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ABSTRACT: Organophosphate (OP) insecticides are utilized throughout the world for protecting crops, people, and animals from pest insect attack and disease transmission. OP compounds are nerve poisons acting at the cholinergic neurons in inhibiting acetylcholinesterase as the primary target. OP insecticides also act on the diverse serine hydrolase targets, thereby revealing secondary or unexpected toxic effects including male reproductive toxicity. The present investigation detects a possible target molecule(s) for OP-induced spermatotoxicity, such as sperm deformity, underdevelopment, and reduced motility, through a chemical standpoint. The activity-based protein profiling (ABPP) approach with a phosphonofluoridate fluorescent probe pinpointed the molecular target for fenitrothion (FNT, a major OP insecticide) oxon (bioactive metabolite of FNT) in the mouse testicular membrane proteome: i.e., FNT oxon phosphorylates the fatty acid amide hydrolase (FAAH) which plays pivotal roles on spermatogenesis and sperm motility acquirement. Subsequently, mice were treated orally with vehicle or FNT (50 or 100 mg/kg/day) for 10 days, and the FAAH activities in testis or epididymis cauda were significantly reduced by the subacute exposure. ABPP analysis revealed that FAAH was selectively inhibited among the FNT-treated testicular membrane proteome. Accordingly, this investigation suggests for the first time that FAAH in mouse testis and epididymis cauda, to modulate the endocannabinoid signaling, is a potential target for OP-induced spermatotoxicity.