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150
YEARS

The scourge of synthetic cannabinoids

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Scourge - “a person or thing that causes great trouble or suffering.”

The scourge of synthetic drugs

Otago Daily Times 2 Aug 2018 +3 more



SYNTHETIC cannabis is causing a spike in deaths in New Zealand, grabbing the attention of Cabinet, health officials, the police and the community at large.

Provisional figures from the coroner showed up to 45 people died from using synthetic cannabis in the year to June, compared with only two deaths in the previous five years.

Anyone witnessing the effects of the manufactured drug will be well aware of some of the awful side effects. A zombielike appearance, vomiting, convulsions, and death, are all part of the journey.

Deputy Prime Minister Winston Peters is calling for a multiagency response, acknowledging it needs to happen as fast as possible. Ministers of Health, Justice, Police and Customs are seeking coordinated advice from their respective agencies on how to urgently reduce the size and supply of the drug.

No solutions have yet been found to implement a turnaround or victory against the people who are peddling

the drug.

The Institute of Environmental Science describes synthetic cannabis as a smokable, dried plant material adulterated with one or more chemical compounds added, known as synthetic cannabinoids. The plant material itself has no psychoactive effect. The active ingredients in synthetic cannabis are not natural compounds, instead manufactured in a laboratory.

It is a lottery which ingredients are included in the synthetic drug. The users will not know which of the many synthetic cannabinoids are present in the plant material and the same packaging does not mean the same cannabinoid is included.

National MP Simeon Brown has a private member's Bill which seeks to increase the maximum jail sentence for selling or supplying synthetic drugs from two years to eight years. This will give police stronger powers to crack down on suppliers and help deter drug dealers in New Zealand from selling these harmful substances, he says.

As well-meaning as Mr Brown is, increasing the maximum jail sentence is ill-directed and will make no dent at all in the supply and use of these dangerous substances.

The National Drug Intelligence Bureau report paints a grim picture of the situation. The synthetic drug is cheap and easy to manufacture, and easy to buy. It rivals P in the ease in which it is manufactured and supplied.

Gangs are said to be associated with the main supply of the drug and the main centres for distribution are said to be Auckland, Wellington and Christchurch.

It is not unlikely Dunedin, Invercargill and Queenstown in particular, have synthetic cannabis available for sale and use.

Any law change needs to put the onus for harm caused directly on suppliers — if they can be found. Changing laws to prevent certain ingredients being included in the manufacture of synthetic cannabis will mean a return to the days of party pills — when one ingredient is removed, another is substituted.

A cheap drug epidemic in New

Related Stories

Synthetic drug deaths hit 45
Otago Daily Times 31 Jul 2018

Synthetic drug deaths worry Govt
The New Zealand Herald 31 Jul 2018

Call to regulate 'lower risk' drugs
Otago Daily Times 2 Aug 2018

Zealand is the last thing anyone wants to see happen. Unfortunately, the nature of the industry relies on people becoming hooked on a cheap and easy-to-find supply.

Authorities will have their work cut out to find a way to stop the supply from overseas of the cannabinoids. Already, police are describing the method of distribution as a “scattergun” approach, similar to what was experienced with the influx of Contact NT — a drug manufactured from a cold and flu remedy before the introduction of methamphetamine.

ESR says it is developing a platform for a national drug monitoring and surveillance system to tackle the wave of synthetic drugs coming into the country. Although the detection of synthetic cannabinoids is complex because of the continual emergence of new varieties, work in stopping the supply of these dangerous substances needs to start immediately.

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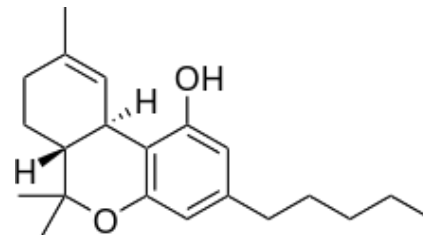




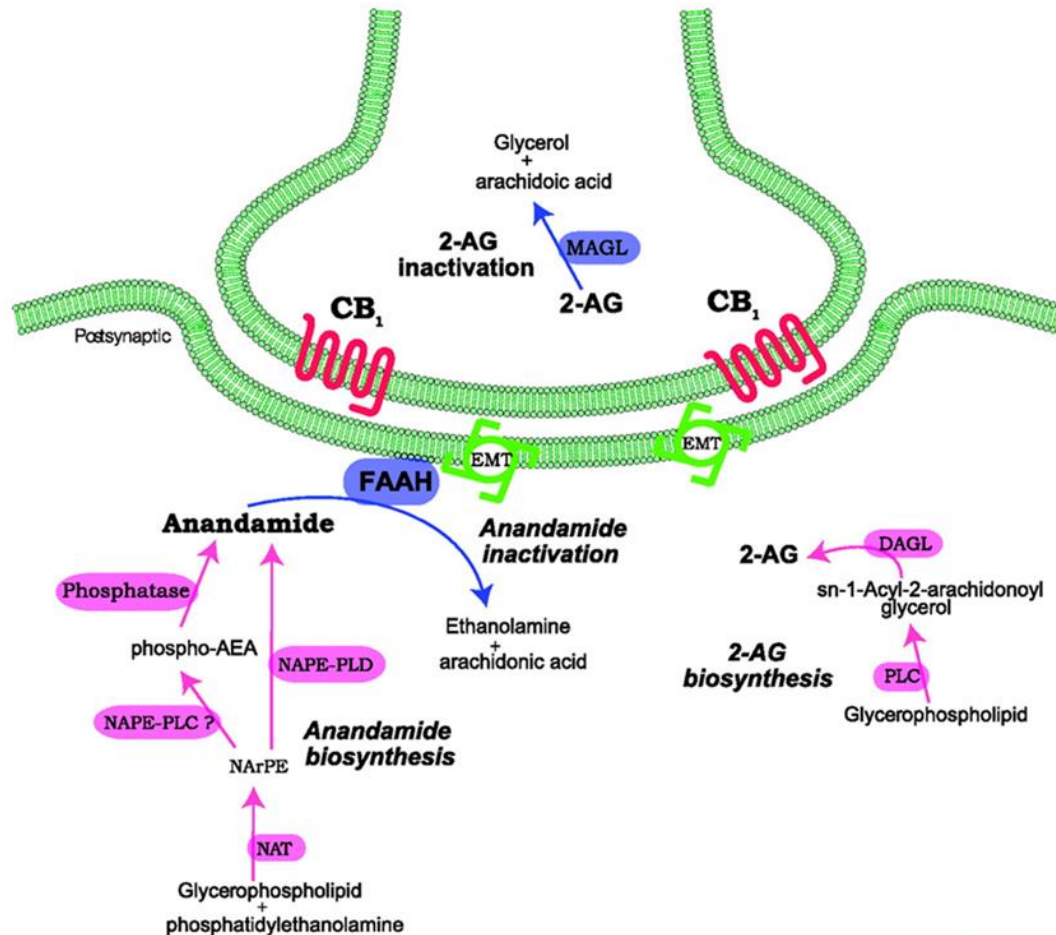
Cannabis



- THC was identified as major psychoactive substance in cannabis (1964)
- Brain cannabinoid receptor (CB1) cloned (1990)
 - discovery of the endocannabinoid system



