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EDITORIAL

Neurotoxicology: an update on epidemiology, mechanisms, and pathology

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The adverse impact of environmental chemicals on the human brain has been recognized as an important endpoint in toxicology. In one of the most influential toxicology textbooks, the authors stated in their introduction that … "the target organ of toxicity most frequently involved in systemic toxicity is the CNS" [1]. Accordingly, the 2nd edition of "Experimental and clinical neurotoxicology", edited by Peter Spencer and Herbert H. Schaumburg [2], listed more than 450 compounds that are suspected or proven neurotoxins/toxicants in humans. Naturally occurring neurotoxins, such as domoic acid (DA) or tetrodotoxin (TTX), are among the most potent poisons that can be found in nature, whereas organic solvents are among the man-made neurotoxicants shown to be associated with severe damage in the central and peripheral nervous system [3]. Already in the early 1980s, Acta Neuropathologica published human biopsy pictures showing demyelination of giant axons taken from the terminal portion of the musculocutaneous nerve of the leg of a patient chronically exposed to *n*-hexane and methylethylketone [4]. Later, details about specific neuropathological changes after chronic solvent abuse via inhalation could be shown in 88 autopsy cases [5]. In addition to macroscopic findings, such as enlarged ventricles, white matter abnormalities, and cerebral atrophy, the study showed that chronic solvent leukoencephalopathy can be identified by birefringent PAS-staining macrophages and reactive microglia in the white matter. However, the study was not able to disentangle the neuropathological effects of the different solvents that the cases abused simultaneously. Nevertheless, such a neuropathological differential diagnosis was possible in the field of aluminum (Al) neurotoxicity. The neurotoxicity of Al is well known and described in detail for various endpoints and species [6]. Al exposure has also been linked to the pathogenesis of Alzheimer's Disease (AD) [7]. Aluminum neurotoxicity is also thought to play a role in dialysis-associated encephalopathy (DAE) where Al-containing drugs are used to control hyperphosphatemia, and dialysis dementia has been frequently observed as clinical outcome. Despite the proven neurotoxicity of Al, another well-conducted neuropathology study by Reusche et al. [8] could show that the changes in human brain tissue in DAE patients differed markedly from AD patients. DAE patients did not show AD-type neurofibrillary tangles (NFT) above the normal or expected age-related changes, even though the Al concentrations in the brain samples were markedly increased. These examples illustrate the valuable contributions of neuropathology to the area of toxicology, in particular neurotoxicology. When searching the electronic archive of Acta Neuropathologica, one can find approximately 120 publications related to neurotoxicology but only a few, like the examples given before, included histopathological analyses in human brain tissue. Moreover, these studies were mostly performed under conditions of high exposures or even intoxication. During the last decades, only a few neurotoxicity studies or reviews have been published that have a strong focus on human neuropathology (e.g., [9]). This deficit has been identified by the former Editor-in-Chief, Werner Paulus, who developed and initiated the idea of a cluster of reviews addressing current hot topics in neurotoxicology. This was a challenging endeavour as there are some differences between these obviously-related disciplines.

Why the disparity between these two disciplines within neuroscience?

There are some reasons for this weak association between neuropathology and toxicology that are inherent to the scientific and societal aims of toxicology. Toxicology tries to contribute to risk assessment procedures, and consequently,

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studies are needed that determine dose–response relationships between the magnitude of exposure and the probability to cause adverse health effects. While the histopathological examination of other target organs (e.g., liver and lung) is still a cornerstone in toxicological guideline studies (e.g., as proposed by the Organization for Economic Cooperation and Development (OECD) [10]), neurotoxicity testing in rodents also relies on functional or behavioral testing (e.g., motor activity [11]). With respect to animal studies, the various regulatory agencies also provide some guidance regarding neuropathology assessment [12], but these examinations are more often a rough estimate of neuropathological changes not fully exploiting the current state of the art in neuropathology. Accordingly, behavioral tests in animals, which have been suggested as an important, sensitive, and apical endpoint in chemical risk assessment, are used more frequently [13, 14], and "safe" levels of exposure are often derived from these endpoints, as in the case of the solvent toluene [15] that also causes neuropathological effects at higher doses [5]. Recently, and related to the efforts of developing alternative methods in toxicity testing [16], behavioral testing in zebrafish has been proposed as a model to investigate adverse outcomes in a whole organism upon exposure to neurotoxic compounds [17]. Accordingly, neuropathology is often only a minor point in neurotoxicity testing, both in guideline studies and scientific research.

