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ELECTROPHYSIOLOGICAL CORRELATES OF SENSORIMOTOR SYSTEM NEUROTOXICOLOGY

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INTRODUCTION

In this review we consider the electrophysiological consequences of neuropathological changes induced by toxic chemicals in sensorimotor systems. A large body of neurotoxicological data is not covered, including that derived from observations of the acute effects of toxic chemicals on neural systems. The toxicological and/or pharmacological effects of such chemical-neural interactions in many cases leave no residual pathology; such data are adequately reviewed elsewhere.

In most instances, too few studies using neurotoxic chemicals have been reported to permit structural-functional correlations. Hence, we have relied on analogous studies from other areas of neurological research, particularly axotomy, on the assumption that while the neuron may be injured in various ways, it can respond to diverse forms of injury in only a few stereotyped fashions.

Systemic exposure to toxic chemicals exposes all levels of the neuron: the perikaryon, the axon, the nerve endings, and the target organs. Possible multiple sites of chemical attack tend to confound cause-effect relationships in a system as dynamic as a neuron and its target(s) of innervation. Particular manifestations of neurotoxicity thus may depend on one or more of the follow-

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ing: the extent of the neuron exposed (1), toxicokinetics of the compound (cf 2–4), duration and route of exposure (cf 5), and species or other variables.

There are instances in which electrophysiological alterations occur without corresponding neuropathological changes. This may reflect the inherent sensitivity of properly chosen electrophysiological techniques in detecting incipient neurotoxicity, or merely that the appropriate ultrastructural correlate has not been examined.

Here we focus on the electrophysiological-neuropathological correlates of neurotoxicology at the level of the neuron. Except for compounds of toxinological interest, we have placed no restrictions on the term "neurotoxic chemical." We have made no attempt to comprehensively review all neurotoxic chemicals; rather, we have selected examples principally on the basis that they have received the greatest research interest. Electrophysiological correlates at the level of neuronal systems can usually be inferred from an understanding of the neurotoxicology of their component parts; space does not permit such a review. Additional information on systems responses in neurotoxicology is available (6).

NEURONAL CELL BODIES IN NEUROTOXICOLOGY

Compared to peripheral axons, neuronal perikarya have received disproportionately little attention in neurotoxicology except from morphologists. This stems, in part, from the greater difficulties in recording from perikarya than from peripheral axons, coupled with a focus on the axonopathic aspects of neurotoxicology.

Exposure of a neuronal cell body, its axon, and its target of innervation to neuropathic agents precipitates a dynamic series of events which has been only partially unraveled. If, as occurs in many cases, the lesion occurs in the axon (or perhaps in the myelin or myelinating cells?), reactive changes are expected in the perikaryon as signals of a shift in metabolic priorities away from maintenance and toward repair mechanisms. The signal for reordering of priorities may be a change in trophic signals from the innervated target. Those reactive changes are presumably stereotypic responses of the cell body to injury, much like those after axotomy, with the specific manifestations a function of the nature and extent of the lesion. It is interesting to speculate that axonal changes might be secondary to or exacerbated by remodeling in the cell body (7).

In axotomy, the lesion is focal, but the situation is likely to be much more complicated when cell body and axon are exposed to toxic agents. A preexisting or coexisting biochemical lesion in the cell body, not detectable by microscopy, could be a triggering or catalytic event for functional or morphological alterations appearing elsewhere. With modifications, this is similar to the concept suggested by Cavanagh (8) some two decades ago.

Perikaryal Responses to Axotomy

HISTOLOGY Injury of axons, or of any portion of the neuron, elicits perikaryal responses that are primarily regenerative (9). Postaxotomy changes, variously referred to as the axon or retrograde reaction, or chromatolysis (10–13), are triggered by an unknown signal from the injury site (14) that may be conveyed by retrograde transport (15, 16). Striking changes occur in DNA-dependent RNA synthesis, evidenced by alterations in RNA-carrying organelles (i.e. chromatolysis), which can be blocked by actinomycin (17). The cell body remodels, apparently shifting protein synthesis priorities away from functional materials (e.g. neurotransmitter-related enzymes) toward membrane and soluble matrix proteins (18–21). Altered demand for cytoskeletal proteins (e.g. neurofilaments) leads to a reduction in slow component *a* of axoplasm transport (20); this in turn causes proximal axonal atrophy (22–25) with correspondingly decreased neurofilament content (cf 26).

Morphologically, the basophilic Nissl substance [containing the ribonucleoprotein of the granular or rough endoplasmic reticulum (RER)] granulates and disperses into the cytoplasm while the cisternae of the RER vesiculate. Swelling is evident in mitochondria and perikarya. The nucleolus and the nucleus enlarge, followed by eccentricity of the nucleus. Lysosomes and Golgi complexes become more prominent (9, 27). Microglial and astrocytic processes cause synaptic reorganization of axosomatic synapses (28), resulting in disjunction of more proximal synapses (29, 30). Disjunction is reversed only if neuromuscular contact is reestablished (31, 32).

ELECTROPHYSIOLOGY Pioneering electrophysiological studies of axotomy-induced changes in motoneurons by Eccles and co-workers (33) tended to emphasize membrane, particularly dendritic, excitability changes. Monosynaptically evoked excitatory postsynaptic potentials (EPSPs) in axotomized motoneurons have a lower peak amplitude and prolonged time to peak (33, 34); this alteration in synaptic efficacy may underlie the diminished monosynaptic reflex (MSR) responses following axotomy (33–35) reported earlier (36). Eccles et al (33) reported finding no change in resting membrane potentials (RMPs), input resistance, membrane capacitance, or afterhyperpolarization potentials (AHPs). In spite of diminished EPSP efficacy, motoneuron excitability, particularly in the dendrites, may be enhanced, evidenced by decreases in somal-dendritic threshold, initial-segment conduction time, greater velocity of action potential upstroke, and a larger than normal number of all-or-none responses in axotomized motoneurons (33). An altered dendritic excitability likely underlies the increased incidence of delayed depolarizations (37–39). Subsequent studies showed shallow initial-segment, somal-dendritic inflections (e.g. 39). Combined with a more rapid voltage upstroke, these lead to achievement of somal-dendritic threshold at a more negative voltage (40).

