

Restless Legs Syndrome

Frank Brennan - Palliative Care Physician
Renal Supportive Care
Department of Nephrology
St George Hospital

- Definition
- Aetiology
- Prevalence
- Pathophysiology
- Management

Definition

1. An urge to move the limbs, usually associated with paresthesias/dysesthesias
2. Motor Restlessness
3. Symptoms exclusively while at rest, with relief (completely or partially) with movement.
4. Symptoms worse at night.

International RLS Study Group – Definition of RLS (1995)

Aetiology

- Familial
- Women in the 3rd trimester of pregnancy
- Chronic diseases – including CKD

Prevalence in the general population :

5 -15 %

What is the prevalence of RLS in patients with ESKD ?

The Prevalence of Symptoms in End-stage Renal Disease : A systematic Review

Murtagh FE et al. *Advances in Chronic Kidney Disease* Vol 14,
No 1 (January) 2007; pp 82-99

A Cross-sectional Survey of Symptom Prevalence in Stage 5 CKD managed without Dialysis

Murtagh FEM et al. J Pall Med (2007) 10;6:1266-1276

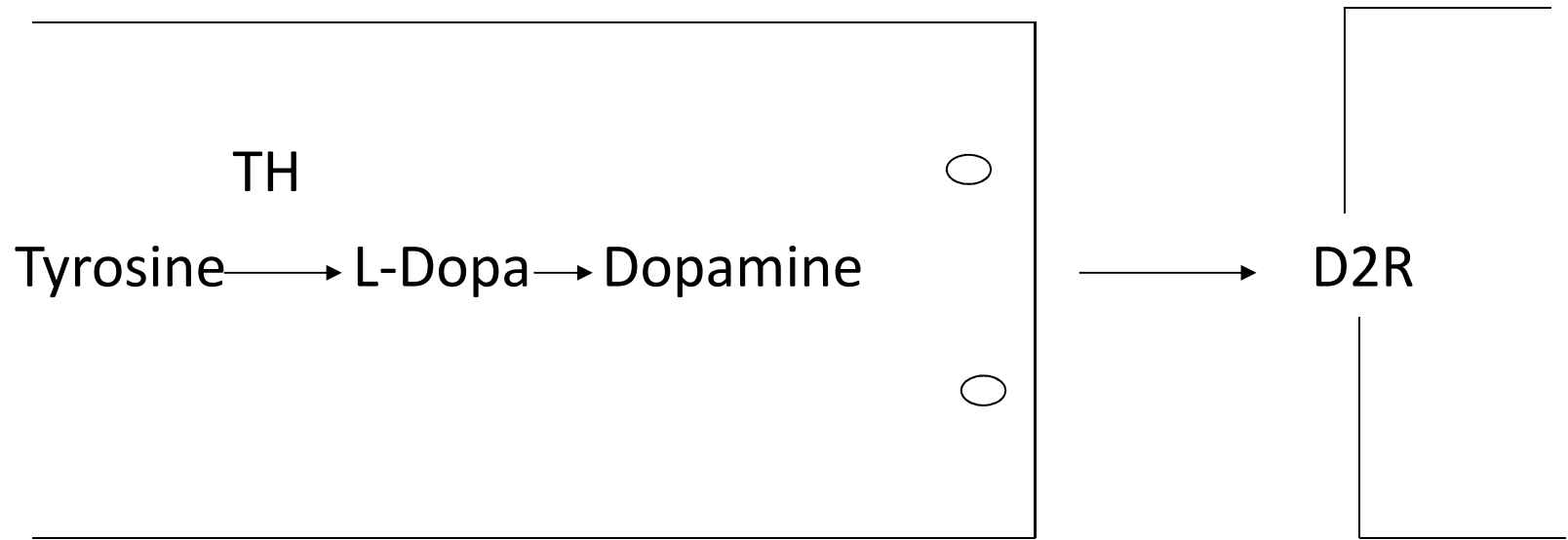
Associations

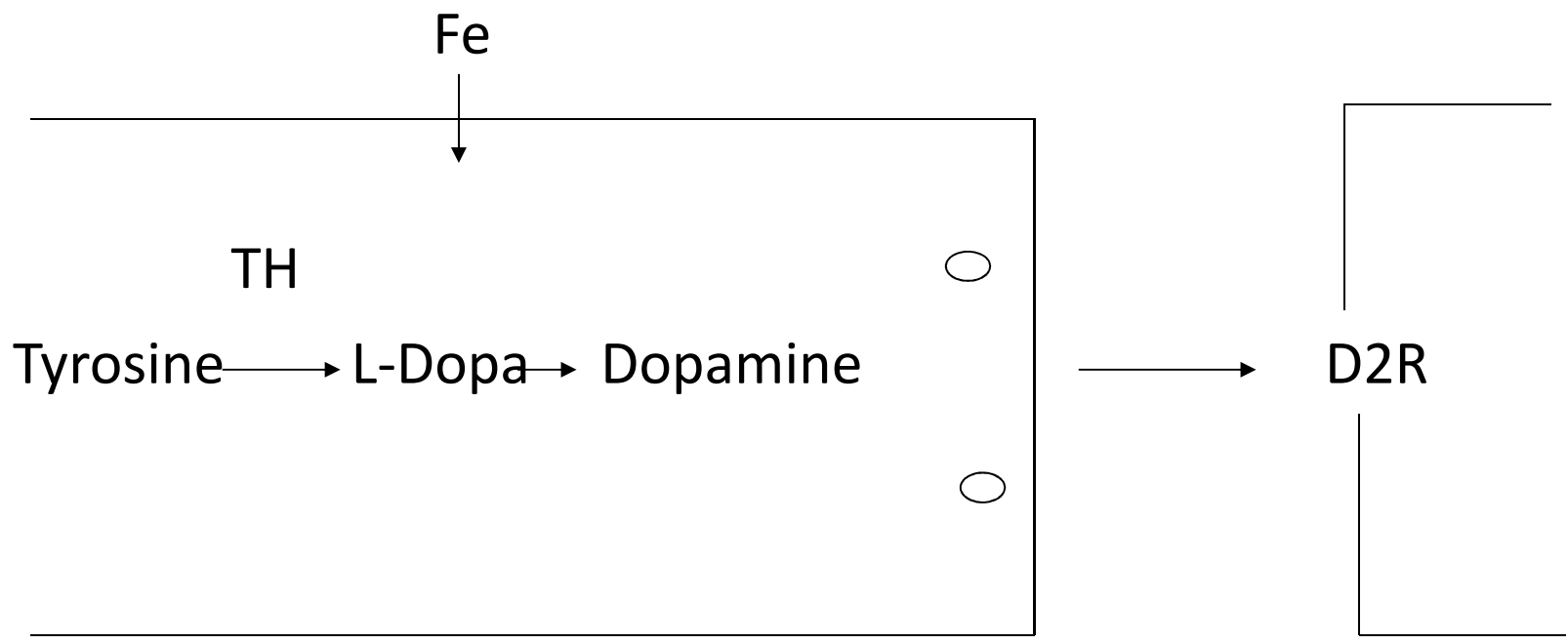
- Sleep deprivation
- Excessive daytime somnolence
- Reduced QOL

Henning W et al. *Sleep Med* 2004;5: 237-246; Merllino G et al. *Nephrol Dial Transplant* 2006;21: 184-190.

Mechanism is not completely understood

Basal ganglia





Fe :

