



# THC and cannabidiol affect CB<sub>1</sub> receptor function

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XXIX W.O. MCCORMICK ACADEMIC DAY CONFERENCE

**Psychiatric Aspects of Cannabis**

Friday April 27, 2018

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## Disclaimer

I do not have any conflicts of  
interest.

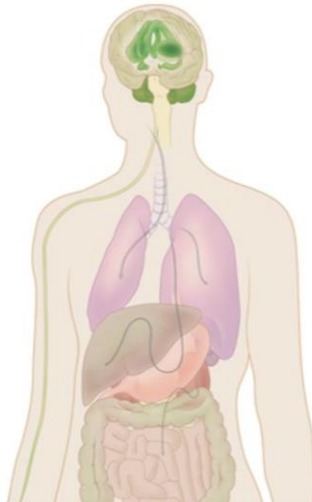
## THC and cannabidiol affect CB<sub>1</sub> receptor function

### Objectives:

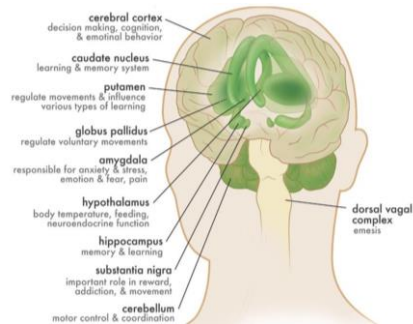
1. To describe the action of THC at the CB<sub>1</sub> receptor as a partial agonist displaying ligand bias
2. To illustrate the important modulatory role of CBD at the CB<sub>1</sub> receptor
3. To highlight some preclinical data on the effect of these drugs in a model of neurodegeneration



## Distribution of CB<sub>1</sub> Receptors



High expression in key CNS areas involved in: reward; mood; anxiety; memory; cognition; posture & movement; autonomic function; stress hormones; blood pressure

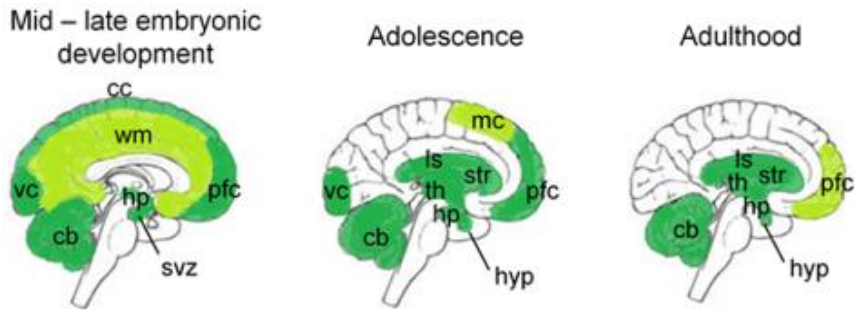


<http://www.ccic.net>

## CB<sub>1</sub> receptor activation

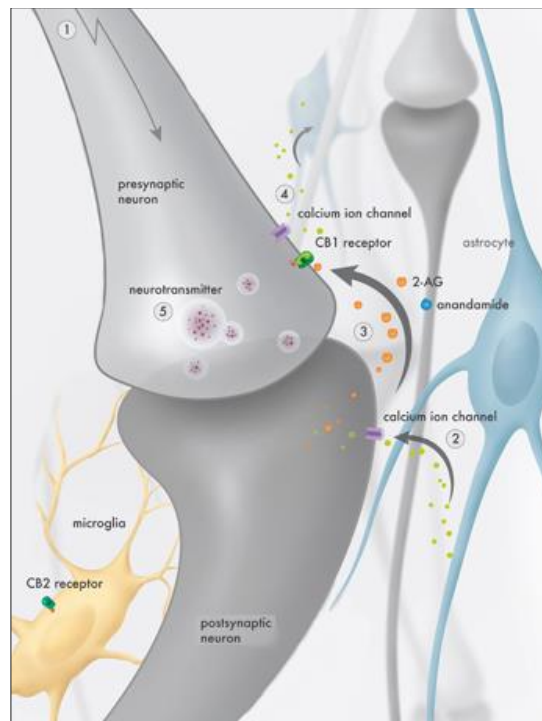
- Alters cognitive function, mood, social interaction
- Affects body temperature
- Increases food consumption; decreases fat mobilization; increases fat storage
- Effect movement and coordination
- Reduce pain and inflammation
- Reduce nausea and vomiting

CB<sub>1</sub> is a modulator of neurotransmitter release in several regions of the CNS. The distribution of CB<sub>1</sub> changes as a normal consequence of aging.

