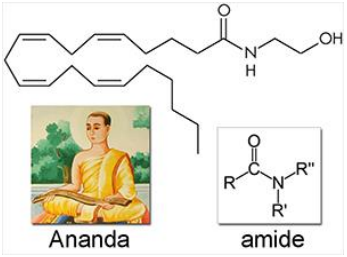
JNJ-42165279: selective and slowly reversible FAAH inhibitor

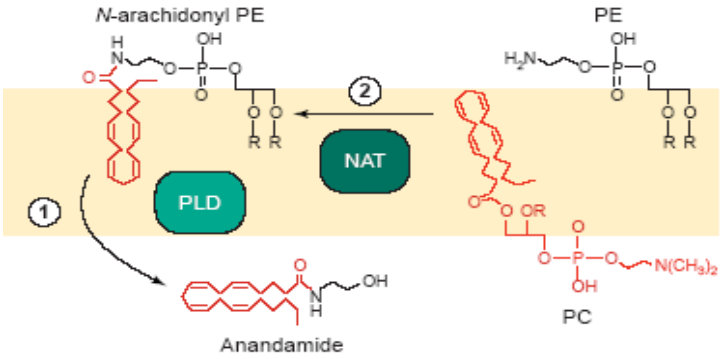
Central and Peripheral PK/PD

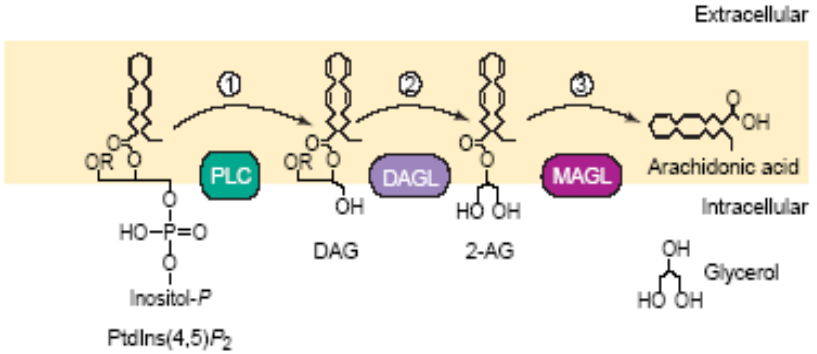
The Endocannabinoid System

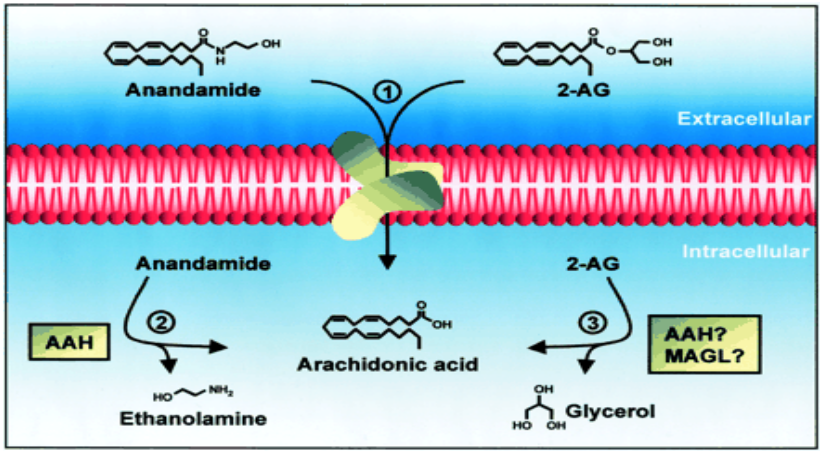


- Research initiated by efforts to elucidate the active substance of Cannabis (THC in 1964)
- First endogenous cannabinoid, “Anandamide” discovered in 1992 closely followed by “2-AG” in 1995
- FAAH identified as the key enzyme controlling the hydrolysis of fatty acid amides (FAAs):
  - AEA (anandamide) →Preferred substrate
    - The original endocannabinoid (CB1/CB2 agonist); weak TRPV1 agonist
  - PEA (palmitoylethanolamide)
    - Anti-inflammatory; analgesic; PPAR-α agonist
  - OEA (oleoylethanolamide)
    - Satiety; PPAR-α agonist; GPR119 agonist?
- Endocannabinoids and their receptors are widely expressed (CNS & PNS, organs, connective tissues, glands, and immune cells
- Whilst in each tissue, the endocannabinoid system performs different roles, their objective remains the same: homeostasis

