CANNABINOIDS BLOCK RELEASE OF SEROTONIN FROM PLATELETS INDUCED BY PLASMA FROM MIGRAINE PATIENTS

Int J Clin Pharm. Res V (4) 243-246 (1985)

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Summary: The effects were assessed of delta-1-THC* (the psychoactive component of cannabis) and CBD and DMHP-CBD (the non-psychomimetic components of marijuana derivatives) on 14C labelled serotonin release from normal platelets, when incubated with patient's plasma obtained during migraine attack. A statistically significant inhibitory effect ($p>0.005$) of 14C serotonin release was found at 10-5M, 10-6M, 10-7M delta-1-THC concentrations. Plasma of migraine patients obtained in attack-free periods revealed no significant inhibitory effect on 14C serotonin release from normal platelets using the same delta-1-THC concentration. CBD and DMHP-CBD had no significant effect on 14C serotonin release from normal platelets when tested either at migraine-free period plasma or plasma obtained during migraine attack.

(*Nomenclature for THC is sometimes different in other countries. delta-1-THC is the same as delta-9-THC.)

Introduction

Several mechanisms are involved in the relationship of platelets to migraine attacks. The first relates to the platelet itself and is associated with hyperaggregation of platelets (1-5) and their activation (6). On the other hand, a plasmatic factor has been reported to induce aggregation of normal human platelets and release serotonin (7-12). Previous reports on the beneficial effect of cannabinoids in migraine (13) raises the possibility that delta-1-3, 4-trans tetrahydrocannabinol (delta-1-THC), the active psychoactive components of the crude extract of marijuana, may be beneficial (14, 15). It is a fact that cannabis has an analgesic effect (16) decreases intraocular pressure (17), has a vasodilatory effect in bronchial asthma (18) and prevents vomiting (19). These various effects of cannabinoids and the effect of delta-1-THC on preventing release of rat brain serotonin induced by reserpin (20) and its effect on platelets in vivo (21, 22) and aggregation of platelets in vitro (23) raised the possibility that it might affect the previously described plasmatic factor in migraine patients responsible for 14C serotonin release of normal platelets (8).

Therefore, we assessed that in vitro effect of three marijuana derivatives: delta-1-THC, the psychoactive component of cannabis (14) and cannabidiol (CBD) which has no psychomimetic effect (24). The effect of both drugs might discern the biological specificity of the marijuana derivatives. Also (6-

hydroxydimethylheptyl) (DMHP-CBD) a homologue of cannabidiol which increases cannabinoid-activity five hundred-fold was also investigated (25).

Material and methods

Plasma was obtained from patients, being followed at the Neurology Clinic of the Ben-Gurion University Medical Center, and diagnosed according to a standard clinical definition of migraine (26). Patients refrained from taking drugs ten days prior to blood donation. Blood samples were obtained (in plastic tubes --- 3.8% sodium citrate 1:10 volume) once during an attack-free period and once during a migraine attack. Simultaneously, samples were obtained from normal controls of the same age and sex and platelet rich plasma was prepared and frozen at -72 degrees C. Plasma samples were incubated at 37 degrees C for ten minutes with the cannabinoids delta-1-THC, CBD and DMHP-CBD. The concentrations of cannabinoids varied from 10 -7M to 10 -3M.

Ethanol 70% was used as control because it is used as the solvent for the cannabinoids. It did not affect the serotonin release during the ten minutes' incubation in comparison with normal saline. 14C labelled serotonin release was determined from normal donor's platelets blood group 0 Rh-, who refrained from taking medications for ten days. The assessment of 14C serotonin release was made with plasma of migraine patients during an attack, and an attack-free period and of normal plasma controls according to Hirshman and Schulman (27). Radioactivity was determined using a liquid Scintillation spectrometer TriCard 3255 Packard.

The results were calculated in percentages, considering the total radioactivity of 14C serotonin uptake by the platelets tested as 100% value. Statistical evaluation was done using the Student's t-test.

Results

Normal plasma incubated with delta-1THC at the range of concentrations 10 -7M to 10 -3M revealed significant increases of 14serotonin release from normal platelets only at 10 -4M and 10 -3M delta-1-THC of 106+ 1.9%, 117.9+ 2.3% respectively ($p<0.05$). The other two cannabinoid derivatives CBD and DMHP-CBD had no effect on 14C serotonin release from normal platelets when incubated with normal plasma, and tested at the same range of drug concentrations.

Table I documents the effect of delta-1-THC, CBD, and DMHP-CBD on 14C labelled serotonin release from normal platelets when incubated with the migraine patient's plasma obtained during a migraine attack. There is a statistically inhibitory effect of 14C serotonin release ($p<0.005$) at 10 -5M, 10 -6M, 10 -7M delta-1-THC concentrations. It should be noted that delta-1-THC added at the same concentrations

to plasma of migraine patients obtained in an attack-free period revealed no significant inhibitory effect on 14C serotonin release compared with normal platelets.

The other two cannabinoid derivatives CBD and DMHP-CBD had no significant inhibitory effect on 14C serotonin release from normal platelets, when tested either with migraine-free period plasma or plasma obtained during a migraine attack. These two derivatives were tested at the same concentrations as described in Table I.

Table I Inhibition of 14C serotonin release from normal platelets. Effect of delta-1-THC, CBD, DMHP-CBD on plasma of migraine patients obtained during migraine attack (mean + s.e. %).

Drug Concentration THC CBD

DMHP-CBD

10 -5M 84.10 + 2.8 107.1 + 3.7

105 + 3.5

10 -6M 86.8 + 2.3 106.6 + 3.7

106 + 3.6

10 -7M 87.8 + 2.5 103.99 + 3.4 108

+ 3.5

Discussion

Plasmatic factor present in migraine patients' plasma was reported to release serotonin in vitro from normal platelets (7, 8). Serotonin release induced by this factor occurred in 60-85% of the patients and is presumed to be a fatty acid (9), prostaglandin (10) or some immunological factor related to decrease in complement (11, 12). Previous reports concerning delta-1-THC, the active component in marijuana derivative (14, 28), documented increased serotonin in rats' brains and prevented release of serotonin induced by reserpine (20). The present studies documented significant inhibition of 14C serotonin release from normal platelets in 10 -7M to 10 -5M delta-1-THC concentrations, when incubated with plasma from migraine patients (Table I).

It should mention that these concentrations induce a psychosomatic effect in marijuana smokers and stabilize red blood cells against lysis (29). It is not clear yet how cannabinoids affect migraine. Is it due to their analgesic effect (16), vasoconstrictor effect (30) or preventive effect on migraine (13)?

The two other non psychomimetic components of marijuana derivatives CBD and DMHP-CBD did not show inhibition activity of 14C serotonin release from normal platelets induced by migraine plasma. It was shown that the psychoactive component of cannabis delta-1-THC did inhibit 14C serotonin release from platelets and it might give a clue to the effect of cannabinoids in vivo in respect of migraine attacks and their inhibition.

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