Findings in axotomized motoneurons were not always consistent. Unlike the finding by Eccles et al (33), later studies revealed the overshoot of action potentials to be increased (41, 42) and axonal conduction velocities decreased (41–43). Significantly, AHP amplitude, duration, and conductance were found to be decreased in soleus [slow; type S (see 44)] motoneurons but unaccompanied by change in RMP or input resistance (37, 39, 41). Conversely, fast motoneurons (i.e. type FF) show no change in AHP following axotomy (but see below) but exhibited decreased RMPs and larger input resistances. Taken in concert, these findings have led to the suggestion that axotomy causes electrophysiological differences between fast and slow motoneurons, particularly AHP and input resistances, to diminish (41, 45). In effect, axotomy causes a "dedifferentiation" of motoneuron electrical properties (42), presumably signaling a stereotyped perikaryal remodeling following axon injury.

Perikaryal Responses in Neurotoxicology

HISTOLOGY The pathological features of neuronal cell bodies in a variety of toxic neuropathies, detailed elsewhere (46, 47), vary from none to complete cellular necrosis. At one extreme is the loss of dorsal root ganglion, but not anterior horn cells, in doxorubicin neuropathy (48). At the other, primary degenerative changes appear uncommon even in neuropathies characterized by widespread axonal involvement. For example, light-microscopic examination of cell bodies has revealed them to be essentially normal in intoxications by acrylamide (49), isoniazid (50), and β,β'-iminodipropionitrile (IDPN) (51, 52). Ultrastructural studies confirmed only mild involvement. Anterior horn and dorsal root ganglion cells showed only mild dispersion of granular endoplasmic reticulum with some dissociation of polyribosomes and single ribosomes in the case of acrylamide neuropathy. Fine structural changes in tri-o-cresyl phosphate intoxication are similarly only slightly more than would be expected from distal axon loss, making them difficult to classify as primary or reactive (cf 49).

Neurofilamentous accumulations in the neuronal cytoplasm, only modest in the above-mentioned neuropathies, are striking features of experimental poisoning with aluminum salts (53, 54). Shelanski & Wisniewski (55) noted the appearance of neurofibrillary tangles to be an early consequence of subarachnoid administration of vincristine. Accumulations of neurofilaments have been observed to engorge the initial segment, proximal dendrites, and cytoplasm of anterior horn cells in a case of fulminating IDPN neuropathy (56). The link between neurofilament derangements in neuronal perikarya and the ultimate expressions of neurotoxicity are unknown; they certainly signal that remodeling has taken place in the cell body.

The principal cell body changes noted in many toxic neuropathies are reactive, usually secondary to axonal degeneration. The reactive changes vary

in intensity depending on severity and duration of intoxication, species, toxic agent, and the neuronal cell body examined. Similar variations in response are observed following surgical axotomy (11); hence the variety of responses in axonopathies is not surprising. Interestingly, axon swellings alone seem not to initiate reactive changes: perikarya remain unremarkable in spite of large axonal spheroids in IDPN neuropathy (51, 52).

Neither the presence of axon swellings nor degeneration may be required to initiate morphological alterations in cell bodies. Recent studies report extensive remodeling after only 6–8 days of intoxication with acrylamide (100–240 mg/kg total cumulative dose), at which time there is no evidence of axonal degeneration (57, 58). Examination of perikarya late in intoxications when axonal degeneration is present is of limited predictive value; initial neuronal alterations that may contribute to development of the neurotoxicity might well be obscured later.

ELECTROPHYSIOLOGY There have been few electrophysiological studies of perikaryal function in neurotoxicity. Those that have been reported, or are in progress, have examined the action potential generating capacity of spinal ganglion cells or spinal motoneurons.

Somjen and co-workers (59) recorded intracellular action potentials from ganglion cells of rats with methyl mercury intoxication, the early manifestation of which is a peripheral sensory neuropathy (60). They reported a marked fragility of the ganglion cells in poisoned animals, leading to difficulty in obtaining successful intracellular impalements; similar difficulties have been experienced in motoneuron recordings from IDPN-intoxicated cats (H. E. Lowndes, D. A. Delio & M. G. Fiori, unpublished observations). Whether this fragility signals physical modifications in neural membranes is a matter of speculation.

Although the values of rheobase and input resistance in methyl mercury poisoned ganglion cells fell within the normal range, Somjen et al (59) noted a paucity of recordings with high rheobase and low input resistance. Based on geometric considerations of perikaryal size, these data suggest that the largest-diameter ganglion cells are the most severely affected. Direct correlation between ganglion cell size and physiological function has not been established. Intracellularly recorded action potentials tended to be markedly prolonged, with durations as great as 15 msec. The long potentials, often characterized by plateaus, appeared to result from delays during the repolarization phase. In addition, the ability of the ganglion cells to follow trains of repetitive stimuli was poor.

Several key features of methyl mercury neuropathy deserve comment. First, the electrophysiological recordings bear no similarity to those from motoneurons undergoing chromatolysis. This is corroborated by the lack of

Table 1 Changes in action potential parameters of motoneurons in IDPN neuropathy

Alteration	Reference
Prolonged latency to onset[a]	52, 63
Shallow initial segment–somal dendritic inflection	52,63
Decreased initial-segment conduction time	52, 63
Decreased somal-dendritic threshold	52,63
Increased overshoot	64
Prolonged M spike	64
Decreased AHP amplitude, duration, and conductance[b]	65
Increased incidence of delayed depolarizations and repetitive firing	63, 65
Increased input resistance[c]	64
Monotonic firing in the primary range	66

[a]Prolonged latencies may reflect the presence of proximal axon swellings that characterize this neuropathy.
[b]In type S motoneurons (see text).
[c]In all motoneuron types (see text).

morphological evidence of chromatolysis (61) and no findings of fiber loss in the neuropathy (60). Lack of early evidence of axon degeneration or chromatolysis, yet with significant alterations in perikaryal function, indicates a direct action of methyl mercury on ganglion cell bodies, the largest diameter cells being most susceptible.