Images: wikipedia



Pál Pacher et al. Pharmacol Rev 2006;58:389-462

CB1 in the brain and peripherally.
CB2 predominantly in immune cells

Endocannabinoid system thought to be involved in:

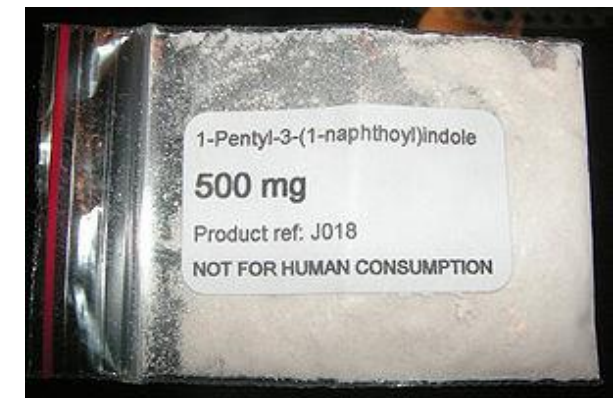
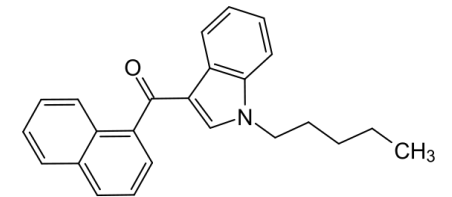
- Pain
- Appetite regulation
- Learning and memory
- Anxiety
- Thermoregulation
- Metabolism
- fertility



What about the synthetics....

- “Spice” on sale around the world since 2002.
- Marketed as a “herbal high” apparently containing:
 - Baybean, Blue Lotus, Lion's Tail, Lousewort, Indian Warrior, Dwarf Scullcap, Maconha Brava, Pink Lotus, Marshmallow, Red Clover, Rose, Siberian Motherwort, Vanilla, and Honey (Silver Spice)
- Dec. 2008; German pharmaceutical company THCPHarm, found the synthetic cannabinoid JWH-018 in 3 versions of Spice.
- Drugs are bought as powder, dissolved in solvent and sprayed onto dry plant material
- Over the next few years a range of other synthetics molecules appeared – now over 240 reported worldwide

JWH-018



Home > Business > Dairies say no to synthetic drugs



Business Nelson Weekly News

Dairies say no to synthetic drugs

By Nelson Weekly - May 15, 2013

456



Nelson police have begun a campaign to rid the region's dairies of synthetic drugs, slamming them as "morally wrong" and urging locals to boycott stores that continue to sell them.

"These drugs may technically be legal, but that doesn't make them safe. Retailers may say they are doing nothing wrong, but in my view it is morally wrong to be preying on the young people in our community and making money by selling them addictive and extremely harmful drugs."

"My officers will be encouraging retailers to think about their responsibilities, not just as business people, but as members of this community."

Nelson Bays area commander, Inspector Steve Grealley



Psychoactive Substances Act 2013

Purpose

- The purpose of this Act is to regulate the availability of psychoactive substances in New Zealand to protect the health of, and minimise harm to, individuals who use psychoactive substances.

Principles

- (a) a psychoactive product that is approved for use by individuals should pose *no more than a low risk of harm* to individuals who use it:
 - If proven, then it could be sold, but the act also puts significant restrictions in place as to where it could be sold and who it could be sold to (R18).

Legal Poison...

- Interim legislation allowed some compounds to stay on sale while they went through “testing”
- Public backlash against effect of outlets on community

Opponents beg for ban on 'legal poison'

By news@dailypost.co.nz, Lydia Anderson

The New Zealand Herald



The New Zealand Herald

Government to ban all legal highs within two weeks

By [Isaac Davison](#) @Isaac_Davison
4:29 PM Sunday Apr 27, 2014

The Government will ban all synthetic drugs within two weeks until they can be proven to be low-risk, Associate Health Minister Peter Dunne has revealed.

The move comes as Labour plans to announce its own policy on psychoactive substances tomorrow, and follows increasing protest from local communities against legal highs.

Mr Dunne told the Herald this afternoon: "Last Tuesday, Cabinet agreed on a proposal from me to introduce legislation under urgency when Parliament resumes to remove the remaining 41 products from the shelves until such time as their low-level of risk can be proven."

Public pressure also lead to a ban on animal testing in proving
“no more than a low risk of harm”

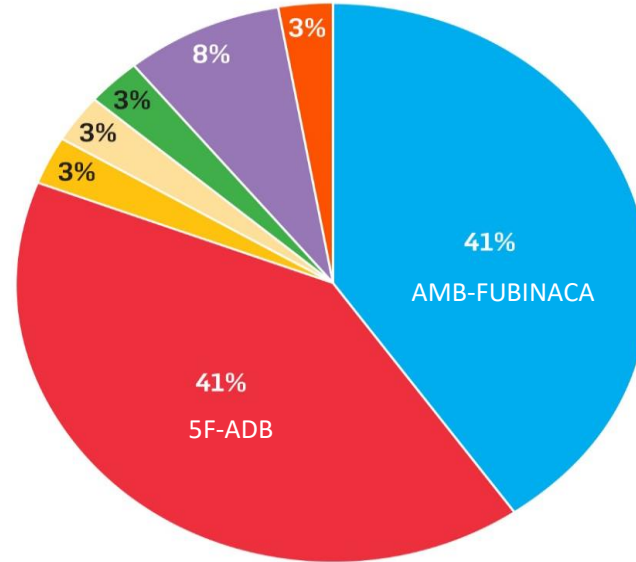
- Section 4(f): inserted, on 8 May 2014, by Psychoactive Substances Amendment Act 2014 (2014 No 24).

(f) animals must not be used in trials for the purposes of assessing whether a psychoactive product should be approved.

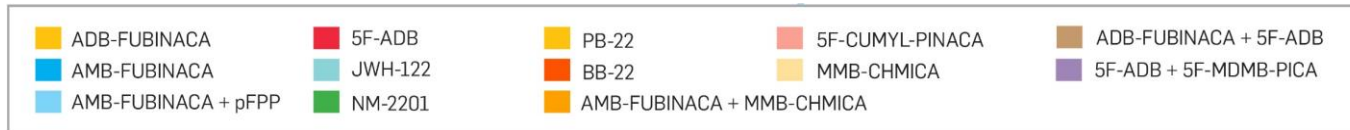


What is happening in NZ ...

