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Review

Biological evidence for the acute health effects of secondhand smoke exposure

Andreas D. Flouris,[1] Constantine I. Vardavas,[2] Giorgos S. Metsios,[3] Aristidis M. Tsatsakis,[4] and Yiannis Koutedakis[3,5]

[1]*FAME Laboratory, Institute of Human Performance and Rehabilitation, Centre for Research and Technology Thessaly, Trikala; and* [2]*Department of Social Medicine, Faculty of Medicine, University of Crete, Iraklio, Greece;* [3]*School of Sport, Performing Arts and Leisure, University of Wolverhampton, Wolverhampton, United Kingdom;* [4]*Centre of Toxicology Science and Research, School of Medicine, University of Crete, Iraklio; and* [5]*Department of Sport and Exercise Science, University of Thessaly, Trikala, Greece*

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Flouris AD, Vardavas CI, Metsios GS, Tsatsakis AM, Koutedakis Y. Biological evidence for the acute health effects of secondhand smoke exposure. *Am J Physiol Lung Cell Mol Physiol* 298: L3–L12, 2010. First published September 18, 2009; doi:10.1152/ajplung.00215.2009.—A vast number of studies on the unfavorable effects of secondhand smoke (SHS) exist within the international literature, the majority of which evaluate longitudinal epidemiological data. Although limited, the experimental studies that assess the acute and short-term effects of exposure to SHS are also increasing in number. They include cellular, animal, and human studies that indicate a number of pathophysiological mechanisms through which the deleterious effects of SHS may arise. This current review evaluates the existing biological evidence regarding the acute health effects of SHS exposure. Analyses on the inhaled toxicants and the carcinogenicity of SHS are included as well as in-depth discussions on the evidence for acute SHS-induced respiratory, cardiovascular, metabolic, endocrine and immune effects, and SHS-induced influences on oxygen delivery and exercise. The influence of the length of exposure and the duration of the observed effects is also described. Moreover, recent findings regarding the underlying pathophysiological mechanisms related to SHS are depicted so as to generate models that describe the SHS-induced effects on different systems within the human body. Based on the presented biological evidence, it is concluded that brief, acute, transient exposures to SHS may cause significant adverse effects on several systems of the human body and represent a significant and acute health hazard. Future research directions in this area include research on the concentrations of tobacco smoke constituents in the alveolar milieu following SHS exposure, individual susceptibility to SHS, as well as the effects of SHS on neurobehavioral activity, brain cell development, synaptic development, and function.

passive smoking; environmental tobacco smoke; cardiovascular disease; respiration; inflammatory markers

"An hour a day in a room with a smoker is nearly a hundred times more likely to cause lung cancer in a non-smoker than 20 years spent in a building containing asbestos."

–Sir Richard Doll (1985)

It is well-known that secondhand smoke (SHS) is a major threat to public health due to its acknowledged adverse health effects (28, 60, 107, 112, 117). Exposure to SHS is related to the ever-increasing frequency of diseases among children and adults, such as respiratory illness, asthma, otitis media, sudden infant death syndrome, vascular dysfunction, and predisposition toward cardiovascular disease and cancer (15, 52, 95, 109). Despite these well-publicized effects of SHS, more than 126 million American and 130 million Chinese adult nonsmokers breathe air polluted by SHS on a daily basis while global estimates include 700 million children and 50 million pregnant women (112, 128a). It is also alarming that despite the adoption of stricter antismoking campaigns worldwide, more people smoke today than at any other time in human history [estimated to be >1.25 billion adults (61, 128a)]. Indeed, the prevalence rates of smoking are steadily increasing (60, 107) primarily among young girls (28, 117), and the tobacco industry predicts a global expansion of the tobacco epidemic in the near future (60). This expansion could be partly fuelled by the scarcity of human experimental studies that assess the acute effects of SHS exposure, leaving the tobacco control movement exposed to a vehement opposition (100, 104) arguing that only chronic SHS exposures increase the risk of cardiovascular disease and that there is limited scientific basis for claims that brief, acute, transient SHS exposures can represent a significant cardiovascular health hazard among nonsmokers.

Address for reprint requests and other correspondence: A. D. Flouris, FAME Laboratory, Institute of Human Performance and Rehabilitation, Centre for Research and Technology Thessaly, 32 Siggrou St., Trikala GR42100, Greece (e-mail: aflouris@cereteth.gr).

