Effects of acrolein on adrenal glands

Kai-Lee Wang1, 2, Wen-Ching Huang1, Paulus S. Wang1, 3, 5, 6, Fu-Kong Lieu4, Sindy Hu7, Shyi-Wu Wang7, 8

1Department of Physiology, School of Medicine, National Yang-Ming University, Taipei 11221, Taiwan
2School of Nursing, College of Nursing, National Taipei University of Nursing and Health Sciences, Taipei 11221, Taiwan
3Medical Center of Aging Research, China Medical University Hospital, Taichung 40402, Taiwan
4Department of Rehabilitation, Cheng Hsin General Hospital, Taipei 11283, Taiwan
5Department of Medical Research, Taipei Veterans General Hospital, Taipei 11217, Taiwan
6Department of Biotechnology, Asia University, Taichung 41354, Taiwan
7Aesthetic Medical Center, Department of Dermatology, Chang Gung Memorial Hospital, Taoyuan 33378, Taiwan
8Department of Physiology and Pharmacology, College of Medicine, Chang-Gung University, Taoyuan 33302, Taiwan, Republic of China

Correspondence: Shyi-Wu Wang or Paulus S. Wang
E-mail: swwang@mail.cgu.edu.tw or pswang3879@gmail.com
Received: August 15, 2016
Published online: September 26, 2016

Introduction

Adrenal glands are the small organs located above the kidneys, surrounded by adipose capsule and renal fascia in mammals. Adrenal glands are one of the most important glands for maintaining electrolyte and energy homeostasis [1]. Each gland has cortex and medulla. The outer part of the gland, adrenal cortex, produces the following 2 steroid hormones, including mineralocorticoids and glucocorticoids, such as aldosterone and cortisol in humans. The primary mineralocorticoid is aldosterone which is important for the long-term regulation of blood pressure by stimulating sodium and water reabsorption and potassium excretion in kidney. Aldosterone secretion is regulated by angiotensin II and
extracellular potassium [2-5]. In contrast, the primary glucocorticoid secreted from adrenal gland is cortisol in humans and corticosterone in rats. Glucocorticoid stimulates glucose, amino acid and triglycerol secretion in response to stress. It is regulated by adrenocorticotropic hormone (ACTH) [6, 7]. Over-production or insufficient secretion of glucocorticoids causes Cushing's syndrome or Addison's disease, respectively. Because both hormones are vital to life, it is crucial to minimize any disruptor that may interrupt the regulations of these two hormones.

Sources and metabolites of acrolein

Acrolein (propenal, acrylaldehyde, CAS No. 107-02-8) is a well-known cytotoxic agent which is an electrophilic α, β-unsaturated aldehyde released during the incomplete combustion. Acrolein can interact and disrupt the structures of DNA, protein and membrane thereby resulting gene mutations, protein dysfunction and cell apoptosis. It is listed as one of 188 hazardous air pollutants (HAPs) in US-environmental protection agency (US-EPA) [8]. The Tolerable Daily Intake (TDI) for acrolein is 7.5 µg/kg body weight, and the LD₅₀ of acrolein is between 7 and 46 mg/kg body weight for rats, mice and hamsters [9].

The sources of human exposure acrolein including environment, dietary and endogenous production [10]. It is a major component of tobacco smoke as well as electronic cigarette (E-cigarette), animals treated with acrolein (≧ 2 mg/kg/day) were wildly used as an animal model to mimic the cigarette smoking [11, 12]. The concentrations of acrolein and nicotine in cigarette are similar, both are about 0.2-0.4 mg per cigarette [13]. Smoker exposure to acrolein and its precursor equals or exceeds the total level of acrolein from all other sources [10, 14]. The levels of acrolein and DNA adduct are about 3-fold higher in the oral tissue of smokers as compared with nonsmokers (1.36±0.90 versus 0.46±0.26 µM guanine, P = 0.003) [15]. Another acrolein exposure resource in the environment is in enclosed fires (up to 500 ppm). Other than tobacco smoke and fires, environmental levels of acrolein are barely measureable [16]. Acrolein is present in cooked foods for instance fried potato chips. It can be find in fruits, vegetables, fish and cheese, too [17]. Endogenous acrolein is produced fromaldophosphamide by spontaneous β-elimination, glucose pyrolysis, glycerol oxidation, and Strecker degradation of methionine and threonine [10, 18].

