May 21, 2020

Online Symposium of the Korean Endocrine Society

Diagnosis and treatment of central diabetes insipidus

Department of Endocrinology and Diabetes,
Nagoya University Graduate School of Medicine

Hiroshi Arima

- Water balance
- Diagnosis of central diabetes insipidus (CDI)
- Treatment of CDI
- Adipsic CDI
- Familial neurohypophysial diabetes insipidus

- Water balance
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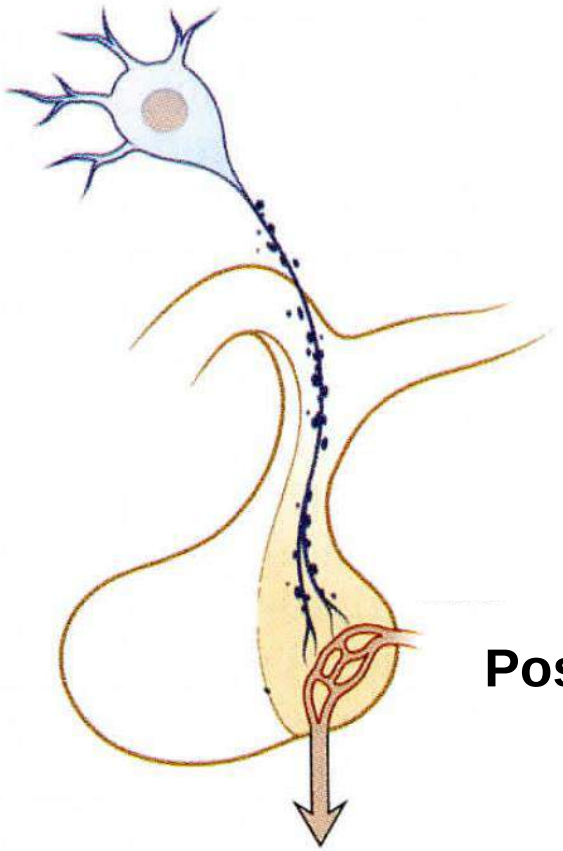
Synthesis and release of arginine vasopressin (AVP)