The Endocannabinoid System

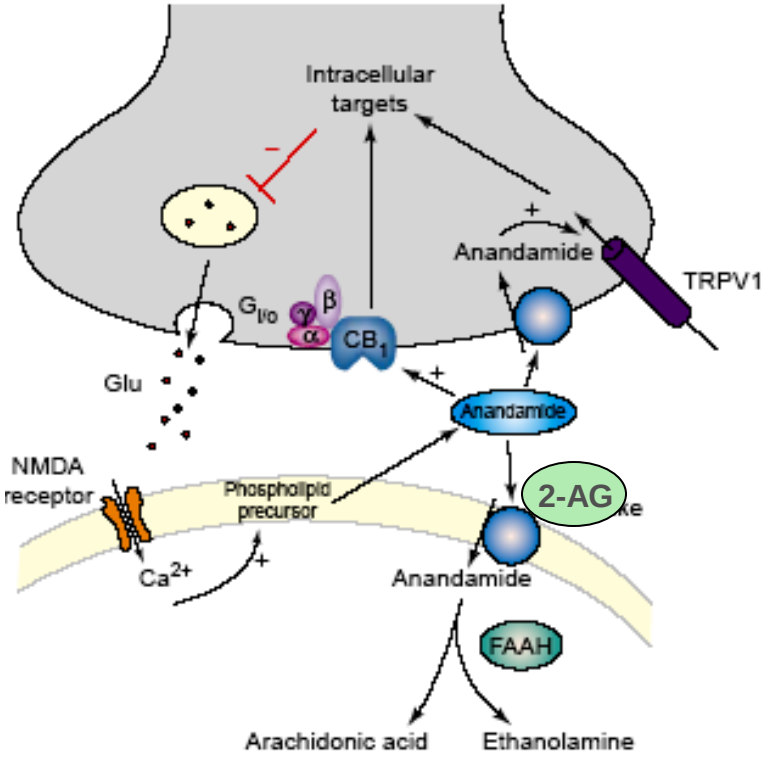






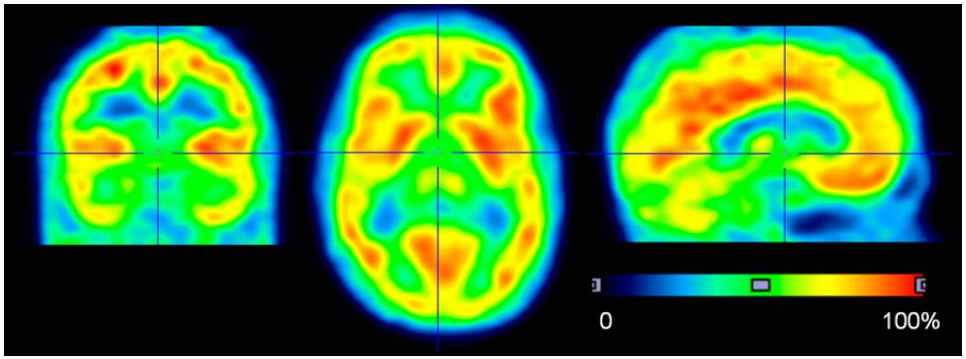
- **Fatty acid amides (FAAs) such as anandamide (AEA) are produced upon demand through activity dependent cleavage of membrane lipid precursors and are released from cells immediately after production.**
- **After release, AEA is rapidly eliminated through two separate mechanism: reuptake into cells and intracellular hydrolysis.**
- **AEA is metabolized by fatty acid amide hydrolase (FAAH)**

Anandamide Signaling in a Glutamate Synapse

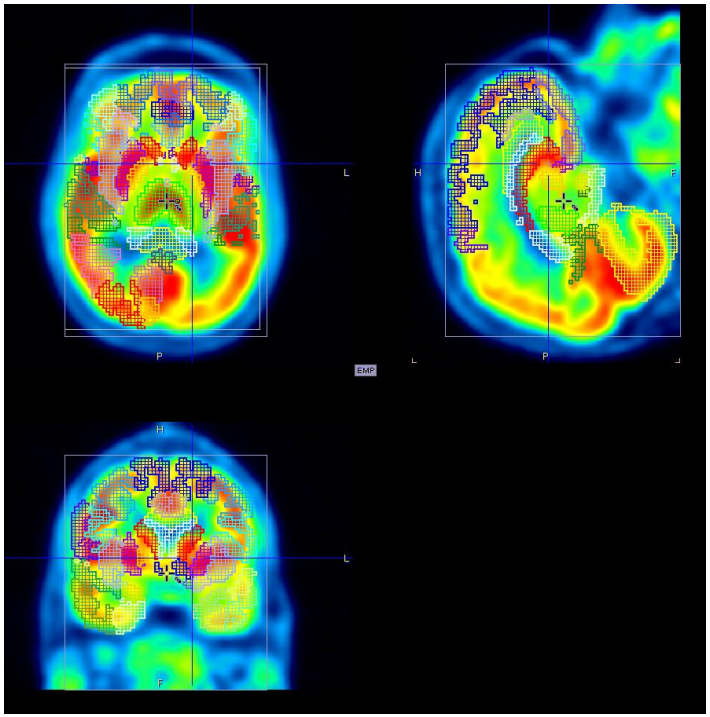


- **AEA is produced as a consequence of excitatory post-synaptic potentials**
- **Presynaptic CB_1 activation by FAAs decreases cAMP turnover, reduces activity of N-type Ca2+ channels, and enhances hyperpolarizing K+ currents**
- **This results in inhibition of glutamate release**

The Endocannabinoid System is Widely Distributed in the Brain

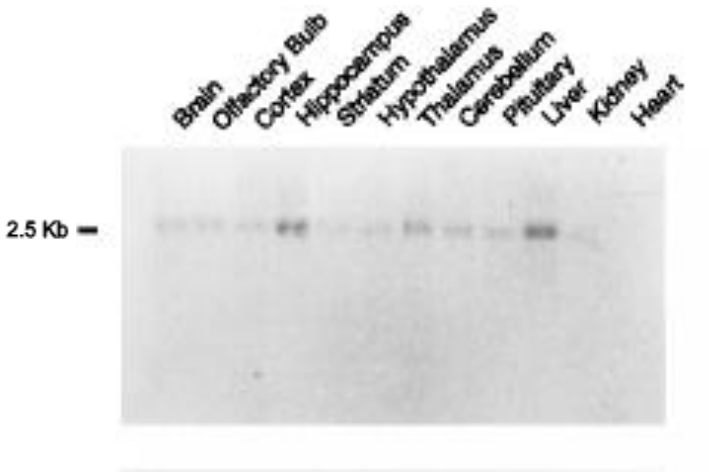


^{18}F-MK-9470 (CB1 inverse agonist)