The aim of the present review is to critically evaluate the existing biological evidence regarding the acute health effects of exposure to SHS. We envisage that the information provided will be valuable not only to physicians and scientists, but also to those interested in personal or public health, politics, and economics. To achieve the above, a comprehensive search in PubMed was conducted using MeSH terms that are germane to SHS (e.g., passive smoking, involuntary smoking, environmental tobacco smoke, secondhand smoke, sidestream smoke) in conjunction with acute physiological and biochemical health effects (e.g., acute manifestation, biochemical pathways, toxicology, pathophysiology, myocardial infarction, cardiovascular disease, respiratory symptoms, immune changes, coronary artery/coronary heart disease). The search also included the articles cited in the identified papers.

INHALED TOXICANTS AND CARCINOGENICITY OF SHS

SHS is an amalgam of 15% mainstream smoke that is inhaled and exhaled by the smoker and 85% sidestream smoke that is emitted from a smoldering cigarette that encompass a few million semiliquid particles per cubic centimeter within a mixture of combustion gases (34). Both mainstream and sidestream smoke are complex mixtures of >4,000 chemical compounds, including carcinogens and potent respiratory toxins (11, 112). The qualitative composition of the components in mainstream and sidestream smoke has been reported as similar (44) or even higher in the latter (71). Chemical analytical research has identified 21 particulate matter and 19 gas-phase compounds in sidestream smoke with known carcinogenic and noncarcinogenic health effects [e.g., hepatotoxic and neurological effects, immune alterations, cardiac arrhythmias, and pulmonary edema (12)], whereas it is estimated that at least 250 chemicals in SHS are toxic or carcinogenic (111). The effects of these compounds are mediated through different mechanisms including direct irritant effects, immunological mechanisms, and mutagenesis (38). Consequently, there is a confirmed link between chronic SHS (lifestyle incorporating frequent SHS exposures) and various types of cancer including lung cancer (10), leukemia (14, 54), breast cancer (47), upper aerodigestive tract carcinomas (106), and nasal cancer (92).

The most studied carcinogenic compounds of SHS include polycyclic aromatic hydrocarbons, nitrosamine compounds, heterocyclic aromatic amines, and other miscellaneous organic compounds. Polycyclic aromatic hydrocarbons are byproducts of the incomplete combustion of organic material and are potent, locally acting carcinogens (98). Tobacco-specific *N*-nitrosamines [particularly 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (commonly known as NNK) and its metabolite, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (commonly known as NNAL)] are chemically related to nicotine and other tobacco alkaloids and are powerful carcinogens that affect various tissues such as the esophagus, the nasal cavity, and the lung often independently of the route of administration (36, 83). Finally, weaker carcinogens inherent in SHS include aromatic amines that are involved in tumorigenesis within various tissues (33), formaldehyde and acetaldehyde that induce respiratory tract tumors (49), butadiene and benzene that are multiorgan carcinogens (44), as well as heavy metals such as nickel, chromium, and cadmium (44). It is noteworthy that both constituents of SHS (i.e., mainstream and sidestream smoke) contain reactive yet long-lived free radicals (84, 85).

Research has indicated that the implantation of mainstream cigarette smoke condensate within rat lungs may induce skin tumors (44), whereas inhalation induces preneoplastic lesions and benign and malignant tumors of the larynx in Syrian golden hamsters (45). However, experiments with mice and rats have shown less consistent results (44, 45). On the other hand, the carcinogenicity of sidestream smoke has not been extensively investigated into despite the fact that sidestream smoke condensate appears to be more carcinogenic than mainstream smoke condensate (69). SHS inhalation experiments in A/J mice have shown increased lung tumor multiplicity and incidence due to a gas-phase component of SHS (121–128). Overall, findings to date have indicated the probable roles of multiple carcinogens inherent in the constituents of SHS, particularly polycyclic aromatic hydrocarbons and the tobacco-specific lung carcinogen NNK in skin and lung carcinogenicity (112). Gas-phase constituents of SHS such as formaldehyde, acetaldehyde, butadiene, and benzene also appear to contribute to tumor induction (112).

