

Supersensitivity of Central Neurons — A Brief Review of an Emerging Concept

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SUMMARY: *The concept that "denervation" or "pharmacological disuse" supersensitivity develops in central neuronal systems subsequent to sustained attenuation of normal neurohumoral mechanisms is reviewed. Particular emphasis is placed on biochemical and electrophysiological parameters of supersensitivity in dopaminergic (striatal) neuronal systems. The possible applicability of theories invoking changes in receptor sensitivity to the phenomenon of narcotic tolerance and physical dependence and to psychoactive drug therapy is discussed.*

RÉSUMÉ: *Le concept impliquant une supersensitivité par "dénervation" ou par "mésemploi pharmacologique" se développe dans les systèmes neuronaux centraux à la suite d'une atténuation soutenue des mécanismes neurohumoraux normaux est passé en revue. Une attention particulière est portée sur les paramètres biochimiques et électrophysiologiques de supersensitivité dans les systèmes neuronaux dopaminergiques (striatum). Les auteurs discutent certaines théories évoquant des changements dans la sensibilité du récepteur dans le phénomène de tolérance narcotique ou de dépendance physique, et évoquent certaines possibilités d'approches thérapeutiques par drogues psychoactives.*

INTRODUCTION

The aim of this article is to provide a critical discussion of some of the available evidence suggesting the occurrence of "denervation" and "pharmacological disuse" supersensitivity in the central nervous system. The potential significance of these phenomena with regard to our understanding of the physiology and pharmacology of the CNS is readily apparent and if validated may have an extensive impact on future attempts by the physician to modify behavior. For authoritative accounts of the development of these concepts, particularly with regard to their applicability to the peripheral nervous system, the interested reader is referred to excellent articles by Trendelenberg (1966) and Fleming et al (1973). Only a superficial synopsis, pertinent to the discussion at hand, is provided below.

Denervation supersensitivity in the peripheral nervous system

As a mechanism of homeostasis, the concept of alterations in transmitter sensitivity or neuro-junctional transmitter efficacy is not new to modern physiology. This is especially true with regard to the peripheral nervous system including both its autonomic and somatic components, where a large body of experimental data has been obtained to validate Cannon and Rosenbleuth's "law of denervation" (1949). Briefly, the notion of denervation supersensitivity suggests that disruption of the normal nerve supply to an organ results in homeostatic compensation, which may have both pre- and post-synaptic components, to restore towards normal the functioning of that organ. For example, it is well known that severing of

motor axons results in a supersensitivity of the denervated muscle membrane so that the whole post-synaptic membrane becomes sensitive to acetylcholine (Axelsson and Thesleff, 1959). This phenomenon is thought to involve gene activation and the synthesis of new cholinergic receptors (Fambrough, 1970). However, the interesting controversy as to whether it is the loss of muscle activity (Lomo and Rosenthal, 1972) or the loss of trophic nerve factors (Guth, 1968) released from motor nerve terminals which initiates the subsequent supersensitivity following denervation still continues.

In the sympathetic nervous system at least two mechanisms resulting in a functional supersensitivity following denervation of sympathetically innervated organs are operative. It has often been demonstrated that following postganglionic lesions and subsequent loss of presynaptic neuronal uptake mechanisms, a relatively specific supersensitivity of neuroeffector junctional transmission develops, principally to directly acting sympathomimetic amines. Thus, the loss of the mechanism which normally inactivates the agonist, presynaptic uptake, explains in large part the exaggerated responsiveness of the tissue to directly acting agonists. This type of supersensitivity is often referred to as a "cocaine" type of supersensitivity since cocaine is known to inactivate the uptake mechanism at adrenergic junctions and produces shifts to the left in dose-response curves. The other type of supersensitivity occurring in sympathetically innervated tissues is the so-called "decentralization supersensitivity" which is characterized by a longer latency of development and relative lack of specificity in that the denervation

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vated structure becomes supersensitive to a wide variety of chemical stimulants. The basis for this type of supersensitivity is thought to reside principally in alterations of the post-synaptic adrenoceptive membrane.

