IN THE NAME OF GOD

WHAT AN ENDOCRINOLOGIST SHOULD KNOW FOR PATIENTS RECEIVING LITHIUM THERAPY

BAHMAN 1402

Lithium In the medical field

Lithium has been recognized as a drug for **bipolar** and **depression** or **schizoid** disorders by the Food and Drug Administration in 1970.

Lithium toxicity

. **Lithium** therapeutic use is limited by its **narrow therapeutic** range

(between **0.6** and **1.2** m Eq/l)

. Measurement of serum level should be carried out at **least 6** to **12 h** after the last therapeutic dose.

.different degrees of **toxicity** that might be **acute** or **chronic**

with **mild**, **moderate**, or **severe** symptoms.

Lithium toxicity

. Nausea, feeling tired, and tremor occur at a blood Lithium level of **1.5** to **2.5** m Eq/L.

. Confusion, tachycardia and hypotonia occur at a blood Lithium level of **2.5** to **3.5** m Eq/L.

. Severe symptoms including coma, seizures, hypotension, and hyperthermia may occur at a Lithium concentration greater than **3.5** mEq/L and can be fatal.

acute toxicity

. **Vomiting** and **diarrhea**, which may result in volume depletion are frequent during acute toxicity, with then distribution of Lithium into the central nervous system causing dizziness and other **mild neurological symptoms**

Acute lithium toxicity treatment

There is **no** specific **antidote** for toxic effect of lithium.

Hemodialysis is more **effective treatment** for acute lithium poisoning

chronic toxicity

non-specific **neurological** symptoms such as nystagmus, tremor, ataxia , and change in mental status

Nephrogenic DI.

Nephrotic syndrome.

Endocrine sys: **hypothyroidism hyperthyroidism hyperparathyroidism**

Lithium and thyroid

Lithium can induce **goiter**, **hypo** and rarely **hyperthyroidism**.

in a cohort of 580 patients, 10% of patients had at least one blood TSH level > 10 mu/l.

and almost 4% at least one TSH < 0.05 mu/l.

This property to induce hypothyroidism is sometimes used as an adjuvant treatment for difficult hyperthyroidism.

Table 2 Thyroid dysfunction in patients receiving lithium therapy

	Patient count	% of total study population	TPO antibodies available	TP an po
	(*n*)		(*n*)	(*n*)
TSH>4.2mU/l	178	30.7	59	30
TSH>10mU/l	60	10.3	23	19
TSH<0.3mU/l	54	9.3	12	5
TSH<0.05 mU/l	22	3.8	8	5

Lithium as an adjuvant treatment for hyperthyroidism

.the rare **hyperthyroidisms** that **resist** to **antithyroid drugs**, to improve control of circulating plasma thyroid hormones

. in case of **liver injury**,

. **leukopenia**

. thyrotoxicosis **crisis** .

the potential toxicity of Lithium limits its application in hyperthyroidism

Lithium Carbonate in the Treatment of Graves' Disease with ATD-Induced Hepatic Injury or Leukopenia

Rendong Zheng et al. Int J Endocrinol. 2015.

Free PMC article

We enrolled **51 GD** patient with **hepatic injury** or **leukopenia** in this study .

thyroid hormone decreased to a certain extent in **all** patient.

TFT was maintained at **NL** in 12 patient (**23**/)who discontinued Li after 36 week.

Only 6 patient (**11.8**/) **relapsed** after Li withdrawal .

33 patient (**64.7**/) could **not reach target :**

25.4/ were **radioactive iodine** . **15.7** / were **operation** therapy.