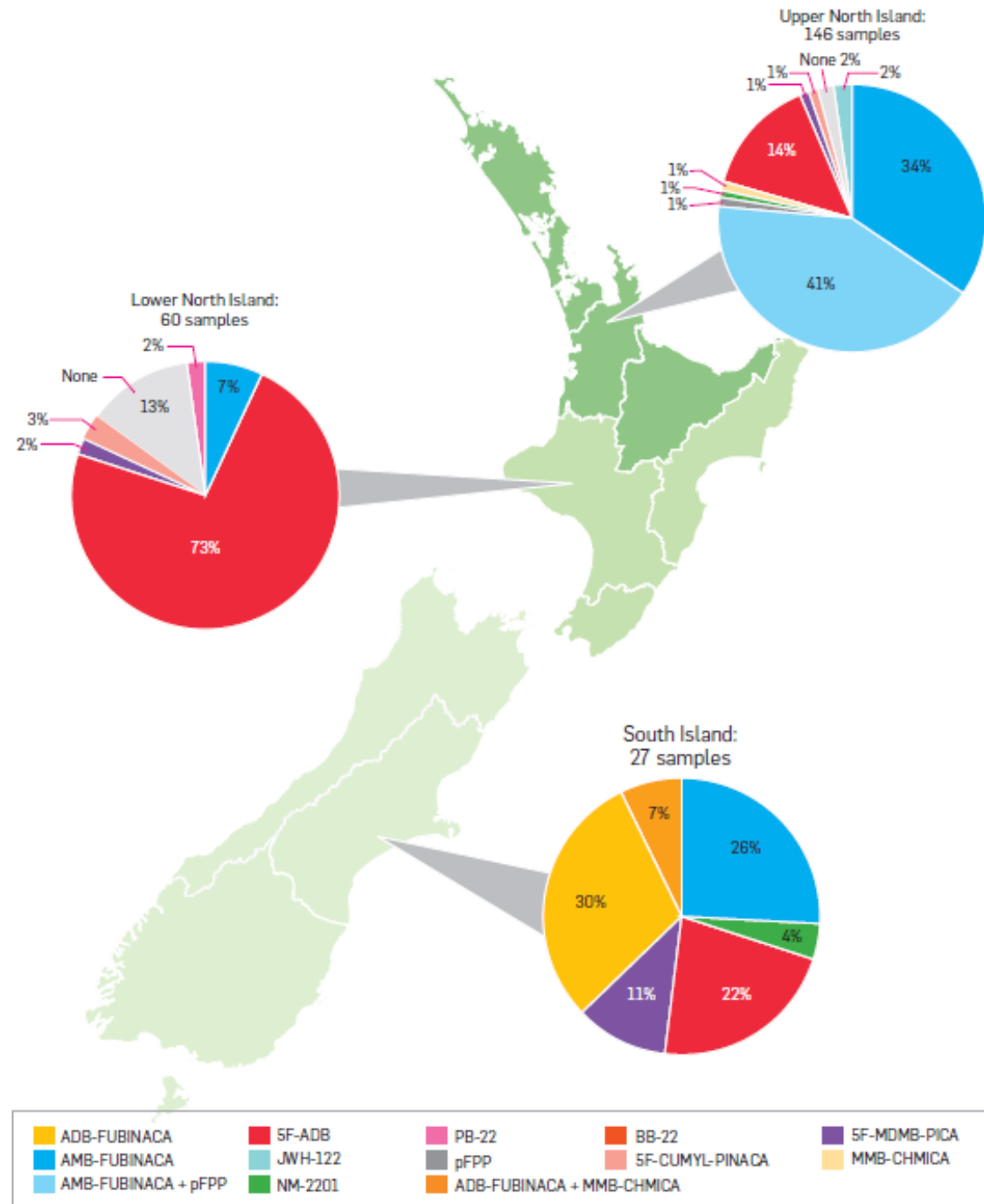
Border seizures – 2017



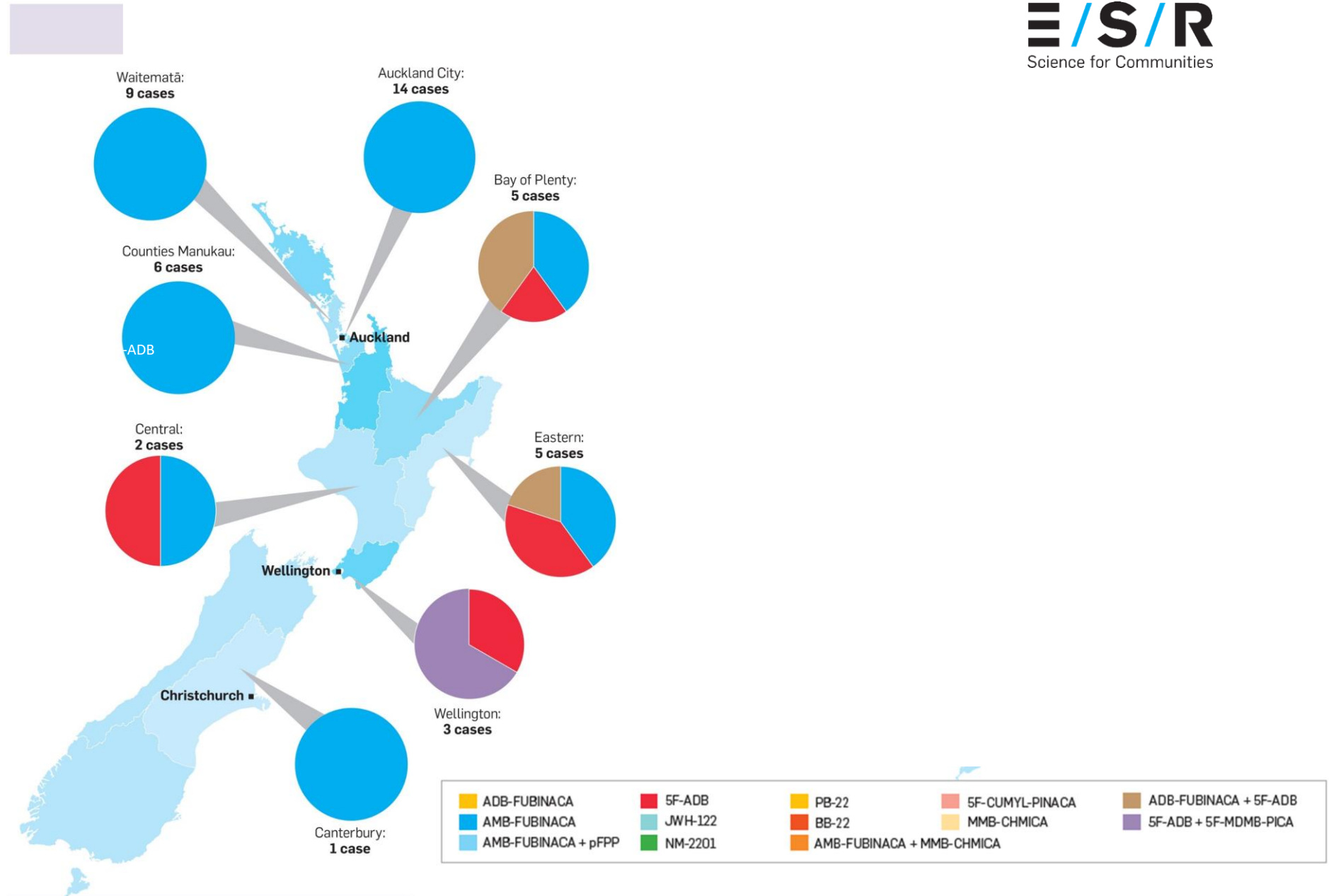
Border seizures



Geographical distribution - Police seizures



Geographical distribution - Coronial deaths



ORIGINAL ARTICLE

“Zombie” Outbreak Caused by the Synthetic Cannabinoid AMB-FUBINACA in New York

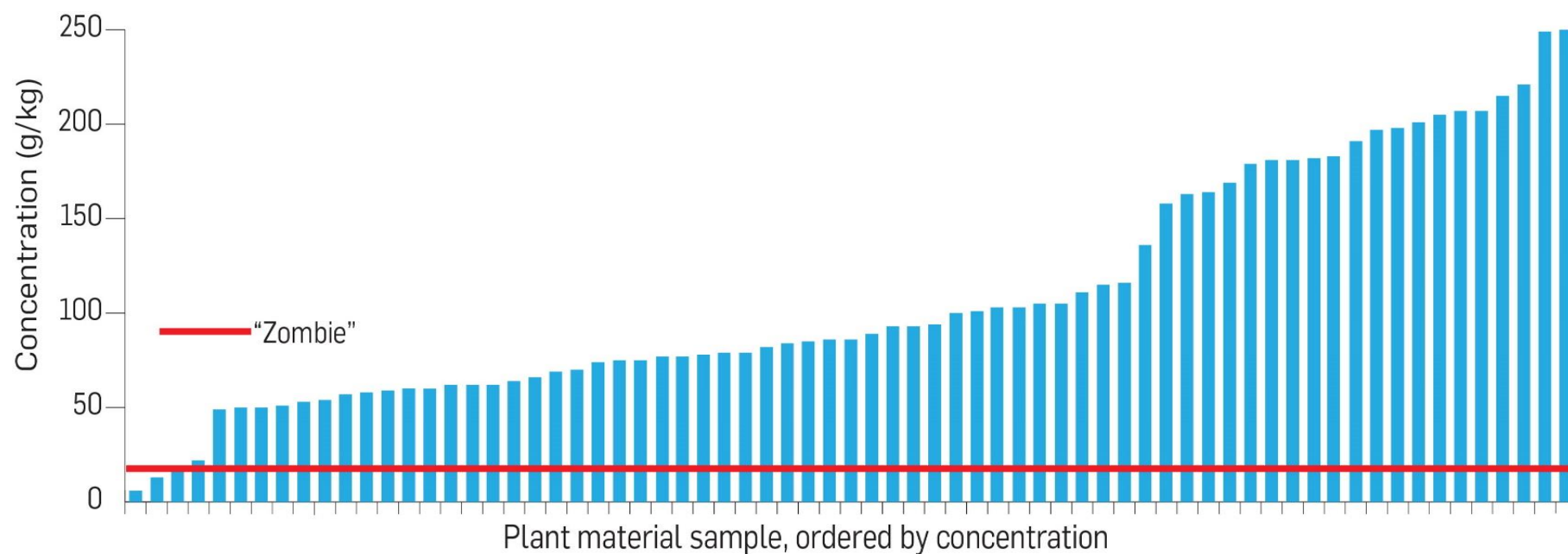
Axel J. Adams, B.S., Samuel D. Banister, Ph.D., Lisandro Irizarry, M.D., Jordan Trecki, Ph.D., Michael Schwartz, M.D., M.P.H., and Roy Gerona, Ph.D.

ABSTRACT

BACKGROUND

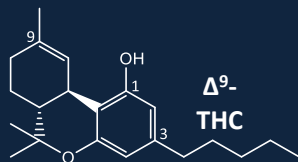
New psychoactive substances constitute a growing and dynamic class of abused drugs in the United States. On July 12, 2016, a synthetic cannabinoid caused mass intoxication