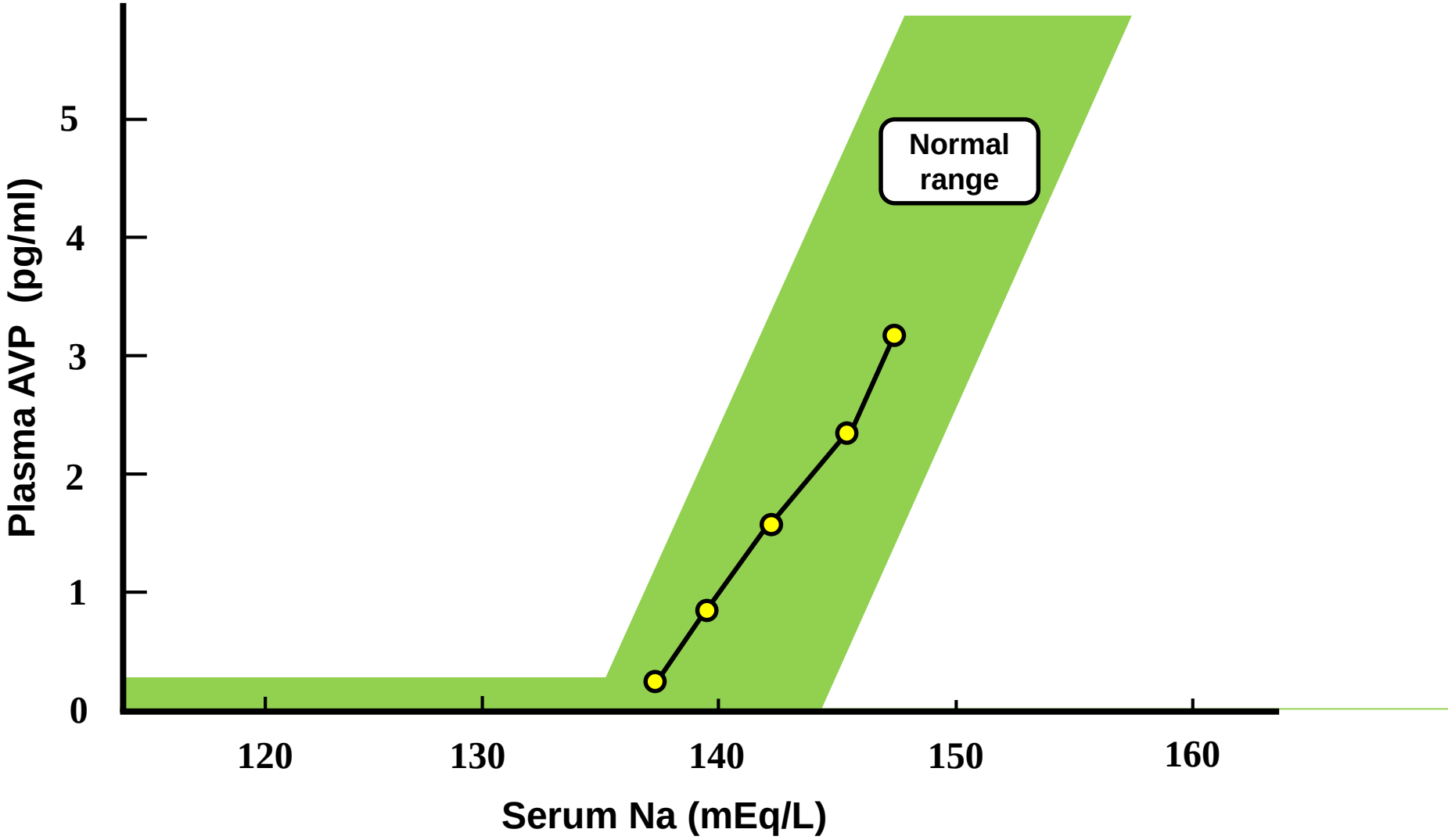
AVP neurons in hypothalamus



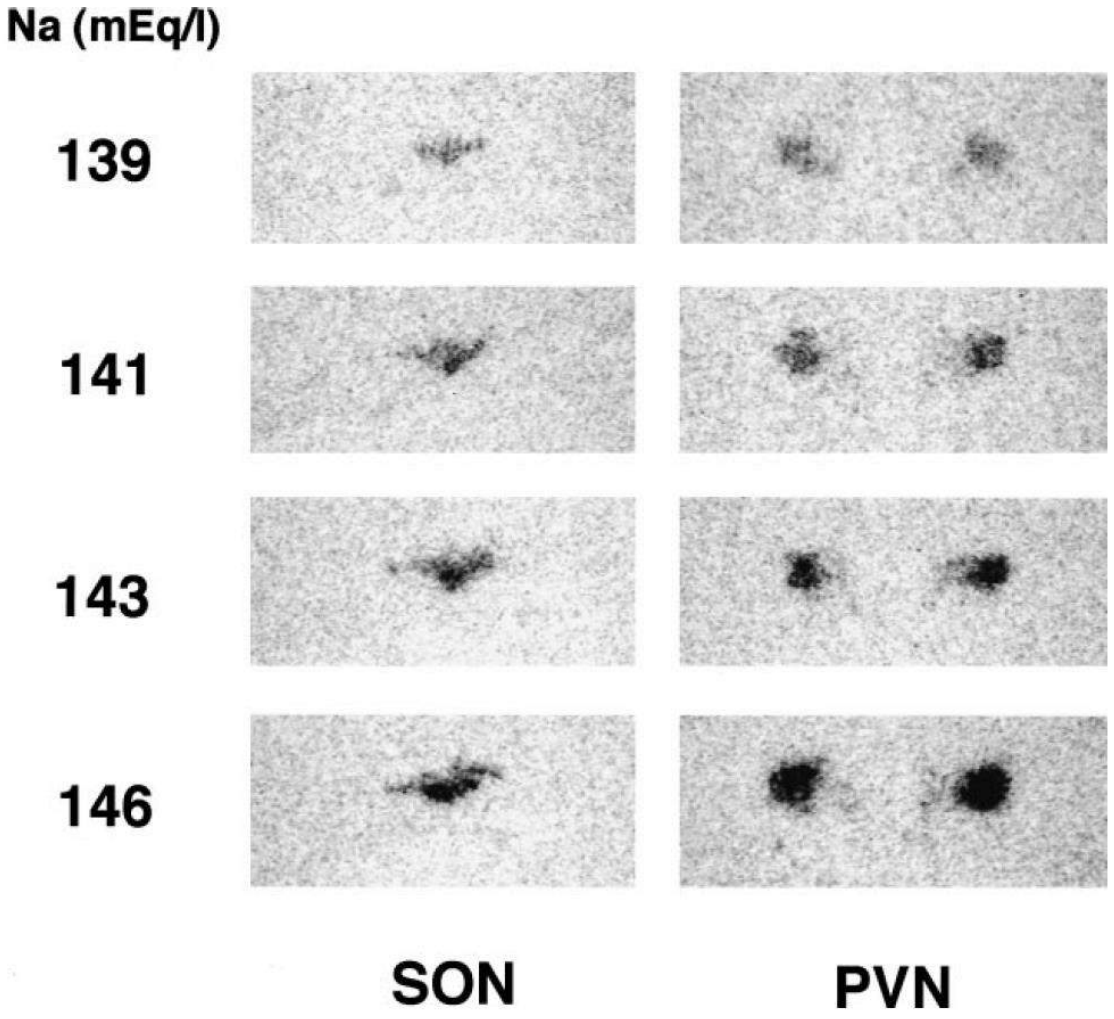
Posterior pituitary

AVP release

AVP is released in response to increases in serum Na



AVP is synthesized in response to increases in serum Na



Arima et al., 1999 J **Neuroendorinol**

Pituitary MRI

Pituitary AVP content is decreased under dehydration

Plasma AVP (pg/ml)	
Base	Dehydrated
1.65 ± 0.04	12.88 ± 2.43^{c}

AVP content (μg/pituitary)	
Base	Dehydrated
1.67 ± 0.10	0.59 ± 0.11^{c}

Arima et al., 1998 **Endocrinology**

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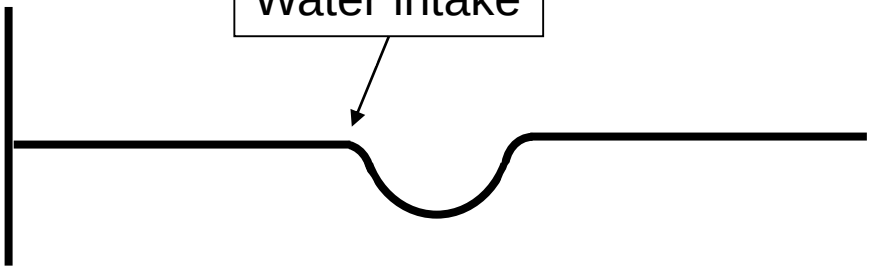
Arima et al., 1998 **Endocrinology**