These finding indicate that Li may be effective therapeutic agent in the treatment of hyperthyroidism due to GD, especially with hepatic injury or leukopenia

Lithium and thyroid

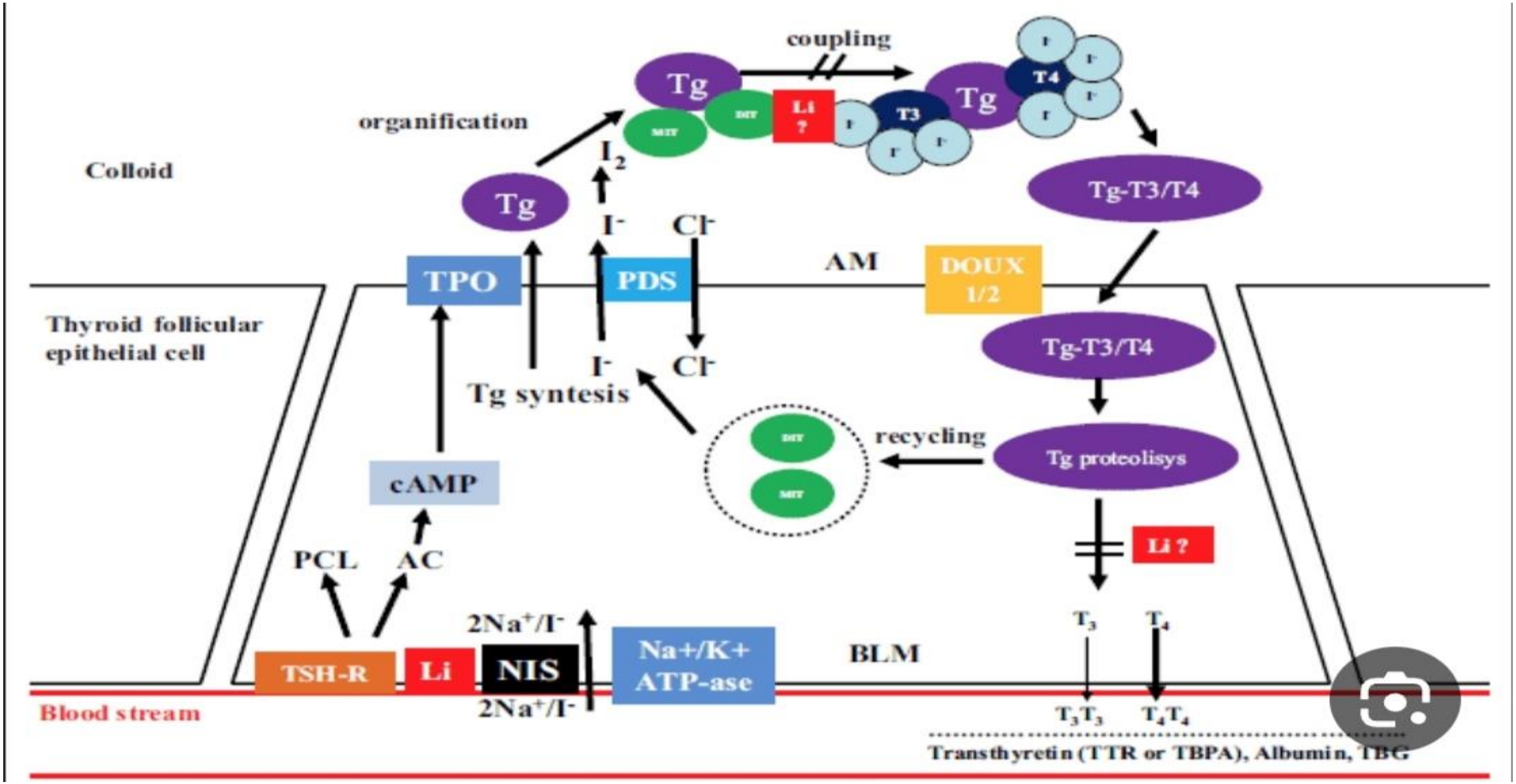
Due to active Na+/I− transport, Lithium, despite its concentration gradient, accumulates in the thyroid at a concentration 3 to 4-fold higher than in plasma.

