An Insight about Doxorubicin induced Neurotoxicity

Asmaa Mahde Kamel Mahde, Ibrahim Amin Ibrahim, Ola Ali Abd El Wahab, Eman S. El-Shetry

Human Anatomy and Embryology Department, Faculty of Medicine, Zagazig University, Egypt

Corresponding author: Asmaa Mahde Kamel Mahde

E-mail: Soma.mahdy98@gmail.com, Ammahdy@medicine.zu.edu.eg, asmaamahde54@gmail.com

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Abstract

Dox (chemical formula: C27H29NO11). It is the active ingredient in the anthracycline class of antibiotics, which are among the most potent chemotherapeutic drugs. It is highly effective against a wide spectrum of malignancies involving both hematological and solid tumors including lymphoma, gastric cancer, small cell lung cancer, sarcoma, and breast cancer. This review aims to summarize the neurotoxic effects of doxorubicin in preclinical (in vitro and in vivo) research. Furthermore, more and more literature reports in the field of basic and clinical research indicate that DOX exposure may induce neurotoxicity, especially in synaptic processes associated with hippocampal neurotransmission. It is known that DOX has a weak ability to penetrate through the BBB. At this point, it is worth mentioning that the mechanism of BBB-mediated drug resistance is complicated by the interaction of P-glycoprotein (P-gp, ABCB1) and breast cancer resistance protein (BCRP, ABCG2), which is successful in removing molecules and drugs from the CNS.

Keywords: Doxorubicin, Neurotoxicity

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Introduction

Dox (chemical formula: C27H29NO11). It is the active ingredient in the anthracycline class of antibiotics, which are among the most potent chemotherapeutic drugs. It is highly effective against a wide spectrum of malignancies involving both hematological and solid tumors including lymphoma, gastric cancer, small cell lung cancer, sarcoma, and breast cancer (Carvalho et al., 2009).

Abd El-Aziz et al. (2012) stated that Dox is metabolized mainly in the liver by the NADPH cytochrome-P450 reductase enzyme, which produces semiquinone radicals, which then react with molecular oxygen in the body to produce reactive oxygen species, which cause oxidative damage to normal cells in body organs.

Su et al. (2015) and Nikerel et al. (2018) reported that Dox acts by many mechanisms in the cancer cell, including intercalation into DNA, which disrupts DNA repair, and the generation of free radicals, which have harmful effects on cellular membranes, DNA, and proteins. Finally, it influences the Bcl-2/Bax apoptosis pathway by activating various molecular signals from AMPK (AMP-activated protein kinase). Apoptosis can be induced by changing the Bcl-2/Bax ratio, which causes downstream activation of several caspases (Fig.1) (Mobaraki et al., 2017).

In addition, Pal et al. (2012) reported that upon administration of Dox, the mitochondrial membrane potential is disrupted, releasing cytochrome C and activating the apoptotic pathway.