There is similarly a striking lack of evidence of chromatolysis in lumbar motoneurons of rats (51) or cats (52) with IDPN neuropathy. Despite the lack of morphological evidence of chromatolysis, electrophysiological studies of the motoneurons point to numerous parallels in action potential features in axotomized motoneurons and those in IDPN neuropathy. Electrophysiological alterations in motoneurons of IDPN treated cats are summarized in Table 1 and elsewhere (62).

Preliminary studies were performed in motoneurons not identified as to physiological type. As in early axotomy studies, this tended to obscure differential responses of the motoneuron subtypes. Subsequent studies in type-identified motoneurons (S, FR, FI, FF) have, in general, supported the original supposition (63) that the electrophysiological changes in IDPN neuropathy are reminiscent of those in chromatolytic motoneurons.

Differences between slow and fast motoneurons (i.e. S vs FF) tend to become

less apparent following interruption of the motor axon. Motoneurons to fast-twitch motor units have for example larger sizes, lower input resistances, and briefer AHPs (45). Axotomy results in a decrease in AHP duration in slow motoneurons and some increase in the normally briefer AHP responses in fast motoneurons (41, 45). Duration of AHP is reduced in types S and FR but unchanged in fast (FI and FF) motoneurons of cats with IDPN neuropathy (D. A. Delio, H. E. Lowndes, unpublished observations). It is noteworthy that AHP duration becomes significantly shorter in slow motoneurons as early as day 14 of the neuropathy.

A second feature showing convergence of electrophysiological characteristics in axotomized motoneurons is an increase in input resistance. Input resistance is significantly greater in all motoneuron types (except FI) by 35 days of IDPN neuropathy (D. A. Delio, H. E. Lowndes, unpublished observations). It has been argued that the change in this passive electrical property may reflect a postaxotomy reduction in perikaryal size and alterations in dendritic geometry as additional features of convergence of motoneuron characteristics (45). It is not profitable to speculate on the possibility of changes in passive motoneuron properties in IDPN neuropathy until further corroborative data (e.g. membrane time constants) are obtained. Further, the small changes in passive properties conferred by alterations in parikaryal size or dendritic geometry are almost certain to be obscured by the preponderant physical changes in the ventral horns resulting from the development of the massive axon swellings.

NEUROTOXICOLOGY AND THE AXON

Wallerian Degeneration

HISTOLOGY Following separation from its parent axon, either by mechanical or chemical lesion, the axon undergoes a stereotypic response first described by Waller (67) and subsequently detailed by several authors (cf 68, 69). Although the following brief description is derived from transection studies in which the precise time and location of the lesion are known, there is no evidence to suggest that the sequence differs following a chemically induced lesion. Focal swelling, with fragmentation of endoplasmic reticulum and accumulation of mitochondria and other organelles, appears within 24 hr adjacent to the transection site (cf 70, 71). Shortly thereafter, neurotubules and neurofilaments lose their longitudinal orientation and fragment; mitochondria swell; and the axolemma becomes occasionally discontinuous. A beaded appearance, reflecting areas of axonal narrowing and swelling (varicosities), is evident by 3 days, followed by fragmentation, usually first observed between nodes of Ranvier. Axonal degeneration is independent of myelin changes, which follow those in the axon (see 72, 73).

Histological features of nerves just proximal to the injury site are similar to

those distal to the lesion; their proximal extent is determined by the nature of the injury (69). It is interesting to note that acrylamide, which induces a "dying-back" neuropathy (8), causes histological changes to appear much more proximal to a nerve ligature than normally (74, 75), regardless of the proximal-distal location of the ligature (7). Isoniazid, 2,5-hexanedione and misonidazole, other neurotoxic agents that have similarly been described as causing a dying-back lesion, fail to augment lesions proximal to a ligature (74).

ELECTROPHYSIOLOGY Cragg & Thomas (23) suggested that nerve fiber diameter may be reduced proximal to sites of axonal injury. This would be consistent with decreases in conduction velocities in this region (41, 76). Presumably, axonal atrophy reflects a diminished supply of cytoskeletal protein, the principal determinant of axonal caliber, following a reordering of protein synthesis priorities in the perikaryon. While atrophy and decreased conduction velocities proximal to a neurotoxic lesion have not been directly investigated, recent studies (5) reveal that exposure to acrylamide can lead to a region of decreased neurofilaments (and axon caliber) that passes centrifugally down the nerve with time.

In contrast to morphological changes which many investigators believe progress centrifugally, electrophysiological alterations appear to progress centripetally. Nerve terminal function, evidenced by loss of repetitive generating capacity (77) within 48 hr, followed by failure of neuromuscular transmission by 4–5 days, is the first compromised, followed by centripetally advancing conduction block (78). Lack of decline in conduction velocities prior to onset of conduction block suggests an all-or-none failure.

Demyelination

PRIMARY DEMYELINATION Primary demyelination independent of axonal alterations or degeneration appears randomly in both proximal and distal portions of nerves, distinct from clusters of demyelinated segments on certain fibers. Primary myelotoxins have been divided into three groups (79):

1. Those that disrupt myelin prior to, or in the absence of changes in either the axons or myelinating cells. Examples include hexachlorophene, isoniazid, cyanate, acetylethyl tetramethyl tetralin, triethyltin, and the salicylanilides. Principal morphological features include edema and vacuolation of myelin.
2. Lysolecithin, which causes direct disruption of myelin without intramyelinic edema.
3. Chemicals that injure myelinating cells (Schwann cells or oligodendrocytes). Examples include pyrithiamine, biscyclohexanone oxalyldihydrazone (Cuprizone®) and chronic exposure to carbon monoxide and cyanide.

A subclass that affects both myelin and myelinating cells includes lead, tellurium, and the hypocholesteremic agents ethidium bromide and diphtheria toxin.

