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Concomitant consumption of marijuana, alcohol and tobacco in oral squamous cell carcinoma development and progression: Recent advances and challenges

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ABSTRACT

Oral squamous cell carcinoma (OSCC) corresponds to 95% of all malignant tumours of the mouth. The association between alcohol and tobacco is the major risk factor for this disease, increasing the chances for the development of OSCC by 35-fold. The plant, *Cannabis sativa* is smoked as cigarettes or blunts and is commonly used in association with tobacco and alcohol. Any type of smoking habit exposes individuals to a wide range of carcinogens or pro-carcinogens, such as polycyclic aromatic hydrocarbons, as well as some ethanol derived substances such as acetaldehyde (AA), and all are genotoxic in the same way. In addition, ethanol acts in the oral mucosa as a solvent and therefore increases the cellular membrane permeability to carcinogens. Carcinogens found in tobacco are also concentrated in marijuana, but the latter also contains high levels of cannabinoids, bioactive compounds responsible for several effects such as euphoria and analgesia. However, Δ^9-tetrahydrocannabinol (Δ^9-THC), the major psychotropic cannabinoid found in plants, causes a reduction of cellular metabolism and induction of apoptosis, both of which are anti-neoplastic properties. Apart from limited epidemiologic and experimental data, the effects of concomitant chronic exposure to marijuana (or Δ^9-THC), tobacco and alcohol in OSCC development and progression is poorly known. This paper reviews the most recent findings on the effects of marijuana over cellular proliferation, as well as in the risk for OSCC, with emphasis on its interaction with tobacco and ethanol consumption.

1. Introduction

In many countries, the oral cancer is among the commonest malignancies, with 900,000 new cases diagnosed annually worldwide. More than 90% of such cancers are oral squamous cell carcinomas (OSCC). OSCC shows a complex, multistage developmental process, and involves several environmental and genetic factors.[1] Exposure to carcinogens, such as those present in tobacco smoke or derived from alcohol intake, is a remarkable element preceding the establishment of disease for most cases.[2] For heavy smokers and drinkers, the consumption of both substances shows a synergistic effect, increasing the risk of OSCC development by up to 35 times.[3] In Western countries, tobacco is usually consumed as cigarettes, and the habit is frequently associated with alcohol drinking.[3,4]

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Among alcoholics, tobacco smoking is also a common addiction, making it hard to evaluate these habits independently from each other.[5,6] Moreover, some smokers and/or drinkers usually take different illicit drugs; however, it is not known if when taken together these habits, could somehow affect the development and progression of malignancies, especially OSCC.

Marijuana is one among many common names for the plant *Cannabis sativa* that is smoked and widely used for recreational purposes. Both tobacco and marijuana consumption cause cellular damage owing to various substances found in inhaled smoke, such as polycyclic aromatic hydrocarbons (PAH). While nicotine is found only in tobacco, the cannabinoids are present in high concentrations in marijuana. These correspond to a class of small bioactive molecules that have various physiological effects mediated by specific cellular receptors and distributed ubiquitously in the human body.[7,8] As with tobacco use, marijuana smoking exposes the oral mucosal tissue to various carcinogens. Conversely, an antineoplastic activity has been associated with cannabinoids,[9] which could affect the extent of the potential carcinogen-mediated damage.

Despite the frequency of its use, the effects of marijuana on the risk for oral cancer have been poorly appreciated, as well as its interaction with tobacco and ethanol abuse. This review discusses current knowledge regarding the effects of marijuana smoke on the control of cellular proliferation, its influence in the relative risk for oral cancer, and its potential epidemiologic and biological impact on oral mucosa when present with tobacco smoke and ethanol.

