Janos Radó: Mechanism of Lithium Induced Polyuria in Historical Perspective

Abstract

The present therapy for lithium-induced nephrogenic diabetes insipidus in man is to counter anti-vasopressin action of lithium by administration of thiazide diuretics, antiprostaglandin compounds (indomethacine) combined with large doses of desmopressin. (Amiloride supplements the "present therapy" drug group). The "future" treatment seems to be (on the basis of recent animal experiments) to enhance the sensitivity of the kidney to vasopressin action by administering pharmacologic blockade of renal P2Y12 receptor. On theoretical basis it is conceivable that the present therapy of lithium-induced nephrogenic insipidus perhaps could be combined with the "future" pharmacologic blockade.

Introduction

In 1978 we found that in response to indomethacine administered to polyuric patient with familial Bartter syndrome, urine osmolality and free water reabsorption increased simultaneously with the decrease in the excretion of prostaglandin E2 (PGE2) (Radó, Simatupang, Boer and Mees 1978). In 2012 Zhang and his coworkers found that lithium-induced polyuria is due to resistance of the medullary collecting duct to the action of arginine vasopressin, apparently mediated by increased production of PGE2 (Zhang, Pop, Carlson and Kishore 2012). Therefore, *PGE2 must be a key factor in the understanding and treatment of lithium polyuria*. My early studies on indomethacine and desmopressin in Bartter polyuria, later studies on indomethacine and desmopressin in lithium-induced permanent nephrogenic diabetes insipidus and the results of the new studies of many investigators working in groups with Zhang and with Zhang and Peti-Peterdi ("Zhang and Peti-Peterdi group") are discussed together.

The purpose of this paper is to review the newer literature concerning the relationship between lithium polyuria and chemical (PGE2 and other), as well as genetic (P2Y12 receptor) factors.

Early Studies

In 1978 we investigated the effect of indomethacin and desmopressin on water excretion in a 32-year-old patient with *familial* Bartter's syndrome in whom urinary concentration was impaired during ad libitum fluid intake without any decrease in maximal concentrating ability (Rado, Simatupang, Boer, Dorhout Mees 1978).

As shown in Figure1 and Table1, in response to indomethacin, urine osmolality and free water reabsorption increased simultaneously with the decrease in the excretion of prostaglandin E2. The indomethacin-induced improvement was, however, *less* than that obtained after desmopressin with or without indomethacin.

Desmopressin (Minirin) was administered in doses of 40 micrograms three times a day intranasally. After a control period (17 days) the effects of daily 200mcg indomethacine was studied during the last 12 days of a month treatment period. One week after discontinuation of indomethacine treatment desmopressin was given again in the same dose as previously.

We compared the urine osmolality findings obtained in healthy subjects and in a polyuric patient with Bartter syndrome without treatment ("no drug") and after administration of desmopressin (DDAVP) or indomethacine, as well as after combined administration of desmopressin and indomethacine during ad libitum fluid intake (Figure 1). Two determinations were done during administration of desmopressin after prolonged water restriction (quadrants).

