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What is the Role of General Activating Systems in Cortical Function?

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Abstract. The term "general activating systems" was used initially in reference to the unknown anatomic substrates that mediated the desynchronized cortical EEG pattern after intense electrical stimulation of the brain stem reticular formation. Most of the reticular formation projections onto cortex were later found to follow classic anatomic patterns with synapses in the thalamus en route to cortex. Nevertheless, the same term was also extended to the aminergic projections to cortex, following the demonstration, largely in rodent brains, that these pontine, midbrain, and diencephalic source nuclei did project monosynaptically onto cortex. In this paper, recent data are reviewed characterizing the anatomic, cellular, and behavioral physiologic properties of these circuits, emphasizing the example of the noradrenergic projections to neocortex. These data indicate to me that the aminergic projections represent at least four (noradrenergic, serotonergic, cholinergic, and dopaminergic) independent nonthalamic afferents to selected target cell populations in selected, functionally defined neocortical target areas. At the cellular level, the ability of these transmitter systems to regulate responsivity and discharge patterns of their targets in neocortex may well rely upon interactions with both intrinsic cortical connections and with other thalamic and cortical afferents. Despite their distinct separation from the classic reticular activating systems, the overall structural and functional properties of the aminergic systems fits well with the hypothetical roles predicted for these systems in being responsible for neither gross excitation or inhibition, but rather creating special conditions for selectively attending to relevant stimuli.

WHAT ARE THE "GENERAL ACTIVATING SYSTEMS"?

The low voltage, fast or desynchronized patterns recorded in the cortical electroencephalogram following stimulation of the "brainstem reticular formation" were interpreted by Moruzzi and Magoun to represent an activating or arousing function. Although the EEG "arousal" was clearly

not behavioral arousal (see discussion by Hobson and Steriade 1986), the concept arose that the reticular core had a diffuse and global activating action on the cerebral cortex. However, there was little understanding of the nature of the circuitry represented by such forms of stimulation, the membrane mechanisms mediating their chemical signals, or the physiological relevance of the general activating phenomenon. The distinctions between the EEG activating response and behavioral arousal were extended through the observations of Jasper and of Dell (cf. refs. in Hobson and Steriade 1986), who viewed the effects of this reticular formation stimulation as different from "gross excitation or inhibition" but rather as "a reorganization of the temporal and spatial patterns of neuronal discharge," and as creating "the conditions for the organism to be actively interested in the outside world" through a "readiness to receive only (relevant) stimuli to the exclusion of others" (see also Maffei et al. 1965).

Despite these thoughtful pioneering observations under less than optimal recording conditions, nearly a quarter century was required to accomplish the chemical and cellular dissection of these behaviorally relevant actions of the "reticular formation." With advances in neuroanatomic circuitry analysis it became clear that most ascending projections from the pons and brain stem did synapse in circumscribed diencephalic nuclei in order to impact on the neocortex. In contrast, these methods supplemented with direct methods for cellular localization of molecular markers of specific neurotransmitter systems, identified additional, defined neuronal elements within the brain stem, pons, and diencephalon that did project monosynaptically onto the neocortex as the likely mediators of the "activating" response. These latter cortical afferent circuits, atypical to the point of initial disbelief for their anatomy, represented cells and fibers containing the aminergic transmitters (see below).

At the synaptic level, these systems were also atypical in operating through membrane mechanisms that are distinct from those employed by the more prevalent amino acid transmitters (see Siggins and Gruol 1986). These systems have been held to offer the possibility of enriching the vocabulary of chemical communication for possible integrative actions (see Bloom 1984a, b). Lastly, our knowledge of the actions of these aminergic projection source neurons on their likely cortical targets has been extended to the behavioral level. This array of data provides a means for some predictions as to their possible roles in cortical function and as an information route that is parallel and interactive with the specific and nonspecific thalamocortical connections.