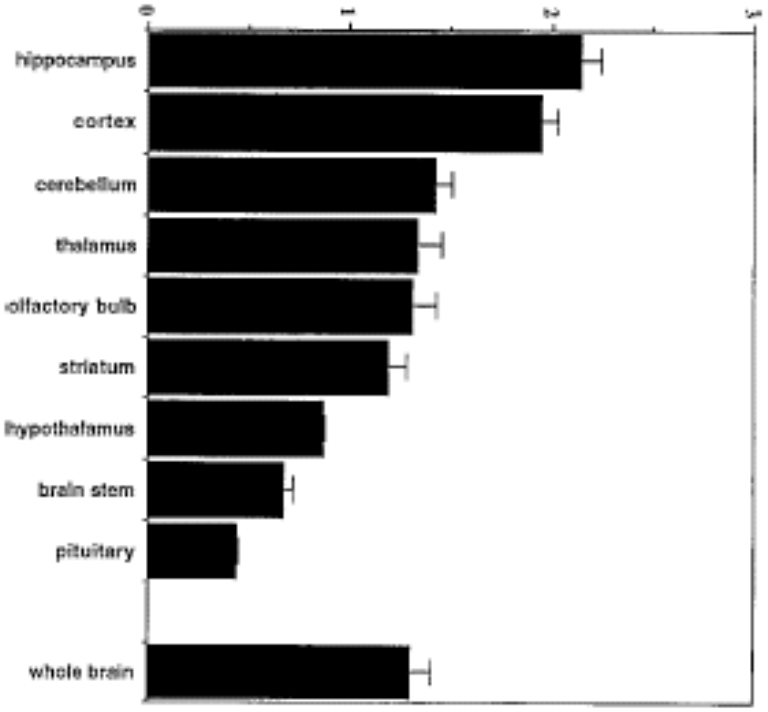
^{11}C-MK-3168 (FAAHi)

Distribution of FAAH in the Body and Brain



Northern blot of FAAH mRNA distribution in rat

- **FAAH is the principal clearance enzyme for fatty acid amides (AEA, OEA, PEA).**
- **FAAH is a membrane-bound enzyme that belongs to the serine hydrolases**
- **Expressed in human brain, liver, pancreas, kidney and skeletal muscle.**

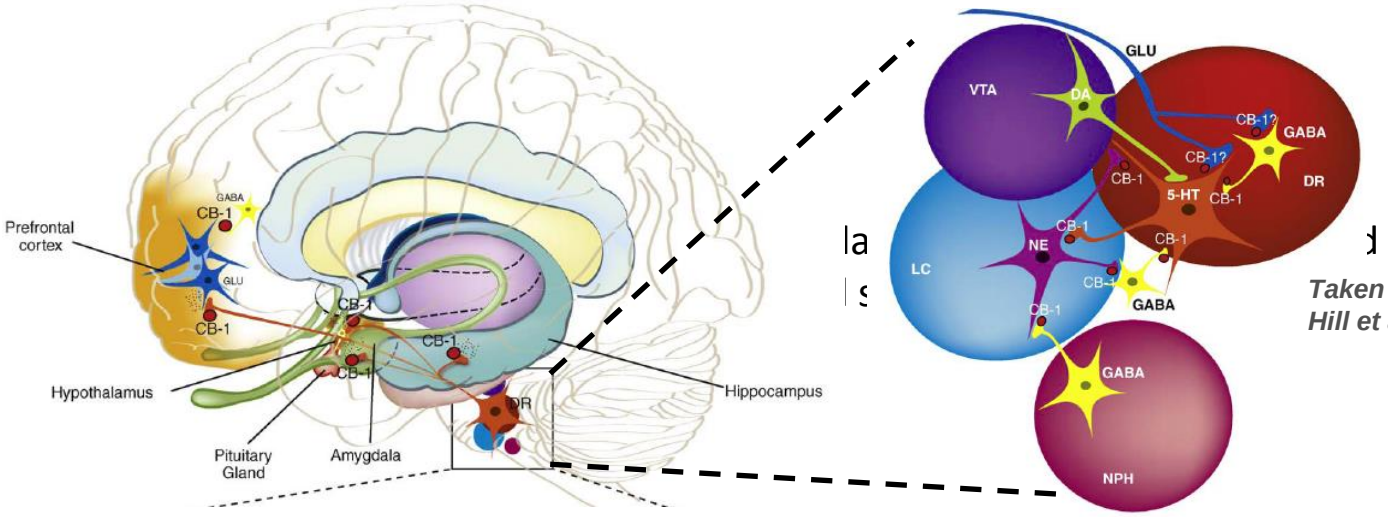


Distribution of FAAH activity in adult rat brain homogenates (hydrolase activity determined by conversion of 14C-labeled oleamide into 14C-Oleic acid during 60 min incubation in 37 min)

Thomas et al., J. Neurosci Res. 1997

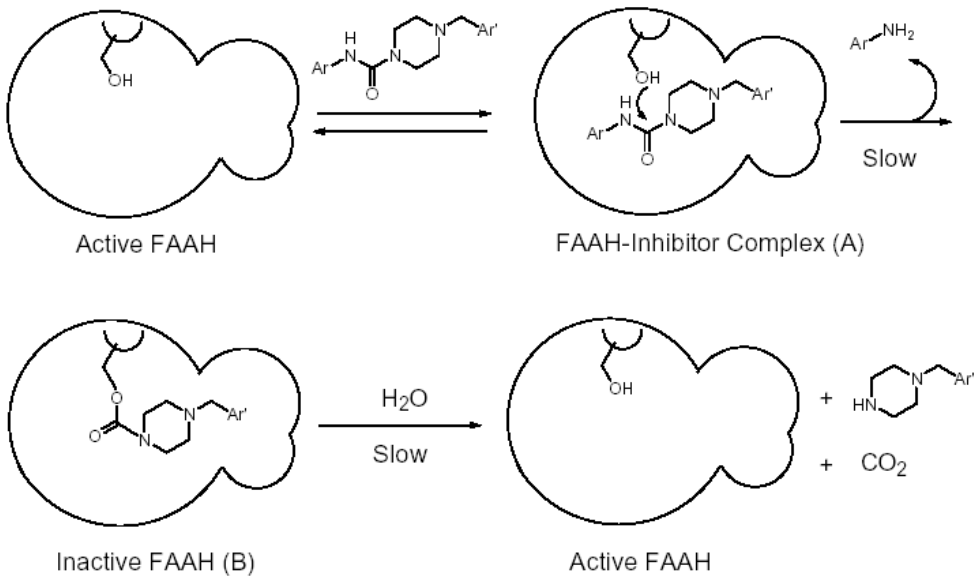
Role of the Endocannabinoid System in Stress, Mood and Anxiety