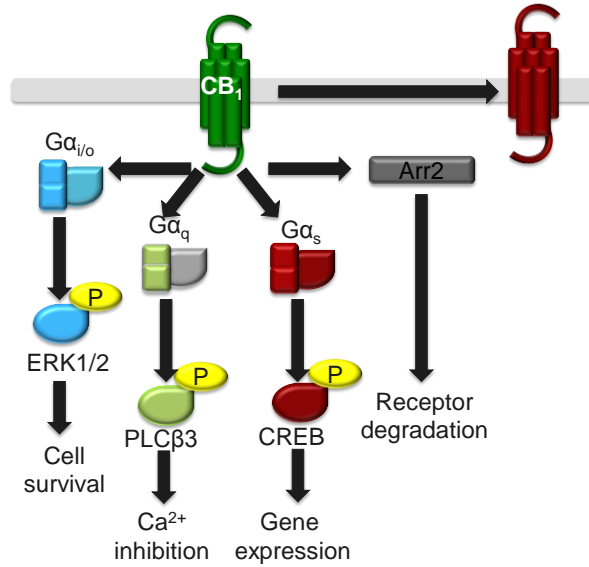


## Cannabinoids as 'synaptic circuit- breakers'

Modified from *Nat Med*  
2008;14(9):923-30

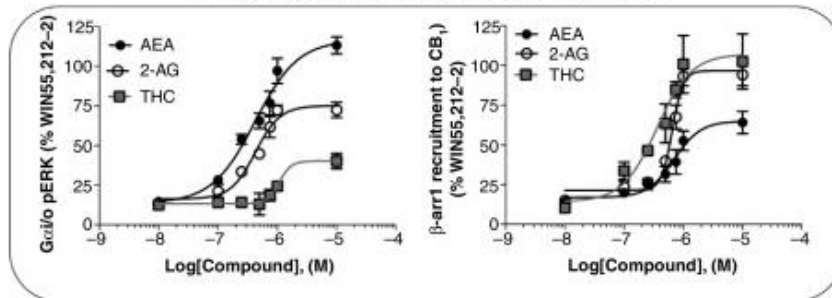


## CB<sub>1</sub> – A G protein-coupled receptor

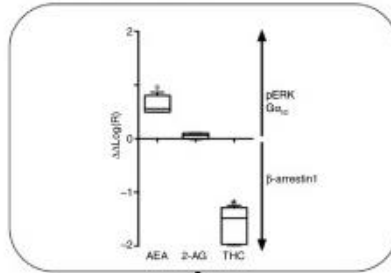
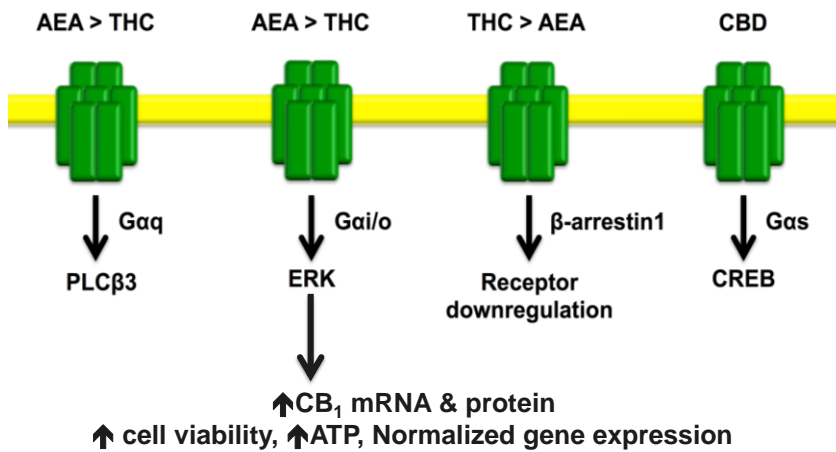