ACUTE HEALTH EFFECTS OF SHS EXPOSURE

Respiratory Effects

Chronic lung disease is generally the result of long-term processes, yet even brief exposure to SHS appear to initiate mechanisms that contribute to its development (30, 31, 67, 99). This notion is in line with evidence that has indicated a reduction in the incidence of respiratory symptoms among hospitality workers following the implementation of smoke-free laws in the context of different countries (25, 27, 53). The acute effects of SHS on the respiratory system are illustrated in Fig. 1. Available data have shown that shortly after the beginning of smoke exposure there is a rapid and marked upregulation of growth factor production as well as production of type 1 procollagen within the small airways (16). Furthermore, spontaneous inhalation of cigarette smoke elicits acute pulmonary chemoreflexes, characterized by apnea, bradycardia, and hypotension through activation of pulmonary C fibers (119). Until recently, the acute effects of SHS on the human respiratory system remained elusive, yet it is now known that even a 1-h exposure to SHS at bar/restaurant levels generates significant decrements on lung function, particularly forced expiratory volume in 1 s (FEV_1), FEV_1-to-forced vital capacity (FVC) ratio, maximum expiratory flow at 75% of expired vital capacity ($MEF_{75\%}$), $MEF_{50\%}$, and $MEF_{25\%}$ (29). The SHS-induced changes in FEV_1 and FEV_1-to-FVC ratio closely resembled the airway obstruction apparent in smokers (26), a notion that was further supported by the SHS-induced changes in $MEF_{75\%}$, $MEF_{50\%}$, and $MEF_{25\%}$ that showed a MEF-volume curve convex to the volume axis with an increasing curve in late expiration. Such results are typical for obstructive diseases such as cystic fibrosis, bronchial asthma, and wheezy bronchitis (131).

The mechanism behind the acute SHS-induced airflow restriction can be related to airway irritation given that SHS elicits irregular breathing patterns, cough reflex, and bronchoconstriction through the activation of vagal afferents (56). However, airway irritation may not be the only mechanism underlying the initial response to cigarette smoke as other lines

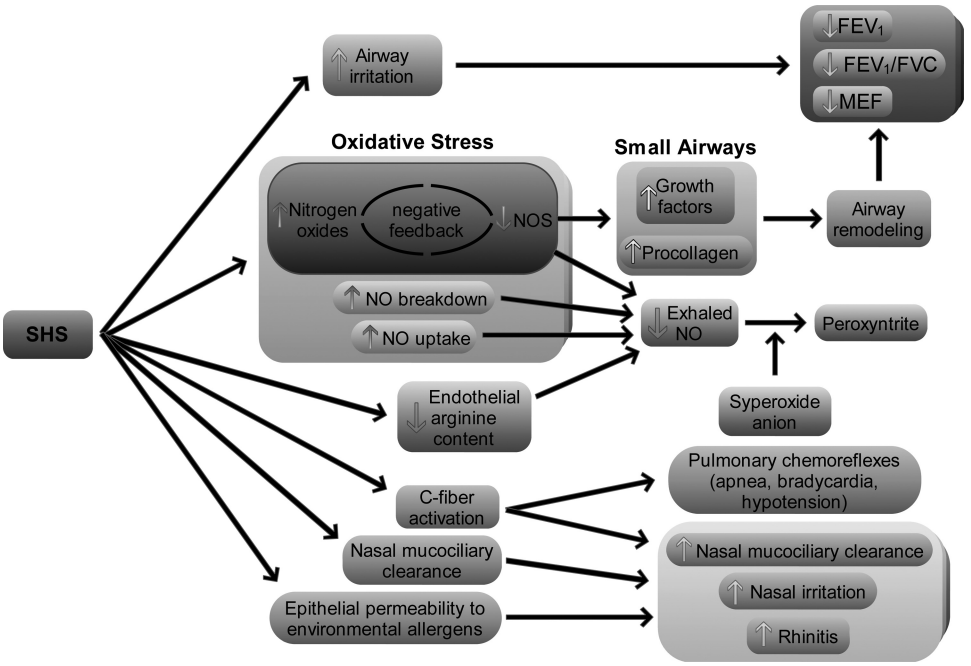

Fig. 1. The acute effects of secondhand smoke (SHS) on the respiratory system. NO, nitric oxide; NOS, NO synthase; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; MEF, maximum expiratory flow.

of evidence suggest that SHS induces rapid profibrotic growth factor production in the walls of small airways through an oxidant mechanism (16). These findings indicate that the initial response to cigarette smoke may not be related to evoked inflammation and may reflect direct induction of growth factors resulting in airway remodeling. Smokers demonstrate various types of airway remodeling in the large and small airways, including fibrosis, inflammation, muscle hyperplasia, and mucous metaplasia/hypersecretion. Fibrosis and the thickening of the airway wall, particularly in the subepithelial compartment within the small airways, are part of the pathogenesis of SHS-induced airflow limitation (19), yet the precise effect of airway remodeling on airflow obstruction remains to be determined (16, 116).