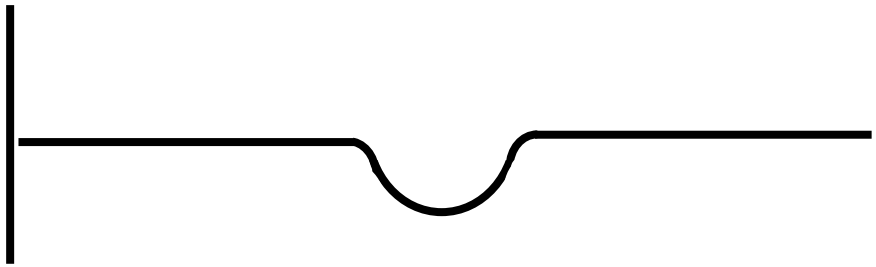
Serum Na

Water intake

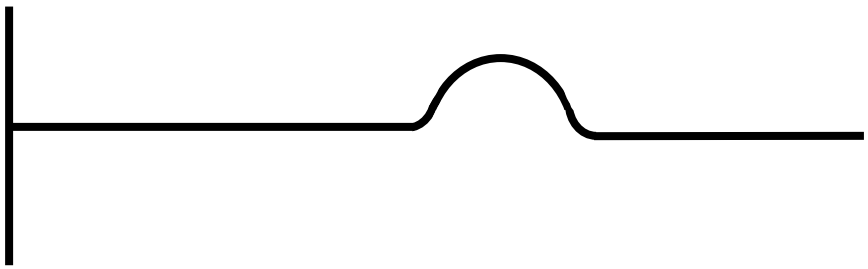
140 mEq/l



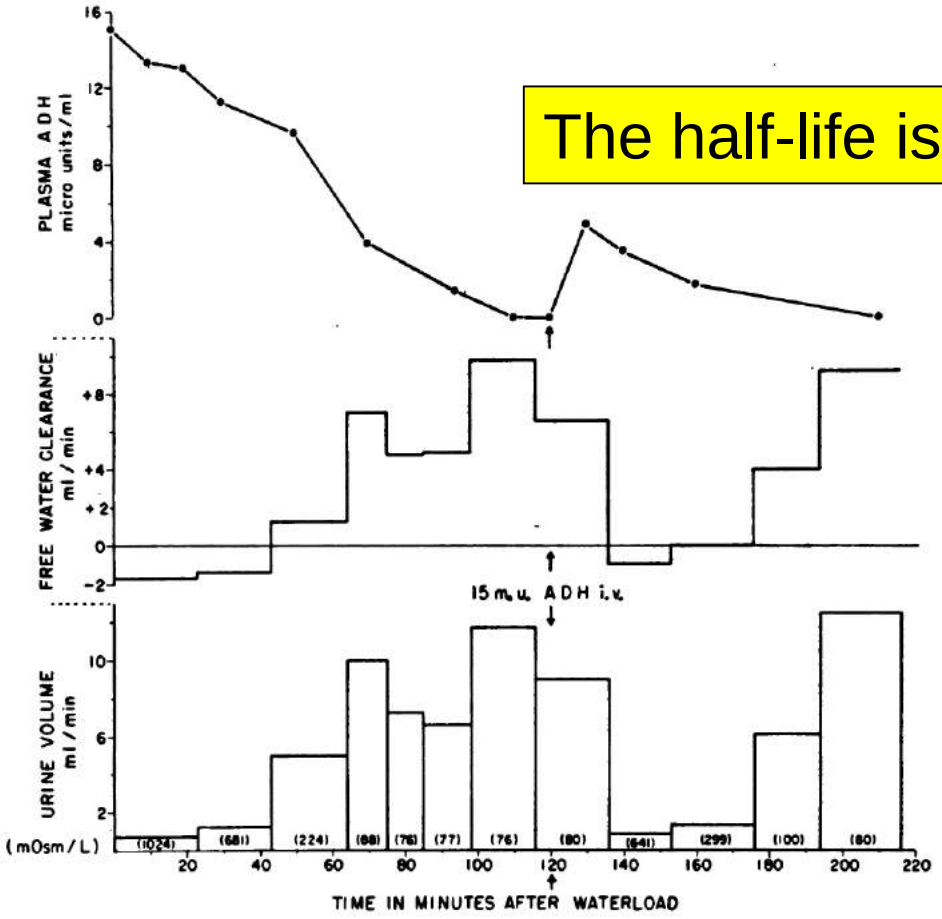
Plasma AVP



Urine output



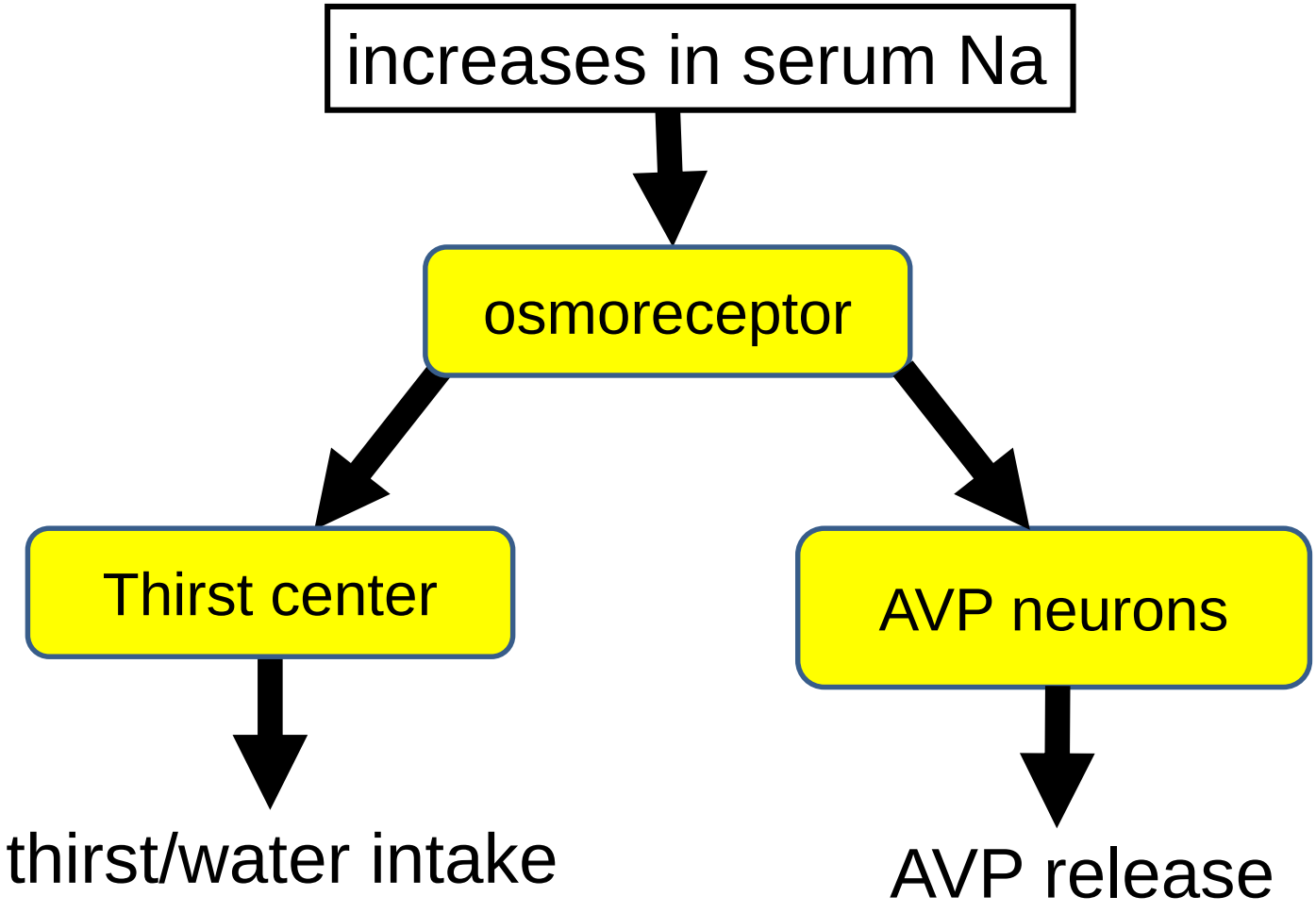