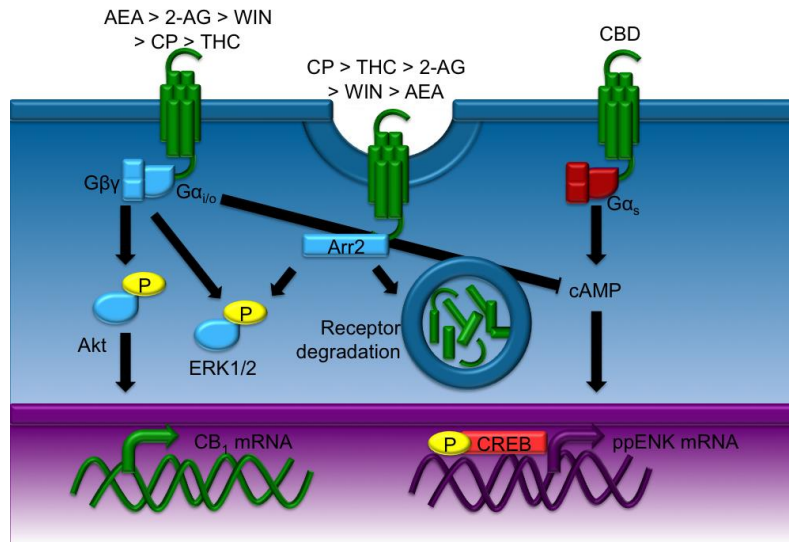
Laprairie *et al.* (2014) *J Biol Chem*

### CB<sub>1</sub> Agonist Assay in Cell Culture



## Calculate Bias

CB<sub>1</sub> ligand biasLaprairie *et al.* (2014) *J Biol Chem*



## Observed effects of CBD prior to Identification of cannabinoid receptors (1970-1995)

In animals, CBD antagonized or inhibited THC-dependent anxiety, catatonia, reduction in movement, aggression and hypothermia

In humans, CBD antagonized THC-dependent anxiety and euphoria

CBD affected sleep, anxiety and psychosis

# CBD targets multiple receptors

CBD is not a direct CB<sub>1</sub> agonist

CBD can increase CB<sub>1</sub> constitutive activity (conformation or number of receptors), augment endocannabinoid tone (FAAH inhibition) and affect CYP-dependent metabolism of THC

CBD is an agonist at TRPV1 channels

CBD inhibits adenosine uptake

CBD affects serotonin receptors

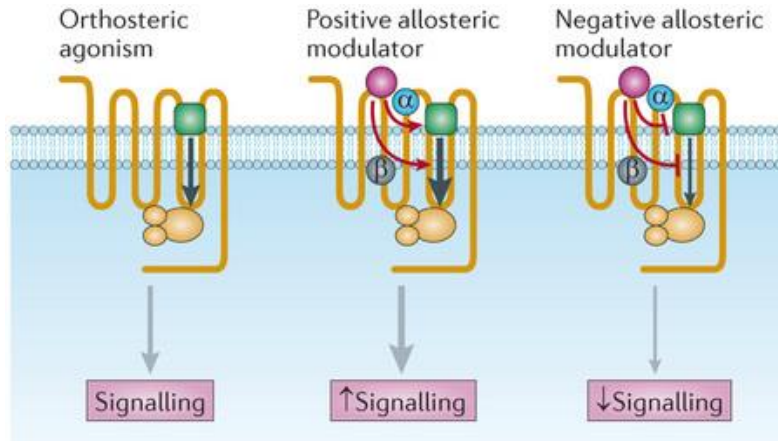
CBD is a PPAR $\gamma$  agonist

McPartland et al., 2015 Br J Pharmacol 172 (3) [PMC4301686](#)