Within the first 15 min of moderate SHS exposure there is a decline in exhaled nitric oxide levels (130), confirming similar in vitro findings (21). This is noteworthy as changes in the production of nitric oxide are implicated in the pathophysiology of airway diseases associated with smoking (7). Nitric oxide reacts rapidly with superoxide anion, producing the deleterious oxidant peroxynitrite, a mechanism similar to that observed in cystic fibrosis where nitrite levels, indicators of nitric oxide oxidative metabolism, are elevated in breath condensate of afflicted persons but exhaled nitric oxide is not (41). The drop in exhaled nitric oxide levels within the first minutes of SHS exposure may be caused by the decreased production of nitric oxide synthase through the mechanism of feedback inhibition, given the high concentrations of nitrogen oxides inherent in tobacco smoke (50). Other possible mechanisms include an increased breakdown or modification of nitric oxide by SHS oxidants or a SHS-induced accelerated uptake of nitric oxide (112).

Regarding clinical implications, research has indicated that moderate SHS exposure develops nasal congestion, irritation, and increased rhinitis within 2 h of exposure (120). A number of potential mechanisms have been examined (93), and research to date shows that nasal mucociliary clearance (9), C-fiber activation (8), and epithelial permeability to environmental allergens (51) are the most likely candidates that may explain the clinical effects of brief SHS exposure on the respiratory system.

Cardiovascular Effects

Existing evidence has demonstrated that even brief SHS exposure may interfere with vascular physiological mechanisms. A model illustrating the acute effects of SHS on the cardiovascular system is illustrated in Fig. 2. In vitro experiments have shown that cigarette smoke condensate promotes the transendothelial migration of monocyte-like cells and induces the surface expression of cell adhesion molecules (63, 72, 96). Animal studies have established that even 5 min of SHS exposure to the smoke of one cigarette elicits the adhesion of leucocytes to endothelial cells (57). Along the same lines, human in vivo experiments have shown that SHS exposure may turn the acetylcholine-induced coronary artery relaxation into a vasoconstriction (108) and reduce the distensibility of the aorta (105). Furthermore, active smoking and SHS appear to have similar inhibitory effects on endothelium-dependent vasodilatation (13), whereas the acute SHS-induced effect on coronary flow reserve (74) and aorta distensibility (105) appears to be more potent in nonsmokers. The underlying mechanisms involved in these endothelial function changes are not completely understood. One likely possibility may be nitric oxide (73), the SHS-induced inactivation of which is discussed in the previous section. This notion is supported by animal studies that show that SHS decreases endothelial nitric oxide synthase activity (46, 129) and the endothelial arginine content (43), effects that are prevented by L-arginine supplementation (43, 132). However, SHS may also show no acute effects on endothelium-dependent vasodilation (48).

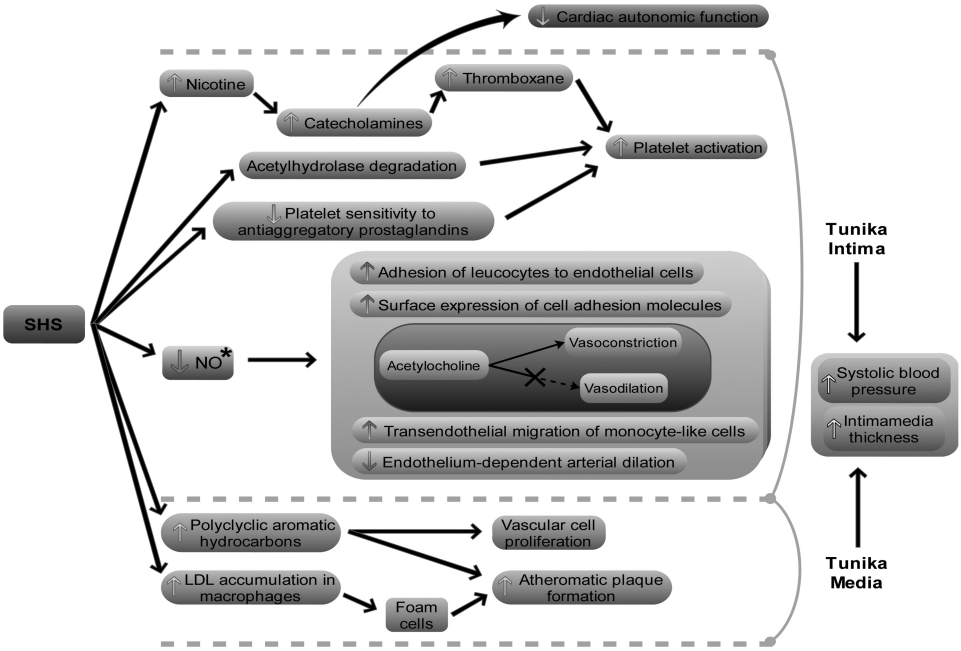

Fig. 2. The acute effects of SHS on the cardiovascular system. *The mechanism by which SHS affects NO is illustrated in Fig. 1.