It inhibits the **formation of colloid** thyrocytes

changes the **structure of thyroglobulin**

decreases the **iodization** of tyrosine

hinders their **coupling**.


coupling
Tg
DIT
MIT
Li ?
T3
T4
I
organification
Colloid
I_2
Tg
Tg-T3/T4
I^-
Cl^-
TPO
PDS
AM
DOUX 1/2
Thyroid follicular epithelial cell
Tg-T3/T4
Tg syntesis
recycling
Tg proteolisys
cAMP
Li ?
PCL
AC
$2Na^+/I^-$
TSH-R
Li
NIS
Na+/K+ ATP-ase
BLM
T_3
T_4
Blood stream
T_3T_3
T_4T_4
Transthyretin (TTR or TBPA), Albumin, TBG

Lithium and thyroid

. Lithium **inhibits thyroid hormone release** from the thyroid gland.

. lithium treatment results in **decreased** serum **T4,T3** and **increase** TSH

.the **proliferation** of normal thyroid **follicles**.

Lithium and thyroid

. it **reduces** the clearance of **FT3** in serum indirectly by reducing the activity of 5-deiodases **type** 1 **and** 2

. **increases** thyroidal **radioiodine retention** and may be effective in reducing administered activity in hyperthyroidism

This study included **40** patient with **graves** disease who where eligible for **RAI therapy** .

Divided **two** groups (20 patient in each group)

All patient were followed for **1** year.

Lithium was administered in a dose of **900** mg per day in **3** divided dose for **6 days**. **Starting on** the day of RAI therapy.

RAI combination with **lithium** had better cure rate (**90**/)compare to **RAI alone** (**70**/).(p 0.11)

Mean **time** taken to **cure** was **4.69** months in RAI plus li and **7.12 months** in **RAI alone** (p 0.001)

There were no side effect of lithium or RAI

Goiter

. the frequency of **clinical goiter** is around **15**%

.Another ultra sonographic thyroid study comparing **90 patients** on long-term **Lithium treatment** (in mean during 19 y) to **39 patients** treated with other psychotropic drugs for psycho-affective disorders, also showed a higher thyroid volume, a higher frequency of goiter, and more nodules (not correlated with the level of thyroid hormones) in the Lithium-treated group as compared to age- and sex matched controls.

.

Goiter treatment

Goiter is **most common** clinical finding

For patient who develop goiter overtime even in the **absence** of **hypothyroidism** (clinical or sub clinical) also consider **LT4 therapy** aimed at restoring normal serum thyrotropin levels.

LT4 is **not effective** in the treatment of **prolonged goiter** due to fibrosis.

Lithium-induced hypothyroidism

Lithium-induced hypothyroidism may reach **25–30%** of cases.

half of them in the **first year** of treatment.

Hypothyroidism is **reversible** in about **40%** of case.

A retrospective cohort study in the Swedish to determine whether **lithium associated hypothyroidism** was **reversible** in patient who subsequently discontinued lithium.

90 patient screened ,27/ had overt hypothyroidism .of **85** / patient available for follow up **41/ stop thyroid replacement** therapy **after lithium discontinuatoin**

It seems prudent to allow **some weeks** for the thyroid gland to **recover** before stopping TRT.

we can expect hypothyroidism to **recur early** after **TRT discontinuation** .

It is advisable to monitor TFT for **3** to **6 months**.

TRT reinsertion should then only be reconsideration if there are unambiguous sign of hypothyroidism such as **persistently high TSH** and **low FT4**

Lithium-induced hyperthyroidism

Lithium may cause hyperthyroidism due to **thyroiditis** or rarely **Graves**' disease.

A **rapid change** in thyroid status can affect mood, and hyperthyroidism may mimic a **manic attack**.

Fifty-two studies support a link between Lithium and hyperthyroidism, but they are of limited quality.

Antibody negative hyperthyroidism is potentially reversible on discontinuation

. Screening and treatment of thyroid complications of Lithium therapy

Goiter and **hypothyroidism** do **not** require Lithium **discontinuation** and usual guidelines may be used.