Pharmacological disuse supersensitivity

It is clear that in order to produce a supersensitivity of some adrenergic structures one does not have to resort to actual surgical denervation. A supersensitivity can be effected by nonsurgical measures that reduce sympathetic tone such as chronic treatment with reserpine, or ganglionic blockers, or chemical sympathectomy with the neurotoxin 6-hydroxydopamine. This concept may have important ramifications for the pharmacotherapeutics of certain mental disease states and has been suggested as the basis for narcotic tolerance and physical dependence (Collier, 1968; Jaffe and Sharpless, 1968). Both of these hypotheses will be given more detailed consideration in subsequent sections of this article.

Applicability to the CNS

The applicability of the concepts of denervation and disuse supersensitivity, developed by analysis of peripheral mechanisms, to central phenomena is tempting but speculative. As early as 1939, Cannon suggested that denervation supersensitivity might be a significant factor in the development of focal epilepsy. However, some of the more direct tests to date of this hypothesis have been negative. Thus, Krnjević et al (1970), studying neurons in isolated cortical slabs (which exhibit prolonged paroxysmal activity), could find no evidence of changes in neuronal sensitivity to iontophoretically applied glutamate, gamma amino butyric acid or acetylcholine consistent with the development of supersensitivity. Similar negative findings have also been reported by Spehlmann (1970). It should be noted, however, that this experimental preparation (i.e., under-cut or isolated cortex) may not have resulted in an adequate disruption of cholinergic (or amino-acid) mechanisms to produce a demonstrable supersensitivity. This is evident

in light of recent conclusive demonstrations by P. L. McGeer and colleagues (1974) of the existence of a high density of intra-cortical cholinergic neurons which might be substantially preserved upon isolation. On the other hand, recently it has been found that deafferentation of the cerebral cortex of cats results in dramatic reductions of noradrenergic terminals (Hirsch et al, 1975). This is not surprising since the noradrenergic innervation of the cortex is thought to be entirely extra-cortical in origin, deriving principally from the locus coerulei in the brain stem. Such a loss could contribute substantially to epileptiform activity in chronically isolated cortical slabs since noradrenaline (NA) is an excellent candidate as an inhibitory neurotransmitter in this area of the CNS (Phillis, 1970). Recently, we have observed an enhanced potency of iontophoretically applied NA on cortical neurons ipsilateral to an electrolytic lesion of the locus coeruleus of rats (Table 1). These findings are compatible with the suggestion that a denervation supersensitivity of cortical adrenoceptive neurons develops after surgical disruption of normal noradrenergic input. Furthermore, enhanced iontophoretic potencies of catecholamines have been observed in various other brain regions after chemical sympathectomy (Feltz and de Champlain, 1972; Hoffer et al, 1971; Segal and Bloom, 1974) but the

tendency has been to interpret these findings as attributable to a simple loss of pre-synaptic uptake elements, analogous to a "cocaine" type of supersensitivity. It is, however, becoming increasingly obvious that such a parsimonious explanation may not account for all the available data, and the possibility of a genuine post-synaptic receptor supersensitivity in the CNS must be considered.

Supersensitivity in central catecholaminergic systems

It is evident that both intra- and interneuronal adaptive changes occur in central aminergic neuronal systems subsequent to chronic pharmacological and non-pharmacological manipulation. With regard to intraneuronal adaptations it has been demonstrated, for example, that repeated administration of reserpine leads to an increase in mid-brain tyrosine hydroxylase (Segal et al, 1971) which is the rate-limiting enzyme in catecholamine synthetic pathways. Similar findings with tyrosine hydroxylase have been reported in the case of chronic non-pharmacological manipulations such as daily immobilization stress (Lamprecht et al, 1972) or cold exposure (Thoenen, 1970). This type of information is consistent with the notion that central catecholaminergic neurons respond homeostatically to chronic attenuation by increasing their transmitter synthetic capacity.