A recent set of data provided evidence that SHS may harm the vasculature not only by directly injuring the vascular endothelium, but also by interfering with the vascular repair system, which may lead to chronic damage with recurrent exposures (37). This was shown by examining endothelial regeneration, a process mediated in part by endothelial progenitor cells circulating in peripheral blood (37). Specifically, 30 min of moderate SHS exposure has been shown to lead to a mobilization of dysfunctional endothelial progenitor cells in response to acute vascular injury that was evident for >24 h. Mechanistically, these effects have been linked to an impairment of nitric oxide production in endothelial progenitor cells, providing further evidence that even brief SHS exposures present significant and persistent vascular consequences.

Given its adverse effects on endothelial function, it is not surprising that SHS activates blood platelets, thereby increasing the risk for thrombus and ischemic heart disease (24, 89). Indeed, within 20 min of SHS exposure, platelet activation reaches levels similar to that of smoking two cigarettes (20). Animal data confirm these findings showing that bleeding time, an indicator of platelet activation, is significantly shortened following brief SHS exposures (133, 134). Although further research is needed to unravel the mechanisms of SHS-induced platelet activation, evidence to date has shown that cigarette smoke may increase platelet activation through toxins that increase platelet function by interfering with and degrading platelet-activating factor acetylhydrolase (68). Furthermore, the SHS-induced decreased platelet sensitivity to antiaggregatory prostaglandins (103) and the increase in thromboxane formation (94) through a nicotine-induced catecholamine secretion (2) have been also proposed as potential pathomechanisms.

In addition to platelet function, research data shows that exposures to SHS induce oxidative stress (42, 52, 89) from oxidants inherent in cigarette smoke (110) as well as free radicals released endogenously from activated neutrophils (89). Active smokers are adapted to this chronic oxidative stress showing increased antioxidant enzyme activity (64). However, nonsmokers demonstrate impaired antioxidant mechanisms in response to SHS (74). For instance, a 5.5-h exposure to SHS in nonsmokers is accompanied by compromised antibiochemical defenses and an increased accumulation of low-density lipoprotein cholesterol in macrophages (113), transforming them into foam cells (70). The oxidization of low-density lipoprotein during SHS induces various effects in the vessel wall (89). These results have been attributed to compounds inherent in SHS that influence the process of incorporating low-density lipoprotein cholesterol into the vessel wall (112). Animal experiments have shown a synergistic effect between SHS and low-density lipoprotein that facilitated the binding of oxidized low-density lipoprotein to the vessel wall during 2-h SHS exposures (91). It is also important to note that polycyclic aromatic hydrocarbons, byproducts of the incomplete combustion of organic material inherent in SHS, bind to lipoprotein subfractions and can be integrated into the atheromatic plaques promoting the proliferation of vascular cells and plaque progression (89, 90).

Regarding parameters of vascular function, research evidence has shown that SHS exposures at moderate levels for up to 2 h are accompanied by unfavorable changes in systolic blood pressure (30, 31, 62, 99) and cardiac autonomic function (82). However, some published studies do not report acute SHS-induced changes in heart rate and blood pressure (67, 74).

Effects on Oxygen Delivery and Exercise

The unfavorable effects of SHS raise concerns for potentially intensified SHS-induced system disruption when additional strains are added such as physical exertion, especially in individuals with (or at risk for) cardiovascular disease, chronic lung disease, or allergies (for instance, an individual being exposed to SHS at home or during a meeting and then having to walk fast for several minutes or climb a few sets of stairs). Understanding the acute and short-term effects of SHS on the