LT4 replacement therapy is preferred more among patient with significant thyroid **enlargement** accompanying compressive syndrome.

Hyperthyroidism is more difficult to treat and **Lithium discontinuation** should be discussed with the psychiatrist.

Lithium and hyperthyroidism

Thyroiditis due to possible **direct toxic effect** of **Li** on the thyroid gland .

another mechanism Li induce hyperthyroidism is related to **autoimmunity** and **auto Ab production**.

Li treatment was shown to **increase B** cell activity.

Patient with Li induce **hyperthyroidism** are best treated with ATD like **carbimazole** with /without **steroid** .

In Li induced **thyroiditis** : **conservative management** with regular follow up is recommended . majority of the patient develop hypothyroidism subsequently

screening thyroid at **least** with a **TSH** measurement and a clinical **cervical palpation**, **yearly** and in case of every intercurrent event

Lithium and calcium metabolism

Chronic or acute **hypercalcemia** is observed in **3** to **30%** of patients treated with Lithium.

Li and hypercalcemia

Li interacts with and renders the **CaSR** in **parathyroid** gland and **kidneys less sensitive** to **hypercalcemia** ,that a **higher threshold** level of serum calcium is required to suppress parathyroid hormone release and to suppress renal tubular calcium reabsorption

The increased renal reabsorption of calcium result in hypocalciuria and mild hypercalcemia, a condition called Li associated hypocalciuric hypercalcemia(**LAHH**)

. Lithium stimulates the growth of parathyroid cells .

The observed **hyperparathyroid** state is possibly **normocalciuric** and not hypercalciuric

. Surgery is only successful in the **third** of **case** related to a **single adenoma** since hypercalcaemia are related to **hyperplasia** in the **two** other **thirds**.

.Five percent of patients may also present with episodes of hypocalcaemia .

The success parathyroidectomy is only 35%, most of patients (75% of cases) showing hyperplasia .

These findings have been recently confirmed in a series of 297 **patients** treated with Lithium .

The median age of the patients was **58 years**, and the median **duration** of Lithium treatment was **16** years. Before the beginning of Lithium treatment, blood calcium level was NL range.

Under treatment, 178 patients (**60**%) remained **normocalcaemic**,

while 102 (**34%)** became **hypercalcaemic** or very suspicious of hyperparathyroidism, including 41% with urine calcium < 4 mmol/day.

Seventeen patients (**6%)** had ≥ 3 intermittent episodes of **hypocalcaemia**.

Screening and treatment of Lithium-induced calcium disorders

screening blood calcium at **least yearly** or in case of **intercurrent event**, especially mood disorder relapse since hypercalcaemia may worsen the mood disorder.

first to check the daily diuresis, to look for clinical signs of **dehydration** and to measure blood **sodium** and **creatinine** .

Diuretics (thiazides) **discontinued** in case of hypercalcaemia and blood **level** of **Lithium** should be checked.

If **hypercalcemia** is **confirmed** after **rehydration** work-up to determine the profile of hypercalcemia and its potential consequences on bone and kidney should be done.

Surgery will be performed mainly in typical hyperparathyroidism phenotypes with a **unique adenoma**.

In other settings, calcimimetic drugs such as **cinacalcet** may be preferable

. **Discontinuation** of **Lithium** may always be discussed with the psychiatrist and is sometimes **sufficient** to **reduce hypercalcemia** .