## Cannabidiol (CBD) modulates the activity of THC

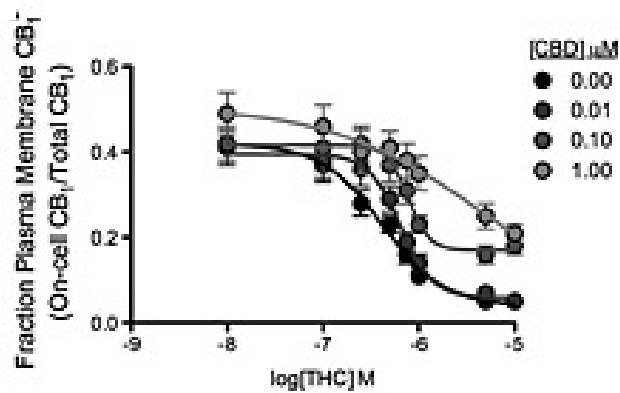


## Allosteric Modulators



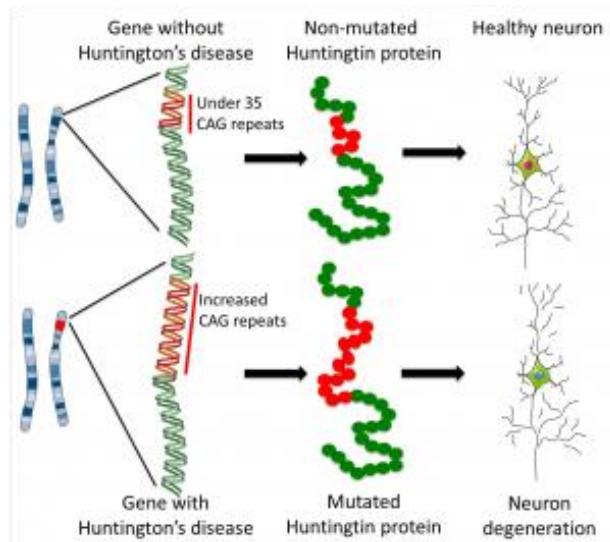
Reduced likelihood for dependence, tolerance, adverse effects because the drug is only effective in the presence of an orthosteric ligand.

Wooten *et al.*, 2013 *Nat Rev Drug Discov*



## CBD is a NAM

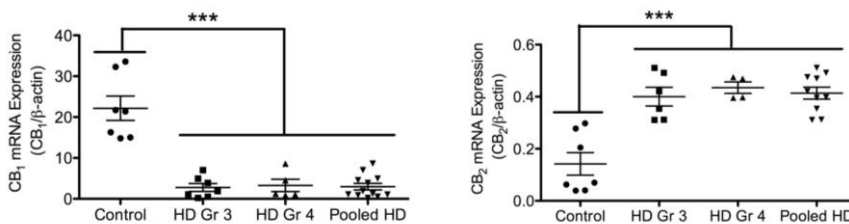
- $\beta$ -arrestin recruitment
- pERK signaling
- PLC  $\beta$ 3 phosphorylation



<http://www.eurostemcell.org/factsheet/huntington%E2%80%99s-disease-how-could-stem-cells-help>

One of the earliest changes in gene expression that occurs during the development of Huntington disease is a decrease in the level of CB<sub>1</sub> receptors

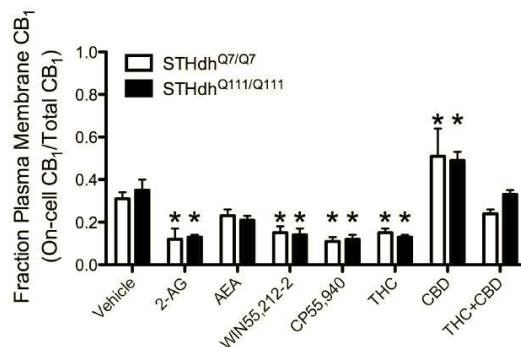
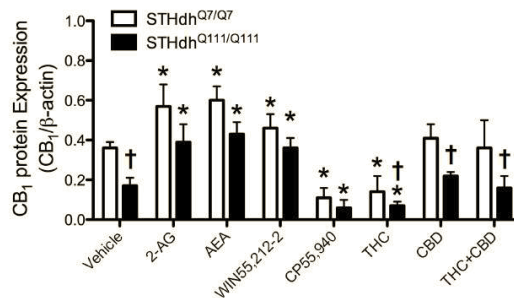
CB<sub>1</sub> levels are decreased, while CB<sub>2</sub> levels are increased in HD patients.