The half-life of AVP in plasma



The half-life is about 15 min

Czaczkes JW et al., 1964 **J Clin Invest**

AVP release and water intake



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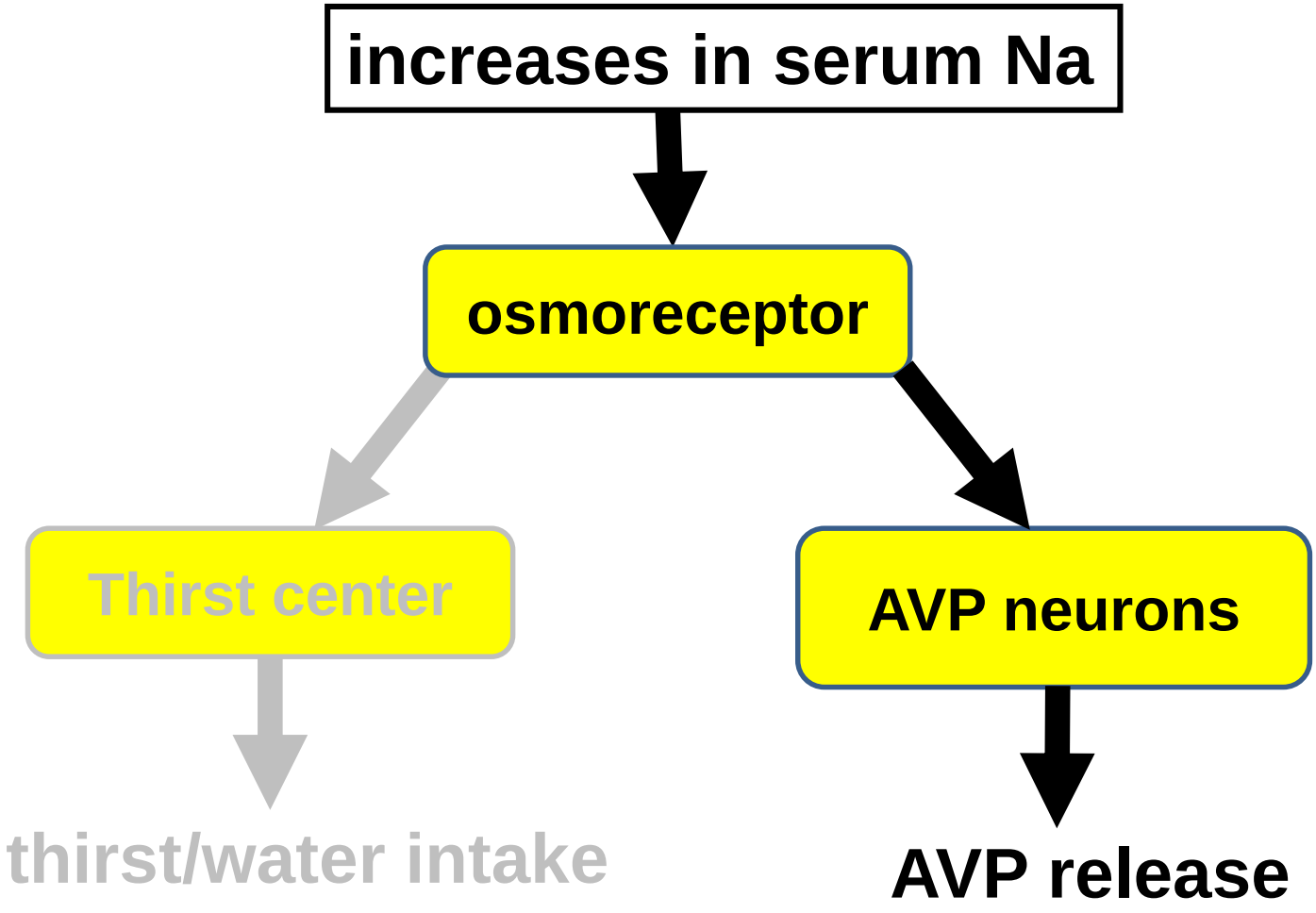