DEMYELINATION SECONDARY TO AXON LOSS In toxic neuropathies in which the axon appears to be the primary target [axonopathies according to the nosology of Spencer & Schaumburg (80)], demyelination is thought to occur as a passive sequel to axonal degeneration.

Secondary demyelination presumably follows a pattern similar to that in Wallerian degeneration [cf (9) for a more detailed description]. The nodes of Ranvier widen and Schmidt-Lanterman incisures dilate distal to the lesion site, either simultaneously or centrifugally over the next 36 hr. Degenerating axon fragments are surrounded by myelin that is fragmented by closures at the incisures (73), forming rows of ellipsoids which subdivide into smaller spheroids. The debris is phagocytized by proliferating Schwann cells and macrophages.

More common in neurotoxic situations is partial demyelination, usually involving only a percentage of the fibers in an affected nerve trunk. This demyelination, which can vary from paranodal to segmental (often in the same nerve fiber and in the presence of ongoing remyelination), can be secondary to focal axon swellings (without degeneration of the parent axon) or a primary effect of myelotoxic chemicals.

Demyelination and Impulse Conduction

Assuming axonal patency, complete block of impulse conduction is an extreme consequence of demyelination, rarely encountered in neurotoxicology. Early work by Denny-Brown & Brenner (81) with compression-induced focal demyelination indicates that the axon remains electrically excitable distal to the site of the demyelinated lesion, in contrast to situations in which the axon is also involved (see 82). In less extreme cases, conduction is altered but preserved. Compound action potentials, reflecting the net electrical activity at the recording site, are reduced in amplitude, delayed, and temporally dispersed. This has been convincingly demonstrated in studies of experimental allergic neuritis (83) and diphtheric demyelination (84, 85).

Caution must be exercised in inferring nerve fiber susceptibility from compound action potential records unless the latter are supported by correlative morphological and, optimally, single-fiber studies. A net slowing of compound action potentials could result from selective involvement of the largest diameter (fastest conducting) axons due to their degeneration, a velocity decrement in all fibers without axonal loss, or a combination of the two. In experimental vincristine neuropathy in the cat, conduction velocity histograms of single soleus afferents retain a bimodal distribution but with lower average velocity

(75–85 m/sec) than normal (90–100 m/sec) in the fastest conducting fibers (86). Morphological studies (87) reveal a combination of proximal axonal swellings and demyelination, with some distal Wallerian degeneration, principally involving the largest diameter fibers. Hence a combination of factors contributed to the apparent conduction slowing in this study. This is frequently the case in neurotoxicology, especially when the animals are tested in advanced stages of the neuropathy. Additional details are available (88).

Conduction velocity slowing due to demyelination has been demonstrated for single fibers in both the peripheral (89, 90) and central nervous systems (91), where the results of demyelination are qualitatively similar.

It should be noted that studies of demyelination have usually focused on the segmental rather than paranodal variety. Even then, myelin alterations at successive internodes are variable (92), associated with variation in internodal conduction times (93). Paranodal demyelination is an early and frequent concomitant in numerous examples of neurotoxicology, particularly those involving axonal swelling (see below). The consequences of paranodal demyelination on conduction velocity are not known with certainty. Slight alterations in nodal morphology do not appear associated with significant changes in conduction velocity (94, 95). Further, conduction velocity returns to normal despite the persistence of myelin vacuolization in triethyltin neuropathy (96).

Numerous morphological alterations occur in cases of neurotoxicity. Not only are parameters of fiber geometrically distorted, but also the properties of excitable membranes, ion concentrations, capacitance and impedance of myelin, axolemma, and axoplasm, and resistance of extracellular pathways to current flow (97). The status of these other determinants of conduction velocities in toxic neuropathies is essentially unknown. Recent studies (98) suggest that retraction of myelin loops from the axolemma (paranodal demyelination), commonly seen in many examples of neurotoxicology, may provide a low-impedence shunt between intra- and extracellular spaces. This could theoretically make the impact of paranodal demyelination on conduction greater than previously suspected.

Computer simulations of impulse conduction in demyelinated axons (95, 99) reveal conduction block to occur only after loss of 97.3% of myelin from a single node or two successive nodes with myelin reduced to 4% of normal. These calculations are based on equivalent changes in cable properties distributed evenly over the length of internodes. Interestingly, the same simulations revealed paranodal demyelination to be more effective in slowing impulse conduction than equivalent changes resulting from myelin loss. Details are reviewed elsewhere (97, 100).

Conduction of impulses in demyelinated axons occurs via either saltatory conduction, albeit with increased delay between excitation of successive nodes, or continuous conduction in demyelinated internodes (93, 101). Bostock &

Sears (101) calculated the velocity of continuous conduction through demyelinated regions (about 0.5 mm) to be only 5% of normal.

The refractory period for impulse transmission, the minimal interval at which the second of two impulses can enter but not transverse a portion of a nerve fiber (91), is markedly prolonged in demyelinated axons (91, 93, 102, 103); the safety factor for transmission is thus reduced, leading to impaired fidelity of transmission of trains of impulses (91, 93, 104, 105). During repetitive transmission across affected internodes, internodal conduction times increase progressively, associated with a progressive decrease in current generation at the node proximal to the affected internode (93).

Axonal Swellings

A common pathological feature of many chemically induced neuropathies is the formation of axon swellings, resulting from abnormal accumulations of cytoskeletal proteins, particularly neurofilaments. These neurofilamentous axonopathies have been observed to result from a diverse group of chemicals (Table 2) and may represent a subset of stereotypic responses of the neuron to certain forms of chemical insult.

MORPHOLOGY OF AXONAL SWELLINGS Although their spatio-temporal location varies with the particular neurotoxic chemical, axon swellings share several features. Their hallmark is an abnormal focal accumulation of 10-nm neurofilaments that first appear distally (acrylamide, hexacarbons, carbon disulfide), proximally (IDPN, vincristine), or occasionally both proximally and distally (IDPN). Aluminum, depending on route of administration, induces accumulations of neurofilaments in proximal axons (107) or in the perikaryon (53). In the neuropathy induced by 3,4-dimethyl,2,5-hexanedione, the locus of the axonal swellings is dose related (110, 111), with higher doses producing the most proximal swellings.