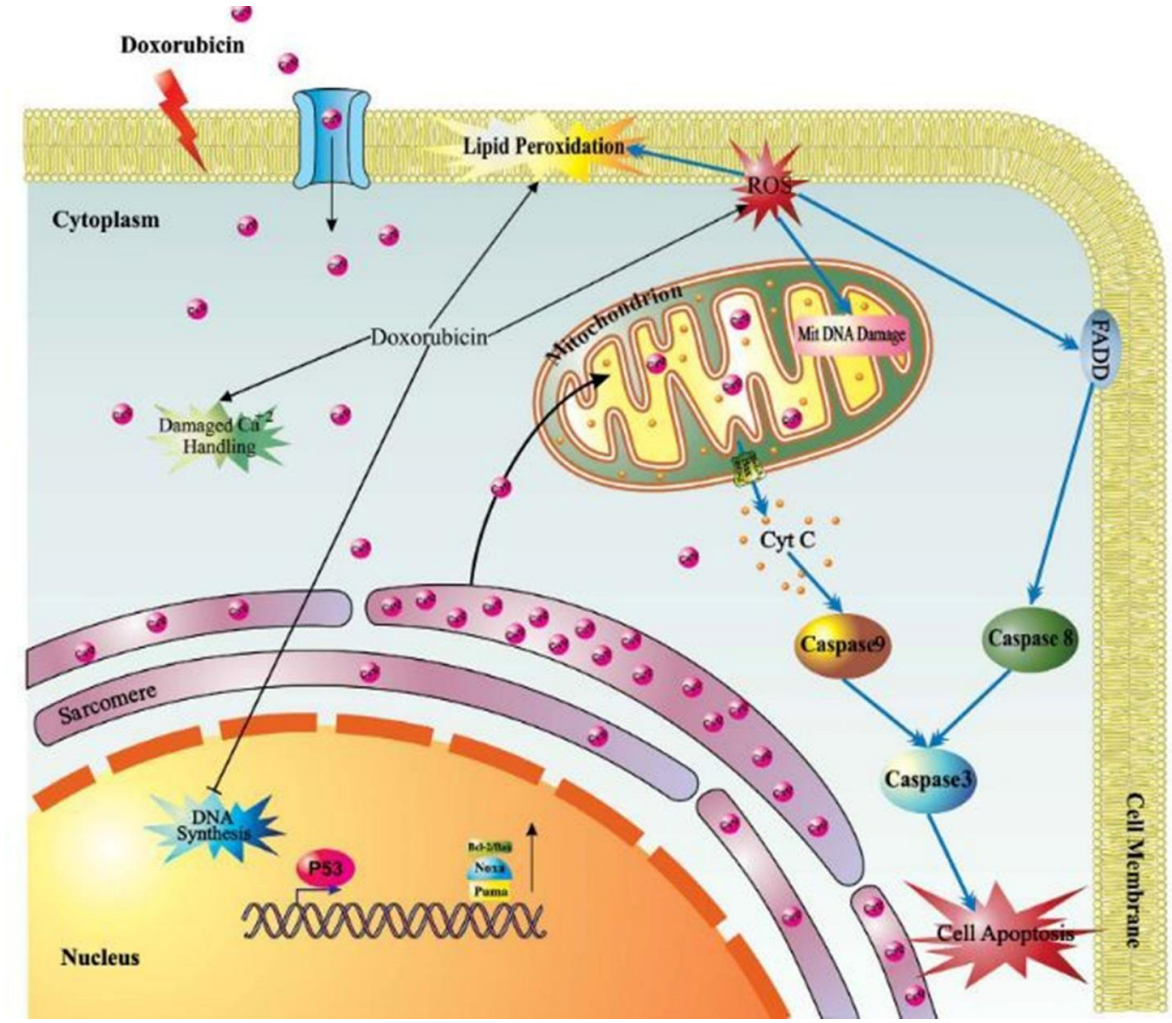

Fig. (1): Doxorubicin effects on cell death. Dox leads to reactive oxygen species formation, lipid peroxidation, DNA and mitochondrial damage, impaired calcium handling, induction of P53, and apoptotic pathways. Calcium channel permeability is increased after Dox entry, which causes an increase in calcium levels in the sarcomere and cytoplasmic and mitochondrial calcium

concentration, which leads to cellular swelling. Upon activation of the P53 pathway, expression of pro-apoptotic proteins (Bcl-2/Bax, Puma, and Noxa) is increased, which triggers cytochrome C efflux from mitochondria to the cytoplasm. Cytochrome C triggers the activation of caspase 9 and then caspase 3 and induces apoptosis. Besides, generated ROS triggers activation of caspase 8 and then caspase 3 and induces apoptosis through interaction with FADD. Furthermore, Dox blocks DNA synthesis by suppressing TOP2b via intercalation into DNA. Cyt C: Cytochrome C, FADD: Fas-Associated Protein with Death Domain (Mobaraki et al., 2017).

Rizk et al. (2017) have reported that Dox-mediated generation of free radicals in the brain tissues increases lipid peroxidation and alters the antioxidant defense system; the endogenous antioxidant enzyme superoxide dismutase (SOD), responsible for scavenging superoxide radicals, was markedly suppressed by Dox, confirming the pro-oxidative effect of Dox on the brain tissues, eventually leading to neuropsychological changes. Moreover, the increased generation of superoxide anions induced by Dox may elevate the level of circulating tumor necrosis factor-alpha (TNF-α), which can directly pass blood–brain barrier, and activate glial cells to initiate the local production of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, TNF-α, Nuclear factor kappa B, and inducible nitric oxide synthase, which exacerbate the oxidative stress and neural apoptosis.

Oxidative stress is a hypothesis for the association of reactive oxygen species with cerebrovascular and neurodegenerative diseases. Reactive oxygen species are generated during oxidative metabolism and can inflict damage on all classes of cellular macromolecules, eventually leading to cell death (Bergamini et al., 2004 and Smith et al., 2005).