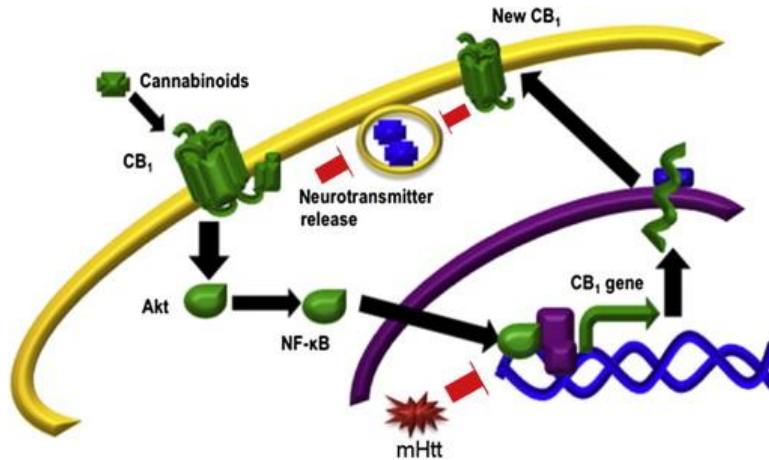
## Therapeutic Potential of Cannabinoids in HD

CB<sub>1</sub> receptor agonists produce motor inhibition, modulate mood, alter energy intake

CB<sub>2</sub> receptor agonists are anti-inflammatory

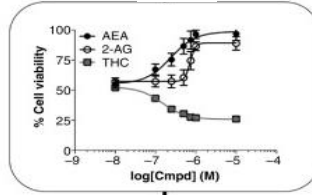


Cannabinoid agonists increase CB<sub>1</sub> levels in *STHdh* cell models of HD via CB<sub>1</sub> activating NF- $\kappa$ B.



Some, but not all, cannabinoids increase CB<sub>1</sub> levels in cells expressing mutant huntingtin

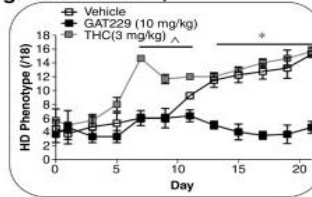
**Correlate Bias and Cell Function**



**Hypotheses to test *in vivo***

CB<sub>1</sub> agonists that favor G<sub>α</sub><sub>i/o</sub>-biased signaling will have positive functional effects *in vivo*  
 β-arrestin-biased cannabinoids will increase symptom severity or promote earlier onset of symptoms

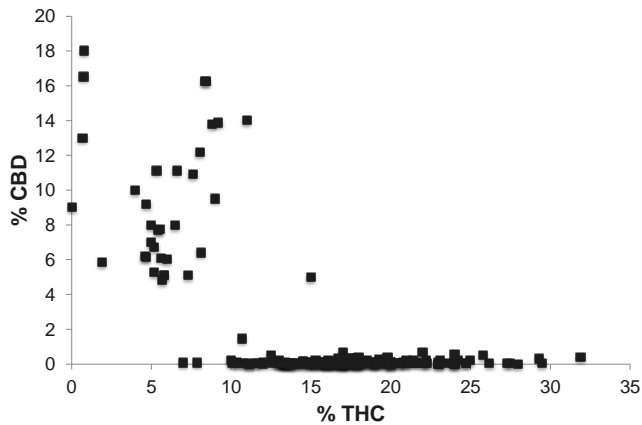
**Test Biased CB<sub>1</sub> Agonist *in vivo***



Current Opinion in Pharmacology

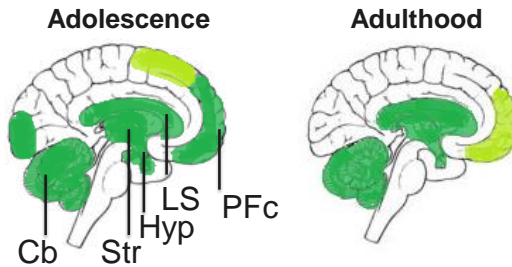
**THC and CBD in Canadian regulated cannabis**

- 15 Licensed Producers
- 206 chemovars for which data was available (2015)



©CCIC unpublished

What stage of HD?