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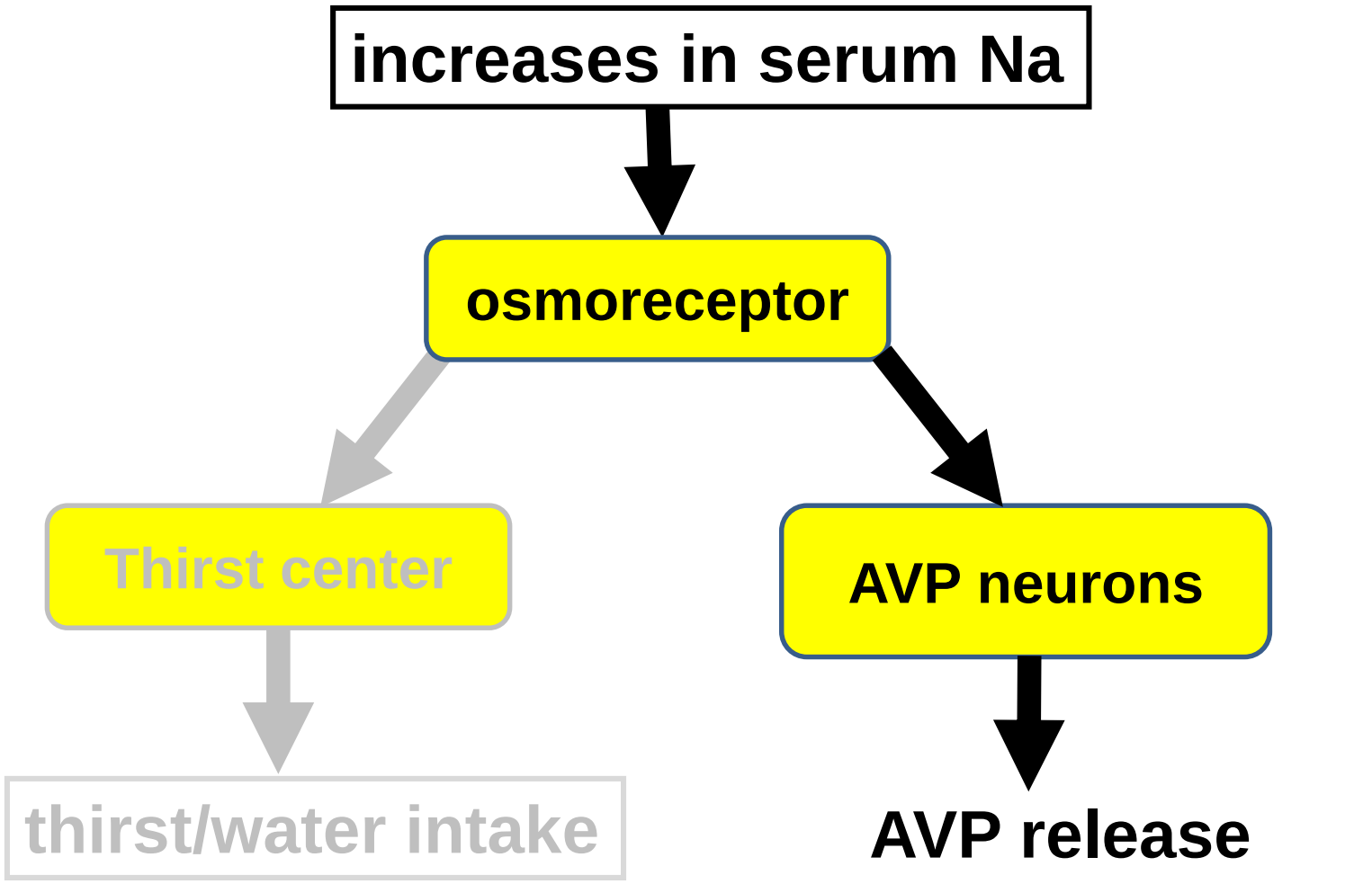

Threshold: Na 140 mEq/L

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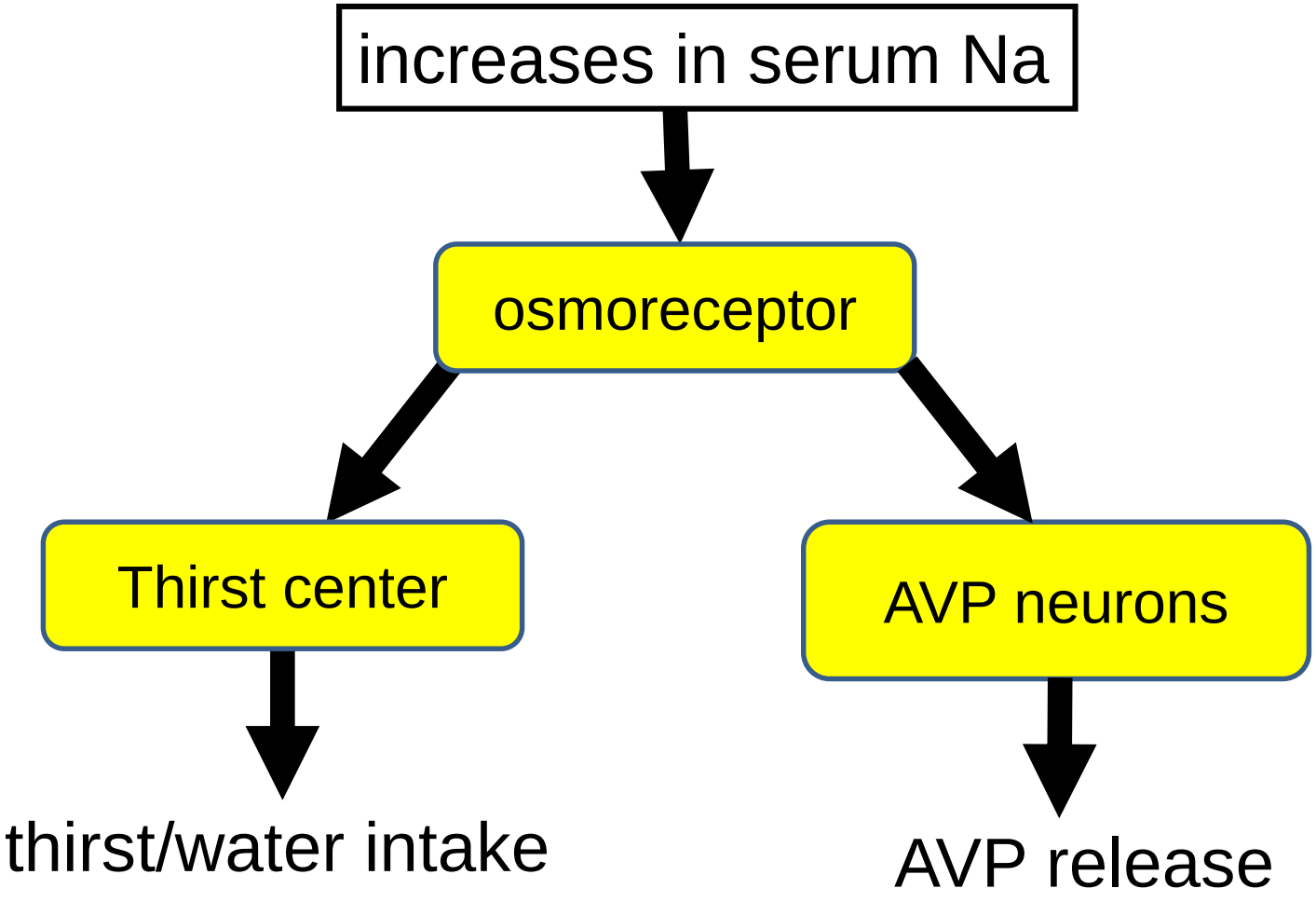

