Moore, 1967) to determine the degrees of synchrony among the simultaneously recorded neurons, and the results could be expressed as synchronization indices (Hamm, Roscoe, Reinking, and Stuart, 1985; Roscoe, Hamm, Reinking, and Stuart, 1985). Coupling coefficients between the driving force of the input processes and synchronization indices (1, completely coupled; 0, completely uncoupled) then could be calculated, provided the driving forces were known. Electrically generated spike-triggering should be avoided, because most natural stimulation within normal functional ranges is believed to occur as a result of spotty quantal release from nerve terminals of depolarizing chemical substances onto excitable membranes.

Many thought experiments were conducted with investigators with expertise in the study of unit activity in a variety of neural systems *in vivo* and *in vitro*. In most instances, one or another of the above requirements could not be met in a manner permitting a definitive test of the hypothesis. A promising experimental paradigm that was devised during conversations with Dudek currently is being pursued in his laboratory. Recordings are being made

simultaneously from a number of visually identified, closely lying pyramidal cells in hippocampal slices. Progressively increasing depolarizing effects are being furnished by adding increasing concentrations of glutamate, a putative excitatory transmitter. The hypothesis predicts that activation by progressively increasing low glutamate concentrations should be accompanied by amplification of differences in activities among the individual neurons. In another set of experiments, progressively increasing concentrations of picrotoxin or bicuculline, substances that block GABA action at receptor sites and can cause seizures, are being added in the presence of a given concentration of glutamate. In the latter instance, it is predicted that variabilities among the cells will decrease progressively with increasing concentrations of GABA receptor blocker even before convulsive, synchronous discharges set in. Additional experimental approaches are being sought.

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