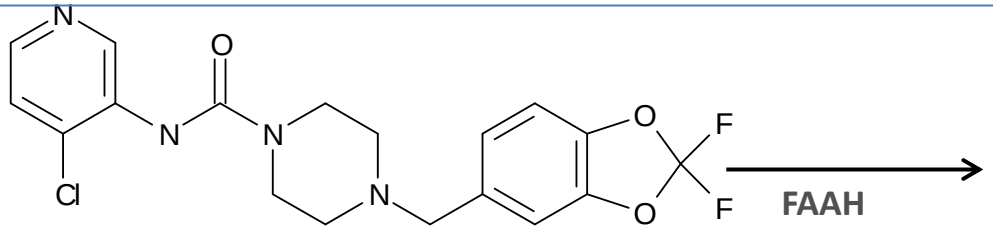
- Emotions are mediated by numerous brain structures, but the prefrontal cortex, amygdala and hippocampus are thought to form a key tri-nodal circuit key for emotion and mood
- CB_1 receptors are found in moderate to high levels throughout these regions, in addition to other forebrain limbic structures linked to mood and emotion
- Effects of [illegible] stress have pro[illegible]



Taken from:
Hill et al., 2009, TIPS

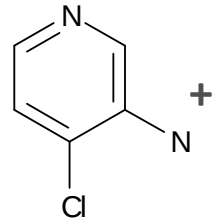
JNJ-42165279 is a Substrate for FAAH with a Slow Off-rate