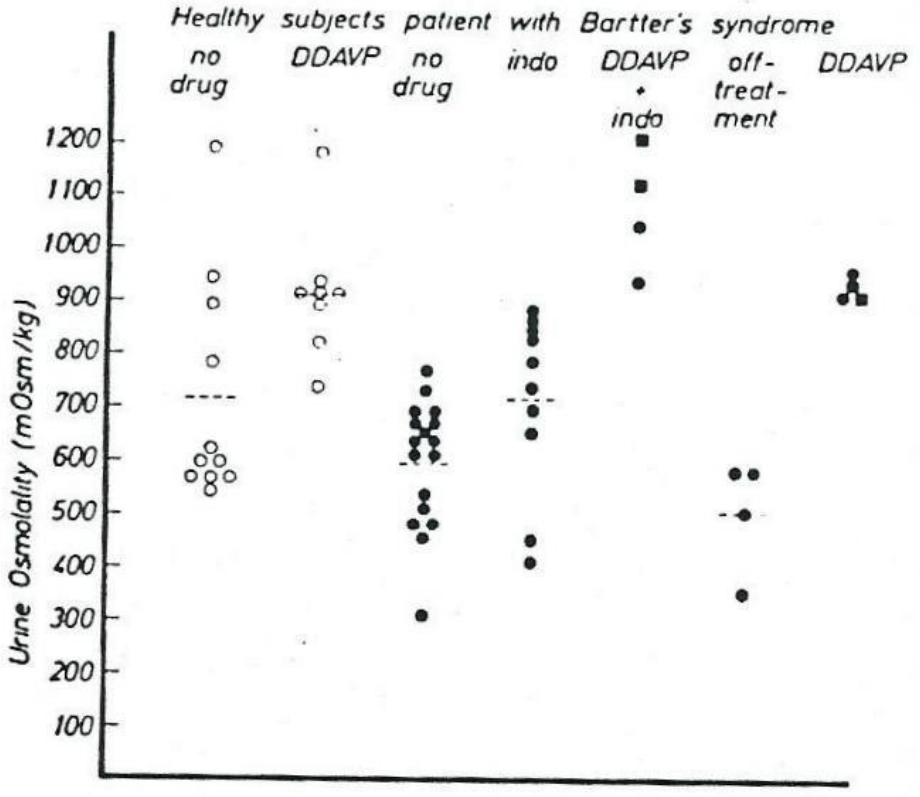

Figure 1. Urine osmolality (U_{osm}) was lower in the untreated patient than in the healthy subjects. After DDAVP this difference disappeared. Indomethacin induced a marked increase in U_{osm} in the patient.

As shown in Figure 1, in the patient with Bartter syndrome indomethacine potentiated the effect of desmopressin (DDAVP). During prolonged water restriction and desmopressin administration, urine osmolality was 924 mOsm/Kg, increasing to 1169 mOm/Kg in response to indomethacine (quadrant).

Table 1 shows the effects of indomethacine, desmopressin (DDAVP) and indomethacine plus desmopressin on specific renal function. Results of statistical analysis are indicated.

	Control	Indomethacin	Indomethacin + DDAVP	Off-treatment Control	DDAVP
n (days)	17	10	2	4	2
Urine osmolality (mOsm/Kg)	594[x] ± 28	713[x] ± 52	990[z] ± 22	504 ± 55	927[z] ± 28
Osmolal clearance (ml/min)	3.17 ± 0.16	2.94 ± 0.23	2.71 ± 0.45	2.91 ± 0.26	2.86 ± 0.22
Free water reabsorption (ml/min)	1.62 ± 0.14	1.70 ± 0.21	1.91 ± 0.25	1.16 ± 0.20	1.98 ± 0.17
Glomerular filtration rate (ml/min/1.73 M^2)	94.1 ± 3.5	92.6 ± 5.3	110.8 ± 12	96.2 ± 9.4	112.6 ± 8.5

x = $p<0.05$. z = contracted: 958 ± 30 ($p<0.001$ as compared to control; $p<0.005$ as compared to indomethacin)
Osmolal clearance and free-water reabsorption is expressed in the percentage of glomerular filtration rate.

Table 1. Effect of Indomethacin and DDAVP on renal concentrating operation during ad libitum fluid intake.

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Effect of indomethacine on prostaglandins

During indomethacin treatment, excretion of PGE2 was decreased from 138.3 ng/24 hrs to 55 ng/24 hrs (normal range: 9-12 ng/24 hrs). PGA decreased from 205 ng/24 hrs to 97 ng/24 hrs (normal range: 71-144 ng/24 hrs), PGB decreased "from 95 ng/24 hrs to 49 ng/24 hrs (normal range: 36-74 ng/24 hrs) and PGF decreased from 146 ng/24 hrs to 64' ng/24 hrs (normal range: 40-83 ng/24 hrs).