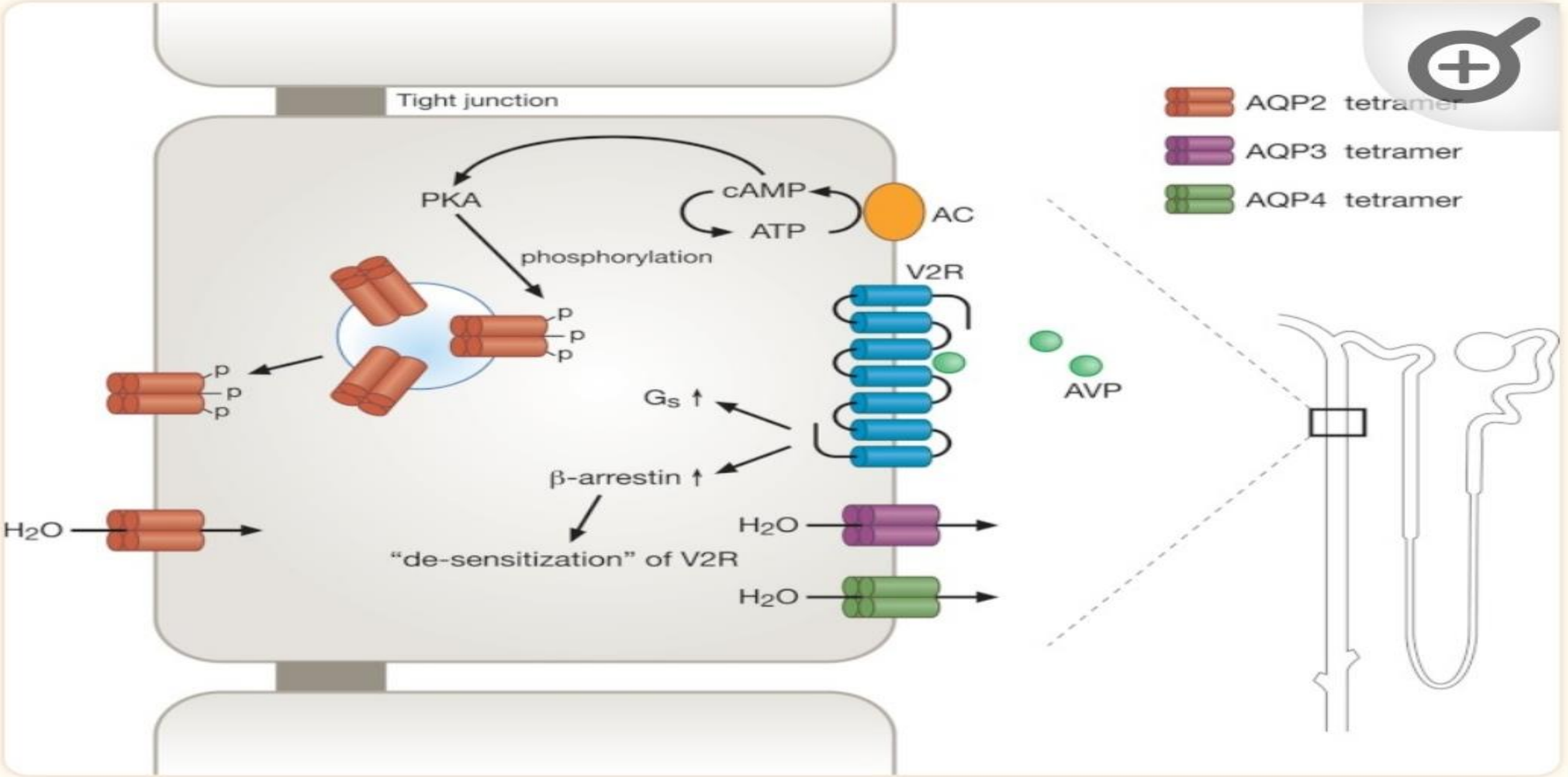
Electrolyte and water balance disturbances Lithium

Nephrogenic diabetes insipidus is related to Lithium-

induced dysfunction of **PKA activation** resulting in

decreased phosphorylation of aquaporin 2 and reabsorption of water.

Vasopressin levels are high in regard of normal or slightly elevated blood sodium levels.


