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Evaluation of the endocannabinoid system in post-mortem human prefrontal cortex of alcoholic subjects

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Introduction: Several reports suggest the involvement of the endogenous cannabinoid system in cerebral mechanisms underlying drug addiction, including alcoholism. Behavioural studies in rodents have shown that the administration of CB1 antagonists and FAAH (fatty acid amide hydrolase, the principal endocannabinoid inactivating enzyme) inhibitors reduce alcohol intake, while CB1 agonists increase it. Furthermore, chronic exposure to ethanol also induces alterations in the endocannabinoid system in animal models: increasing endocannabinoid content, while decreasing FAAH activity and CB1 receptor density and functionality. In parallel, human genetic studies have suggested the involvement of particular CB1 and FAAH coding polymorphisms in alcoholism. A recent report described an increase in CB1 receptor expression and density in prefrontal cortex of alcoholic suicide victims when compared with chronic alcoholics dying from causes other than suicide [1].
Aims: The purpose of this study was to evaluate the endocannabinoid system in post-mortem human brain of subjects with a previous history of alcoholism. Thus, the protein expression of the CB1 receptor, its functional coupling at the G-protein level and at the adenylate cyclase (AC) activity, and the activity of FAAH were assessed.
Methods:

1. Expression of the CB1 receptor was determined by immunoblot experiments.
2. Functional coupling of CB1 receptor to G-protein was evaluated by WIN 55,212–2 (10^{-12}-10^{-3} M, 10 concentrations) stimulated [^{35}S]GTPγS binding.
3. AC activity was evaluated as basal activity, forskolin (10^{-5} M) activated cAMP accumulation and the inhibition of forskolin-stimulated cAMP accumulation evoked by WIN 55,212–2 (10^{-8}-10^{-4} M).
4. FAAH activity was determined by the hydrolysis of N-arachidonoyl-[^{3}H]ethanolamine (1, 5, 20 μM).

These different assays were performed in preparations of human prefrontal cortex from 1) non-suicide alcoholic subjects (n = 11), 2) alcoholic suicide subjects (n = 11), 3) non-alcoholic suicide subjects (n = 11), and 4) controls (n = 11). All groups were matched for sex, age and post-mortem delay.
Results:

- A significant increase (126% of control) was observed in the protein expression of CB1 in the prefrontal cortex of the alcoholic suicide subjects.
- The potency (EC_{50} = 1.0–1.8 μM) and the maximal effect (E_{max} = 175–196%) of WIN55,212–2 to stimulate [^{35}S]GTPγS binding was found to be unchanged among the different populations.
- A significant decrease (42% of control) was observed in the basal activity of AC in the non-suicide alcoholic subjects. However, no statistically significant differences were found either in the potency (EC_{50} = 0.4–1.2 μM) or the maximal effect (I_{max} = 35–44%) of WIN55,212–2 for inhibition of AC activity.
- FAAH activity was found to be unaltered among the groups (K_m = 3.3–3.6 μM and V_{max} = 6.8–7.1 nmol/min/mg prot)

Conclusions: These data indicate an increase in CB1 receptor expression in the cortex of alcoholic suicide subjects, which agrees with the results previously reported [1]. However, no change was observed in the functionality of the CB1 receptor, either at G-protein or AC levels. FAAH activity was also found to be unaltered in the cortex of alcoholic subjects.
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