

## ABSTRACT

Studies were conducted to elucidate the effect of tobacco smoking and marihuana on respiratory functions in both animals and human subjects. The airway resistance (Raw) was measured in apparently healthy Wistar rats using whole body plethysmograph. Histopathological and histochemical observations were also made to ascertain the damage induced by the inhalation of tobacco or marihuana smoke. Various pneometric tests viz. Vital Capacity (VC), Functional Residual Capacity (FRC), Residual Volume (RV), Total lung Capacity (TLC), Forced Expiratory Volume in one second (FEV<sub>1.0</sub>), Mean Transit Time (MTT), Peak Expiratory Flow Rate (PEFR) and Closing Volume (CV) were carried out in chronic tobacco, marihuana smokers and clinically assessed asthmatic patients. The effects of crude aqueous marihuana extract on specific airway resistance (sRaw) as well as on various pneometric parameters were observed both in animals and human subjects respectively.

### Animal Studies

Inhalation of either marihuana or tobacco smoke

significantly increased ( $P < 0.01$ ) airway resistance (Raw), functional residual capacity (FRC) and specific airway resistance (sRaw) as compared to the control rats. Apparent increases in the airway resistance were observed after the first week of exposure but significant differences were only noted in rats exposed for a period of 12 weeks or more.

The smoking of either marihuana or tobacco increased the sensitivity of airways to acetylcholine from 18 weeks of exposure onwards.

Attempts to elucidate the mechanism of action suggested that the increase in airway responsiveness of alpha adrenoceptors and increased vagal activity which may have resulted in the narrowing of the airways. This has been suggested on the basis of the following observations:

- i) Intraperitoneal administration of adrenaline (400 ug/kg body weight) following propranolol (2 mg/kg body weight) resulted in an increase in sRaw, whereas a decrease was observed following phentolamine (2 mg/kg body weight).

ii) Intramuscular administration of atropine (2 mg.kg body weight) decreased sRaw. Bilateral vagotomy also decreased the value of sRaw in 36 weeks of marihuana or tobacco smoke to exposed rats.

iii) The administration of subthreshold concentrations of acetylcholine (0.25 ug and 0.5 ug Ach) in 36 weeks smoke exposed rats significantly increased sRaw in contrast to control rats. The administration of atropine prior to acetylcholine in subthreshold concentrations prevented such increase in sRaw in smoke exposed rats indicating the involvement of vagus in inducing the hypersensitivity.

The possible existence of bronchitis in marihuana and tobacco smoke exposed rats from 12 weeks onward has been further supported by histopathological and histochemical changes which include inter alia catarrhal inflammation resulting into ulceration of the bronchial mucosa, squamous cell metaplasia, increased goblet cell, increased sulphation of mucus, focal alveolitis and alveolar collapse.

The intraperitoneal administration of 1 ml aqueous crude marihuana extract (1.27 gm/100 ml) significantly decreased the value of sRaw in both marihuana and tobacco smoke exposed rats. This is suggestive of its broncho-dilatory effect and has been further demonstrated to be acting through beta adrenoceptors.

The cessation of smoking for one month resulted in a decreasing trend of sRaw in rats exposed to either marihuana or tobacco smoke for period of 36 weeks. This suggests that improvement in the lung picture may be achieved if a longer recovery period is allowed.

### Human Studies

The comparison of lung functions in chronic marihuana smokers and non-smokers indicated narrowing of both central and peripheral airways as demonstrated by slight decreases in  $FEV_{1.0}\%$  and PEF and increases in  $RV/TLC\%$ ,  $CV/VC\%$  and  $CC/TLC\%$ . These lung functions were found to be more affected in chronic smokers.

The bronchodilatory effect observed immediately after smoking a single dose of marihuana to the chronic marihuana smokers may be due to the presence of THC. This bronchodilatation was followed by bronchoconstriction when observed after 60 minutes of marihuana smoking. The mechanism of initial bronchodilatation is at present unclear but may be due to a direct effect of THC on the bronchial smooth muscle. The bronchoconstrictory effect of marihuana or tobacco smoke is probably due to increased vagal activity and increased responsiveness of alpha adrenoceptors as observed in the animal studies. The presence of a low responsive and a high responsive group of subjects in chronic marihuana smokers has been demonstrated. The high responsive group seems to be more susceptible to marihuana smoke as exemplified by greater decrease in  $FEV_{1.0}\%$  and increase in  $CV/VC\%$ . These changes further indicate that the impairment occurs predominantly in the larger airways even though there are signs of onset of small airway disease.

The decreases in  $FEV_{1.0}\%$  and PEF in the asthmatic subjects indicated abnormalities in the larger airways.

Significant increases in MTT, CV/VC% and CC/TLC% is suggestive of obstruction in the peripheral airways. Administration of 30 mls aqueous extract (200 mg/100 mls) of marihuana to asthmatic subjects resulted in the improvement in lung functions after 30 minutes with the maximum improvement being observed at 60 minutes post administration. The bronchodilatory effect of marihuana extract was quite comparable to a known bronchodilator, ventolin (Salbutamol 200 ug), used in this study. However, the effect of ventolin was faster than aqueous marihuana extract. The bronchodilatory effect of aqueous marihuana extract may be due to the presence of some active ingredient other than THC and may be partly due to the increased activity of beta adrenoceptors.