Tight junction
PKA
cAMP
ATP
AC
phosphorylation
V2R
p
p
p
Gs ↑
β-arrestin ↑
AVP
H2O
H2O
H2O
"de-sensitization" of V2R
AQP2 tetramer
AQP3 tetramer
AQP4 tetramer

Treatment of nephrogenic diabetes insipidus

Nephrogenic diabetes insipidus may respond to **discontinuation** of **treatment**, especially at the beginning of symptoms.

It frequently persists if chronic kidney disease is present . and is therefore very **difficult** to **treat.**

Lithium should be discontinued as soon as diabetes insipidus is diagnosed and psychiatrist agrees.

Besides the current treatments of nephrogenic diabetes insipidus, other treatments such as **AMPK activators** are investigated.

Some of them are commercially available such as **statins**, **metformin** which can be effective.

Other AMPK inhibitors such as **ND5033** or **cyclooxygenase NrF2** (independent of aquaporin 2) are not currently available yet

.Rehydration

.Lithium discontinuation in accordance with the psychiatrist Low sodium **hypo osmolar** diet

.Distal diuretics Thiazide (**indapamide**)

.Inhibitors of ENaC or epithelial sodium channel, by which Lithium penetrates the main cells of the collecting tube (**triamterene** and **amiloride**)

.Cyclooxygenase inhibitors (**indomethacin**) despite its potential nephrotoxicity

Kidney transplantation is a very effective treatment in case of kidney

failure .

Kidney complications

progressive renal failure due to **chronic tubulointerstitial** nephropathy.

Segmental and focal **glomerulosclerosis,**

acute renal failure

more rarely severe **nephrotic** syndrome have also been reported.

Lithium, pregnancy and breastfeeding

Lithium must be **avoided** during **pregnancy** and **lactation**.

Nevertheless, the risk of **mood disorder relapse** should be weighed against the **risk** of **lithium** treatment during pregnancy, especially during the first trimester.

Lithium exposure during the **first trimester** was associated with an **increased risk** of **major malformations** .

Maternal **Lithium** requirements may be **increased during pregnancy** and in case of prescription

Lithium, pregnancy and breastfeeding

maternal serum levels should be monitored frequently **after childbirth** and the **dosage reduced** if necessary.

Stopping Lithium 24 to **48** hours **before cesarean** delivery or at the **onset** of **spontaneous labor** and resuming

the pre pregnancy Lithium dose immediately after delivery should minimize the infant's serum Lithium

concentration at birth.

Recommendations vary in the postpartum period: monitor serum **lithium** and **creatinine** of **mother** and **infant**,

and **TSH** at **2**, **10**, **30** and **60 days**, or only at 10 days, or only if clinical signs, or every 4 at 12 weeks

Lithium and breastfeeding

Lithium in breast milk **inhibits** the **uptake** of **thyroid iodine** and the production of hormones in the **infant**.

Of 344 initial studies, 13 case/series reports with 39 mother-

child dyads . The **infants** were breastfed an average of **59** ± 83 **days**.

and **lithium blood** range was **0.73** ± 0.26 mEq/L.

Lithium concentrations in **breast milk** was **0.84** ± 0.14 mEq/L

with infant's **lithemia** being **0.23** ± 0.26 mEq/L.

Lithium and breastfeeding

80% (*n* = 26) of **infants** had blood **Lithium levels** ≤ **0.30** mEq/L without adverse effects.

Eight (**20**%) experienced a transient adverse event (i.e., acute toxicity or thyroid damage).

In conclusion, the current studies on Lithium and lactation are **heterogeneous** and of **low quality**.

Most infants have Lithium ranges **below 0.3** mEq/L **without** apparent **side effect**, but no long-term evaluation is available. Therefore, if possible and as recommended by French health authorities, this treatment should be avoided each time it is possible

. Prevention of side effects lithium

bariatric surgery may favor **lithium intoxication** whatever the type of surgery (Rouxen-Y Bypass, sleeve gastrectomy or gastric banding).

Surgeons should be aware of the pharmacokinetic alterations requiring **close monitoring** after **bariatric surgery** in patients receiving Lithium.