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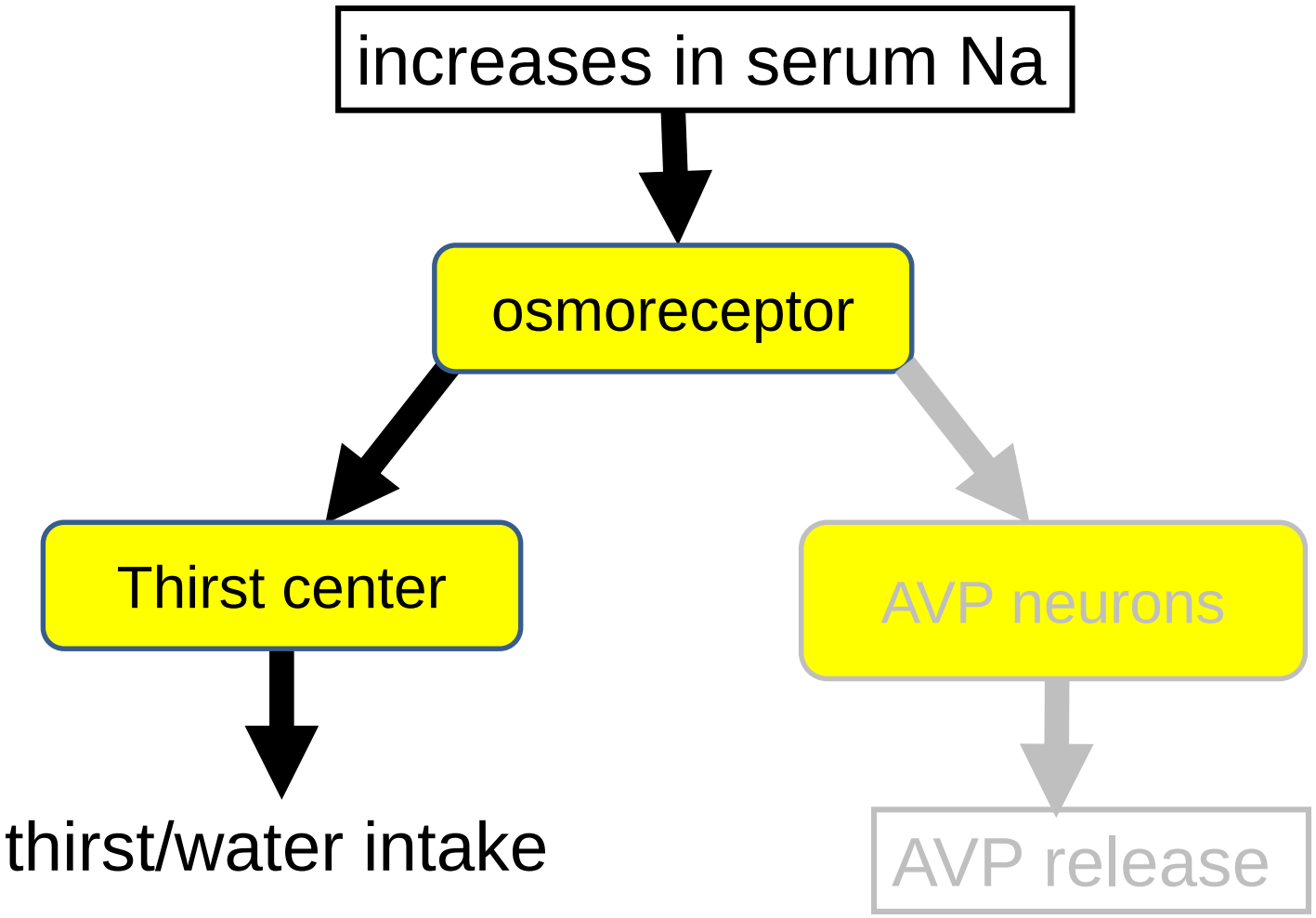