Acrolein can be dissolved very well in water thereby can enter body tissues rapidly. The metabolic routes of acrolein can be seen everywhere [17, 19]. It is metabolized by Michael-type addition with glutathione (GSH) as mercapturic acid metabolites. Ninety percent of acrolein is excreted in the urine within 24 h (maximal urine concentration at 2-4 h and reaching almost basal level at 6-8 h [20]). S-(hydroxypropyl)-mercapturic acid (3-HPMA) the main metabolite of acrolein found in urine can be used as acrolein exposure biomarker [17].

Toxicity of acrolein

Acrolein exposure may cause oxidative stress through the depletion of GSH and formation of adducts with proteins, nucleic acids and other cellular components. The mechanisms of acrolein toxicity can be grouped as: induction of oxidative and ER stress, cause mitochondrial dysfunction, increasing of protein and DNA adducts, and thereby deregulation of signal transduction pathway and alteration systemic functions [19]. Some of these lesions are considered to be associated with oxidative stress-related diseases such as inflammation, neurodegenerative disorders, cardiovascular diseases, diabetes and cancer [21].

More and more evidences suggest that acute acrolein exposure causes cardiopulmonary toxicity. Acrolein inhalation (>100 ppm) for 30 min is deathful [16]. Acute acrolein vapor exposure may cause eye, nasal and respiratory tract irritations through activation of transient receptor potential ankyrin 1 (TRPA1) protein [16, 22]. It could also cause bronchial smooth muscle hypercontractility, edema and interrupt cell cycle and abolish proliferation of lung epithelial cells [16, 23]. Acrolein exposure (at relatively low levels ≦ 10 ppm) could increase heart rate, blood pressure, mean arterial blood pressure and minute volume in hypertensive rats [24, 25], and cause the dysfunction of endothelium and cardiovascular reflex both in vivo and in vitro [10, 26]. However, the mechanism is still unclear.

Acrolein also affects other systemic function. It may disrupt the function of cystic fibrosis transmembrane conductance regulator (CFTR) and influencing the pancreatic juice secretion [27]. It may also correlate with the acceleration of brain infarction or other brain disease through increasing intracellular calcium concentration by NMDA receptors activation [28, 29]. It may also associate with lung and bladder cancers through induction of DNA adducts, inhibition of DNA repair, and induction of cell transformation [30]. Moreover, acrolein can also interact with zidovudine, an anti-HIV drug which can inhibit nucleoside reverse transcriptase, and cause hepatocyte toxicity [31]. High concentration of acrolein exposure (4~6 mg/kg bw/day) results in maternal mortality, spontaneous miscarriages, increased resorption rates of the fetuses [32]. Inflammatory gene expression induced by acrolein is resistant to suppression by the endogenous hydrocortisone [33]. It may also impair cholesterol absorption by modification of
high-density lipoprotein (HDL) particles that might promote atherosclerosis progression [34].

**Acrolein on adrenal glands**

Recent evidence indicates that smoking stimulates plasma aldosterone levels, however, the mechanisms are still obscure. In our current studies, we are focused on the adverse effects of acrolein on the hormone secretion in adrenal glands. We found that intraperitoneal (i.p.) injection of acrolein (2 mg/kg/day) for 3 days could significantly increase plasma levels of angiotensin II and aldosterone. It can also stimulate aldosterone secretion in zona glomerulosa cells in vitro, and the stimulatory effects of acrolein is, at least in part, though elevation of enzyme activity of P450scc, the enzyme regulates the rate-limiting step of aldosterone synthesis [35-36]. In contrast, plasma corticosterone secretion was reduced in response to adrenocorticotropic hormone (ACTH) injection. This phenomenon may associate with lower activity of P450scc [37]. Meanwhile, data from our study suggest that acrolein alters the physiological function of adrenal glands.

**Conflicting interests**

The authors have declared that no conflict of interests exist.

**Author contributions**

K.L. Wang conceived the study concept. K.L. Wang and W.C. Huang prepared the manuscript. F.K. Lieu and S. Hu edited the manuscript. P.S. Wang and S.W. Wang reviewed the manuscript.

**References**