cardiorespiratory and immune response to moderate exertion is essential because the physical and metabolic changes that occur during physical activity can increase the risk of acute coronary complications and life-threatening myocardial ischemia even in apparently healthy individuals (18). The literature on SHS and exercise contains only three germane experiments in healthy individuals (58, 66, 79) and three additional experiments in coronary artery disease patients (3, 5, 97). Taken together, these experiments suggest that SHS adversely affects exercise performance in healthy individuals and exacerbates myocardial ischemia in coronary artery disease patients. Specifically, these experiments reported increased respiratory quotient, perceived exertion, levels of lactate in venous blood (66), increased heart rate (5, 79) and prolonged time to heart rate recovery (58), increased systolic and diastolic blood pressure (5), as well as similar FVC and FEV_1 but lower $MEF_{25\%}$ (79). On the other hand, no changes in submaximal oxygen uptake have been reported (66), whereas maximal oxygen uptake has been found both decreased (58, 66) and increased (79). Finally, evidence from animal experiments demonstrate that in addition to the well-known smoke-induced reduction in blood oxygenation (40), SHS may reduce the energy capacity of the heart with a 25% reduction in cytochrome oxidase activity within 30 min (35).

Metabolic and Endocrine Effects

Existing research has indicated that active smoking increases resting energy expenditure (115), the primary indicator of human metabolism (81). The first study on the metabolic effects of SHS was recently conducted by our group (67) demonstrating that a 1-h SHS exposure to levels similar to those of bars/restaurants is accompanied by a statistically significant increase in metabolism. Specifically, resting energy expenditure was increased by ~6% following SHS (67), resembling the ~7% increase previously reported in response to active smoking (115). It should be noted that the SHS-induced effects on metabolism were dose-dependent, similarly to that of active smoking (17, 78). Based on knowledge gained from research on active smoking (1), these results suggest that chronic SHS may influence normal catabolic processes resulting in adverse changes in body composition.

The SHS-induced increase in metabolism is accompanied by a statistically significant increase in the secretion of thyroid hormones 3,5,3′-triiodothyronine (T_3) and free thyroxine (fT_4; Ref. 67). This phenomenon is not attributed to a direct anterior pituitary response through increases in thyroid stimulating hormone levels but to the–probably short-term–effects of a different mechanism (67). Further work by our group demonstrated a lower T_3-to-fT_4 ratio, despite the increase in T_3, following SHS (31). This suggests an inhibited extrathyroidal T_4 deiodination to T_3, resulting in larger amounts of unbound hormone, which is available for uptake into cells and interaction with nuclear receptors, as well as a smaller circulating hormone storage pool. Consecutively, this may be due to a lower circulation of binding proteins or interaction of binding proteins with fT_4 and T_3 (23).

Data from some SHS experiments show more pronounced effects in men compared with women (32, 62, 77). This is also true for the SHS-induced changes in thyroid hormone secretion (31). For instance, the T_3-to-fT_4 ratio in women remains unaffected following SHS exposure (31), suggesting the involvement of estrogens that are known to influence serum total T_4 and T_3 concentrations by increasing the glycosylation of thyroxine-binding globulin–a protein heavily involved in T_4 and T_3 binding–and by slowing its clearance from the blood (23). Indeed, following SHS exposure, changes in estrogen are linked with changes in the T_3-to-fT_4 ratio in both sexes as well as inversely with fT_4 in women (31), reflecting an increase in thyroxine-binding globulin concentration. In turn, this increase in hormone binding reduces fT_4 concentration by increasing the clearance of thyroxine. Analogously, an observed decrease in the T_3-to-fT_4 ratio following SHS exposure in men as well as an inverse association between testosterone and T_3 suggest the involvement of androgens (31), which are known to decrease the glycosylation of thyroxine-binding globulin (23). These results are accompanied by an SHS-induced reduction in the secretion of luteinizing hormone and follicle-stimulating hormone by the anterior pituitary gland (31). It can be postulated, therefore, that the decrease in T_3-to-fT_4 ratio and possibly the increases in T_3 and fT_4 secretion–resulting in the increased metabolism–may be a result of a SHS-induced effect in the anterior pituitary gland reducing the secretion of luteinizing hormone and follicle-stimulating hormone that, in turn, reduce the secretion of gonadal steroid hormones resulting in a downregulation of thyroid gland hormonogenesis. This model is illustrated in Fig. 3. Based on these results and data from chronic active smoking, it can be suggested that chronic passive smoking (lifestyle incorporating frequent exposures to passive smoke) may have clinical implications such as thyroid and gonadal abnormalities in both sexes.