Brain tissues have unique characteristics that make them especially susceptible to damage due to low levels of antioxidant defenses (Barichello et al., 2006). The brain has defenses against reactive oxygen species, including dietary free radical scavengers (ascorbate and α- tocopherol), the endogenous tripeptide glutathione, and enzymatic antioxidants superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX), there is considerable evidence that oxidative damage directly or indirectly, due to free radical production and reactive oxygen species, can lead to brain injury (Dal-Pizzol et al., 2010).

However, despite its wide clinical applications, it has been noted that long-term use of Dox tends to induce neurotoxicity and may cause neuropsychiatric diseases including depression, anxiety, and impaired cognition function (Merzoug et al., 2011; Christie et al., 2012 and Merzoug et al., 2014).

According to a study by Tangpong et al. (2006), animals treated with Dox have higher levels of TNF-α in the hippocampus and cerebral cortex. Studies have shown that administration of Dox causes oxidative stress in the brain, heart (Kuzu et al., 2018), kidney, liver (Qin et al., 2008), and blood plasma (Aluise et al., 2009), which has been linked to Dox-induced organ damage, including neurotoxicity. Oxidative stress is a risk factor for neuronal cells, and it plays a key role in the mechanism of Dox-induced neurotoxicity (Alkreathy et al., 2010).

A clinical study showed that Dox therapy has a deleterious effect on cognitive function in breast cancer patients (Jansen et al., 2011). In addition, that study demonstrated that long-term Dox use resulted in brain apoptosis and successfully created depression-like behaviours in rats (Wu et al., 2016).

Dox-induced cognitive dysfunction manifests in several forms, including changes in various components of visual, verbal, episodic, spatial, and working memories, as well as a lack of concentration, difficulty in multitasking, attention, planning, and lower processing speed with impaired executive function (Berndt et al., 2009 and Joly et al., 2011).

The principal mechanism of action of DOX is still not fully understood but is related to DNA intercalation and inhibition of macromolecular biosynthesis (Fornari et al. 1994; Tacar et al. 2013). This inhibits the progression of topoisomerase II, an enzyme that relaxes supercoils in DNA, thus facilitating the transcription process (Pommier et al. 2010). DOX stabilizes the topoisomerase II complex after the DNA chain is broken for replication, preventing the release of the DNA double helix and thus stopping the replication process (Tacar et al. 2013). It can also increase the production of quinone-type free radicals (FR), thus contributing to its cytotoxicity (Rossi 2013). The flat aromatic chromophore portion of the molecule intercalates between the two DNA base pairs, while the daunosamine six-membered sugar is located in the smaller groove and interacts with the flanking base pairs immediately adjacent to the intercalation site as evidenced by several crystal structures (Pigram et al. 1972; Frederick et al. 1990). DOX is also able to induce the eviction of histones from transcriptionally active chromatin via intercalation (Pang et al. 2013).

As a result, DNA damage response, epigenome, and transcriptome are deregulated in the cells exposed to DOX action (Pang et al. 2013). The cytotoxic effect of DOX results from a complex system of multiple modes of action related to FR and reactive oxygen species (ROS) formation, intercalation of the drug into DNA, induction of DNA breaks and chromosomal aberrations, and alterations in cell membranes. In vitro studies in cells treated with DOX suggest that apoptosis also may be involved in the drug's mechanism of action (Tomankova et al. 2015, Pilco-Ferreto and Calaf 2016).

Like the other anthracyclines, DOX has a lot of adverse effects. Patients respond differently to chemotherapy. Some experience few side effects, while others experience more. The most common symptoms of DOX adverse effects include nausea, vomiting, stomatitis, loss of appetite, stomach pain, diarrhea, increased thirst, unusual tiredness or weakness, dizziness, hair loss, separation of fingernail or toenail from the nail bed, ocular pain or red discoloration of urine. However, the progressive cardiotoxicity usually occurring after the completion of treatment with anthracyclines limits the use of DOX (Simůnek et al. 2009). Dilated cardiomyopathy, leading to congestive heart failure is the most dangerous side effect of it (Chaterjee et. al. 2010). DOX cardiotoxicity can be acute, with a prevalence of about 11%, and chronic, with an estimated incidence of about 1.7%. Acute cardiotoxicity occurs within the first 2–3 days of DOX administration, while chronic

cardiotoxicity usually manifests clinically within 30 days of administration of its last dose, but it may occur even after 6–10 years after its completion (Von Hoff et al. 1979; Takemura and Fujiwara 2007). The acute cardiomyopathy induced by DOX is usually manifested through chest pain due to myopericarditis and/or palpitations due to sinus tachycardia, paroxysmal nonsustained supraventricular tachycardia, and premature atrial and ventricular beats. The incidence of DOX-induced cardiomyopathy is related to its dose. It is about 4% when the dose is 500–550 mg/m2, 18% when 551–600 mg/m2, and 36% when 600 mg/m2.