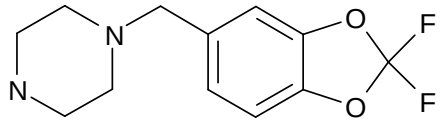


JNJ-42165279

FAAH



JNJ-42280667

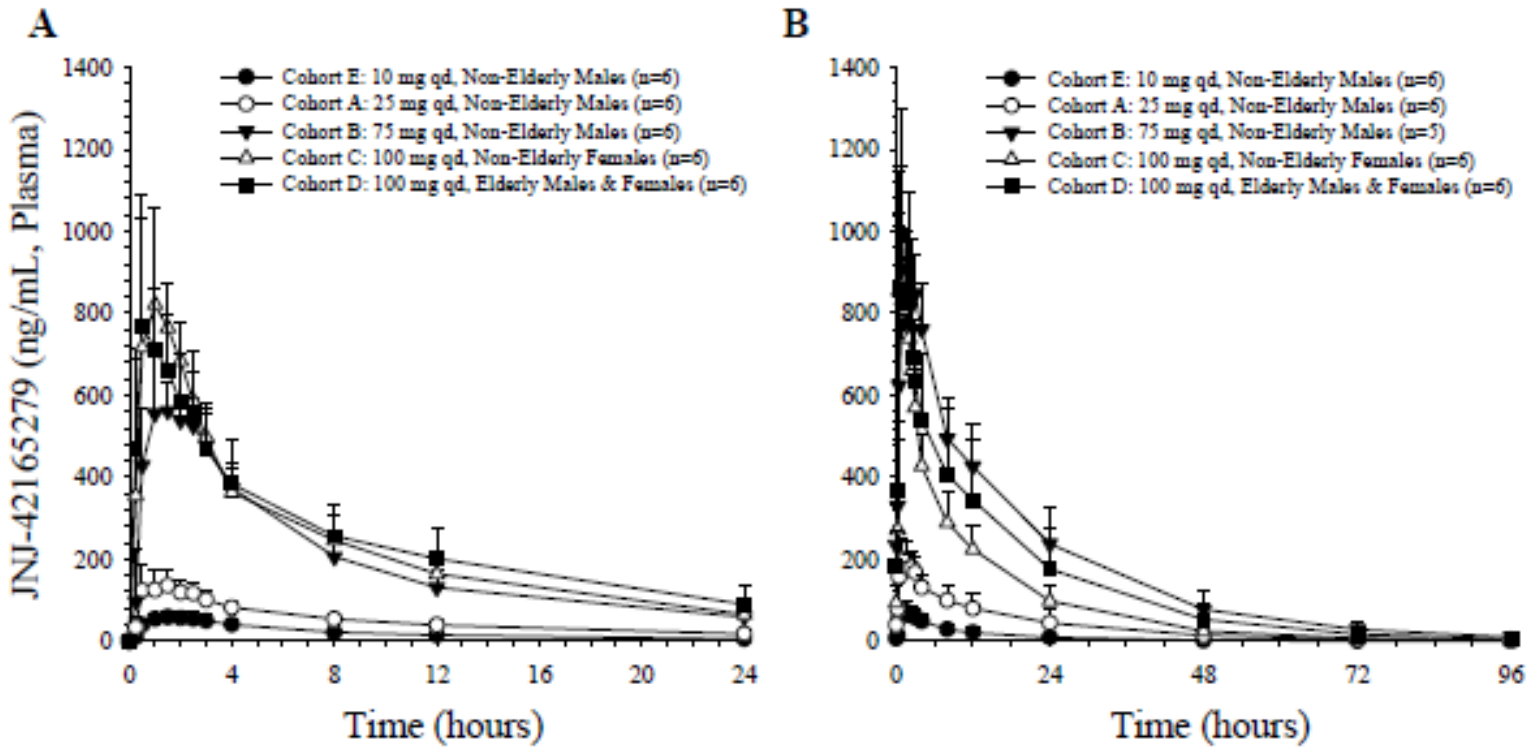


JNJ-39544258

Pharmacokinetic Profile after Repeat Dose

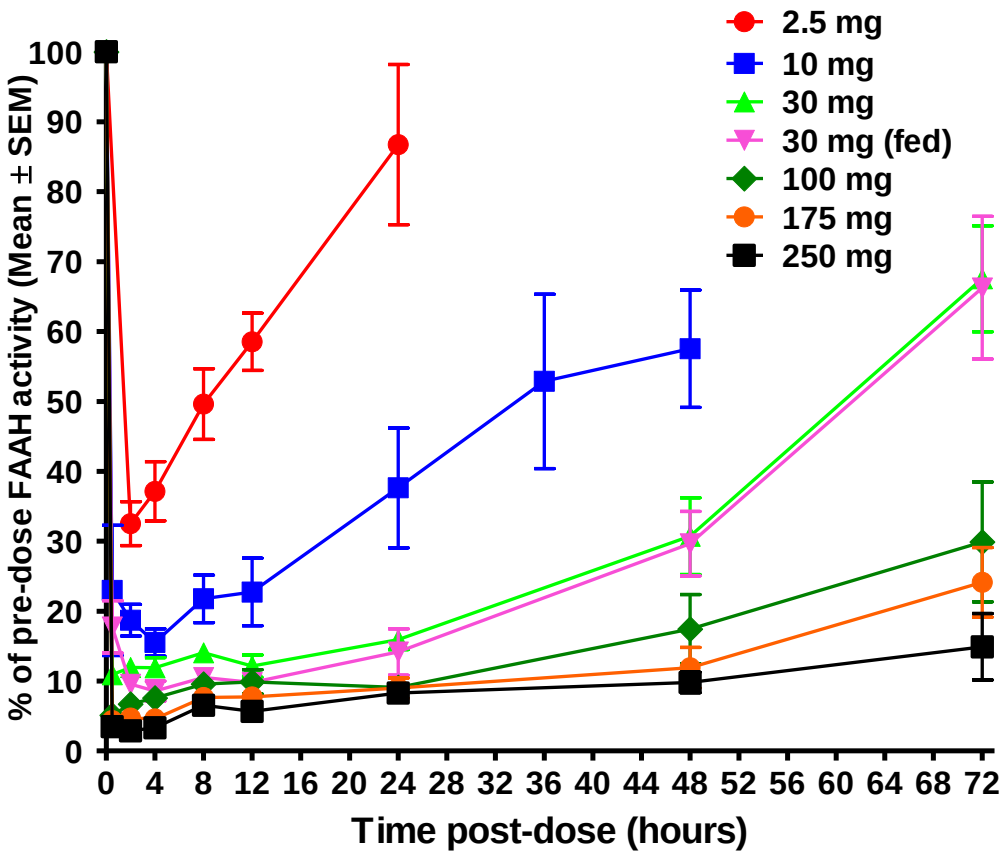
Figure 25: Arithmetic Mean (+SD) JNJ-42165279 Plasma Concentration-Time Profiles

(Study 42165279EDI1002: Pharmacokinetic Data Analysis Set)



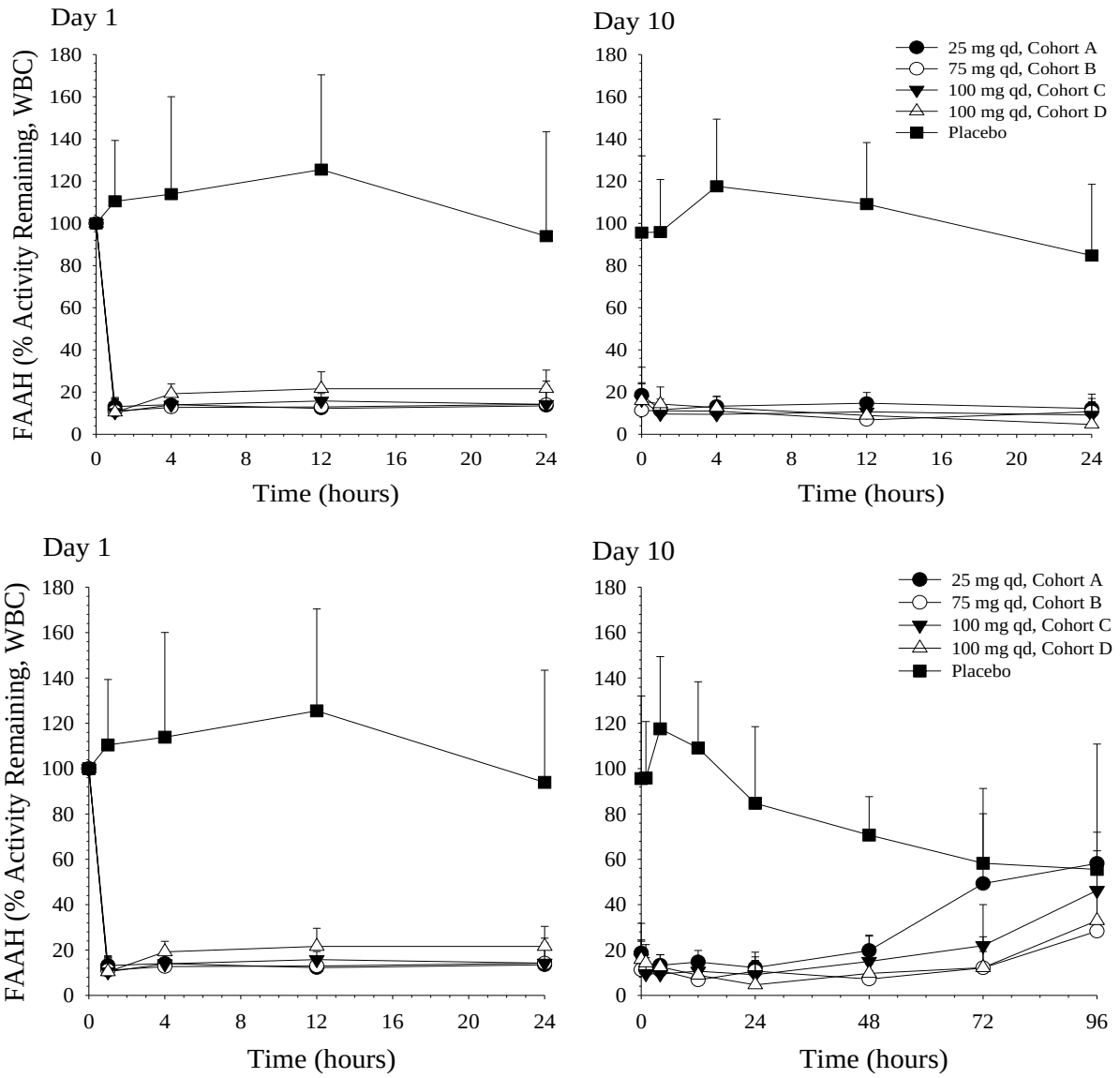
A: Day 1, 0 to 24 hours postdose; Day 10, B: 0 to 96 hours postdose