THE EXTRATHALAMIC CORTICAL AFFERENTS

At least four substantial extrathalamic systems project to neocortex, each bearing the markers for one of the four major aminergic systems:

acetylcholine (Ach), noradrenaline (NA), dopamine (DA), or serotonin (5-HT) (see Foote and Morrison 1987 for review). Initial detailed studies of the circuitry of these systems and their ultrastructure within the rodent neocortex offered little evidence of any degree of anatomic specificity, and the systems were frequently viewed as diffuse, amorphous, and nonspecific. However, subsequent studies with more refined methods of orthograde and retrograde circuitry analysis, and of synaptic terminal identification, as well as extension of the studies to primate cortex, have revealed these afferents to be much more highly organized than was initially thought (see Foote and Morrison 1987 for review).

The existence and nature of these cortical afferents raises major questions about cortical organization and function, as has been pointed out in several recent reviews (Foote et al. 1983; Hobson and Steriade 1986; Foote and Morrison 1987). Thalamocortical and corticocortical systems appear to be organized to implement both serial and parallel processing of information through rapidly conducting components that are interconnected with precise topography and functional segregation. Thus, the well-known columnar, radial organization of neocortex would appear to be disregarded by the tangentially organized extrathalamic afferents in which single axons may innervate not only different columns within a functional region but several different functional areas. In this position paper, I review the essential features of circuitry and synaptic function for the locus coeruleus, the noradrenergic member of this tetrad of nonthalamic cortical afferents, and comment more briefly in passing on the degree to which data on the cholinergic (see Aston-Jones, Shaver et al. 1985; de Lima and Singer 1986; de Lima et al. 1985; Stichel and Singer 1985; Dutar et al. 1986; Lamour et al. 1984, 1985, 1986), dopaminergic (Miller et al. 1983; Schultz 1986; Schultz and Romo 1987), and serotonergic (Jacobs et al. 1984; de Lima et al. 1987) components exhibit similar general features.

GENERAL FEATURES OF THE AMINERGIC PROJECTION CIRCUITRY

The principle organizational features of the aminergic afferent circuits to neocortex are: a) circumscribed clusters of several hundred neurons, generally homogeneous in transmitter marker expression, from which multiple branching and highly collateralized axons projecting towards selected terminal fields arise; b) cortical terminal fields which reveal pronounced regional and laminar specialization and which are transmitter system specific across the major cytoarchitectonically defined cortical areas and their internal cortical laminae; c) an innervation of thalamic and other subcortical structures that follows the aminergic cortical patterns (also see Aghajanian and van der Maelen 1986; Bjorklund and Lindvall 1986; de Lima et al. 1985; Stichel and Singer 1985; Foote and Morrison 1987). It is not year clear whether a

similar histamine-containing direct cortical projection, demonstrated most convincingly at present only in the rodent (see Schwartz et al. 1986), will exhibit these same general properties. It is also probable that the monoamine-containing direct cortical projections were in some ways more easily defined since their cell bodies have been thought to be exclusively outside of cortex (but see below). A reported direct diencephalic cortical projection composed of cytochemically defined GABAergic fibers (Vincent et al. 1983) would have been difficult to distinguish from its intracortical GABA circuitry. However, if such long GABAergic projection data are reproducible, the "aminergic" model circuit may not be restricted to the amine systems.

NA INNERVATION OF NEOCORTEX

The NA innervation of neocortex arises solely from the nucleus locus coeruleus (LC) which is located in the pontine brain stem (reviewed in Foote et al. 1983). This nucleus innervates every major region of the neuraxis even though it is composed of a relatively small number of neurons (approximately 1,600 per hemisphere in rat, 5,000 per hemisphere in monkey, and 13,000 per hemisphere in human (see Foote and Morrison 1987)). Individual LC neurons often innervate widely separated brain regions, indicating that these axons must be highly divergent. The individual rodent LC neurons innervating different cortical and subcortical regions show distinctive morphological features and distinctive groupings within the main nucleus (see Loughlin et al. 1986). The NA fibers within cortex travel mainly parallel to the cortical surface within the subcortical white matter, particularly in deep layer VI where they are oriented predominantly in the anteroposterior plane, forming a continuous sheet of longitudinal fibers overlying the white matter (see Morrison 1979).