Furthermore, more and more literature reports in the field of basic and clinical research indicate that DOX exposure may induce neurotoxicity, especially in synaptic processes associated with hippocampal neurotransmission (Alhowail et al. 2019). This aspect of DOX's negative effects has not yet been well-studied.

It is known that DOX has a weak ability to penetrate through the BBB. At this point, it is worth mentioning that the mechanism of BBB-mediated drug resistance is complicated by the interaction of P-glycoprotein (P-gp, ABCB1) and breast cancer resistance protein (BCRP, ABCG2), which is successful in removing molecules and drugs from the CNS (Löscher and Potschka 2005). Despite those facts in vitro and in vivo data on models of malignant glioma suggest that this drug is an effective anti-tumor agent (Liang et al. 1991; Muldonn and Neuwelt 2003).

Neurotoxicity of Doxorubicin

It was believed that DOX is completely unable to cross the BBB, however, many preclinical studies on animal models reported neurotoxicity associated with its administration in various doses (Mohamed et al. 2011; Rizk et al. 2017; Liao et al. 2018). Moreover, research on animals has also shown that DOX low levels were detected in the brain after intraperitoneal (*ip*) administration (Sardi et al. 2013). Currently, research is being conducted to increase the availability of DOX in the brain to treat cancers that occur there. However, this may exacerbate its neurotoxicity.

Later, it was suggested that DOX can cross the BBB through vascular-associated apical projections of neural stem cells. Thus, it can establish direct membrane-membrane contacts with the endothelial cells in specific regions of the irregular endothelial basement membrane, and have abundant vesicular activity (Licht et al. 2020; Du et al. 2021).

In Vitro Studies

Research conducted by Lopes (2008) proved that DOX is neurotoxic to serum-free cultures of cortical neurons of Wistar rats – the primary cultures of cerebral cortex obtained from embryos (E17-18). DOX concentrations up to 0.5 μM, induced cell death through an apoptotic pattern, while for higher concentrations (5, 10, 20 μM) necrosis becomes dominant (Lopes et al. 2008).

A study by Petrovic et al., showed that DOX (1μM for 17 h) affects the expression of proteins of pathways related to neuronal development (CNS neuron differentiation, neuron projection

membrane, soluble Soluble N-ethylmaleimide-Sensitive Factor Attachment Proteins attachment proteins receptor activity) of the MCF-7 breast cancer cell line, using the precursor acquisition independent from ion count mass spectrometry method (Petrovic et al. 2015). This research found that proteins like myotrophin, mitochondrial 2- oxoglutarate dehydrogenase, eukaryotic translation initiation factor3 subunit, robable E3 ubiquitin-protein ligase microtubule-associated protein 2 involved in the above-mentioned pathways, which are crucial to physiological processes in the central nervous system, are down-regulated when exposed to treatment with DOX. These findings might explain the development of cognitive impairment symptoms which occur after chemotherapy in cancer patients (Petrovic et al. 2015).

The experiment performed by Ramalingayya et al. (2017a) demonstrated that IMR32 cells exposed to DOX (1μM for 24 h) exhibit increased apoptosis, and intracellular ROS generation with simultaneous inhibition of neurite growth (Ramalingayya et al. 2017a).

In another research, a hippocampal cell line (H19-7/IGF-IR) along with rodent hippocampal slices was tested to evaluate the acute neurotoxic effects of DOX at a concentration 0.25, 0.5, 0.75, and 1 μM (Alhowail et al. 2019). The reduction in long-term potentiation (LTP) in hippocampal slices with DOX was observed. In addition, the markers of oxidative stress - lipid peroxidation and caspase-3 expression were increased in investigative cells at a long site with extracellular signal-regulated kinase 1/2 (ERK1/2), p38 mitogen-activated protein kinase, and Akt (Gururaj et al. 2005, Alhowail et al. 2019).