The swellings, containing maloriented skeins of neurofilaments and other organelles, distend progressively with the duration of the neuropathy, ultimately achieving diameters of 30–50 μm in hexacarbon intoxication. Swell-

Table 2 Chemicals causing neurofilamentous axonopathies

Chemical	Reference
Acrylamide	49, 106
Aluminum	53, 54, 107
Carbon disulfide	108, 109
Dimethylhexanedione	110, 111
Hexacarbons	112, 113
β,β'-iminodipropionitrile	51, 114, 115
Vinca alkaloids (vincristine)	87

ings with diameters of 100–150 μm have been observed in IDPN-treated cats (52). In hexacarbon neuropathy, swellings first develop on the proximal side of nodes of Ranvier (116).

As the axon swelling enlarges, myelin is altered at the involved node(s). Initially, terminal loops become detached from the axolemma (paranodal demyelination). Larger swellings and/or more severe intoxication result in slippage or remodeling of myelin, resulting in thin, patchy, or absent myelin (51, 117).

The axon distal to axonal swellings undergoes Wallerian-like degeneration in many, but not all, neurofilamentous axonopathies. Axon loss is a hallmark, at least in the advanced stages of intoxication with acrylamide (49, 106, 118), hexacarbons (47) and carbon disulfide (119), and dimethylhexanedione (110, 111). Apparently, the presence of axon swellings is a necessary but insufficient condition for axon degeneration. Fiber loss does not occur in rodents chronically exposed to IDPN, despite the presence of enormous proximal axonal enlargements (120, 121). On the other hand, IDPN intoxication of felines results in not only typical proximal swellings, but also occasional contemporaneous distal swellings; mild fiber loss appears to accompany coexisting proximal and distal swellings in this neuropathy (115).

ELECTROPHYSIOLOGICAL CONSEQUENCES OF AXONAL SWELLINGS

Conduction block Block of impulse conduction could arise from one or more consequences of axonal swellings: (*a*) Wallerian degeneration distal to the swelling; (*b*) demyelination of several successive internodes; (*c*) compromise of axolemmal mechanisms supporting action potential generation and propagation; and (*d*) enlargement of the axoplasm to an extent inconsistent with impulse propagation.

When a neuropathy has progressed to the stage in which axons degenerate (i.e. Wallerian degeneration), profiles of compound action potentials reflect the influence of loss of subpopulations of susceptible fiber diameters (see above). In most toxic neuropathies, these tend to be the largest diameter fibers subserving proprioceptive and α-motor axon functions. The dying-back hypothesis (8) predicts that with continued intoxication, axon degeneration should progress centripetally; hence the profile of compound action potentials would reflect not only the duration of intoxication, but also the proximo-distal location of the recording. Sumner (82) has detailed an experimental procedure for evaluation of centripetally advancing Wallerian degeneration in peripheral nerves.

Wallerian degeneration associated with axon swellings induced with toxic chemicals is essentially similar to that following axotomy; the two differ only in the nature of the lesion. Similarly, demyelination at several successive in-

ternodes would be expected to have direct consequences analogous to those following demyelination with diphtheric toxin (reviewed in 97).

Axon swellings represent abrupt discontinuities in axonal caliber; their size could be principal determinants of their influence on impulse conduction. Small increases in axonal caliber, such as occur in the early stages of neurofilamentous axonopathies, might be predicted to slow impulse conduction (122; reviewed in 123). The net effect on conduction velocity is difficult to determine since paranodal or nodal demyelination often accompanies even small swellings, and the relative influences of small degrees of demyelination and axon swelling are unknown. For example, conduction latencies in single motor axons of cats with IDPN neuropathy are significantly prolonged as early as 7 days of intoxication, when the proximal axons are very mildly distended; however, internodal and paranodal myelin thickness appear modestly reduced (52), confounding interpretation of the influence of the axon swelling alone.

Very large swellings (e.g. greater than 60–70 μm) such as occur in IDPN intoxication (51, 52, 115) are predicted to block impulse conduction regardless of the influence of demyelination. Parnas et al (124) calculated that a 5 : 1 ratio between the diameters of the enlargement and normal adjacent axon would be the critical point at which longitudinal currents through the enlarged portion of the axon would become insufficient to support impulse propagation. At this point, the axon swelling would represent an impedance mismatch with the contiguous axon and impulse conduction would be blocked. Experimentally this has been tested by recording intracellularly from a spinal motoneuron of cat with IDPN neuropathy and attempting to evoke motoneuron action potentials via orthodromic, then antidromic stimulation. Orthodromic stimulation (via dorsal roots) was effective in eliciting a motoneuron action potential; but antidromic stimulation, with a presumed intervening axonal swelling, frequently was not (63). Since the incidence of such recordings increases with duration of intoxication, during which there is progressive enlargement of axon swellings, it is probable that impulse conduction is blocked in the largest swellings.

Later studies of single motor units confirmed that the incidence of impulse blockade increases with the duration of IDPN intoxication and that all motor unit types (FF, FR, S) are equally susceptible (D. A. Delio, H. E. Lowndes, unpublished observations).

Impulse reflection and repetitive discharge At some critical size, an axon swelling retards impulse conduction sufficiently that the just depolarized (i.e. nonswollen) portion of the axon repolarizes while the impulse is still transversing the swelling. Under such conditions, action potentials can be initiated in both forward and reverse directions and, in effect, the impulse is reflected back to its origin (123). Impulse reflection has been demonstrated in a number of

models and experimental situations (125–129). This has not been tested in neurotoxic states.