of 33 persons in one New York City neighborhood, in an event described in the popular press as a “zombie” outbreak because of the appearance of the intoxicated persons.

Plant material – concentration of AMB-FUBINACA

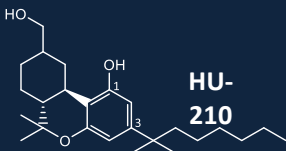


Synthetic Structures

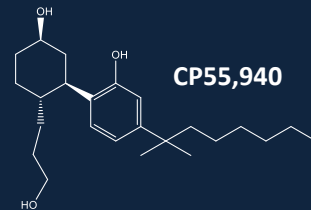
Classical



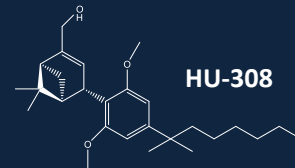
- Dihydrobenzopyra n-type structure
- Dimethylheptyl derivatives



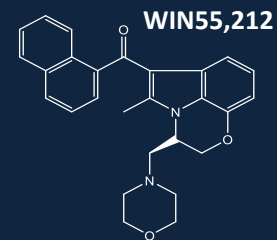
Non-Classical



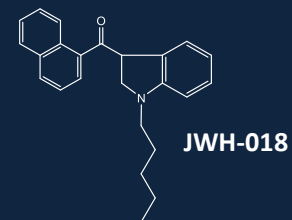
- Lack of dihydropyran ring
- Increased potency



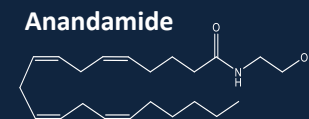
Aminoalkylindole



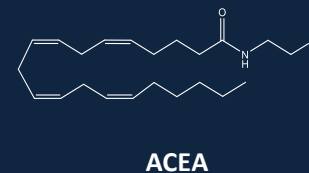
- Morpholinoethyl groups and aromatic rings