Rapid and Reversible Inhibition of WBC FAAH Activity* after Single-Dose

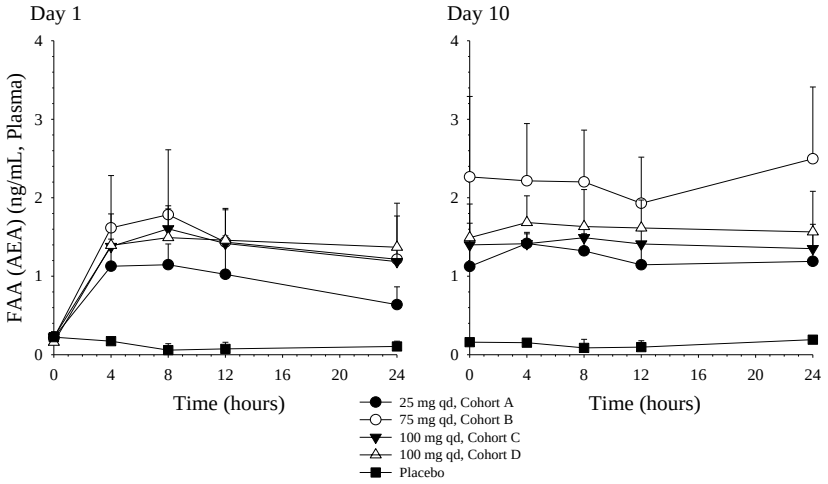


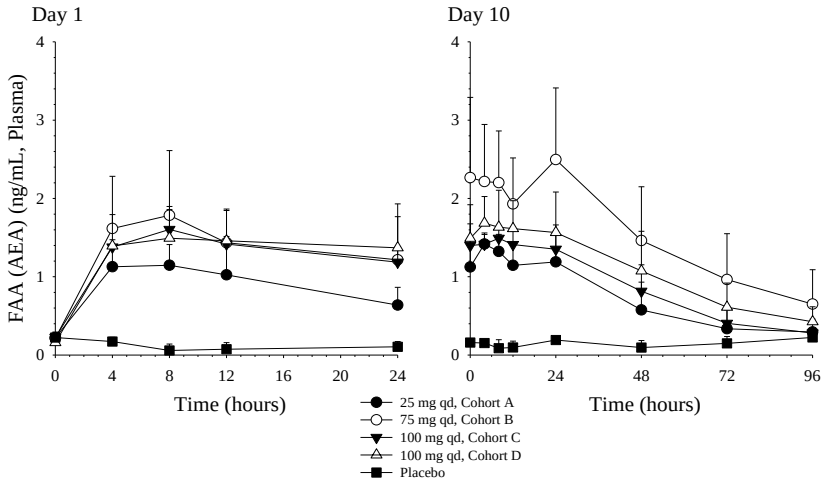
***Reported as percent FAAH activity remaining relative to predose values**

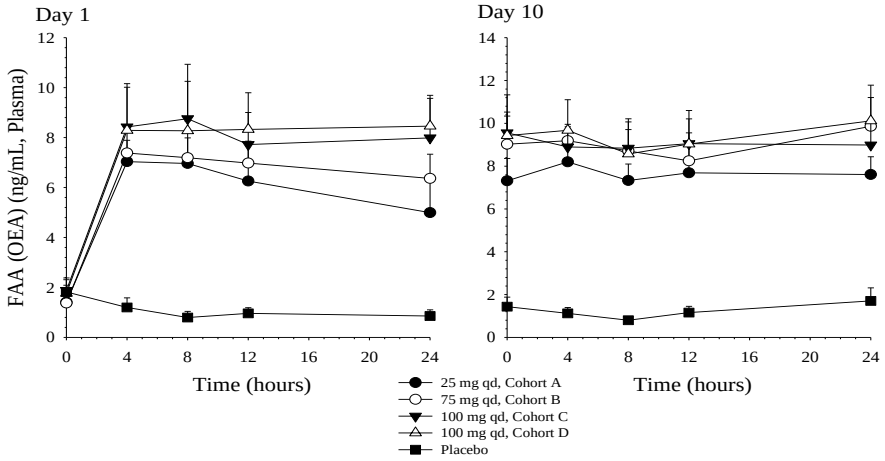
WBC FAAH Activity after Single Dose and at Steady State