A possible sequel to the slowing of the impulse in an axonal swelling is repetitive activation of the adjacent, presumably normal, axon. Single stimulation of soleus or medial gastrocnemius afferents in cats with IDPN neuropathy gives rise, in certain instances, to multiple action potentials in the dorsal root input (130). Large axonal swellings occur in the stem processes of dorsal root ganglia in IDPN treated animals (51). The multiple dorsal root discharges may arise from repetitive activation of the afferent fiber in the region of these axon swellings. Repetitive activation, again perhaps reflecting the influence of proximal axon swellings in alpha-motor axons, are also observed in ventral root recordings even in the absence of multiple potentials in the dorsal root input (130).

While the repetitive discharges arising in the dorsal root ganglia are likely related to the axon swellings, it is less certain that swellings in motor axons are the sole contributors to repetitive action potential discharges recorded in motoneurons. A high incidence of delayed depolarizations is observed in motoneuron recordings (63, 65); their possible contribution to repetitive activation of the motoneuron cannot be overlooked.

Axonal/perikaryal crosstalk Axon swellings, whether in nerve trunks or the spinal/CNS interparenchyma, are grossly distended structures which must compress and abut upon neighboring neuronal elements. Their physical size, coupled with concomitant demyelination that leaves them electrically "uninsulated," give rise to the possibility of abnormal electrical interactions. Granit and co-workers (131, 132) observed the formation of an "artificial synapse" at the site of acute cut or crush injury in cat sciatic nerve. Ephaptic transmission, or crosstalk, occurs between pairs of spontaneously active nerve fibers in dystrophic mice, in which the spinal root axons are devoid of myelin and closely opposed in midroot (133–136). Crosstalk has also been observed in experimental neuromas (137).

The only studies of crosstalk employing neurotoxic agents have involved tullidora (buckthorn) (138) and β,β'-iminodipropionitrile (52, 63).

The neuropathy caused by IDPN is characterized by large, demyelinated swellings which fill spinal ventral horns and abut on axons, motoneurons, and each other (52, 56, 115), giving rise to crosstalk between numerous neuronal elements. Preliminary estimates suggested that about 12% of motoneurons were capable of crosstalk at 5 weeks of the neuropathy (63). More detailed studies revealed that all motor unit types are approximately equally involved, the incidence of crosstalk increased with duration of the neuropathy (presumably reflecting ever-enlarging axon swellings), and crosstalk occurs between

both cell bodies and axon swellings (139). In late (i.e. 70 days) stages of the neuropathy almost one half of neuronal elements tested exhibited crosstalk. True ephapse formation between neuronal elements does not occur in IDPN neuropathy (140), and the exact location where crosstalk is initiated (soma, dendrites, axon, axon swelling) has not been determined. It has been suggested that the axon–axon interactions in this neuropathy may be mediated by activity-driven accumulations of extracellular potassium (99, 138).

Axonal Atrophy

IDPN neuropathy presents a unique opportunity to examine the influence of true diminution of axon diameter on impulse conduction. Proximal giant axon swellings enlarge at the expense of cytoskeletal proteins destined for maintenance of axon caliber (141), leading to axonal atrophy (51). Maximum motor conduction velocities in rat sciatic nerve trunks are diminished in animals chronically administered IDPN, in direct correlation with the observation of a reduction in the number of large axons and an increase in small-diameter fibers (i.e. axonal atrophy) (142). Studies of conduction velocities in single soleus and gastrocnemius motor axons (B. G. Gold, H. E. Lowndes, unpublished; 62) at 50 and 100 days of the neuropathy reveal a progressive decline until at 100 days average conduction velocities are reduced to nearly one half normal. At early stages of the neuropathy (7–35 days) a progressive decline in single fiber conduction velocities is also observed in all types of motor axons (S, FR, FF), but the fastest conducting axons (innervating type FF motor units) tend to exhibit the earliest and most severe reduction in velocities (64). It is interesting that the extent of axon swelling in IDPN neuropathy covaries with axon caliber (143), perhaps related to the greater neurofilament density in larger-diameter axons.

Recent studies reveal that the caliber of proximal axons is reduced during chronic administration of acrylamide (5). These authors suggest that the diminished delivery of neurofilaments underlying the atrophy may reflect a reordering of slow axoplasmic transport as a neuronal response to toxin-induced axonal injury. The electrophysiological correlates of acrylamide-induced axonal atrophy have not been reported.

NERVE TERMINAL FUNCTION IN NEUROTOXICOLOGY

In almost all examples of neurotoxicity investigated, nerve terminal function appears somehow compromised, regardless of whether the primary lesion occurs in the soma, axon, or myelin. In the case of axonopathies, many of which are distal, impaired terminal function as an early manifestation of

neurotoxicity is consonant with the dying-back hypothesis (8). While terminal dysfunction is an obvious sequel to axon degeneration, it is less clear why deficits in terminal function occur prior to the appearance of neuropathology, whether a causal relationship exists between the two, whether they share a common initiating event [e.g. impaired axoplasmic transport (144)], or whether one or both are consequences of interrupted bidirectional trophic maintenance between the nerve cell body and its target of innervation. These are some of the major unanswered questions in neurotoxicology.

Sensory Terminals

Subjective sensory impairment is often the earliest symptom of incipient neurotoxicity in man. This is exemplified by clinical reports of acrylamide intoxication (118) and is borne out by experimental studies which confirm that sensory impairment precedes motor involvement (145, 146). In some instances, sensory neuropathy is the first manifest but is inevitably followed by motor involvement with progression of the neuropathy. In other cases, profound sensory involvement occurs without an apparent motor counterpart, as in the cases of doxorubicin (147; see however 148) and cisplatin (149) neurotoxicity.

The apparently greater susceptibility of peripheral sensory structures to the neurotoxic effects of certain chemicals may reflect toxicokinetic influences. Jacobs (3, 4) described finestrae in the "blood-nerve barrier" surrounding the dorsal root ganglia. Such finestrae would result in potentially greater exposure of these sensory perikarya to neurotoxicants than their motor counterparts, which enjoy relatively greater protection behind the "blood-brain barrier" of the CNS. While this is an intuitively appealing argument, it fails to take into account chemicals that cause a predominantly motor neuropathy or the simultaneous appearance of sensory and motor impairments with still other toxic chemicals (150, 151).

