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CANNABINOID ADDICTION: BEHAVIORAL ASPECTS AND NEUROCHEMICAL CORRELATES

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The hemp plant, Cannabis sativa, has been used for over 4000 years as a recreational drug due to its mind-altering effects. Marijuana, the common name for cannabis, is by far the most commonly used street drug world wide today. These compounds exert their psychoactive effects by binding at specific membrane receptors, the CB1 cannabinoid receptors coupled with G proteins.
Animal models of cannabinoid addiction allowing the exploration of neural correlates of cannabinoid abuse have been developed only recently. These models have provided a better understanding of the neurobiological mechanisms involved in cannabinoid actions and have revealed commonalities between cannabinoids and other drugs of abuse with respect to the addictive processes.

The present work was organized to correlate the behavioral alterations present in rats made tolerant and physical dependent to either natural (Δ^9-tetrahydrocannabinol -THC-) or synthetic (CP-55,940) cannabinoid with the cellular modifications present in the central nervous system of treated animals. Moreover in line with cannabinoids effects on brain rewarding circuits, we assumed that repeated cannabinoids exposure might also induce behavioral sensitization. This phenomenon plays a part in drug seeking behavior that persists long after discontinuation of drug use.
To give further insights in all these aspects we surveyed the changes in CB1 receptor binding, receptor-G protein coupling and cAMP cascade in tolerant, abstinent and sensitized animals.

Behavioral and neurochemical correlates of cannabinoid tolerance
Tolerance to the analgesic effect of THC and CP-55,940 was induced by a chronic treatment consisting respectively of twice a day injections of 15 mg/kg i.p. of THC or 0.4 mg/kg i.p. of CP-55,940 for 6.5 days. At the end of this period animals developed a full tolerance to the analgesic effect as demonstrated by a reduction in the area under the time-response curve (AUC).
In the brain of THC tolerant rats we observed a significant reduction in CB1 receptor and [^{35}S]GTPγS binding in all cerebral regions that contain this receptor. In contrast, the down regulation and desensitization produced by chronic CP-55,940 appeared more localized. Moreover cAMP system was up-regulated only in THC tolerant rats whereas no changes were observed after chronic CP-55,940.

Behavioral and neurochemical correlates of cannabinoid withdrawal
To characterize the behavioral and neurochemical aspects of the cannabinoid withdrawal we injected the cannabinoid antagonist SR141716A (5 mg/kg i.p.) in rats made tolerant to CP-55,940. The most characteristic somatic manifestations that we observed in dependent rats were turning, chewing and digging. The physical dependence was less marked in our study than with other drugs of abuse, such as opioids, and appeared to be resolved completely within 24 h. At the receptor level we observed a tendency to return to basal levels in the striatum and cortex, whereas the specific binding remained lower in the hippocampus and cerebellum. The receptor/G protein coupling recovered its efficiency in all the cerebral areas except for cerebellum where a trend to overcome the control amounts was present. Moreover the stimulation of cAMP cascade was localized only in the cerebellum of abstinent rats suggesting an important role of this area in the mediation of the motor component of abstinence.

Behavioral and neurochemical correlates of cannabinoid sensitization
To assess the presence of behavioral sensitization to THC, rats were treated twice a day for 5 days with increasing doses of THC (5, 10, 20, 40, 40 mg/kg ip) or its vehicle and after 20 days of suspension were challenged with 5 mg/kg ip of the drug and their behavior was monitored. The challenge with THC induced a syndrome of motor inhibition in control rats, while in animals pre-treated with THC elicited a complex behavioral manifestation characterized by a trend of increase in non stereotyped activity and a significant enhancement in stereotyped items suggesting the presence of cannabinoid behavioral sensitization. We also investigated the cellular adaptations present in the sensitized rats and we observed a significant up-regulation of CB1 receptor confined to the cerebellum and an increase in the net [^{35}S]GTPγS binding only in the striatum and cerebellum suggesting a better CB1 receptor/G protein coupling in these areas. These alterations were followed

also by changes at the intracellular level, both in the cAMP cascade and in cAMP-related transcriptional factors activation.

Concluding the present work is part of a growing body of evidence indicating that cannabinoids develop behaviors typical of addiction, including tolerance, physical dependence, self-administration and behavioral sensitization. The neurochemical alterations correlated to these behaviors are mainly localized in striatum and cerebellum that appear specific areas for cannabinoid addiction. Our finding further demonstrate that marijuana resembles other drugs of abuse with respect to addictive processes.

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