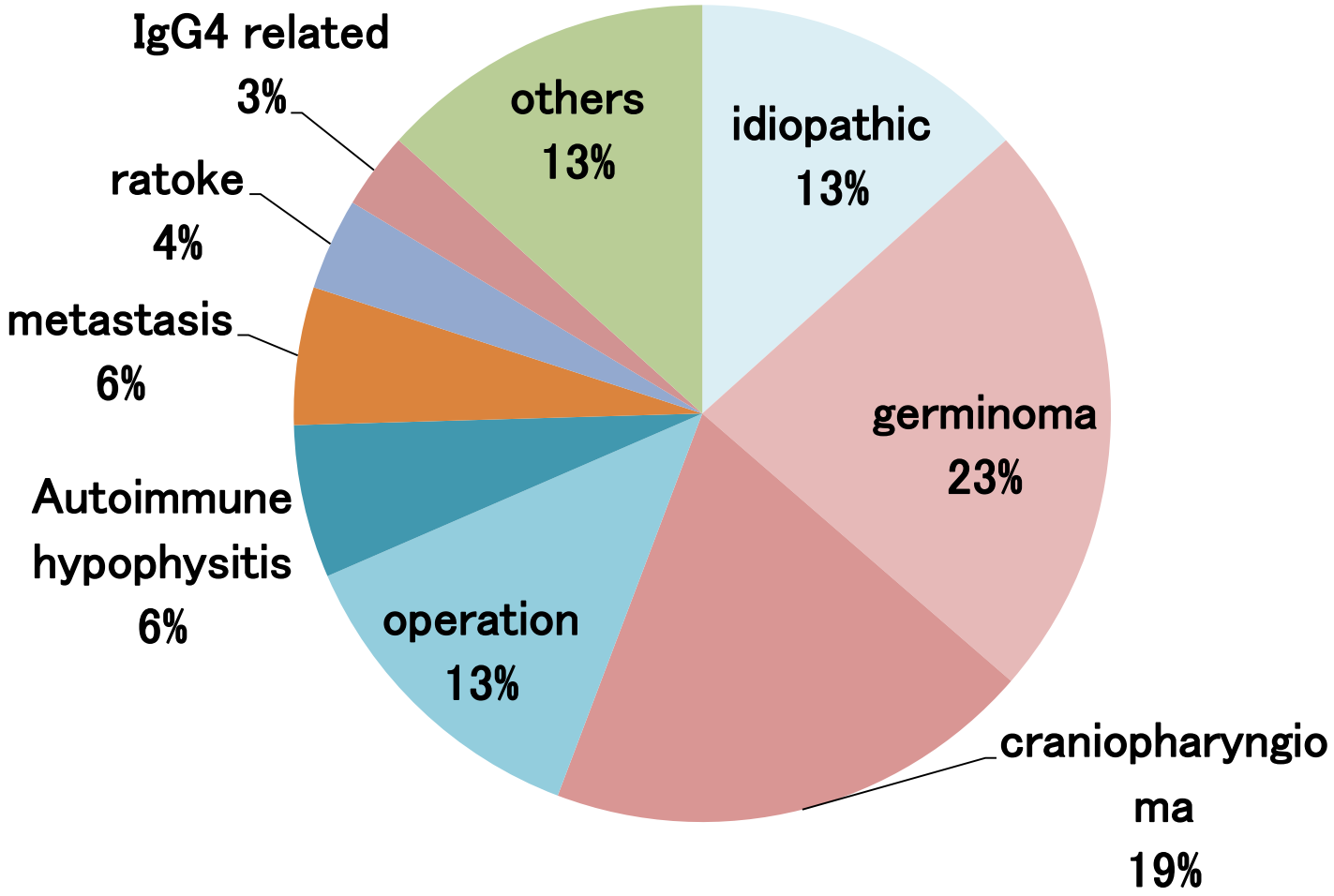
threshold：Na 145 mEq/L

Pituitary MRI

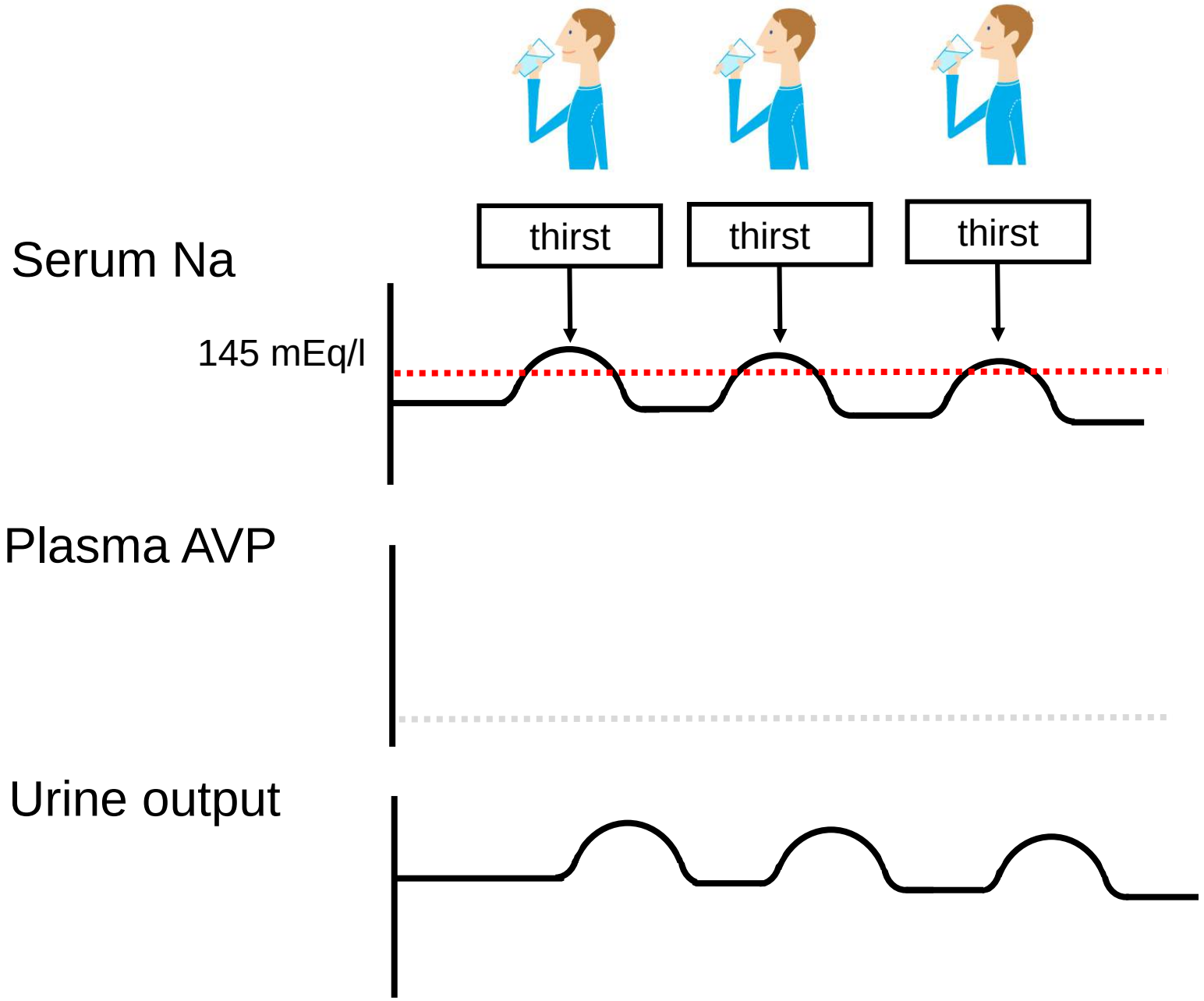
Healthy control

CDI

Etiology of central diabetes insipidus



Arima H et al., 2016 **Nagoya J Med Sci**


thirst
thirst
thirst
Serum Na
145 mEq/l
Plasma AVP
Urine output

Research on hypothalamic pituitary disorder Ministry of Health, Labor, and Welfare

Guidelines for diagnosis and treatment of hypothalamic pituitary disorders

published in 2019 (in Japanese)

1. Acromegaly
2. Cushing disease
3. Prolactinoma
4. Diabetes insipidus
5. SIADH
6. Congenital nephrogenic diabetes insipidus
7. Gonadotropin producing pituitary tumor
8. Central precocious puberty

Guidelines for diagnosis and treatment of hypothalamic pituitary disorders

published in 2019 (in Japanese)