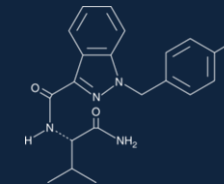
Eicosanoid



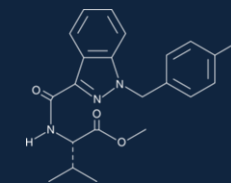
- Substitutions of amide group



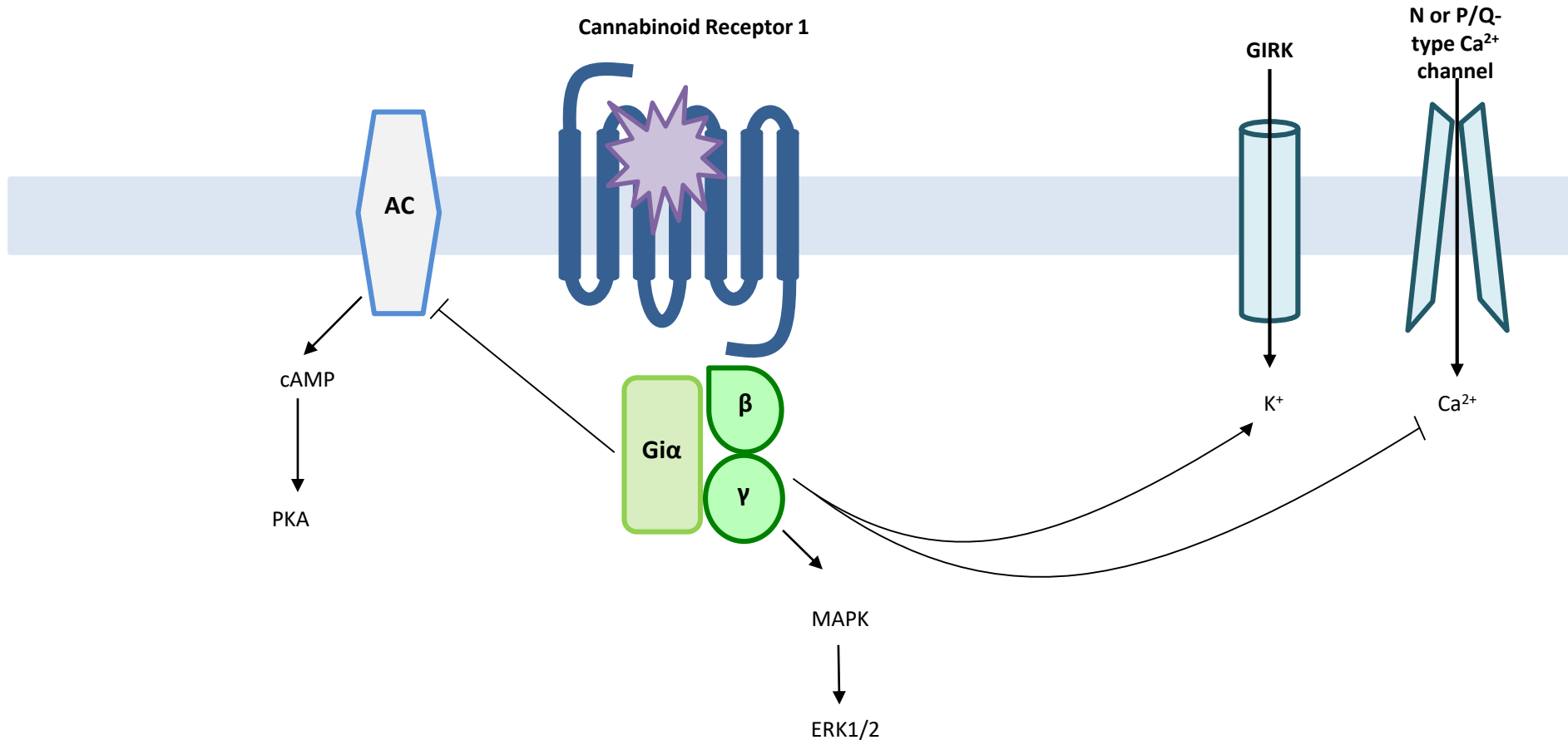
Novel



- Indazole-derived

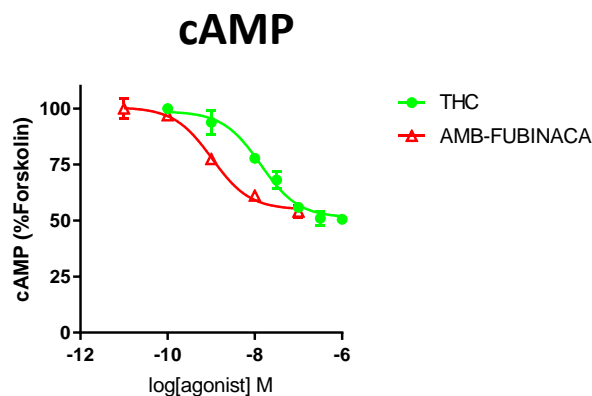


What do the synthetics do at the receptor compared to THC?



AMB-FUBINACA

CB1 vs [3H]CP55,940 – pKi 8.7 ± 0.06 (2nM)
 CB2 vs [3H]CP55,940 – pKi 8.91 ± 0.05 (1.2nM)

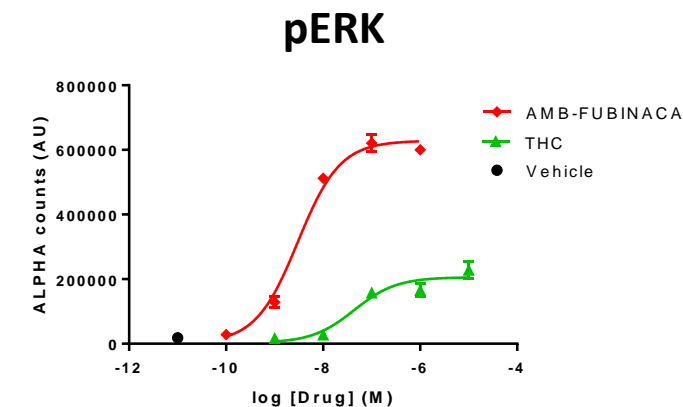


AMB pEC50 8.9 ± 0.09 (1.3nM) (n=4)

THC pEC50 7.7 ± 0.17 (19nM) (n=5)

THC

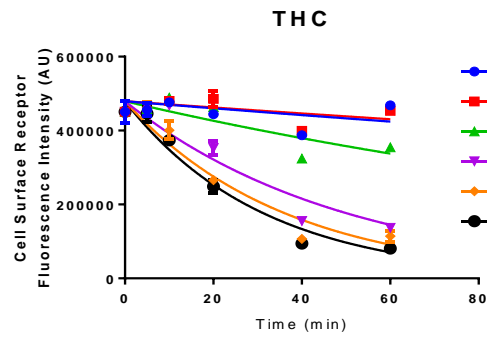
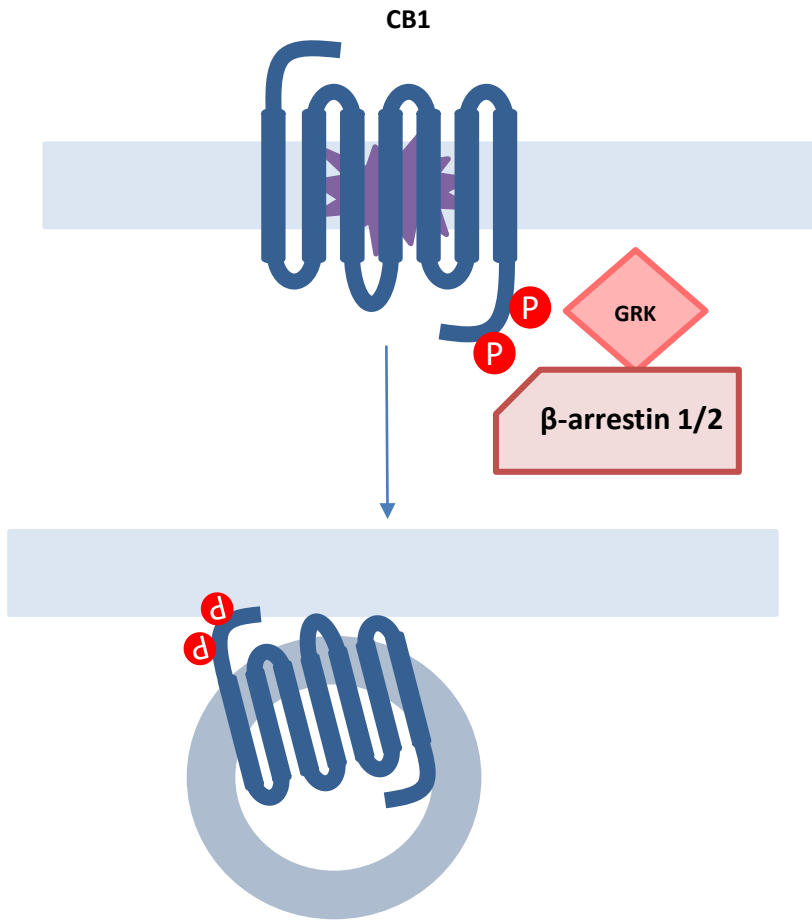
CB1 vs [3H]CP55,940 – pKi 7.3 ± 0.03 (50nM)
 CB2 vs [3H]CP55,940 – pKi 7.0 ± 0.04 (100nM)