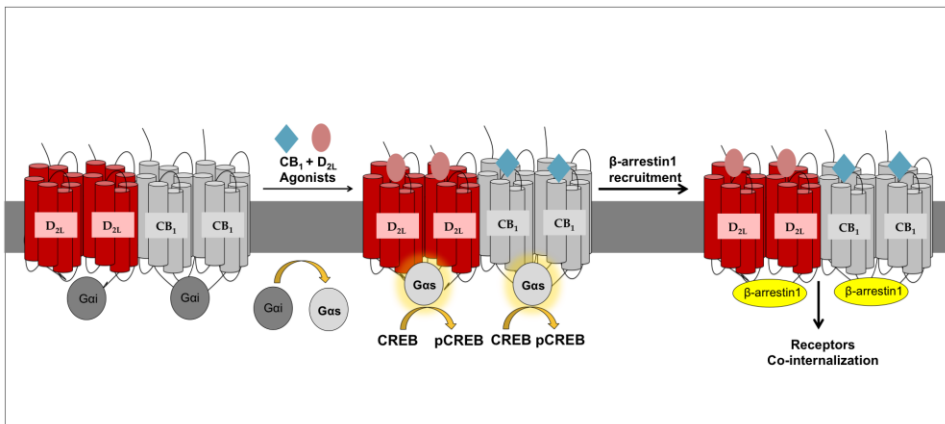
Huntington Society of Canada

To date, there is no strong evidence that pure THC, pure CBD or 1:1 combinations of THC and CBD are effective at managing the range of symptoms for HD

What happens when patients combine cannabinoids with other medicines?



CB<sub>1</sub> heterodimerizes with other GPCRs including D<sub>2</sub> and A<sub>2A</sub> receptors





# Main Points

- THC is a weak partial agonist of CB<sub>1</sub> receptors
- CBD is a NAM of CB<sub>1</sub> and acts at many other sites to alter the activity of THC
- Cannabinoids show bias (functional selectivity)
- Cannabinoids may be useful in neurodegenerative disorders
- The pharmacology of CB<sub>1</sub> receptors and their ligands is complex and may be complicated by receptor complex function



**Dr. Robert Laprairie**  
**University of Saskatchewan**

**Dr. Amina Bagher**  
**King Abdullah University**

**Dr. Melanie Kelly**  
**Dalhousie University**

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Huntington Society of Canada  
Izaak Walton Killam Trust  
Dalhousie Medical Research Foundation

## Selected References

Bagher et al, 2016 Mol Pharmacol 89:652-666

Bagher et al, 2017 Eur J Pharmacol 813:66-83

Katona and Freund 2008 Nature Med 14:923-930

Laprairie et al, 2014 J Biol Chem 289:24845-24862

Laprairie et al, 2015 Brit J Pharmacol 172: 4790-4800

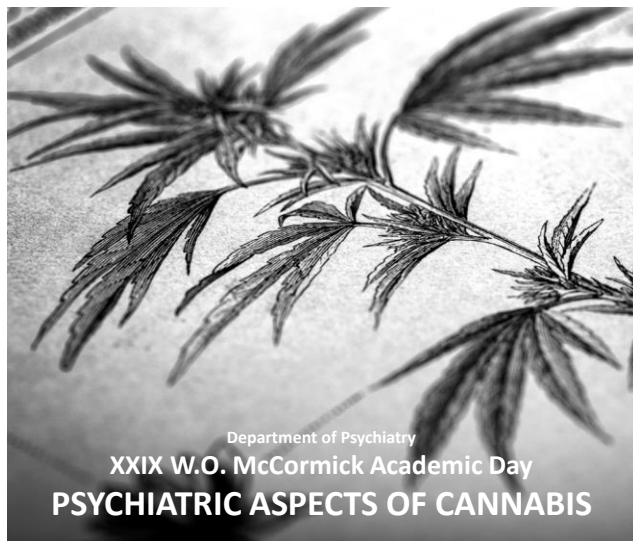
Laprairie et al, 2015 Mol Pharmacol 89:864:875

Laprairie et al, 2017 Curr Opin Pharmacol 32:32-43

MacCallum and Russo (in press) Eur J Int Med [http://www.ejinme.com/article/S0953-6205\(18\)30004-9/pdf](http://www.ejinme.com/article/S0953-6205(18)30004-9/pdf)

MacPartland et al, (2015) 172:737-753

Wooten et al, 2013 Nat Rev Drug Discov 12: 630-640



## Q&A

Please line up  
behind the  
microphones

evaluation:

<https://surveys.dal.ca/opinios?s=41941>



## Recycle Name Badges

Return your name  
badge at the 2:15  
break to enter a  
draw for a door prize