The blood level of PGE1 also decreased from 38.9 pg/ml to 23.2 pg/ml (normal: 5.5 ± 0.8 pg/rnl). PGA changed from 241 pg/ml to 269 pg/ml (normal: 94 ± f 5 pg/rnl), PGB from 129 pg/ml to 107 pg/ml (normal: 1 il9 ± 14 pg/nil) and PGF from 22 pg/ml to 9.4 pg/ml (normal: 17.2 ± 3.3 pg/ml).

(We are greatly indebted to Prof. Dr. A. Hornych, Hopital Broussais, Paris, who kindly performed the prostaglandin determinations).

Later Studies on Indomethacine and Desmopressin

In "use of modern antidiuretic agents in the treatment of permanent lithium-induced nephrogenic diabetes insipidus" (Radó 2018a) we found that administration of excessive doses of desmopressin resulted in clinically relevant antidiuresis, enhanced by indomethacine and abolished by calcitonine. A theory was proposed why the presumed antidiuretic drug calcitonine exerted a "diuretic" action by abolishing the effect of desmopressin (Radó, Zdravkova 1991, 1993; Radó 2018b). These results and thoughts were discussed by Gordon Johnson (2018) and Hector Warnes (2019). Renal toxicity of lithium was reviewed in a balanced manner, considering both the renal insufficiency and end-stage renal disease, as well as the *prominant* tubular abnormality of nephrogenic diabetes insipidus (Radó 2019b). In this review the role of the large doses of desmopressin was analyzed in counteracting polyuria in congenital as well as in lithium-induced nephrogenic diabetes insipidus during combined administration of many different drugs (thiazide diuretics, indomethacine, piroxicam, calcitonine, etc.). Other drugs also having antidiuretic properties but without coadministration with desmopressin were also mentioned (metformin, statins, sildenafil, clopidrogel, prasugral etc.). Finally, antidiuretic drugs which could have been combined with desmopressin, but not promising in the treatment in lithium-induced nephrogenic insipidus, i.e., chlorpropamide, clofibrate and carbamazepine, were also included. From these compounds carbamazepine is an exception: its weak antidiuretic effect, combined with desmopressin, may be advantageous when it is otherwise indicated from psychiatric point of view (Radó 2019a)

New Investigations of the Zhang and Peti-Peterdi Group

Zhang and his coworkers found that lithium-induced polyuria is due to resistance of the medullary collecting duct to the action of arginine vasopressin (AVP), apparently mediated by increased production of PGE2. Genetic deletion of the $P2Y_2$ receptor offered significant resistance to development of lithium polyuria. This change was accompanied by alterations in PGE_2 signaling mediated by a marked decrease in the prostanoid EP_3 receptor protein abundance thus attenuating the decrease in cAMP, modulator of arginine vasopressin, in the renal medulla (Zhang, Pop, Carlson and Kishore 2012; Zhang, Hansson, Liu , Kishore 2019).

P2Y12 Receptor Localizes in the Renal Collecting Duct

P2Y12 receptor signaling reduces cellular cAMP levels, the central modulator of arginine vasopressin. It was hypothesized that if expressed in the renal collecting duct P2Y12 receptor may play a role in renal handling of water in health and in nephrogenic diabetes insipidus. *P2Y12 receptor mRNA expression in rat kidney, and immunolocalized its protein and aquaporin-2 in collecting duct principal cells was found* (Zhang, Peti-Peterdi, Müller et al. 2015).

Short-Term Studies in the P2Y12 Receptor Knockout Mice

In the P2Y12 receptor knockout mice, enhanced vasopressin activity and increased renal sodium conservation was found. These animals were less sensitive not only to the diuresis enhancement induced by lithium, but also to the lithium-induced natriuresis and kaliuresis due to the attenuation of down regulation of the major natrium or kalium transporter/channel proteins in the collecting duct (Zhang, Li, Kohan et al. 2013).