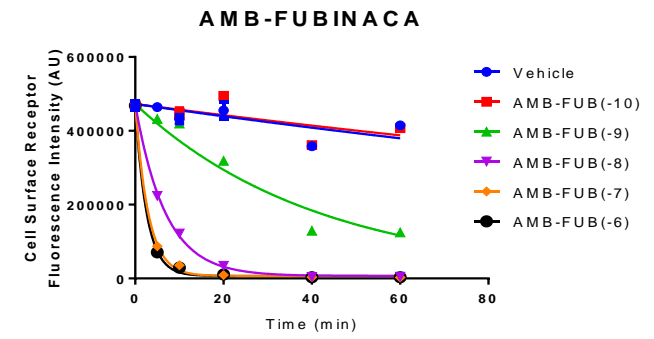
pEC50 8.7 ± 0.1 (2nM) Emax = 100% n=5

pEC50 7.4 ± 0.1 (40nM) Emax $\approx 30\%$ n = 5

Internalisation of the receptor

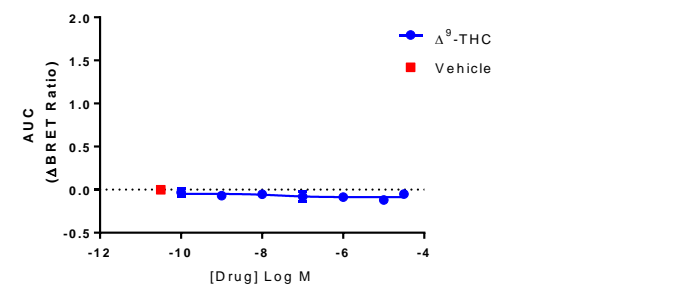
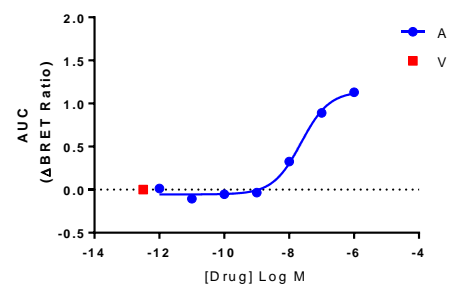
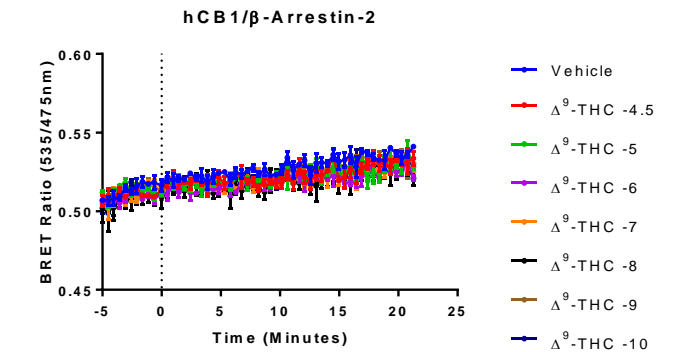
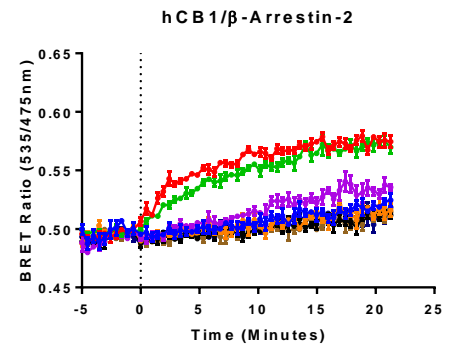
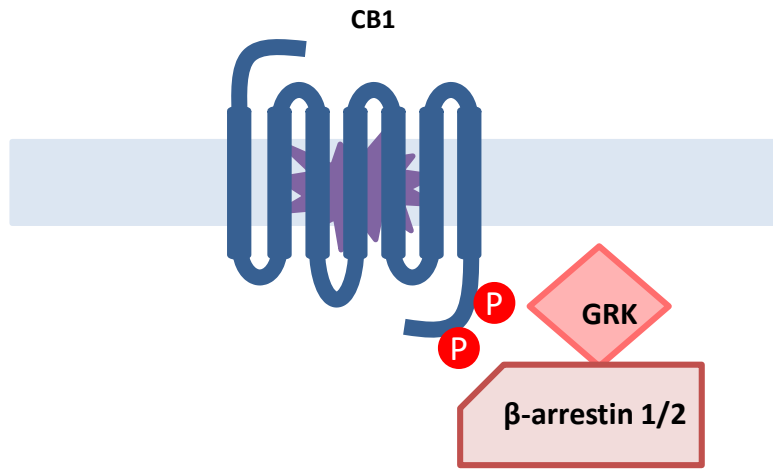