Immune Effects

Experimental data from different laboratories suggest that even brief exposures to SHS cause marked changes in IL-1β (29, 31), IL-4, TNF-α (29), white blood cell count, C-reactive protein, homocysteine, fibrinogen (75), as well as leukocyte counts accompanied by an immune cell activation (4). Moreover, the SHS-induced inflammatory reaction appears to be more potent in men compared with women given that some of the aforementioned inflammatory cytokines increase only in men, while there is a significant sexual difference in IL-5 and IL-6 as well as IFN-γ following exposure to SHS (29, 31).

The inflammatory markers that increase following brief SHS exposure are closely associated with the chronic lung inflammation and structural changes observed in pulmonary disease patients (76). The SHS-induced inflammation may also be reflected in the induction of bronchial hyperreactivity following SHS (55). Therefore, it has been suggested that chronic SHS may have clinical implications–especially in men, given their increased inflammatory response–such as increased susceptibility to infection, chronic lung inflammation, as well as pathological airway changes including chronic obstructive pulmonary diseases (29). Indeed, SHS-induced changes in IL-5 and IL-6 as well as IFN-γ is associated with the marked decrements in lung function. In turn, impaired lung function is associated with a greater prospective risk of cardiovascular mortality among nonsmokers (22).

The effects of SHS on inflammatory markers, particularly IL-1β, are known to influence the hypothalamic-pituitary-adrenal axis (86, 88) and may play a role in the SHS-induced

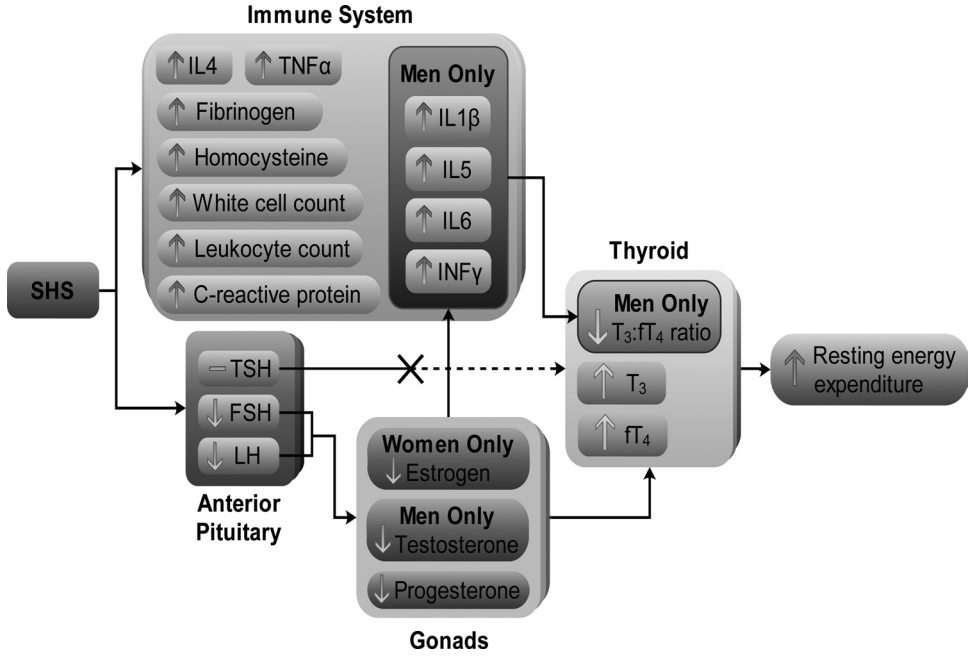

Fig. 3. A model describing the SHS-induced effect on the endocrine and immune systems resulting in an increased resting energy expenditure. It is postulated that the increases in thyroid hormone secretion is not a direct result of anterior pituitary response since SHS does not change thyroid stimulating hormone levels. In contrast, SHS reduces the secretion of luteinizing hormone and follicle-stimulating hormone that, in turn, decrease the secretion of gonadal hormones. Gonadal hormones affect thyroid gland hormonogenesis directly as well as through the well-known anti-inflammatory effect of estrogen, resulting in a higher resting energy expenditure. T_3, 3,5,3′-triiodothyronine; fT_4, free thyroxine.

changes in thyroid hormone secretion (described in detail in the previous section). IL-1β inhibits differentiated thyroid cell functions (87) including human thyroid cell adenylate cyclase and thyroglobulin release (86, 88). Consistent with this notion is the finding that IL-1β demonstrates significant SHS-induced changes only in men (29, 31), reflecting an anti-inflammatory effect of estrogens that is well-supported by previous research (101). These mechanisms are illustrated in Fig. 3. Further research is required to fully elucidate the relationship between circulating inflammatory markers and thyroid hormone secretion during/following SHS.