In rat, Morrison, Molliver, and their colleagues interpret their data to demonstrate that these very fine caliber fibers branch to innervate all six layers of neocortex, and to indicate that the pattern of NA axon distribution possesses a geometric orderliness and distinct laminar pattern that is consistent throughout lateral neocortex (see Foote and Morrison 1987; Morrison et al. 1982; Levitt et al. 1984). In contrast to the rather uniform innervation patterns of the rodent cortex, the NA innervation of primate cortex exhibits striking regional specialization in both density and laminar pattern of innervation, while retaining a strong tangential, intracortical orientation (see Morrison and Foote 1986; Morrison et al. 1982; however, see Levitt et al. 1984 for different views). For example, primary somatosensory and motor regions are densely innervated in all six laminae while temporal cortical regions are very sparsely innervated. In primary visual cortex the density of innervation is intermediate, with mainly radial, presumptive fibers of passage coursing through lamina IV.

Although no modality specific innervation patterns have yet emerged from these and related data on other aminergic systems, the visual cortical and subcortical systems have offered a means to compare the qualitative distribution of these fiber systems within a well defined sensory modality (see Morrison and Foote 1986). Cortical areas 17 and 18, as well as visual areas in the temporal and parietal lobe, also differ in their patterns of NA innervation. Specifically, layer IV of area 18 contains more NA-containing fibers than layer IV of 17, and the overall density of these fibers is higher in area 18. The inferotemporal cortex was found to be very lightly innervated by NA fibers, while area 7 of the parietal lobe was much more densely innervated. These immunohistochemical findings confirm and extend previous biochemical analyses of NA in primate cerebral cortex (Brown et al. 1979; Brown and Goldman 1977) and agree in most interpretations with similar cytological studies (Levitt 1982).

In addition, according to the analysis of Morrison and Foote (1986), visual thalamic nuclei also exhibit pronounced variations in NA innervation density. The lateral geniculate was found to be virtually devoid of NA fibers, while the pulvinar-lateral posterior complex was densely innervated. In the mesencephalon, the superficial layers of the superior colliculus were found to be densely innervated by NA fibers.

These patterns of innervation indicate to Morrison and Foote (1986) that, in the primate, functionally separable yet visually related cortical regions share common and distinguishable densities of NA innervation. Specifically, tecto-pulvinar-juxtastriate structures are more densely innervated than geniculo-striate and inferotemporal structures. These relationships suggest that, within the visual system, NA fibers preferentially innervate regions involved in spatial analysis and visuomotor response rather than those involved in feature extraction and pattern analysis. This is especially interesting given the proposed involvement of the LC-NA system in attentional mechanisms (see below).

ACTIVITY OF AMINERGIC SOURCE NEURONS IN BEHAVIORALLY RESPONSIVE SUBJECTS

LC neurons in unanesthetized, nonparalyzed rat, cat, and monkey have been shown to be most active during waking, less active during slow-wave sleep, and silent during rapid-eye-movement sleep (Maffei et al. 1965; Foote et al. 1983; Aston-Jones et al. 1980; Steriade and Hobson 1986; also see Aston-Jones, Shaver et al. 1985; and Jacobs et al. 1984, for extension to other projection systems). Within the waking state, the mean discharge rates of LC cells increase when enhanced levels of arousal or attentiveness are exhibited by the animal. In monkey, for example, discharge rates vary from second to second, anticipating by several hundred milliseconds subsequent

EEG signs of increased or decreased levels of alertness. Primate LC axons projecting to neocortex exhibit more rapid conduction velocities than rat (e.g., approximately 34% were greater than 1 m/s) thereby resulting in similar conduction latencies to distant target areas for the two species (Aston-Jones, Foote et al. 1985).