TABLE 1
Noradrenaline and 5-hydroxytryptamine depressant potencies (A) and comparative potencies (B) on the firing of cerebral cortical neurons

		Cortical cells inhibited ¹	
A.	NA	Denervated ³ 31/32 (97%)	Intact ⁴ 41/64 (64%)
	5HT	22/32 (68%)	42/64 (65%)
		Comparative depressant potencies ²	
B.	NA > 5HT	Denervated ³ 25/32 (79%)	Intact ⁴ 22/64 (34%)
	NA = 5HT	4/32 (12%)	25/64 (39%)
	NA < 5HT	3/32 (9%)	17/64 (27%)

¹Up to 100 NA for up to 60 sec. of NA and 5HT were tested on each cell.

²Equal doses (ejection currents and times) of NA and 5HT were compared on each cell.

³In 5 of 6 lesioned animals a significant depletion of ipsilateral cortical NA occurred. The mean NA content of these cortices was 0.15ug/g \pm SEM 0.04 as compared with 0.45ug/g \pm SEM 0.09 ($P < 0.05$) in the intact cortices. The data in this group was derived only from cortices in which NA depletion was observed.

⁴Includes cells from one cortex ipsilateral to the lesion in which no NA depletion occurred.

Interneuronal responses to chronic alterations in aminergic systems — biochemical correlates

The responsiveness of adenylyl cyclase systems of neuronal tissues is thought to provide an index of catecholaminergic receptor activity. An enhanced responsiveness of pineal gland adenylyl cyclase to noradrenaline after chemical or surgical sympathectomy (Strada and Weiss, 1974) and increases in cerebral adenylyl cyclase responses to NA after chronic reserpine (Williams and Pirch, 1974) or 6-hydroxydopamine (Palmer, 1972) have been reported. The most interesting work at the moment derives from studies on denervation supersensitivity in the nigrostriatal dopaminergic projections. While Von Voigtlander et al (1973) were unable to find a "supersensitive" adenylyl cyclase response to dopamine (DA) in the striatum of mice pretreated with 6-hydroxydopamine (6-OHDA) or alpha-methyl-p-tyrosine, positive findings in this regard have recently been reported (Mishra et al, 1974) in the caudates of rats subsequent to 6-OHDA injections into the substantia nigra. In addition, the findings of Fibiger and Grewaal (1974) that substantia nigra lesions resulted in enhanced levels of striatal acetylcholine in response to apomorphine (a directly acting DA-receptor agonist) were interpreted to indicate neurochemical evidence for a denervation supersensitivity in this structure.

Sulser and his colleagues (Vetulani et al, 1975), studying a NA-sensitive adenylyl cyclase from limbic forebrain areas of the rat, have found an enhanced response of this enzyme to NA following reserpine or intraventricularly administered 6-OHDA and decreased responses following chronic tricyclic antidepressants or monoamine oxidase inhibition. These data are compatible with the idea that noradrenergic interneuronal mechanisms respond homeostatically to chronic facilitation (resulting in post-synaptic subsensitivity) or disruption (resulting in post-synaptic supersensitivity) of noradrenergic transmission.

However, considerable caution should be attached to the interpretation of the studies summarized above since they are almost all predicated on the assumption that *in vitro* adenylyl cyclase responses provide an accurate reflection of catecholamine receptor activation. In light of the known glial adenylyl cyclase system (Gilman and Shrier, 1972) and the possible involvement of adenylyl cyclase in the regulation of catecholamine synthesis (Anagnoste et al, 1974), which may be essentially presynaptic in nature, the relevancy of this enzymatic system to transmitter receptor mechanisms is not entirely clear.

Behavioral correlates of supersensitivity

There exists a large body of behavioral studies, beyond the scope of this review, on the functional manifestations of so-called "dopaminergic receptor supersensitivity" (see Ungerstedt, 1974). The principal tenet of this hypothesis is that sustained attenuation of dopaminergic transmission by surgical, pharmacological or pathological means results in exaggerated motor responses to dopaminergic agonists and antagonists which has as its underlying mechanism a development of supersensitive dopaminergic receptors. Presumably, this concept is applicable to other CNS neuronal systems although there is less (or none in the case of serotonergic systems) information to support such predictions.

