Synaptic mechanisms of cadmium neurotoxicity

Andrei N. Tsentsevitsky, Alexey M. Petrov

Cadmium (Cd) is a toxic heavy metal ubiquitously distributed in the environment (water, air, food, smoke) with extreme ability to enter human body and accumulate with delayed clearance (half-life time 15–30 years). Consequently, prolonged exposure to low doses of Cd causes multi-organ toxicity. Remarkably, the central and peripheral nervous systems are considered as one of the most vulnerable targets. Excessive Cd exposure can profoundly aggravate common neurodegenerative diseases and peripheral polyneuropathies as well as lead to mental deficits in children (Branca et al., 2020). Conceivably, that Cd-induced defects in synaptic neurotransmitter release from neurons could be triggering events in Cd neurotoxicity. Numerous studies have discovered the disturbances at the synaptic levels in response to both acute and chronic Cd administration. Furthermore, release of Cd, captured by neuronal tissue, into extracellular space is increased by stimulation of synaptic vesicle (SV) exocytosis (Minami et al., 2001), pointing to Cd accumulation within the SVs in presynaptic terminals. Being a divalent cation, Cd can enter cells through various ways (such as active transporters, carriers, channels, and endocytosis), which serve to transport physiologically essential cations (Ca, Mg, Cu, Mn, Zn). An important route for Cd penetration into neuronal cells relies on zinc transporters (ZnTs). Among them, ZnT3 is highly abundant in the membranes of the SVs and responsible for maintaining the vesicular Zn pool in brain (McAllister and Dyck, 2017). Presumably, presynaptic terminals containing from hundreds to thousands of SVs could be reservoirs for Cd accumulating in the SVs due to ZnT3 activity. Furthermore, SV membranes are enriched with anionic negatively-charged lipids that can electrostatically attract bivalent cations, including Cd, as they are present in close proximity to the SVs (Minami et al., 2001). Cd is produced inside the nerve terminals that could affect a plethora of processes, consequently disturbing various presynaptic functions, notably neurotransmitter release. The resulting synaptic defects can produce “devastating signals” which are propagated to the neuronal bodies. Such retrograde pattern of pathology spreading is observed in some neurodegenerative disorders. Recently, we have found that at very low concentrations Cd can desynchronize neurotransmitter release from motor nerve terminals (Tsentsevitsky et al., 2020). A focus on the mechanism behind this phenomenon (Figure 1) can delineate the early events in Cd neurotoxicity and reveal a bridge between Cd action and neurodegeneration.

Synchrony (timing) of neurotransmitter release is an important factor that determines the efficacy and plasticity of synaptic communication. The neurotransmitter release occurs shortly (within hundreds of microseconds) after action potential (AP) to maintain precise transfer of frequency-coded information. This synchronous mode of neurotransmitter release allows fast and flawless exchange of information between neurons, establishing the basis of proper neuronal network activity and delivery of instructions to external targets (e.g., muscles, visceral organs). Although a synchronous release usually dominates, a neurotransmitter may be released asynchronously during tens to hundreds of milliseconds after an AP. This asynchronous release is an essential modulator of neurotransmission by affecting the duration of postsynaptic inhibition and activation; neuronal excitability and network activity; and coincide detection by neurons. Meaningfully, a prominent increase in asynchronous release was found in models of Alzheimer disease, epilepsy and spinal muscular atrophy characterized by loss of motor neurons. Also, IgGs from sporadic amyotrophic lateral sclerosis patients selectively bind to presynaptic membrane of motor neurons and enhance asynchronous release (Pagani et al., 2006). Accordingly, excessive Cd can aggravate neurodegenerative diseases and epileptic seizures via an increase in asynchronous release. It should be noted that SVs which mediate synchronous and asynchronous exocytosis can use separate endocytic routes. Particularly, adaptor protein-3 dependent endocytic recycling is utilized for the replenishment of the SV pool responsible for the asynchronous release. The same pathway generates SVs and endosomes with Zn/Cd-translocating ZnT3 and the vesicular Zn facilitates the participation of these SVs in the neurotransmitter release. It is tempting to suggest that accumulation of Cd and Zn in the subpopulation of the SVs contributes to the enhancement of asynchronous release. Supporting this notion is that both Zn and Cd desynchronized neurotransmitter release in the motor nerve terminals (Tsentsevitsky et al., 2020). Like Cd poisoning, excess Zn might exacerbate neurodegenerative disorders as well as epilepsy. Accordingly, the severity of Cd neurotoxicity can be interconnected with alterations in Zn homeostasis. Indeed, we found that Znenhanced Cd-induced desynchronization of neurotransmitter release (Tsentsevitsky et al., 2020).