LENGTH OF SHS EXPOSURE

The majority of published experiments investigating the acute effects of SHS in humans used exposure durations of up to 2 h, whereas animal experiments have used exposures of up to 5.5 h. In this light, the available evidence has shown SHS-induced effects on the respiratory system within the first few minutes of smoke exposure (16, 119). Exposure of 5 min to the smoke of one cigarette elicits the adhesion of leucocytes to endothelial cells (57), whereas within the first 15 min of moderate SHS exposure there is a decline in exhaled nitric oxide levels (130). Other lines of evidence have shown that within 20 min of SHS exposure, platelet activation reaches levels similar to that of smoking two cigarettes (20). Exposure of 1 h to moderate SHS is accompanied by increased metabolism and thyroidal secretion of T_3 and fT_4 (67) as well as marked changes in IL-1β, IL-4, and TNF-α (29, 31). Two hours of moderate exposure to SHS is accompanied by unfavorable changes in systolic blood pressure (30, 31, 62, 99) and cardiac autonomic function (82) as well as the development of nasal congestion, irritation, and increased rhinitis (120). Exposures to SHS for up to 3 h may also cause marked changes in leukocyte counts accompanied by an immune cell activation (4). Finally, longer SHS exposures for up to 5.5 h are accompanied by increased oxidative stress (70, 91, 113).

DURATION OF SHS EFFECTS

Recent evidence demonstrated that the SHS-induced effects on lung function appear to recede within 60 min but inflammatory cytokines remain elevated for at least 3 h following SHS exposure (29). This finding alludes to chronic low-grade systemic inflammation in individuals exposed to SHS on a daily basis and/or at higher smoke concentrations. This is particularly true for the case of IFN-γ (29) that is closely linked with chronic obstructive pulmonary disease and asthma (59). At present, the physiological mechanisms linking low-grade systemic inflammation and pulmonary disease are not entirely understood (102). However, a number of studies have reported higher levels of systemic fibrinogen and C-reactive protein of individuals with impaired lung function (6) and in patients suffering from chronic obstructive pulmonary disease (80).

CONCLUDING REMARKS

The first evidence on the danger of SHS arose in 1981 from a study showing that nonsmoking Japanese women married to men who smoked had an increased risk for lung cancer (39). Since then, many studies have appeared on the unfavorable effects of SHS, most of which evaluated longitudinal epidemiological data. In contrast, exposure studies assessing the acute and short-term SHS effects are limited. However, this knowledge is essential and of the utmost importance for elucidating the underlying physiological mechanisms involved in SHS-induced system disruption (65, 114).

Since the first study on SHS, research in this topic has spread into different areas, and new scientific evidence continues to accumulate. Thus far, the cellular, animal, and human studies conducted indicate a number of mechanisms by which the deleterious effects of SHS may arise. However, many germane studies incorporate limitations. For instance, a large number of epidemiological studies base SHS exposure on self-report without an objective measurement of exposure, they adopt a

cross-sectional design, and they provide little data on the duration of the exposure. On the other hand, the majority of mechanistic exposure studies rely on animal models or in vitro experiments, both of which are inherently limited, particularly in relation to the level and duration of the exposures as well as their relevance in humans. Nevertheless, the literature also contains outstanding experiments that have provided novel evidence on the underlying pathophysiological mechanisms related to SHS exposures.

The aim of this review was to critically evaluate the existing biological evidence regarding the acute health effects of SHS exposure. Based on the presented evidence, we conclude that even brief exposure to SHS may generate significant adverse effects on several systems of the human body. This information has been summarized herein into three models in an attempt to put forward an elegant and consistent theory. However, as Albert Einstein wrote, "No fairer destiny could be allowed to any physical theory than that it should itself point out the way to introducing a more comprehensive theory in which it lives on as a limiting case."

Notwithstanding the recent attention on the biological effects of brief SHS exposures and the excitement for the new discoveries in this area, we remain largely naïve to issues as critical as the concentrations of specific tobacco smoke constituents following SHS exposure in the alveolar milieu as well as the interactions among the various constituents of SHS. Furthermore, future research should address individual susceptibilities, an approach that will lead to the recognition of genetic profiles that influence susceptibility to adverse SHS induced effects and will provide insights into the underlying mechanisms of the health consequences. Finally, investigation of the effects of SHS exposure on brain cell development, synaptic development and function, as well as neurobehavioral activity should be projected in future studies.

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DISCLOSURES

The authors have no conflict of interest to declare for this study.

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