Of particular relevance to our interests, however, are recent efforts to use behavioral paradigms to test the hypothesis of Jaffe and Sharpless (1968) that the development of tolerance and manifestations of physical dependence with chronic narcotic administration might result from a "pharmacological disuse supersensitivity" induced by sustained interference by narcotics with normal neurotransmitter mechanisms. A similar hypothesis based on a change in receptor sensitivity has been advanced by Collier (1968). Vasquez et al (1974) suggested that an increase in receptor (cholinergic, adrenergic and dopaminergic) sensitivities in

morphine-tolerant animals could account for their findings of altered behavioral responses to peripherally administered substances thought to affect these receptors. Studying the effects of intraventricularly administered transmitter candidates on body temperature in morphine-tolerant rats, Lagerspetz et al (1974) concluded that central cholinergic receptors involved in thermoregulation may be supersensitive in this state whereas Medon and Blake (1973) could find no evidence of such a mechanism. Puri and Lal (1974) have speculated that tolerance to the acute motor effects in chronically morphinized rats may involve the development of DA-receptor supersensitivity as have Eidelberg and Erspamer (1975) who investigated narcotic effects on motor activity in mice. As discussed below, these positive findings are difficult to reconcile with single-cell studies on central neurons in chronically morphine treated animals.

Electrophysiological correlates of receptor supersensitivity in aminergic neuronal systems

Evidence of a rather direct nature has been obtained, using the microiontophoretic technique, to support the hypothesis that a supersensitivity of dopaminergic striatal neurons develops after chronic disruption of presynaptic input. Thus, Siggins et al (1974) have demonstrated an enhanced responsiveness to iontophoretically applied DA and apomorphine of caudate cells following unilateral 6-OHDA substantia nigra lesions. We have obtained highly compatible information employing electrolytic lesions of the substantia nigra (Table 2). In addition, a supersensitivity of caudate neurons to iontophoretically applied DA and apomorphine has been shown to occur in rats treated chronically with the DA-receptor antagonist, haloperidol (Yarbrough, 1975). The use of apomorphine in these studies may allow one to extrapolate directly to the post-synaptic dopaminergic receptor since this substance is thought to be a directly acting dopamine receptor agonist (Ernst, 1967; Anden et al, 1967)

whose action is not terminated by uptake into presynaptic dopaminergic terminals. The use of haloperidol to induce "supersensitivity" is even more pertinent on this point, since this substance is not known to have any direct effects on DA uptake mechanisms and in these studies the dopaminergic neurons remained intact. The possibility does exist, however, that a loss or decrease in activity of the enzyme catechol-O-methyl-transferase might accompany dopaminergic neuronal degeneration or chronic dopamine receptor blockade. Since this enzyme, which is associated with post-synaptic catecholaminergic receptors (Axelrod, 1971), is involved in the degradation and catabolism of catechol compounds, including apomorphine (McKenzie, 1974), a

reduction in its activity might potentially account for apparent increases in the potencies of these substances when iontophoresed onto caudate neurons. Further work is required to eliminate or confirm this possibility.

With regard to the possible development of supersensitive receptors in chronically morphinized animals, the most direct tests to date (i.e. quantitative assessment of iontophoretically applied transmitter substances) have failed to demonstrate any changes consistent with this hypothesis. Thus, Bradley and Dray (1974) found no differences in the effects of serotonin, noradrenaline or acetylcholine on brainstem neurons in rats chronically ingesting morphine (or in the withdrawn state). Likewise, we were unable to demonstrate changes in the

acetylcholine sensitivity of cortical cells or in the dopamine, serotonin and gamma amino butyric acid sensitivities of caudate neurons in rats receiving chronic injections of morphine (Yarbrough, 1974; Table 3). These studies do not easily accord with the premise of a receptor supersensitivity underlying the development of tolerance to narcotic drugs, but clearly further investigation is warranted.