LC-NA EFFECTS ON CORTICAL NEURONAL ACTIVITY

There have been numerous physiologic studies of the possible impact of LC-NA projection on putative target cells in various neocortical regions, based on earlier studies of LC-NA synaptic actions on identified target cells in cerebellum and hippocampus (see Foote et al. 1983 for review). In the neocortex of unanesthetized monkeys, target cells in auditory cortex with vigorous reproducible responsiveness to behaviorally relevant functional stimuli were tested before, during, and after iontophoresis of NA; these tests showed not only dose-dependent inhibition of spontaneous and vocalization-evoked activity, but also that a given dose of NA reduced spontaneous activity more than the activity evoked by acoustic stimuli. During auditory responses, segments with lower discharge rates were reduced proportionately more than segments with higher discharge rates. Those data, combined with earlier observations on cerebellar and hippocampal neurons (see Siggins and Gruol 1986 for refs.) fit the hypothetical view that the LC-NA enhances elicited activity relative to spontaneous activity, thereby "enabling" (Bloom 1984a, b) or increasing "signal-to-noise" characteristics of the target cells (Foote et al. 1983) to afferent stimuli active during periods of enhanced LC activity.

Analogous experiments in anesthetized rats (see Waterhouse et al. 1980) showed a similar reduction of background activity relative to stimulus-elicited activity in the somatosensory cortex. As in cerebellum and hippocampus (see Siggins and Gruol 1986), both excitatory responses and inhibitory responses were enhanced or "enabled" by NA application or LC activity. The effects of LC electrical stimulation alone are generally to depress spontaneous cortical neuronal activity (reviewed in Foote et al. 1983; Siggins and Gruol 1986).

Taken together, the anatomic data concerning LC projections, the functional data on activity of LC source neurons, and the synaptic effects of the transmitter on specific target neurons indicate that the LC is activated during alerting or arousal and releases NA onto target neurons in many brain regions, including specific targets in neocortex. This transmitter then acts to enhance the selectivity and vigor of responses of target neurons to contemporaneous afferent stimuli to the target neurons. The LC may well also play a role in more tonic behavioral state changes, such as the sleep-wake cycle (see Hobson and Steriade 1986). An alternative view describes

the function of LC as altering behavioral modes from internally oriented and generated states such as sleep, grooming, and food consumption to an externally oriented mode which involves active matching of appropriate behaviors with novel, stressful, or informative stimuli (e.g., Aston-Jones and Bloom 1981a, b).

Although the light microscopic details of the neocortical monoaminergic systems have progressed substantially over the past 15 years, the nature of the cells to which these fibers project in cortex has become more certain. When the data are based upon direct cytochemical localization of boutons containing the synthetic enzymes for the catecholamines or the direct localization of 5-HT itself, it is clear that both 5-HT and the two cortical catecholamines typically form conventional specialized "synaptic"-like contacts with their target neurons in frequencies (20–50% of boutons within an area of a terminal target field) that suggest that nearly all their cortical boutons probably do so (see Bloom 1984a for review). The interpretations of Molliver (see Molliver et al. 1982) are quite similar to ours (see Foote et al. 1983) and hold also for 5-HT and cholinergic projections to primate area 17 (de Lima and Singer 1986; de Lima et al. 1987).

MONOAMINES IN SPATIAL, TEMPORAL, AND OTHER DOMAINS

Despite their aberrant anatomy and physiology, the availability of these data plus a broad pharmacological armamentarium combined to allow monoamines to be among the first chemically defined systems to satisfy rigorous criteria as central transmitters (see Siggins and Gruol 1986; Bloom 1984a). The noradrenergic and other monoaminergic systems provide an excellent illustration of the time and space features by which chemically labeled neuronal systems may be distinguished and compared (see Bloom 1984a, b). The spatial domain of a neuron is the total target cell area to which that neuron sends information. The highly divergent efferent morphology of the aminergic systems has characterized these systems as having a far broader structural domain of potential influence than other systems.