In humans, epidemiological studies of exposed populations (e.g., occupationally or environmentally) are the only source to derive dose–response relationships, and here, the availability of brain tissue is limited. Even in cases like the solvent abusers [5], it is difficult to link individual exposure data to these brain samples. Therefore, in human studies, neurobehavioral testing has been the only or at least most important endpoint for the assessment of adverse health effects to the human brain [18]. In addition to the strong focus on behavioral measures as a "surrogate marker" of impaired brain functions, the deficit of neurophysiological and even pathological human data in neurotoxicology was also caused by (a) the lack of non-invasive methods to investigate brain functions in vivo, and (b) the limited availability of neuroimaging techniques, such as functional and structural Magnetic Resonance Imaging (MRI). Various neurophysiological techniques have become increasingly available in epidemiological studies among workers, e.g., manganese-exposed welders [19], and thereby, the knowledge about neurotoxic mechanisms can be used for the selection of sensitive, neurophysiological endpoints in experimental or epidemiological studies [20, 21]. Later, the validation of such neuroimaging findings in brain tissue could provide conclusive information about dose-dependent neuropathological changes after neurotoxic exposures. Thereby, the impact of neurotoxic exposures could also be evaluated more precisely as these findings can be compared to the neuropathology of aging [22] or neurogenerative diseases [23].

Recent developments that might facilitate interactions between neuropathology and toxicology

The ongoing paradigm shift towards toxicological testing strategies that are based on mechanistic knowledge about the perturbations of molecular and cellular events within neural cells and networks [24, 25] might promote or revive the integration of neuropathology into toxicology. One conceptional tool that is relevant here is the idea of an "Adverse Outcome Pathway" [26] that has be adopted by neurotoxicity [27]. Here, the molecular initiating event (MIE), e.g., the chronic antagonism of *N*-methyl-d-aspartate receptors (NMDARs) during brain development, should cause impairment of learning and memory abilities in children. The apical endpoint of this adverse effect might be the reduced IQ of children as shown for low-level lead exposures [28]. Such adverse effects of environmental toxicants have also been addressed in neurophysiological and pathological studies, as summarized for prenatal exposure to maternal cigarette smoking (PEMCS) [29]. In particular, the MRI readouts were able to detect adverse neurotoxic effects in exposed children, such as thinner orbitofrontal, middle frontal, and parahippocampal cortices in smoke-exposed children [30]. These morphometric readouts were more sensitive than the Wechsler Intelligence Scale for Children. Moreover, in this review, neuropathological findings from animal studies were able to provide more details about the pathological changes in the brain of rats (e.g., increased spine density in the granule cells, and terminal and basal dendrites of the pyramidal neurons of CA3 and CA1 of the hippocampus). These examples clearly showed that the paradigm change in neurotoxicology might be a chance to intensify the collaboration between neuropathology and neurotoxicology.

The present neurotoxicity review cluster is intended to be a first step in this direction and might encourage researchers from both disciplines to intensify collaborations. Two hot topics from neurotoxicology, namely the exposure to pesticides [19] and polychlorinated biphenyls (PCBs) [31], will be addressed in detail. Both reviews will provide some information about the history of these neurotoxicants, their diversity with respect to chemistry, and their ability to persist in the environment and human tissue even for decades. Summaries of in vivo and in vitro studies describing the different neurotoxic mechanisms that have been discovered are presented, and their relevance for the epidemiological findings has been discussed. While the review on PBC has a stronger focus on developmental neurotoxicity, the pesticide review will also address possible associations of this class

of neurotoxicants with neurodegenerative diseases. Finally, both reviews focus on the need for a comprehensive characterization of the neurotoxic properties of new chemicals that may be developed to substitute the two groups of chemicals reviewed in this cluster.

I am confident that this cluster of two reviews is an excellent starting point to stimulate the dialogue between these two "neuro" research areas.

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