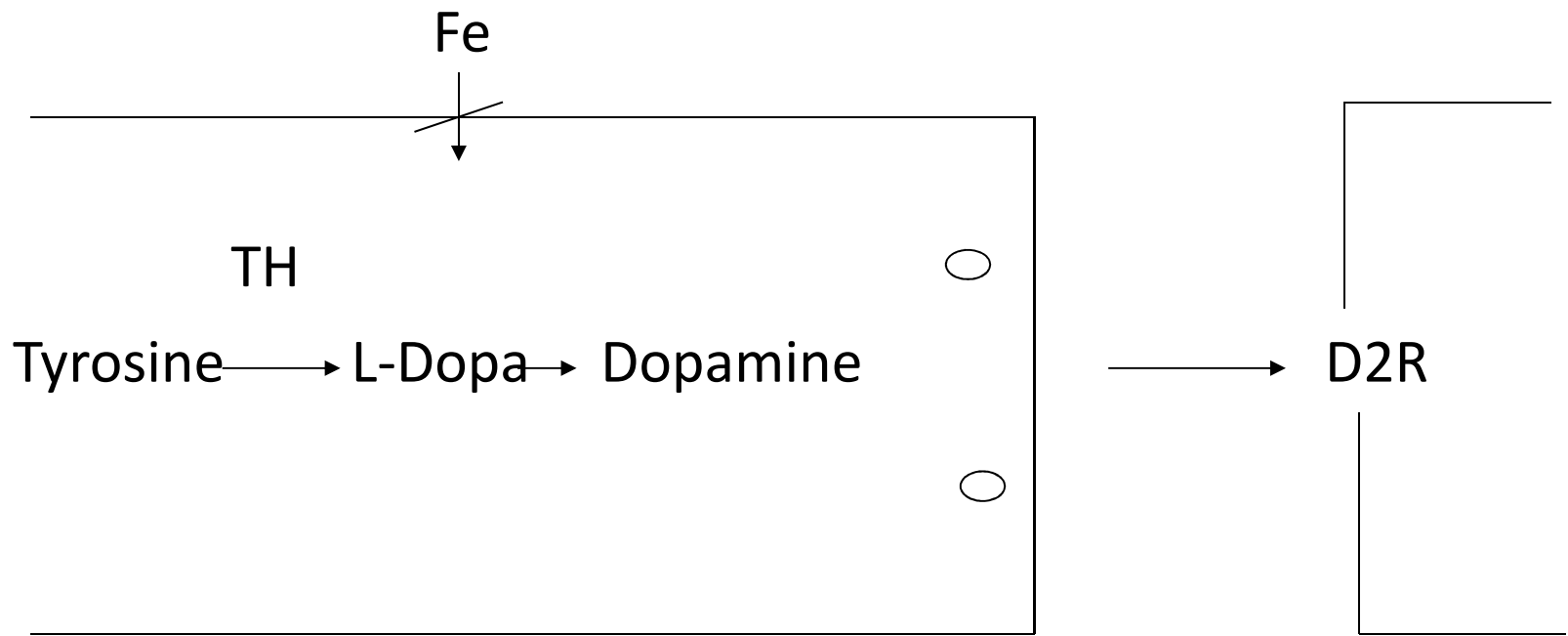
1. Is a co-factor for Tyrosine Hydroxylase (TH).
2. Is involved in the packaging process of Dopamine into vesicles.
3. Is part of the D2R.

There is a circadian rhythm in :

- Fe metabolism
- Activity of TH
- Activity of the D2R

There is a connection between the Basal Ganglia and the Hypothalamus – circadian centre

There is a defect in Fe transport into the cells causing a significant disruption to Dopamine metabolism



The sole source of spinal dopamine lies in the
A11 cell group – in the hypothalamus

– effect is predominantly inhibitory.

Clemens S et al. *Neurology* 2006;67: 125-129.

Management

Management

Clonazapem

0.5mg – 1mg nocte

Dopamine agonists

- Ergot-Dopamine Agonists (Pergolide, Cabergoline)
- Non-Ergot Dopamine Agonists (Pramipexole, Ropinirole, Rotigotine)

Ergot-Dopamine Agonists (Pergolide, Cabergoline) can result in valvulopathy and retroperitoneal fibrosis and “should no longer be used in the treatment of RLS, except for those patients whose symptoms are refractory to all other treatments and in whom the benefits outweigh the risks.”

International Guidelines. Sleep Medicine 2013;15(4): 677-684.

- Augmentation
- Rebound
- Impulse control disorders

Ropinirole

Randomised, double blind, placebo-controlled trials
Significant improvement in RLS, sleep quality, QOL.
Generally well tolerated.

Boyanek et al. *Mayo Clin Proc* 2006; 81(1): 17-27; Bliwise DL et al. *Sleep Med* 2005;6(2): 141-147.

Ropinirole v L-Dopa in patients with ESKD on HD

Pellucchia MT et al. *Clin Neuropharmacol* 2004;27:178-181.

Open label, cross over trial.

Ropinirole was more effective than L-Dopa.