Similarly, the temporal domain is the time course of the neuron's effects on its targets, especially the duration and pattern of its activity and that of its synaptic targets. It is only through evaluation of synaptic actions documented to be transmitted by specific agents that one can assess the minimum latency for onset of effects. *In situ*, data exist for only a few monoaminergic systems (see Siggins and Gruol 1986 for review). The *in vivo* data suggest that endogenous noradrenergic systems may have a synaptic latency that approaches 100–150 ms and that their own sensory activation

requires 35–75 ms depending on the modality (Aston-Jones and Bloom 1981a, b; Foote et al. 1983; Siggins and Gruol 1986).

The aminergic neurons are thought to be extensively interconnected through recurrent collateral innervation within their source nuclei. Since most monoamines tend to respond to their own amine by depression of discharge sensitivity, such recurrent interconnections tend in general to yield similar, succinct excitatory responses to sensory activation, followed by more prolonged inhibition and refractoriness to sensory activation (see Foote et al. 1983 for review; Schultz 1986; Schultz and Romo 1987). However, recent data from the cholinergic neurons in rat projecting to neocortex suggest that these neurons are far more hetergeneous in their response patterns (Aston-Jones, Shaver et al. 1985; Dutar et al. 1986; Lamour et al. 1984, 1985, 1986). The latter studies also point to the fact that the cholinergic neurons may be excited by their own transmitter, thus tending to release and augment activity once activated.

The monoaminergic systems also offer insight into a third comparative axis that may be termed "mechanistic" (see Siggins and Gruol 1986) or energetic (see Bloom 1984a) domain. For the LC-NA system, virtually all of its synaptic actions *in vivo* and *in vitro* can be attributed to the ability of NA to activate within target neurons the rapid synthesis of cAMP and thereby to modify the postsynaptic cell promptly. For example, postulated changes in a cAMP-mediated activation of a protein kinase could lead to phosphorylation of membrane proteins that would account for the observed increase in membrane resistance. This would alter the postsynaptic membrane in a manner that "enables" it to respond more effectively and in a more enduring manner to its other afferent inputs (see Siggins and Gruol 1986; Madison and Nicoll 1986a, b). While past data have emphasized the beta adrenergic receptor-mediated responses of NA target neurons, more recent data suggest that the alpha-1 adrenergic receptor may well interact on the same target cells (see below). Within the LC, alpha-2 adrenergic responses are prominent; such receptors also occur throughout the NA terminal fields, but their functional roles and effects remain uncertain (Arnsten and Goldman-Rakic 1985a).

INTERACTIONS BETWEEN VASOACTIVE INTESTINAL POLYPEPTIDE AND NA IN RAT CEREBRAL CORTEX

The aminergic activating systems thus possess temporal, spatial, and mechanistic interactions that can extend and lengthen the effects of this system on cortical targets. A specific example of this interaction (see Magistretti et al. 1986 for refs.) is the neurochemical and physiological interaction of the NA afferent cortical system with intrinsic cortical neurons that contain the peptide transmitter, vasoactive intestinal polypeptide (VIP).

Several lines of evidence support a role for VIP as a neuronal messenger in cerebral cortex, particularly the biochemical data on its presence, release, binding, and the ability to stimulate cyclic AMP formation in cortical slices somewhat more potently than NA (see Magistretti and Morrison 1985; Magistretti et al. 1986 for refs.). Cytochemically, VIP- and NA-containing circuits show a contrasting but complementary cortical anatomy: VIP neurons are intrinsic, bipolar, radially oriented, intracortical neurons while the NA innervation arises only from locus coeruleus and innervates a broad expanse of cortex in a horizontal plane. From our unpublished ultrastructure data (Bloom, Morrison, and Battenberg), the two fiber systems may have the same targets, the pyramidal cells, as do many other cortical afferents.