2. Molecular biology of alcohol and tobacco as risk factors for OSCC

When an individual smokes a tobacco cigarette up to 3000 different substances are inhaled, of which at least 50 are assumed as carcinogens or pro-carcinogens.[10] It includes tobacco-specific nitrosamines [*e.g.* 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone], aromatic amines (4-aminobiphenyle), acetaldehyde (AA) and PAH, all of these demanding enzymatic activation to exert carcinogenic activity.[11] For example, 7,12-dimethylbenz[a]anthracene (DMBA) is a PAH that is widely used to induce OSCC in model animal.[12] Its activation occurs via cytochrome P450 superfamily (CYP) enzymes and the final epoxy products are reactive species that have affinity to DNA, thus increasing the occurrence of mutations.[13]

Alcohol itself is not a carcinogen, but its first endogenous metabolite, AA, is genotoxic and causes DNA damage due to N^2-ethyl-2′-deoxyguanosidyne stable adducts formation,[14] making alcohol a co-carcinogen. Ethanol metabolism is required to form AA, catalyzed by the systemically distributed aldehyde dehydrogenase, which allows extra-hepatic metabolite formation.[15] Moreover, microbial oral colonization is also involved in the process, forming AA in the mouth and potentiating its local carcinogenic activity.[6] Oral and foreskin keratinocytes in culture, with attached with acetaldehyde producer *Streptococci* spp. bacteria, are remarkably affected in that they have an increase in the metabolic production of AA from added alcohol.[2] This pattern of attachment resembles that observed in the formation of oral microbial biofilms which occur among individuals with poor oral hygiene. Whereas AA formation derived from alcohol intake requires enzymatic conversion, tobacco smoke is a direct source of this carcinogen. Human cells treated with ^{13}C-labelled AA show unquestionable DNA damage resulting from the formation of both N^2-ethyl-2′-deoxyguanosine and N^2-propano-2′-deoxyguanosine adducts.[16] But it is also noticeable that cannabis smoke is also rich in AA, and strong experimental evidence support that such smoke can indeed be harmful to the DNA of exposed cells, again due to formation of N^2-ethyl-2′-deoxyguanosine adducts. Thus, there is evidence that *C. sativa* consumption can somehow be implied in cancer development by direct DNA damage associated with smoke compounds other than cannabinoids.[14]

Ethanol metabolism also involves CYPs, which are central in the detoxification/oxidation of xenobiotic, such as PAH and other carcinogens. Thus, when alcohol activates the CYP members, it is stimulated by carcinogenic hydrocarbons and other combustion products.[17] Furthermore, genetic epidemiological studies suggest that gene polymorphisms in CYP2E1 are risk factors for head and neck SCC (squamous cell carcinoma), since their expression products are enzymes for tobacco-derivate oxidation.[11] Hence, alcohol intake may change the carcinogen-activation pathway related to substances found in cigarette smoke.

Locally, ethanol affects cellular membrane permeability and, due to morphological changes, mucosal atrophy and acts as a liquid phase into which carcinogens are dispersed in low-concentrated media, such as smoke. Ethanol facilitates the penetration of molecules, such as PAH, into the intracellular domain of mucosal epithelial cells in the mouth.[6] The increased membrane permeability causes changes in the diffusion/uptake patterns of other substances, for which ethanol can also act as solvent, *e.g.* cannabinoids found in marijuana smoke.

3. Endocannabinoid system

Since the discovery of endocannabinoid system, several efforts have been performed to understand the role of endocannabinoids in diverse biological processes, due to its ubiquitous presence in organs and tissues. Specific receptors CB1 and CB2 have emerged as potential drug targets, and synthetic cannabinoids have been proved useful in inducing responses modulated by such receptors in both *in vitro* and *in vivo* experiments. The use of medicinal marijuana has undesirable side effects related to psychoactive properties of CB1 agonists, namely Δ^9-THC. Indeed, more potent non-psychoactive analogues, such as ajulemic acid, have been proved useful in several diseases in pre-clinical essays, such as systemic sclerosis and other inflammatory conditions.[18]

Despite noticeable advances in research, the development and growing availability of synthetic cannabinoids has turned into a new concern for healthcare, since they have been used, from 2008, as psychoactive substances mixed to herbal smoking products, sold legally on internet or *coffeshops*, under names as Spice Gold, Spice Silver, Yucatan Fire and others.[19] Toxic effects similar to those due to cannabis use have been