A series of studies by Jantas and co-workers, who investigated cell death evoked by DOX in human neuroblastoma SH-SY5Y cells (Jantas et al. 2008; 2015; 2018a; Chwastek et al. 2017), showed that DOX at the concentration of 0.5 μM caused the apoptotic fragmentation of DNA in undifferentiated -SHSY5Y cells (UN-SHSY5Y) without being harmful to retinoic acid-differentiated -SHSY5Y cells (RA- SHSY5Y) (Jantas et al. 2008). It was also proved that 1 μM of DOX produced necrotic changes in undifferentiated -SHSY5Y and evoked apoptosis in retinoic acid-differentiated -SHSY5Y (Jantas et al. 2008). Furthermore, the group investigated the cell-damaging effect of DOX in the primary cortical, hippocampal and striatal neurons (Jantas and Lasoń 2009). The data revealed that cerebellar neurons were the most resistant to DOX-induced apoptosis when compared to neuronal cell cultures derived from the forebrain (Jantas and Lasoń 2009). Moreover, programmed cell death induced by DOX in a concentration-dependent manner had a higher damaging effect in immature neurons (Jantas and Lasoń 2009). Jantas and co-workers (2018b) proved also that DOX is neurotoxic for cortical glia cell cultures (Jantas et al. 2018b).

Animal Studies

Behavioral tests

In the study of Liedke et al. (2009) the effect of a single dose of DOX 8 mg/kg (equivalent to the human dose of 60 mg/m2) on memory for inhibitory avoidance conditioning in 2 to 3 months old Wistar rats was investigated. The experiments showed a decrease in exploratory behavior assessed by the number of rearings during the exploration of an open field in DOX-treated rats. The results indicate that an exposition to a systemic administration of DOX might impair long-term learning (Liedke et al. 2009).

In another study, it was presented that rats (strain not specified in the cited article) exposed to DOX action (4 mg/kg/week for 4 weeks, *ip*) exhibited a significant decrease in the number of arm entries, and spontaneous alternation percentage compared to control in the Y-maze test, which suggests the reduction in short-term and long-term memory (Alharbi et al. 2020). Additionally, 6-week-old athymic (T-cell deficient, partially immunocompromised) male mice (NCr nude) treated with DOX (5 mg/kg for 5 weeks, *ip*) demonstrated impaired performance in the Y-maze and a significant reduction in the hippocampal long-term potentiation (Alhowail et al. 2019).

According to Ramalingayya and co-workers' study, animals treated with DOX (2.5 mg/kg, i.p., every 5 days for 50 days) showed an insignificant difference in exploration time of the novel or familiar object in comparison to the control group in the novel object recognition test (NOR) (Ramalingayya et al. 2017b). In the Moretti et al. study (2021) DOX was administered (2.5 mg/kg/week for 4 weeks, *ip*) to male rats (Wistar), which showed short-term and long-term memory impairments in NOR test at 3 and 24 h after habituation (Moretti et al. 2021). Furthermore, this study suggests that DOX induces hippocampal gene expression changes, which is related to an increase in anxiety behavior in young animals (Moretti et al. 2021). These studies are in line with previous research which documented increased anxiety and impaired spatial cognition in rodents after DOX injection (2- 2.5 mg/kg for 4 weeks, *ip*) (Kitamura et al. 2015; Philpot et al. 2016). What is interesting, the DOX-induced changes in cognitive behavior may be more severe in female than in male animals (Cavalier et al. 2021). In contrast, in the studies of Aziriova et al. (2014) and Kitamura et al. (2015), no anxiety-like behavior was statistically demonstrated after DOX administration (Aziriova et al. 2014, Kitamura et al. 2015). Additionally, no differences were reported after DOX administration in the open field test where locomotion and rearing frequencies were measured during the 4-week-long experiment (El-Agamy et al. 2018).

In research (Merker et al. 1978) on rhesus monkeys, DOX was perfused through the ventriculo-cisternal and ventriculo-lumbar spaces at concentrations from 1.5 to 100 μg/ml for 190 min. The neurotoxicity after perfusion manifested in body weakness, tremors, severe to slight hypokinesia, excitation, nervousness, or depression. In the brains of three monkeys a distinctive necrotizing angiopathy that was noninflammatory was found (Merker et al. 1978).

On the contrary, in the study by Flanigan et al. (2018) where DOX (2 mg/kg) and cyclophosphamide were administrated to C57BL/6J mice, only sporadic effects due to chemotherapeutic treatment were observed (Flanigan et al. 2018).

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