Also unexplained are the electrophysiological consequences at higher integrating centers (i.e. the cerebellum and cerebrum) of impaired sensory terminal function. Clinically, the consequences appear as anesthesias, parethesias, and symptoms suggestive of deficits in proprioception typified by ataxia and areflexia. While the consequences of altered proprioceptive inputs on spinal reflexes have been examined in the experimental neuropathies induced by acrylamide (152, 153), vincristine (86), and IDPN (63, 130), their supraspinal influences remain unexplored.

Muscle Spindles

HISTOLOGY The neuropathologic features of muscle spindles and Pacinian corpuscles in various neurotoxicities have been described in detail (106, 113, 154).

ELECTROPHYSIOLOGY Muscle spindles provide two types of proprioceptive information concerning a muscle: the rate and amount of its extension. The rate of lengthening is signaled by a dynamic discharge frequency proportional to the velocity of extension (the velocity or dynamic component of spindle discharge) while the length per se is signaled by a more constant discharge rate reflecting muscle length (the length or static component). Information concerning both the static and dynamic state of the muscle are critical to proprioception.

Sumner & Asbury (155) first demonstrated spindle defects in acrylamide intoxication. Subsequent detailed studies revealed the static and dynamic sensitivities of muscle spindles to be reduced in striking correlation with the appearance of clinical signs of the intoxication, especially ataxia (145). Loss of static responsiveness, particularly in secondary endings, coincided with the appearance of neurological deficits after 7 days administration of 15 mg/kg/day acrylamide to cats; doubling the dose to 30 mg/kg/day halved the time to onset of equivalent neurological impairment. The amount of muscle extension necessary to elicit a given discharge from a spindle was greater at this time, indicating an elevation in threshold, along with the loss in fidelity of static sensitivity. While there are contemporaneous lesions in the cerebellum even at these early stages of the neuropathy (156), the temporal link between muscle spindle dysfunction and neurological impairment is apparent.

The tendon reflex (knee jerk) is initiated by the dynamic discharge from primary muscle spindle endings activating homonymous motoneurons via spinal monosynaptic reflexes. The attentuation of dynamic sensitivities of the spindle endings early in acrylamide neuropathy provides a rational explanation for the areflexia that accompanies this neurotoxicity (157).

In contrast to acrylamide neuropathy, the dynamic but not the static sensitivity of muscle spindles is attenuated in vincristine neuropathy (86). Static responsiveness is retained only by those endings capable of any discharge; as many as 80% of presumed spindle endings become totally afunctional during the course of vincristine intoxication.

Position sensitivity of spindle endings is also impaired in diisopropylfluorophosphate (DFP) neuropathy (151). As in the case of acrylamide poisoning, secondary endings appear more susceptible to the neuropathic effects of DFP than their primary counterparts. Dynamic sensitivities are not attenuated in cats chronically intoxicated with DFP (151) or subacutely poisoned with soman (158).

The mechanism underlying muscle spindle dysfunction in the toxic neuropathies is unknown. Among other possibilities are: early degenerative events

in the nerve membrane subserving mechanical transduction (i.e. the generator potential); impaired impulse conduction in the preterminal, intramuscular branches of the sensory nerve ending; and pathological alterations in capsular tissue surrounding the spindle endings. The latter would result in incorrect or incomplete transmission of physical forces from the muscle to the spindle ending. Additional details are given elsewhere (159).

Pacinian Corpuscles and Other Peripheral Cutaneous Receptors

ELECTROPHYSIOLOGY Pacinian corpuscles from cat mesentery lose the ability to initiate generator potentials in proportion to the severity of acrylamide poisoning (160). Total doses in excess of 60 mg/kg result in corpuscles unresponsive to mechanical stimuli. Analogous studies of cutaneous mechanoreceptors (field, rapidly adapting, and slowly adapting types 1 and 2) similarly show a greater incidence of failure during acrylamide intoxication (161). An apparent shift in the distribution of relative numbers of these receptors, with an increase in rapidly adapting but a decrease in slowly adapting types, likely results from loss of position sensitivity (static responsiveness) in slowly adapting receptors, making them appear functionally to be rapidly adapting [i.e. retaining a pseudodynamic response (159)].

Frequency-response relationships of mechanoreceptors are unaltered following subacute soman administration, but the total number capable of responding is reduced by one third (158). Slowly adapting type 1 receptors have elevated thresholds and more irregular firing patterns, following even a single dose of vincristine (162).

Central Projections of Sensory Receptors

HISTOLOGY The central projections of peripheral sensory receptors, being distally located from their cell bodies, might be expected to be involved early in the course of neurotoxic events for the same reasons as their peripheral counterparts. For example, the projections of primary afferent fibers (i.e. from muscle spindles) projecting onto the cells of origin in the dorsal spinocerebellar tract (Clark's column) show changes early in the course of acrylamide neuropathy reminiscent of those in peripheral terminals. By 10 days of the intoxication, the synaptic boutons on cells in Clark's column contain modest accumulations of neurofilaments and a depleted number of synaptic vesicles (B. S. Jortner, H. E. Lowndes, unpublished observations). These consequences of this defect, coupled with the coexisting deficit in muscle spindle ending function, must further compromise transmission of proprioceptive information.

In a stereological examination of synaptic boutons on anterior horn cells (lumbar motoneurons) of rats intoxicated with 2,5-hexanedione, Sterman &

Sposito (163) noted morphological changes including partial and occasionally complete detachment of the boutons; some synaptic degeneration also occurred, with involvement of microglia and astrocytes. These boutons are the terminals of primary afferents subserving spinal monosynaptic reflexes. These findings could indicate a primary lesion in the sensory neuron or its terminals. Alternatively, they could result from a remodeling of the motoneuron itself following a neurotoxic lesion at some level of the motor axis. Synaptic disjunction of temporarily redundant synapses is known to occur following section of motor axons (28).

