The Effect of the Enzyme Inhibitor Phenylmethylsulfonyl Fluoride on the Pharmacological Effect of Anandamide in the Mouse Model of Cannabimimetic Activity[1]

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ABSTRACT

Anandamide is an putative endogenous cannabinoid ligand that produces pharmacological effects similar to those of D^9-tetrahydrocannabinol, the principle psychoactive constituent in marijuana. There is considerable evidence that the enzyme inhibitor phenylmethylsulfonyl fluoride (PMSF) is capable of altering the actions of anandamide *in vitro* by blocking its metabolism. Therefore, studies were conducted in mice to determine whether PMSF could produce cannabinoid effects by altering endogenous levels of anandamide as well as determining whether PMSF could potentiate the effects of exogenously

mg/kg) or vehicle (1:1:18) before treatment with various doses of anandamide. The dose-response curves demonstrating the effect of PMSF on anandamide-mediated responses are demonstrated in figures 4 to 6 and summarized in table 3.

PMSF pretreatment produced a parallel shift to the left in the anandamide dose-response curve in the tail-flick antinociception measure (fig. 4). The ED_{50} value for anandamide was 17 6 2 mg/kg. The potency of anandamide was somewhat less than that previously reported [6.2 mg/kg (Smith *et al.*, 1994)], although very similar to that observed for other measures. PMSF produced a statistically significant shift in that value to 3.3 6 .3 mg/kg. This 5-fold increase in the potency of anandamide was obtained in experiments in which the re-

However, a PMSF dose of 85 mg/kg produces only about 30% inhibition of brain acetylcholinesterase activity, and this effect occurs 18 hours after drug administration (Moss *et al.*, 1985). Thus, it seems unlikely the interaction of 30 mg/kg of PMSF with anandamide is compromised by changes in esterase activity, but it does seem plausible that the effects ob-