Identified cortical pyramidal neurons, like most identified potential target cells, are depressed in spontaneous firing by iontophoresis of either NA or cAMP (see Foote et al. 1983). Biochemically (see Magistretti et al. 1986 for refs.), VIP and NA can act synergistically to increase cAMP in cerebral cortex. Furthermore, in single unit electrophysiologic tests (Ferron et al. 1985) application of VIP during subthreshold NA administration causes pronounced inhibitions of cellular discharge regardless of the effect of VIP (none, speeding, or slowing) prior to NA.

Magistretti and Schorderet (see Magistretti et al. 1986 for refs.) showed that the synergism of VIP by NA was blocked by phentolamine, an alpha adrenergic receptor antagonist, and mimicked by phenylephrine, the alpha receptor agonist. This result was supported by the electrophysiologic tests, showing the NA-VIP synergism could be replicated by phenylephrine, an alpha adrenergic agonist. An apparently similar, cAMP-mediated enhancement by beta receptors of noradenergic target cell responsiveness to alpha adrenergic agonists has been reported for other cellular systems (see Ferron et al. 1985). If NA- and VIP-containing fibers do indeed converge on the same cortical target cell, it is feasible that cAMP is the intracellular mediator of their synergistic interaction, underlying the "enabling" type action (also see Madison and Nicoll 1986a, b).

"SATELLITE" EXTENSIONS OF THE AMINERGIC ACTIVATING SYSTEMS

Two further issues form the LC-NA example of the aminergic activating systems to neocortex merit further research and discussion.

1) Pyramidal cells are the main output cell of the neocortex, both between and within cytoarchitectonic regions. When aminergic afferents converge on these target neurons with the afferents from cortical interneurons, such as VIP, a synergistic combination of signals emerges to extend and perhaps strengthen the signals of the activating afferent alone. In the case of the VIP interaction with NA, additional metabolic regulation for the target

neurons may augment the electrophysiologic activation (see Magistretti and Morrison 1985 for discussion). Other reported interactions, such as that between the intracortical somatostatin neurons and the cholinergic afferents (but not other efferents such as glutamate) (Mancillas et al. 1986) may represent a similar "conditional" electrophysiologic synergism (Bloom 1984a, b). Given the degree to which intracortical GABA-containing interneurons may be further distinguished by different peptide co-transmitters (see Jones and Hendry 1986), it will be important to determine whether these interactions will also show similar modifiability of response patterns as the peptide-amine interactions. On a more comprehensive level, such mechanisms could represent an avenue for all converging afferents to interact on selectable subsets of neurons within the global terminal domain of a divergent afferent and in which the global afferent produces conditions that both enhances and differentiates the specific local responses. The ability of exogenous amines to augment the responsiveness of specific target neurons to other afferent transmitters provides a means for selective regulation of responsivity, Jaspar's concept of some 30 years ago. Clearly, an open critical question is to specify the precise target neurons of the aminergic afferents, both anatomically and functionally.

2) The aminergic afferent-intracortical neuron interactions may also suggest an evolutionary device that expands the limited repertoire of electrophysiological signal categories mediated by discrete neurochemical response mechanisms, such as cyclic nucleotides and other second messenger systems (see Bloom 1984a, b; Siggins and Gruol 1986). The necessary component would be a remote aminergic type neuron acting as an amplifying co-transmitter relay, with the threshold requirement that activity within both the aminergic and co-afferent systems would ordinarily be needed to reach an interactive threshold and enable the full extent of the conditional action. In this light it may be of interest that in the retina and olfactory bulb, local aminergic interneurons have already been found (see Bloom 1984a for refs.); furthermore, at least two groups have observed antityrosine hydroxylase immunoreactive neurons within primate neocortex (J. Pearson, personal communication; J. Morrison, D. Lewis, and M. Campbell, personal communication).