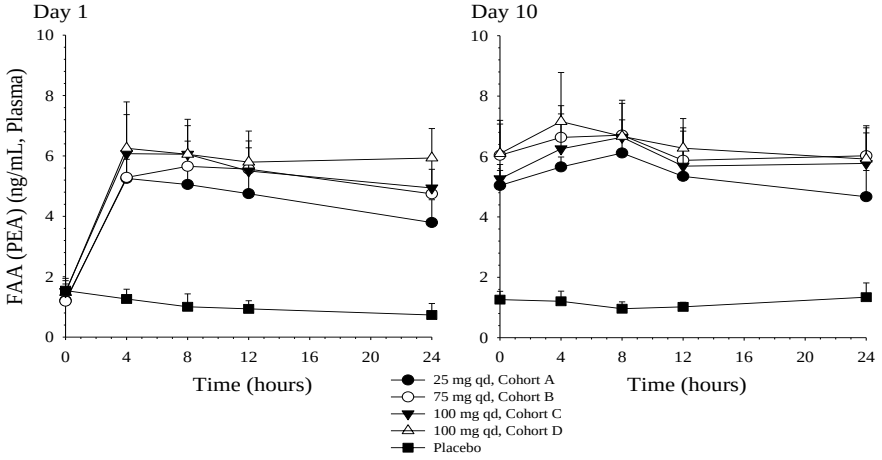


FAAs in Plasma after Single Dose and at Steady State









FAA Concentrations in CSF

OEA ng/ml 10mg qd

	D1	D7
N	6	6
Mean	21.16	139.24
SD	5.33	41.96
Min	13.3	75.1
Median	22.12	154.19
Max	26.5	182

OEA ng/ml 25mg qd

	D1	D7
N	6	5
Mean	20.2	117
SD	10.2	26.1
Min	7.84	91.4
Median	18.0	108
Max	35.0	159

OEA ng/ml 75mg qd

	D1	D7
N	6	5
Mean	20.2	150
SD	8.25	34.6
Min	9.56	114
Median	20.2	146
Max	32.6	186

AEA ng/ml 10mg qd

	D1	D7
N	3	6
Mean	0.56	12.57
SD	0.04	4.86
Min	0.5	4.8
Median	0.57	13.89
Max	0.6	18.1

AEA ng/ml 25mg qd

	D1	D7
N	6	5
Mean	0.522	21.2
SD	0.158	7.39
Min	0.346	13.8
Median	0.524	19.5
Max	0.711	32.3

AEA ng/ml 75mg qd

	D1	D7
N	6	5
Mean	0.377	28.9
SD	0.210	9.52
Min	BQL	14.5
Median	0.423	34.6
Max	0.607	35.9

PET Study of Dose Related Occupancy of FAAH by JNJ-42165279 in Human Brain

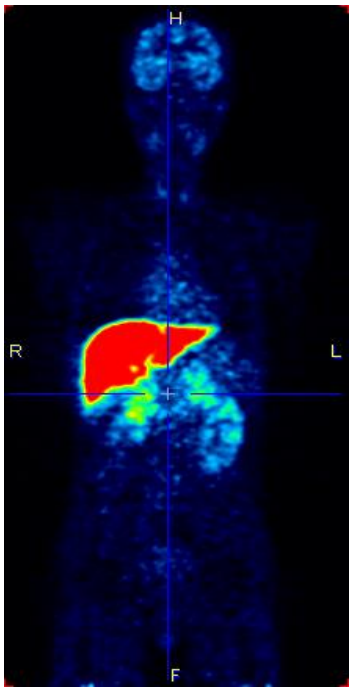
Objectives:

To measure enzyme occupancy by blocking of the retention of ^{11}C-MK-3168 in the human brain by pre-treatment with JNJ-42165279.

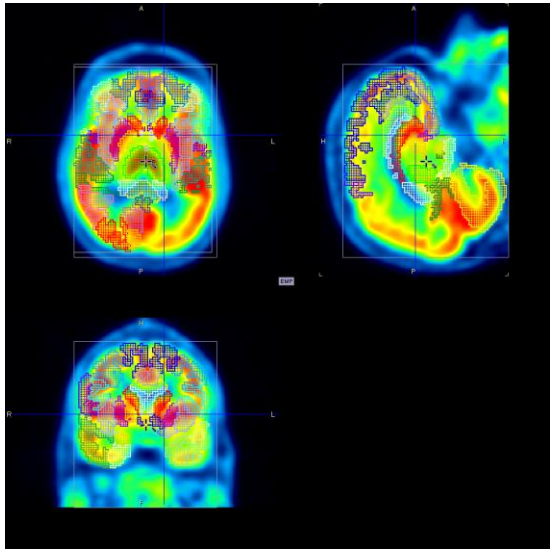
a) At t_{max} after a single dose

b) After multiple dose: at 24 hours after first dose and at steady state plasma levels of JNJ-42165279 at 24 hours after 7 once-daily doses of JNJ-42165279 (saturation).