Asynchronous release is determined by influx of extracellular Ca2+ and its utilization inside the nerve terminal. Mitochondria occupy ~1–5/13 volume of presynaptic compartment and they are present in close proximity to the SVs (Figure 1). Mitochondrial Ca2+ uptake markedly restrains a time frame for neurotransmitter release after arriving an AP, thus the compromised mitochondrial function leads to an increase in asynchronous release. Additionally, mitochondria damage in synapses leads to an overproduction of reactive oxygen species (ROS) (Zakyrianova et al., 2020), which can enhance Ca2+ influx into nerve terminal through voltage-gated Ca2+ channels (VGCCs), which are reversibly blocked by Cd, reside densely at the presynaptic site can concentrate Cd, facilitating direct Cd action on both mitochondrial ROS production and the asynchronous release in the motor nerve terminal. Mitochondrial Ca2+ uptake markedly restrains a time frame for neurotransmitter release (Figure 1). The ability of Zn to amplify Cd action on both mitochondrial ROS production and the asynchronous release in the motor nerve terminals emphasizes the link between Cd effect on mitochondria and the asynchronous neurotransmitter release (Tsentsevitsky et al., 2020). Zn is known to have dual actions by acting as either an antioxidant or prooxidant (Branca et al., 2018; Lee, 2018). One explanation to this paradoxical effect of Zn is that antioxidant action of Zn such as Cd levels, may determine the prooxidant properties of Zn. As an oxidant Zn, can inhibit mitochondrial function at the level of the electron transport chain complex I, III and IV as well as a-ketoglutarate dehydrogenase complex of tricarboxylic acid cycle (Lee, 2018). In neuronal cell lines, only higher concentrations (10–20 μM) of Cd 12–48 hours after administration disturbed mitochondrial function and significantly enhanced ROS levels (Branca et al., 2020). A plausible explanation for this is that exposure of neurons to low concentrations of Cd (1–10 μM) can increase the expression and activity of antioxidant enzymes, thereby protecting neuronal cell bodies against ROS overproduction (Branca et al., 2018). Presynaptic nerve terminals are distinctly located from mitochondrial in the nerve terminals, Cd-induced changes in the gene expression have no influence on the antioxidant capacity of the presynaptic compartment, which faces to a stronger oxidative stress in response to Cd neurotoxication. Furthermore, glutamate receptors membranes have a specific lipid composition and are enriched with poly-unsaturated fatty acids and cholesterol (Krivoi and Petrov, 2019). These lipids are highly susceptible to free radical oxidation and the resulted products could affect TRPV1 channel activity directly or indirectly by acting via alterations in lipid raft integrity (Ciardo and Ferrer-Montiel, 2017). Additionally, a strong lipid peroxidation perturbs the mitochondrial permeability transition pore and contribute to cell death. In many cell types, organs and brain regions, Cd-induced damages were associated with a prominent lipid peroxidation (Branca et al., 2020). We also detected lipid peroxidation of the synaptic membranes brought about by low concentration of Cd. Probably, lipid peroxidation could also contribute to an increase in TRPV1 channel activity and, hence, desynchronization of neurotransmitter release (Figure 1). Additionally, Cd-induced enhancement of asynchronous release (Figure 1) might affect the autophagic flux (Zou et al., 2020) can block the utilization of the impaired membranes and, consequently, facilitate the spreading of pathological signals. For instance, oxidized lipids, such as oxysterols, can easily escape from the affected membranes and modulate neurotransmitter release (Krivoi and Petrov, 2019).
In many electrophysiological studies, Cd at a broad concentration range (from 1 µM to 1 mM) is used as a non-specific VGCC antagonist, which suppresses AP-evoked fast neurotransmitter exocytosis. However, the abilities of Cd at lower concentrations (0.1–0.5 µM) to induce transmitter release and provoke oxidative changes in synapses suggest a more complex nature of Cd synaptic action. Only higher concentrations (2.5–100 µM) of Cd can exhibit toxicities and oxidative damage in numerous cell studies. According to the observed synaptic effects of Cd at the ultra-low doses point to the presynaptic site as a primary target. Given that levels of Cd in blood are normally low (nanomolar range) and concentrations above 0.05 µM can lead to signs of toxicity (Branca et al., 2018), Cd-induced disruption in synapsosome neurotransmitter release and function of synaptic mitochondria can be considered as early and/or as triggering events in Cd poisoning. There are numerous open questions in the synaptic mechanism of Cd action. First, the precise pathways for Cd penetration into the synapses need to be revealed. Secondly, understanding how Cd can be retained in synapses and the role of SV pools in this work in progress. Next, the reasons for high susceptibility of synaptic mitochondria to Cd and molecular mechanism of Cd-mediated disruption of redox status in the nerve terminals are still to be identified. A promising strategy for future studies is a detailed assessment of Cd-induced changes in synaptic membranes and the contribution of oxidized lipids to Cd toxicity. If initial events in the progression of Cd neurotoxicity occur in synapses then a hypothetical retrograde mechanism might deliver the pathological signal to the neuronal soma. Finally, in vivo studies connecting Cd-related changes in behavioral performance with aberrations in synaptic transmission can capitalize a relevance of the synaptic deficits in Cd poisoning. Noteworthy that developing target delivery of Cd and possible modulators of sensory TRP channels (e.g., capsaicin) can improve this question. Furthermore, generated oxidized lipids (particularly, oxysterols and derivatives of polyunsaturated fatty acids) can modulate TRPV1 channels (top scheme; in box). Increased TRPV1 channel activity augments asynaptic neurotransmitter release. Thus, Cd can cause synaptic dysfunction via affecting the timing of neurotransmitter release and redox status. Furthermore, generated oxidized lipids (particularly, oxysterols) can diffuse into extracellular space and exert an influence on neighboring synapses.

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Olguin-Albuerne M, Moran J (2018) Exogenous antioxidants can impair axonal retraction which implies maintaining of the ROS actively regulate axonal growth and provoke oxidative changes in synapses. Thus, Cd can cause synaptic dysfunction via affecting the timing of neurotransmitter release and redox status. Furthermore, generated oxidized lipids (particularly, oxysterols) can diffuse into extracellular space and exert an influence on neighboring synapses.

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