$T_{1/2} = 17.3 \pm 2.4$ min



$T_{1/2} = 2.4 \pm 0.3$ min

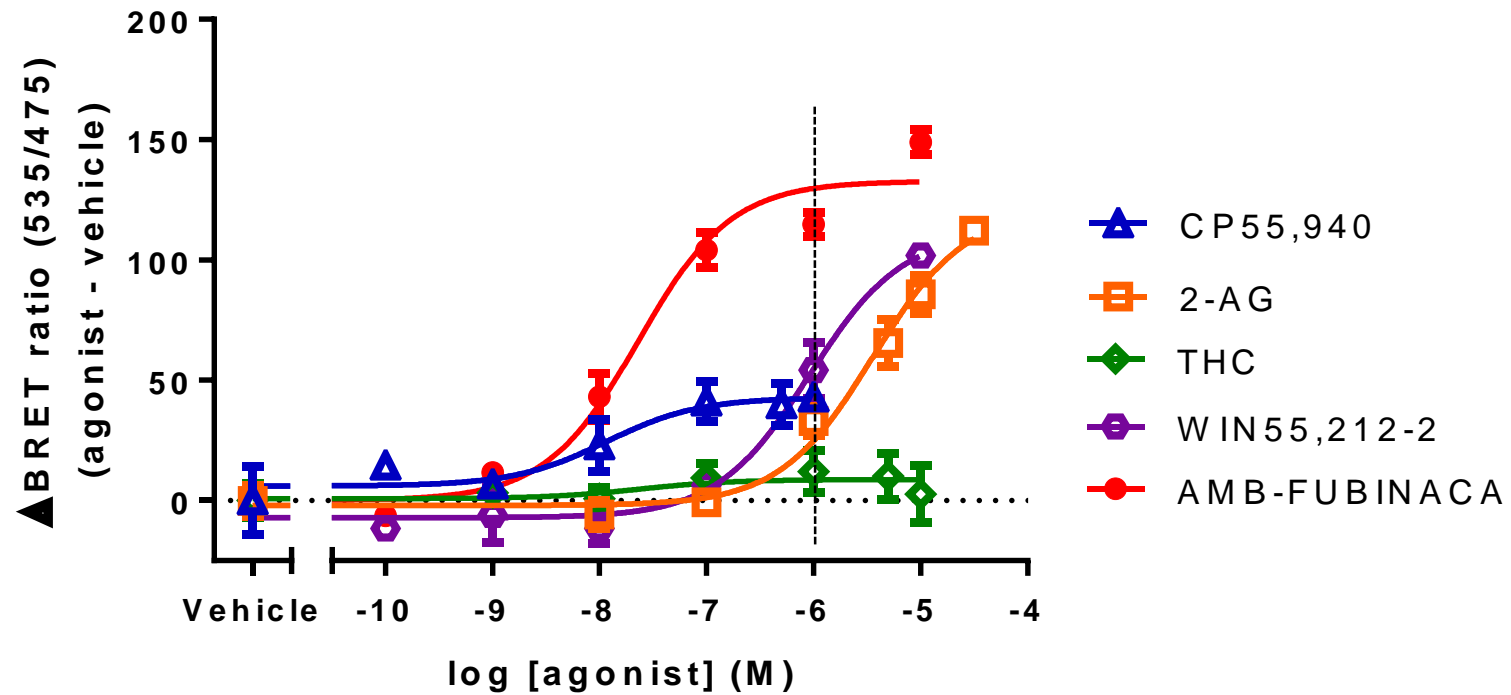
β-arrestin-2 recruitment



pEC50 7.7 ± 0.08 (20nM)
 N=5

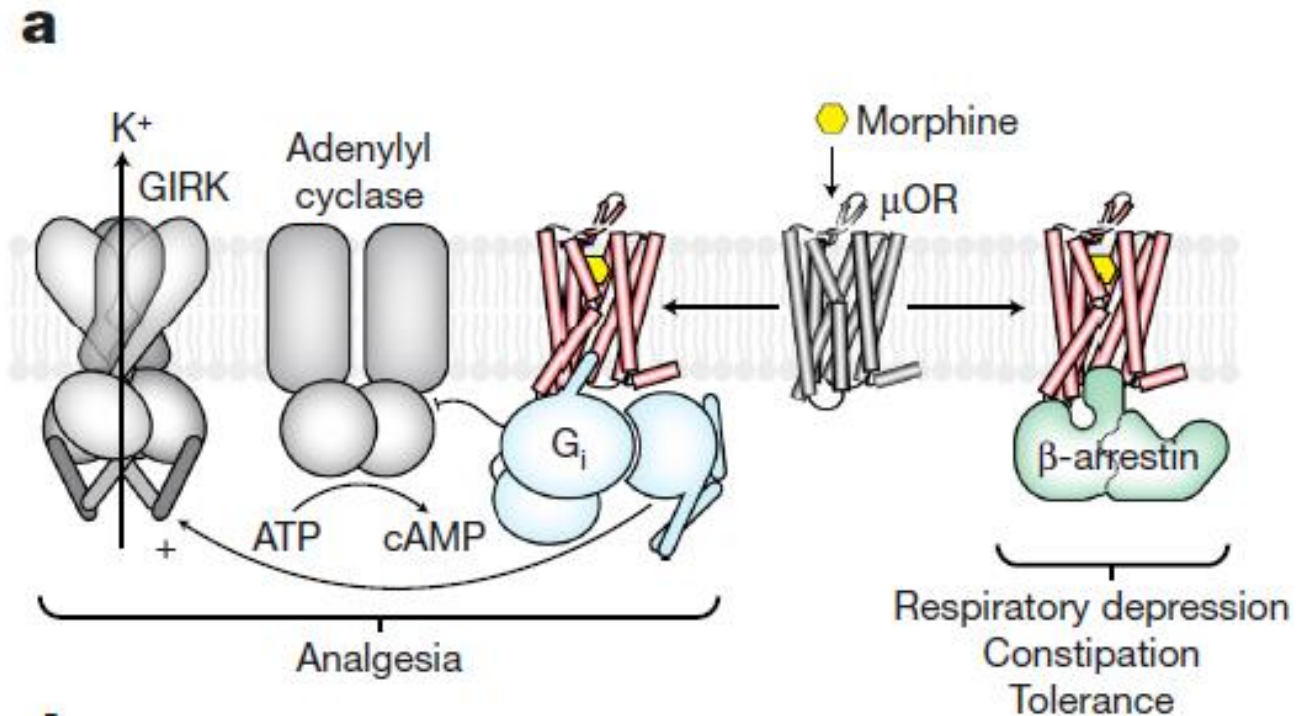
What about other cannabinoids?