Clioquinol neuropathy has the remarkable neuropathological feature, at least in experimental animals, of principally involving the distal ends of centrally projecting sensory axons, with relative sparing of axons of the peripheral nervous system (164).

ELECTROPHYSIOLOGY A number of electrophysiological studies of primary afferent terminal function in acrylamide intoxication reveal that these central projections to spinal reflexes are affected at doses that have no visible effect on peripheral terminal (muscle spindle ending) function. Greater sensitivity of central projections may reflect underlying differences in the neurochemical substrates supporting central and peripheral projections. Unconditioned but not conditioned (posttetanic) monosynaptic reflex responses are reduced in cats given acrylamide (152). This defect in the primary afferent terminals to spinal monosynaptic reflex pathway results partly from a diminution of transmitter turnover (153). A motoneuron (perikaryal) contribution to the decreased monosynaptic reflexes was ruled out by studies demonstrating motoneuron responses to quipazine to be unchanged in acrylamide-treated animals (165). Additional evidence for an afferent terminal deficit is that dorsal root potentials cannot be evoked even with very large stimuli (166).

Monosynaptic reflexes are also altered in IDPN neuropathy (130). While it is probable that a sensory defect occurs in this neuropathy, direct experimental proof is lacking. However, the motoneuron involvement in this neuropathy is so extensive as to confound interpretation of a possible primary afferent terminal contribution to overall dysfunction. Similarly, studies of the delayed neuropathy resulting from tri-ortho-cresyl phosphate revealed attenuation of monosynaptic reflex responses (167); determination of the status of terminal projections in this neuropathy awaits precise assessment of the motoneuron contribution. Additional details are given elsewhere (168).

Motor Nerve Endings

HISTOLOGY Neurotoxic agents can cause morphological damage of nerve endings. Using a model in which a localized organophosphorus-induced neuro-

pathy is produced in a hind limb of cats (150, 169), various investigators (170–173) found ultrastructural changes in motor nerve endings. In this context, motor nerve endings are the final portion of peripheral motor axons that extend from the distal or last node of Ranvier and include the unmyelinated terminals. Typical morphological alterations include the presence of extensive lamellar whorls in both the axons and intramuscular axons, the disruption and retraction of nerve terminals from the synaptic cleft, and a dispersion of the basal lamina.

ELECTROPHYSIOLOGY The morphological damage occurs contemporaneously with the loss of electrophysiological responsiveness of the motor nerve endings: This is evidenced by the loss of the capacity of motor nerve endings to generate repetitive discharges after conditioning by high frequency stimulation or facilitatory drugs in DFP (150, 169), acrylamide (146), and IDPN (174) neuropathies.

The neurotoxic agent dithiobiuret also affects motor nerve terminal function: The quantal release of acetylcholine is depressed, as well as the minature end plate frequency (175). These prejunctional toxic effects adversely affect the posttetanic potentiation evoked by high frequency conditioning of motor nerves (176).

Lead presumably affects motor nerve ending function by competing with calcium for prejunctional sites. Calcium uptake into the nerve terminal is thereby blocked and transmitter release is interrupted (177–179).

Interestingly, in acute methyl mercury toxicity, an increase in the spontaneous release of transmitter first occurs followed by the cessation of all activity at the neuromuscular junction. This agent increases the probability of transmitter release while causing reduction in the quantal content and the immediately available store of transmitter (180). Miyamoto (181) has postulated that the mercury ion has a high affinity for intracellular sulfhydryl groups that are involved in transmitter releasing mechanisms. This bimodal type of activity of methyl mercury at the neuromuscular junction is similar to that caused by black widow spider venom (182). Morphological studies have shown that a disruption of the motor nerve terminal and an absence of synaptic vesicles within the nerve ending occur after black widow spider venom treatment while the postjunctional structures are unaffected. The effects of some other neurotoxic agents on neuromuscular function are listed in Table 3.

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Table 3 Electrophysiologic effects of neurotoxic agents at the neuromuscular junction

Agent	Effect	Reference
Aliphatic alcohols	EPP amplitude ↑ and then ↓ → 0	199, 200
	quantal content (m) ↑	200
	immediately available store ↓	
	mepp amplitude ↑	
	EPP decay phase ↑	
	mepp decay phase ↑	
Dithiobiuret	EPP amplitude ↓	
	RMP no change	
	mepp frequency no change or ↓	175, 198
	quantal content (m) ↓	175
	mepp amplitude ↑	
2,5-Hexanedione	mepp frequency ↑ and then ↓	201
	mepp amplitude ↑	
	mean quantal content (m) ↓ or no change	
Lead	ACh output ↓	183
	mepp frequency ↑	178
	EPP amplitude ↓	177
	Ca uptake by nerve terminals ↓	184
	quantal content (m)	
	↓ immediate available stores	185
	mepp amplitude ↓	186
	RMP ↑	187
	slowing of recovery of RMP	
	↓ spontaneous spike activity	
	↓ input resistance	
Mercury	EPP amplitude, ↑ and then ↓ → 0	188
	mepp frequency ↑	181
	mepp frequency ↑ and then ↓ → 0	180
	mepp amplitude no change	
	RMP no change	
	quantal content (m) ↓	
	p (probability of release) ↑	
	immediately available store ↓	
Organophosphorus anti-cholinesterase agents	EPP decay phase ↑	192, 193
	EPC decay phase ↑	194, 195
	EPP amplitude ↑	196
	At high doses or long duration	195
	EPP and EPC ↓	197
	mepp frequency ↑	193

Table 3 *(continued)*

Agent	Effect	Reference
	mepp amplitude ↑	193
	quantal content (m) ↓	196
	mepp decay phase ↓	196
Organotin (triethyltin)	EPP ↓ amplitude	189
	mepp amplitude no change	
	mepp frequency no change	
	ACh release during tetany ↓	190
	RMP ↓	191

Abbreviations: ACh, acetylcholine; EPP, end plate potential; mepp, miniature end plate potential; RMP, resting membrane potential

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