Neurological, **gastrointestinal**, **cardiac** (severe bradycardia) or **renal** (nephrogenic diabetes insipidus) complications may occur in the immediate perioperative period or later.

Lithium intoxication may be explained by change in **diet**, **intestinal absorption**, **liver metabolism**, concentration of plasma **binding proteins** in association with the decreased volume of distribution related to weight loss.

Thyroid complications occur more frequently in **women**

. **Goiters** are **4** times more frequent than in the general population.

Hypothyroidism can reach **30%** of cases, **more frequently** if thyroid **autoimmunity** pre exists.

Hyperthyroidism, likely to worsen mood, is present in **5%** of cases.

Increase in serum **calcium** and **PTH** levels are found in **30%** of cases with a moderate risk of hyperparathyroidism, more often related to hyperplasia;

hypercalcemia is **5 times** more frequent than in the general population, but hypocalciuria is frequent and surgery rarely successful because of concomitant alterations of CaSR.

The most serious complications are **nephrogenic diabetes insipidus** and acute or progressive

Kidney insufficiency.

Dehydration with hypernatremia may be severe.

General advice to avoid complications of treatment with Lithium

. assessment before the prescription of the drug should include **pregnancy test**, **blood control** and possibly **electrocardiogram**

.The border between the effective dose and the toxic dose is narrow: so, recommend the

patients to take the medication regularly and **never double** a **dose** if he/she forgets the previous dose

.Any **dehydration** (profuse sweating, vomiting, diarrhea, fever) leads to toxicity and **serum**

Lithium concentration must be **checked**

.The absorption of **alcoholic** beverages is **not recommended** since it increases **drowsiness** and **fluctuations** in blood **Lithium**

.The following **drugs** may **interact** with serum **Lithium concentrations** and their prescription, if needed, should be strictly monitored :

NSAID, Diuretics ,ACE.I,ARB, Neuroleptics or carbamazepine ,SSRI, Methyldopa, Verapamil

.Look for the lowest effective dose of Lithium

.Beware of post-bariatric surgery including sleeve-gastrectomy Monitor regularly clinically goiter and diuresis and biologically serum lithium, **sodium**, **calcium**, **cr ,** and **TSH** levels, as well as urine albumin

	Clinical symptoms to search for	Blood test	Investigations to be perform in second line	Treatment
Thyroid *Goiter (15%) *Hypothyroidism (8–30%) *Hyperthyroidism (5%) - Graves disease - Thyroiditis Lithium induced	- Exacerbation of psychiatric symptoms- Body weight variations- Fatigue- Digestive disorders- Goiter palpation	TSH 1x/year	- FT4 FT3- Anti-TSH receptor antibody- Thyroid ultrasound examination if nodular goiter- -	No systematic lithium discontinuation is necessary
Parathyroid ***Hypercalcemia*** (3–30%) *Dehydration *Hypercalcemia hypocalciuria syndrome *Hyperparathyroidism -Hyperplasia (2/3) -Adenoma (1/3) ***Hypocalcemia*** (5%)	- Polyuria-polydipsia- Fatigue- Digestive troubles	Serum calcium 1x/year	- PTH- 25OH Vit D- 24H urine calcium If surgery considered parathyroid ultrasound +-MIBI-I123 scintigraphy	Discontinuation of lithium can be discussed if possible
Kidney *Nephrogenic diabetes insipidus *Kidney insufficiency Tubulointerstitial Glomerulosclerosis *Nephrotic syndrome	- Polyuria-polydipsia> 3L/day- Nocturia	-Natremia 1/year– Blood creatinine 1x/year	-Early morning plasma and urine osmolality- Combined natremia and AVP measurement if natremia > 145- Fluid restriction test (only if normal blood sodium) to confirm diabetes insipidus- Therapeutic desmopressin test to confirm nephrogenic diabetes insipidus if no response- Kidney ultrasound- Biopsy	Need to stop lithium in accordance with psychiatrist