Consideration of clinical significance

The potential clinical importance of the postulated post-synaptic adaptive changes in neuronal systems is very extensive. It should be noted that psychotherapeutic drugs in man often have a lag time of days to weeks before the amelioration of symptomatology begins to appear. Without disregarding purely pharmacodynamic considerations, the question can be asked as to whether or not the efficacy of some of these drugs is related in part or whole to the homeostatic adaptive changes they induce in neuronal systems. Unfortunately, the vast majority of information available to the neuropharmacologist regarding the mode of action of psychotropic drugs is based on experimentation conducted on an acute basis (within six hours of giving the drug to an experimental subject). Historically, the clinician has been in the best position to observe (albeit indirectly) possible adaptive neuronal changes since psychoactive drug therapy (including L-DOPA), narcotic abuse and degenerative central diseases are invariably chronic phenomena in man. The applicability of ideas on changes in receptor sensitivity to the clinic is illustrated by the recent claim that L-DOPA-induced dyskinesias in patients with Parkinson's disease may be related to the development of dopamine receptor hypersensitivity attendant with chronic L-DOPA therapy (Klawans et al, 1975). An equally controversial suggestion is that an amphetamine-induced subsensitivity of catecholamine receptors (due to overstimulation) may underlie the therapeutic efficacy of this com-

TABLE 2

(A) The inhibitory effects of iontophoretically applied dopamine (30 nA) and apomorphine (40 nA) on the firing of neurons in intact and "denervated" caudates and (B) the threshold current intensities for dopamine inhibition of firing of neurons in intact and "denervated" caudates.¹

	Intact	Denervated ²
(A) Dopamine	10/35 (29%)	27/38 (71%)
Apomorphine	11/33 (33%)	28/38 (74%)
(B) Dopamine threshold current	56.3nA \pm SEM 4.0 (n = 32)	30.6nA \pm SEM 2.6 ³ (n = 38)

¹ Unilateral electrolytic lesions were placed in the substantia nigra of rats 14-28 days prior to testing the potencies of apomorphine and/or dopamine on caudate neurons. The same electrodes were used to examine neuronal responses between intact and denervated caudates. All caudate cells examined were chemically induced to fire by regular repeated applications of glutamate and dopamine or apomorphine was applied for one glutamate pulse cycle (20 sec.) in each trial. The average amounts of glutamate used to excite cells was not different between intact and denervated caudates.

² Fluorometric determinations of endogenous dopamine concentrations were conducted on intact and denervated forebrain hemisectons subsequent to the iontophoretic experimentation. There was a depletion of dopamine ipsilateral to the lesion in each animal tested ranging from 73% to 10% of the concentrations observed on the intact sides.

³ $p < 0.05$ using Student's T-Test.

TABLE 3

Inhibitory effects of dopamine, 5-hydroxytryptamine and gamma amino butyric acid on caudate neurons in control and chronically morphine treated rats.¹

	Caudate cells inhibited ²		
	DA	5-HT	GABA
Chronic saline	17/39 (44%)	22/39 (56%)	26/37 (70%)
Chronic morphine	21/51 (41%)	21/41 (52%)	31/43 (72%)

¹ Rats were injected every eight hours with saline or increasing doses of morphine (up to 45 mg/kg/injection) for 11-22 days. Iontophoretic testing was conducted 1-6 hours after the last injection.

² Caudate cells were induced to fire by regular repeated applications of glutamate, and the agonists were ejected with constant doses [DA(35) nA; 5-HT(40nA); GABA(35nA) for one glutamate pulse cycle (20 sec.)].

pound in relieving the hyperkinetic syndrome associated with minimal brain damage in children (Arbuthnott and Murray, 1975).

CONCLUSIONS

There is an increasing body of evidence, deriving from diverse lines of experimentation, suggesting that central catecholaminergic neurons may exhibit a post-synaptic supersensitivity after disruption of normal transmitter input. At this time, however, neither the nature of this supersensitivity nor its functional manifestations are evident, but as an area for future research, both clinical and basic, it appears promising.

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