LPS (1 ng/ml) and/or DMPO (50 mM) for 24 h. LPS induced cell activation as showed by inducible nitric oxide synthase expression and production of inflammatory mediators such as $^{\bullet}$NO, TNF-α, and IL-1β. However, DMPO blocked these inflammatory responses. LPS-induced TNF-α and $^{\bullet}$NO are known to induce ER stress and apoptosis. ER stress was shown by activation of PERK and induction of CHOP, which is known to be involved in apoptosis. Notably, DMPO downregulated LPS-induced ER stress. Furthermore, LPS decreased anti-apoptotic protein 14-3-3 expression, but increased caspase-3 activation. As expected, DMPO restored 14-3-3 expression but, unexpectedly, has a synergistic effect on caspase-3 activation by LPS. Even though upregulating the apoptotic marker caspase-3, DMPO protected cells from LPS-induced DNA damage as showed by inhibiting phosphorylation of histone H2A, acetylation of histone H2B, and phosphorylation of DNA damage sensor p53 and checkpoint Chk1. In order to understand the mechanistic basis of DMPO for the above-mentioned effects, we determined the phosphorylation of Akt, mitogen-activated protein kinases (MAPKs), and IκB-α that are linked to NF-κB activation. DMPO inhibited phosphorylation of Akt, MAPKs (ERK, JNK/SAPK and p38), and IκB-α, which led to inhibition of NF-κB activation. Taken together, DMPO prevented macrophage activation, ER-stress and DNA damage triggered by LPS throughout the blocking of Akt and MAPKs signaling pathways. The analysis of DMPO effects on signaling and gene expression in "inflamed" cells would help us develop new therapeutic applications of this old nitrone spin trap. Supported by NIEHS 5R00ES015415.

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Diesel Exhaust Particles from Diesel Engines Induced Oxidative Stress in Immortalized Human Brain Endothelial Cells

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Diesel Exhaust Particles (DEP), a prominent and persistent air pollutant, has been associated with an increased incidence of cardiovascular and respiratory diseases. However, there has been no studies to indicate that DEP can affect the blood-brain barrier (BBB) function, which might lead to neurodegenerative diseases. DEP contains a large portion of the polynuclear aromatic hydrocarbons (PAHs) found in diesel exhaust. In the current study, we used immortalized human brain endothelial cells (HCMEC/D3) as a BBB model to study whether DEP can induce oxidative stress. Our studies showed that DEP significantly decreased the levels of intracellular glutathione (GSH) and glutathione peroxidase (GPx). Malondialdehyde (MDA) levels increased dramatically after DEP treatment, and generation of reactive oxygen species (ROS) increased after DEP exposure as well. In order to determine whether DEP-induced oxidative stress in BBB cells alters BBB integrity, permeability and trans-endothelial electrical resistance (TEER) tests were performed. Cells exposed to DEP (50ug/ml) showed significant increases in cell permeability and significant decreases in trans-endothelial electrical resistance compared to those of control. These results strongly suggest that DEP induce oxidative stress in human brain endothelial cells and disrupt the integrity of the BBB. We hypothesize that DEP induced oxidative damage may contribute to the increase incidences of neurodegenerative diseases. Therefore, an antioxidant should be recommended in the areas with excessive DEP exposure.

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Smoking Cessation Effect of Tea Component Theanine Through Inhibition of Nicotine Acetylcholine Receptor

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Cigarette smoking is the major risk factor for a series of life threatening diseases and due to the addictive nature of nicotine, quitting smoking is extremely difficult. We reported an unprecedented smoking cessation effect of tea when it was used in cigarette filters. In a double-blind study, the volunteer smokers decreased their cigarette consumption by 85% after smoking with the tea filter for 60 days; and 32% of them quitted smoking. Animal experiments showed that theanine in the filter exerted smoking cessation effect similar to nicotine acetylcholine receptor (nAChR) inhibitor. Theanine significantly inhibited the nicotine-induced expression of $\alpha 4$, $\alpha 7$ and β2 subunits of nAChR, c-fos and tyrosine hydroxylase and the release of dopamine in the mouse brains and neuron cells. Animal studies also revealed that tea filters could significantly scavenge the free radicals generated from the cigarette smoke, reduce the acute toxicity, mutagenicity, lung damage and COHb levels in the blood caused by cigarette smoking. This work suggests that smoking using the tea filter may be a new effective method to combat the tobacco epidemic.

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Mechanism of Protection by Suberoylanilide Hydroxamic Acid (Vorinostat) against Tetrahalogenated Quinone-induced Cytotoxicity: Suicidal Nucleophilic Attack Coupled with Unusually Mild and Facile Double Lossen Rearrangement

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Suberoylanilide hydroxamic acid (SAHA, also called Vorinostat) has recently been approved by US FDA and used clinically for the treatment of cancer through inhibition of the zinc-containing enzyme histone deacetylase. Here we show that SAHA could effectively protect against the cytotoxicity induced by the carcinogenic tetrahalogenated quinoid metabolites of the ubiquitous environmental pollutants pentahalogenated phenols. Further investigations demonstrate that SAHA could dramatically accelerate the conversion of the highly toxic tetrahalogenated quinones to their much less reactive and toxic dihydroxylation product, with rate accelerations of up to 100,000-fold. In contrast, no enhancing effect was observed when the hydroxamate group of SAHA was blocked by metal chelation. The major reaction product of SAHA was isolated and identified as *O*-suberoylanilidecarbamyl suberoylanilide hydroxamate. On the basis of these data and oxygen-18 isotope-labelling studies, we proposed that suicidal nucleophilic attack coupled with unusually mild and facile double Lossen rearrangement reaction was responsible for this remarkable acceleration of the detoxication reaction. This is the first report of a novel mode of action for SAHA, which is independent on its metal-chelating property.

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