Those data must be documented and their functional meaning established. However, the working concept would be that there exist satellite co-transmitter neurons whose transmitter might be the same as the aminergic global afferent or might be a completely different transmitter, such as one of the many possible peptides. The latter cellular and chemical combination would allow for novel recombinant actions at a convergent target neuron. The satellite co-transmitter neuron would exist to complete an auxiliary circuit for afferent systems that under some conditions provide global cortical activating signals (but within the precise anatomic constraints of the terminal

field of the global projection system). Under other conditions the global afferents operating at subthreshold levels of activity could rely upon parallel input to the remote satellite neurons for local intensification of the activating signal.

EXTRATHALAMIC MODULATION OF CORTICAL FUNCTION

What are the implications of our knowledge of the cellular anatomy and physiology of these extrathalamic systems for speculations concerning their roles in normal and abnormal brain function? According to some views (see Foote and Morrison 1987), while the source neurons for these systems are outside of the major sensory and motor pathways, they clearly innervate those primary and secondary sensory and motor structures. Thus, these projections could impose the long recognized (see Maffei et al. 1965), state-dependent regulation onto the highly topographic systems. Although the final picture is not yet at hand, given the anatomic differences, the DA and ACh systems may well exert these influences with a greater degree of topographic specificity than do the NA and 5-HT systems (see Bloom 1984a; Foote and Morrison 1987). Nevertheless, each of the four aminergic systems clearly has preferred regions and laminae of termination both within and across sensory modalities and motor control areas. This suggests that their effects on neocortex should not be viewed as generalized, parallel, and redundant but rather as region-specific enhancement or diminution of activity in limited neuronal ensembles during certain stages of information processing. The cellular physiologic data provide well-defined actions on the response properties of target cells to weight the effectiveness of selected combinations of sensory stimuli.

These systems are not tonically active but show specific behavioral state-related levels of activity (see Foote and Morrison 1987; Hobson and Steriade 1986). NA neurons are most active during waking but also exhibit further increased bursts of activity during episodic increases in attentiveness during waking. 5-HT neurons appear to be more responsive to the sleep-wake cycle per se and might well initiate and maintain more tonic effects of behavioral state on target neuron function (see Jacobs et al. 1984). The activity of DA and ACh neurons has been less extensively studied in behaving animals. DA neurons (see Miller et al. 1983; Schultz 1986; Schultz and Romo 1987) appear to be involved in orienting or movement initiation behaviors while ACh neurons (see Aston-Jones, Foote et al. 1985) are most active during relatively specific conditions involving motivated, or perhaps emotional, behaviors. Finally, because each monoamine innervates diverse functional systems, one would not expect a simple correlation of "one transmitter-one behavior."

In both normal and abnormal states, each of these transmitters for a presumptive general activating system must influence a variety of behaviors. Several studies have examined the effects of catecholamine depletion and pharmacological antagonism on cortical function in primates (Brozoski et al. 1979; Arnsten and Goldman-Rakic 1985b). From these studies it appears that limited lesions and pharmacological manipulations of these aminergic systems can produce profound impairments in carefully controlled behavioral paradigms.

It would appear that a discrete molecular and cellular foundation has been established by the anatomic, cytochemical, and electrophysiologic studies of the past decade to begin to document the highly perceptive interpretations developed by Jasper and by Dell when the phenomena of general activation of the neocortex by electrophysiologic signs were first noted. Then, as now, what remains to be established is the degree to which such electroencephalographic or cellular evidence of an induced state of enhanced responsiveness to sensory stimuli represent epiphenomena of behavior or the actual mechanisms which can enhance or diminish the probability that a specifiable behavioral repertoire may be elicited or initiated.

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