Long-Term Studies in the P2Y12 Receptor Knockout Mice

Age matched wild type and P2Y12 receptor knockout mice were fed regular or lithium-added diet for five months. There was a steady increase in lithium-induced polyuria, nariuresis and kaliuresis in wild type mice, but increases in these parameters were very low in the knockout mice. Lithium-induced collecting duct proliferation was significantly lower in the knockout vs wild type mice. The results demonstrate that genetic deletion of P2Y12 receptor protects against the key structural and functional alterations in lithium-induced nephrogenic diabetes insipidus. Genetic deletion of P2Y12 receptor offers long-term (five months) protection against lithium-induced polyuria, natriuresis, kaliuresis and collecting duct remodeling and cell proliferation (Zhang, Riquier-Brison, Liu et al. 2018)

The most widely studied purinergic receptor in the kidney is ATP-activated P2Y12 receptor which is expressed in the collecting duct. Signaling mediated through P2Y12 receptor antagonizes the vasopressin action by enhancing the production of PGE_2 (Kishore, Carlson, Ecelbarger et al. 2015).

The present therapy for lithium-induced nephrogenic diabetes insipidus in man is to counter *anti-vasopressin action of lithium.* The future treatment *is to enhance the sensitivity of the kidney to vasopressin action* (Kishore, Carlson, Ecelbarger et al. 2015).

Administration an Irreversible Inhibitor of the P2Y12 Receptor (*clopidogrel)*

Clopidogrel bisulfate significantly increased urine concentration and aquaporine protein in the kidneys of Sprague–Dawley rats but did not alter urine concentration in Brattleboro rats that lack arginine-vasopressin. Clopidogrel administration also significantly ameliorated lithium-induced polyuria, improved urine concentrating ability and aquaporine protein abundance *and reversed the lithium-induced increase in freewater excretion*. ***Selective blockade of P2Y12 receptor by the reversible antagonist PSB-0739 in primary cultures of rat inner medullary collecting duct principal cells potentiated the expression of aquaporine and cAMP production induced by desmopressin*** (Zhang, Peti-Peterdi, Müller et al. 2015).

Clopidrogel alone increased renal aquaporin 2, Na-K-2Cl cotransporter, Na-Cl cotransporter and the subunits of the epithelial Na channel (ENaC) in renal medulla. When combined with lithium, clopidrogel prevented downregulation of aquaporin, Na-K-ATPase and Na-K-2Cl cotransporter but was less effective against downregulation of cortical sodium channel (α- or γ-ENaC). *Thus, clopidrogel primarily attenuated lithium-induced downregulation of proteins involved in AVP-sensitive water conservation* (Zhang, Peti-Peterdi, Heiney et al. 2015)

Clopidrogel is an antiplatelet drug of the thienopyridine group extensively used in cardiological clinical medicine. Another such drug is *prasugral* and both are ADP antagonists *acting on the P2Y12 receptor*. Administration of *prasugral* completely suppressed lithium-induced polyiuria and polydipsia in rats (Zhang, Peti-Peterdi, Brandes et al. 2017)

Pharmacologic Blockade of Renal P2Y12 Receptor

*Pharmacologic blockade of renal P2Y12 receptor in rodents increases urinary concentrating ability by augmenting the effect of vasopressin on the kidney and ameliorates lithium-induced nephrogenic diabetes insipidus by potentiating the action of vasopressin on the renal collecting duct (*Zhang Peti-Peterdi, Müller et al. 2015*). This strategy may offer a novel and effective therapy for lithium-induced nephrogenic diabetes insipidus in man..*

Conclusion

Pharmacologic blockade of renal P2Y12 receptor may be combined - at least theoretically - with anti-prostaglandin agents (non-steroidal anti-inflammatory compounds) and supplemented with large doses of desmopressin in the treatment of lithium-induced nephrogenic diabetes insipidus. Lithium-induced excessive prostaglandinuria (increased excretion of PGE_2) can be prevented by pharmacologic blockade of the renal P2Y12 receptor and antagonized by the administration of indomethacine.

We are all definitely convinced by the enormous work of Ban (2017), Blackwell (2014), Rybakowski (2017), Severus, Taylor, Sauer et al. (2014) and others that millions suffering from bipolar disorder need lithium treatment and making it safer by eliminating (at least partly) its most frequent side effect lithium polyuria, is a decent goal for both the investigators and physicians.

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