No adverse effects with Ropinirole

- Ropinirole is almost entirely inactivated by hepatic metabolism.
- Less than 10 % excreted unchanged in the urine.
- None of the major metabolites have pharmacological activity

Gabapentin

Two RCTs have shown efficacy for Gabapentin in the treatment of RLS in Dialysis patients

- Study A – Placebo controlled – Thorp et al (2001)
- Study B – Gabapentin compared to Levo-dopa – Micozkadioglu et al (2004)

On Dialysis

Gabapentin 100mg after each Dialysis and
titrate to effect

On conservative management

If eGFR < 15 :

Gabapentin 100 mg every 2nd night and titrate
to effect

On conservative management

If eGFR > 15 :

Gabapentin 100 mg every night and titrate to effect

Gabapentin Enacarbil was approved by the US FDA for the management of moderate to severe RLS in 2011.

Iron supplementation

Sloand A. *Am J Kid Diseases* 2004;43: 663-670.

Randomised, double blind, placebo controlled trial

- IVI Fe 1g v placebo.
- Significant benefit in RLS.
- Treatment benefit at 1 week.
- Maximal benefit at 2 weeks.
- Lost significant benefit at 4 weeks.
- No adverse effects.

Improvement in RLS occurs after Renal transplantation

Large case series – Winkelmann J et al. *Mov Disord* 2002; 17; 1072-1076.

What international guidelines exist ?

International RLS Study Group

Evidence based guidelines and clinical
consensus best practice guidance

Sleep Medicine 2013;15(4): 677-684.

European guidelines on management of RLS :
Joint Task Force of the European Federation of
Neurological Societies, The European
Neurological society and the European Sleep
Research Society

Eur J Neurology 2012;19: 1385-1396.

The use of Gabapentin

Several reasons :

1. The concurrent presentation of :

(a) Uraemic Pruritus. There are several RCT showing significant efficacy for Gabapentin in the management of UP.

(b) Diabetic painful peripheral neuropathy.
The Gabapentinoids play a central role in managing neuropathic pain.

2. Cost.

3. Flexibility in dosing

Challenges in dosing :

1. Excellent control except a flare of RLS *during* the dialysis.
2. At Gabapentin 100mg some control, at 200mg intolerant with side effects

Excellent control except a flare of RLS during the dialysis.

A dose prior to and directly after dialysis.

At 100mg reasonable control, at 200mg intolerant

The use of a Compounding Pharmacist to make up 25 mg doses allowed us to carefully titrate doses in very small increments.

A 77 year old man

- ESKD secondary to Diabetic Nephropathy
- Moderate to severe RLS for “at least 6 months, maybe more”
- Also had moderate Uraemic Pruritus
- Very disrupted sleep

- Commenced on Gabapentin 100mg after each dialysis
- Some improvement but remained troubled.
- Increased dose to 200mg – drowsy, “shaky”.

Adjusted dose to 125 mg post dialysis.

Surge in RLS in the final hour of dialysis

Introduction of a pre-dialysis dose

- Gabapentin 75mg pre and 150 mg post dialysis.
- Finally reached stable dose with good effect “virtually all gone... Mild only”

Other research questions

Given that RLS is classically worse at night
what effect does RLS have on sleep ?

In this cohort of patients what are their levels of Insomnia ?

And the corollary – what changes occur to insomnia in this cohort over this period with management of RLS ?

The Sleep Dividend

What effect does the management of RLS have a patient's overall quality of life ?

Conclusion

- RLS is a symptom secondary to RLS
- When present it may be deeply disturbing to patients
- It may disrupt sleep, cause daytime drowsiness and impact on QOL

Mechanism is not completely understood.

- Dopaminergic dysfunction
- Brain Fe metabolism
- Supraspinal inhibition

- A small number of medications have been shown to be of benefit.
- Gabapentin has an advantage in its simultaneous efficacy in the management of other symptoms in ESKD patients.
- The Dopamine agonists have a clear role.

Acknowledgements

- Gemma Collett, Renal Research Officer
- Liz Josland, Renal Supportive Care Nurse
- Heads of Departments of Nephrology and Palliative Medicine – Professor Mark Brown, Dr Jan Maree Davis