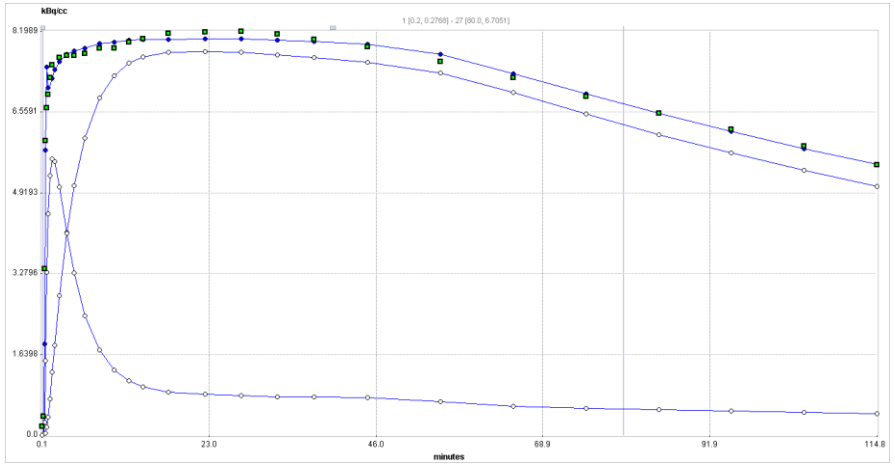
Distribution and Tissue Kinetics of ^{11}C-MK-3168



Biodistribution and metabolism of ^{11}C-MK3168

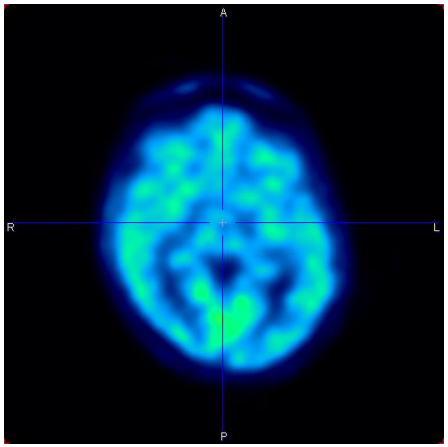


Brain activity summed from 2-30 minutes

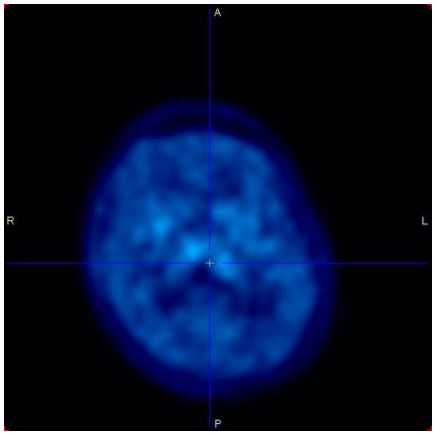


- Slow clearance results in little separation between free (k1/k2) and bound compartments (k3).
- Most robust kinetic parameters are Vt for 1T and 2T reversible models, and BP for 2T model with fixed k1/k2.
- Little regional difference in uptake and retention.
- Tracer metabolism is rapid
- No brain penetrant metabolites identified

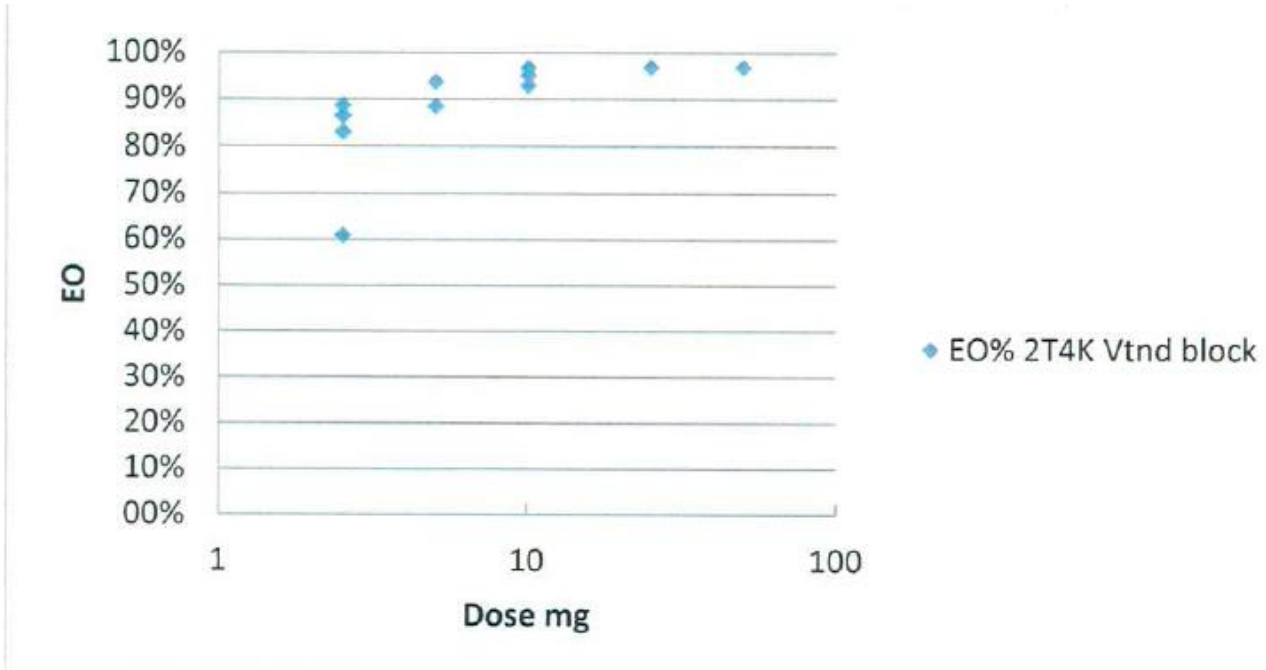
Retention of ^{11}C-MK-3168 after Single Dose



Baseline



After 10 mg JNJ279



Occupancy after Multiple Dose

	Dose	Day 1	Day 8
• Subject 1	2.5 mg	EO=56%	EO=57%
• Subject 2	2.5 mg	EO=44%,	EO=16%
• Subject 3	10 mg	EO=85%,	EO=86%
• Subject 4	10 mg	EO=80%	EO=82%

- Occupancy is sustained throughout the dosing interval with 10 mg
- No evidence of accumulation occurring with repeat lower doses

Inhibition of WBC FAAH in the PET study