β -arrestin 2

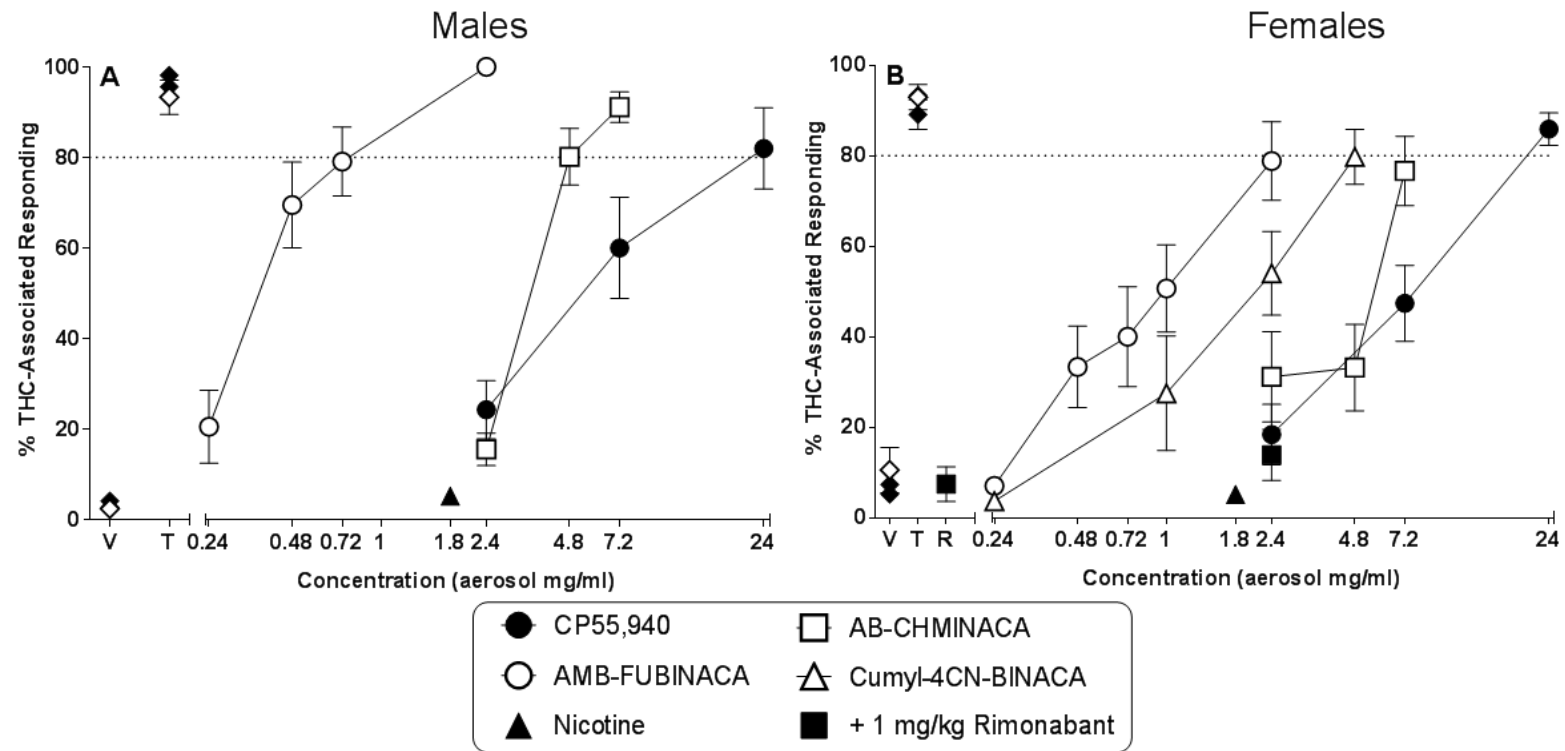


Structure-based discovery of opioid analgesics with reduced side effects

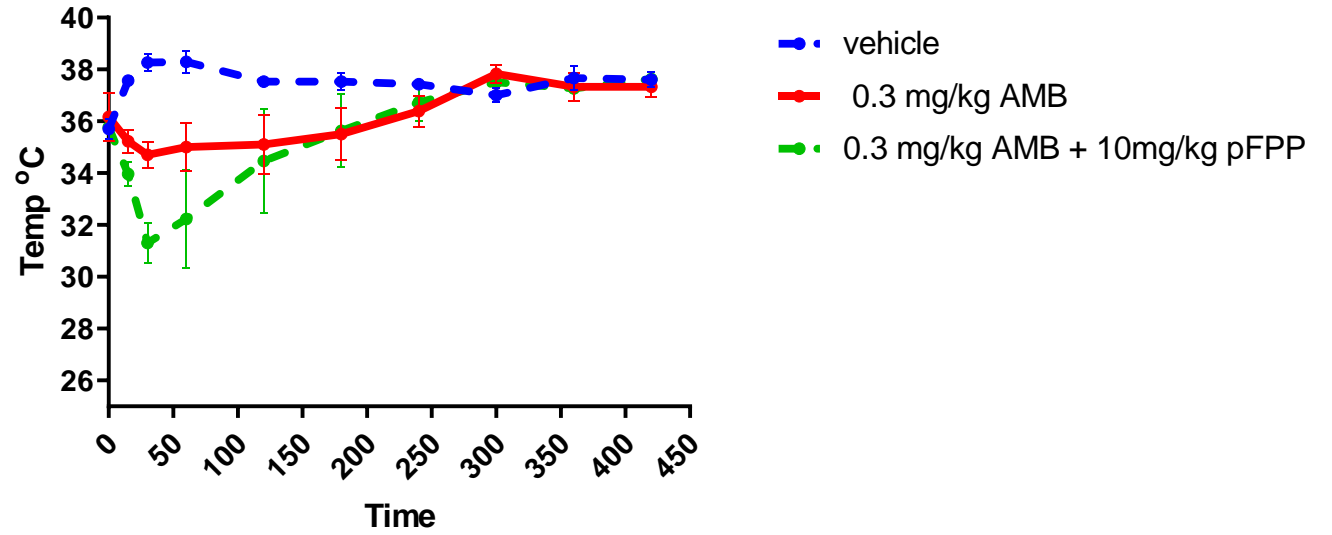
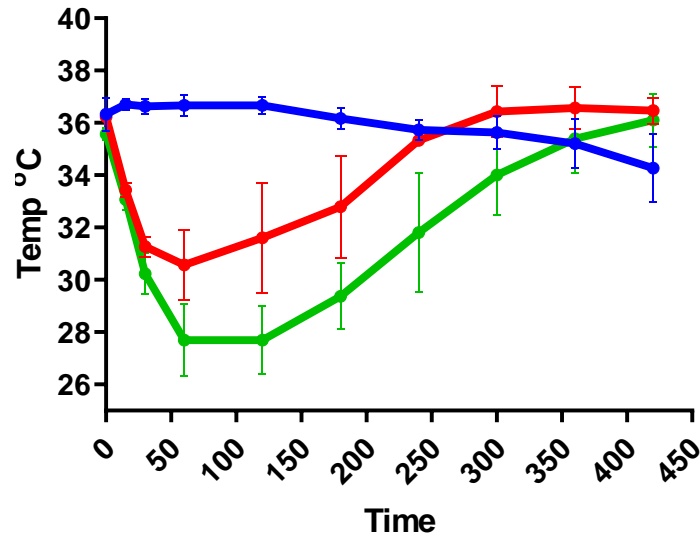
Aashish Manglik^{1*}, Henry Lin^{2*}, Dipendra K. Aryal^{3*}, John D. McCorvy³, Daniela Dengler⁴, Gregory Corder⁵, Anat Levit², Ralf C. Kling^{4,6}, Viachaslau Bernat⁴, Harald Hübner⁴, Xi-Ping Huang³, Maria F. Sassano³, Patrick M. Giguère³, Stefan Löber⁴, Da Duan², Grégory Scherrer^{1,5}, Brian K. Kobilka¹, Peter Gmeiner⁴, Bryan L. Roth³ & Brian K. Shoichet²



AMB FUBINACA substitutes for THC in drug discrimination tests – but is more potent in males



Do AMB and pFPP interact?



Pilot data from n=3 animals per group.

Concluding Remarks

- AMB-FUBINACA is a high affinity, high efficacy CB1 agonist linked to deaths in NZ
- It drives rapid internalisation of the receptor – biological impact?
- The recruitment of arrestin-1 and 2 were the most potent and efficacious we have documented.
- The challenge now is determine if this activity links to the toxicity in vivo
 - How does it compare to other commonly abused synthetics?
 - Are the toxic effects CB1 mediated?
 - **How should we best treat this?**



Thank you

Current Lab members:

David Finlay

Jamie Manning

Monica Patel

Christa Macdonald (UOA)

Collaborators:

Sam Banister (Lambert Institute)

Mary Jane McCarthy (ESR)

Jenny Wiley/Brian Thomas (RTI)



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