9. TSH producing pituitary tumor
10. GH deficiency short stature
11. Transition from child to adult in GH deficiency
12. Adult GH deficiency
13. ACTH deficiency
14. Prolactin deficiency
15. Gonadotropin deficiency
16. TSH deficiency
17. Incidental pituitary tumor
18. Autoimmune hypophysitis
19. IgG4 related hypophysitis

Diagnosis of central diabetes insipidus

Ⅰ. Main symptoms

1. thirst
2. polydipsia
3. polyuria

Ⅱ. Inspection findings

1. Daily Urine volumes >3,000 ml or >40 ml/kg in adult
   >2,000 ml/m^2 in child

2. Urine osmolality < 300 mOsm/kg

3. Increases in AVP release during hypertonic saline injection are attenuated

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3. Increases in AVP release during hypertonic saline injection are attenuated

Questions which should be asked before hypertonic saline injection test

- How much volume of water do you drink every day?
  （how many PET bottles?）
- How often do you go to the bathroom at night?
  （Don’t you drink water or alcohol before going to bed?）
- Do you drink water when you wake up at night?
  （Do you feel thirsty at night?）

AVP RIA in Japan

	AVP RIA 「Mitsubushi」	AVP RIA Neo 「SML」	AVP kit 「YAMASA」
Period	Until March, 2012	From June 2012 to February, 2017	Since march 2015
sensitivity	0.2 pg/mL	0.8 pg/mL	0.4 pg/mL
Cross-reactivity with DDAVP	0.1%	0.88%	< 0.001%

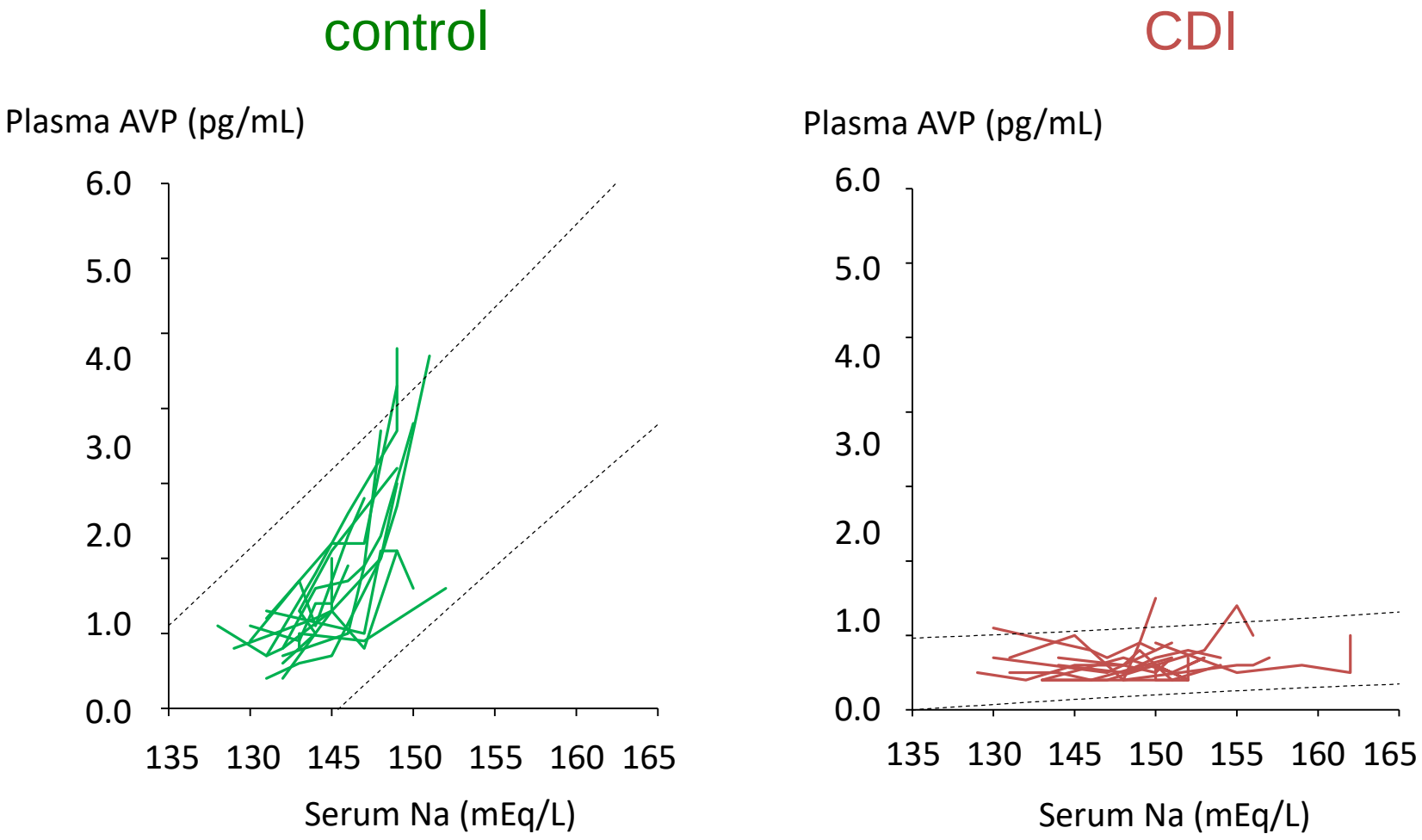
Control

Case	Gender	age	disease	Urine volumes (mL/day)	Urine volumes (mL/kg/day)	Urine osmolality (mOsm/kg)	evaluation
1	F	38	Craniopharingioma	638	11.3	468	Before TSS
2	F	26	normal	1,300	30.7	496	-
3	M	45	acromegaly	1,400	20.2	607	After TSS
4	F	76	acromegaly	2,150	35.6	484	After TSS
5	M	63	acromegaly	1,850	21.0	498	After TSS
6	F	63	normal	1,800	44.1	311	-
7	F	72	acromegaly	1,145	24.2	419	Before TSS
8	F	57	AGHD	2,110	36.1	575	After TSS
9	M	53	acromegaly	1,655	19.9	950	-
10	M	49	acromegaly	1,300	14.9	639	After TSS
11	M	71	acromegaly	1,250	20.4	618	After TSS
12	F	75	normal	1,500	25.0	290*	-
13	M	65	acromegaly	1,780	18.1	531	After TSS

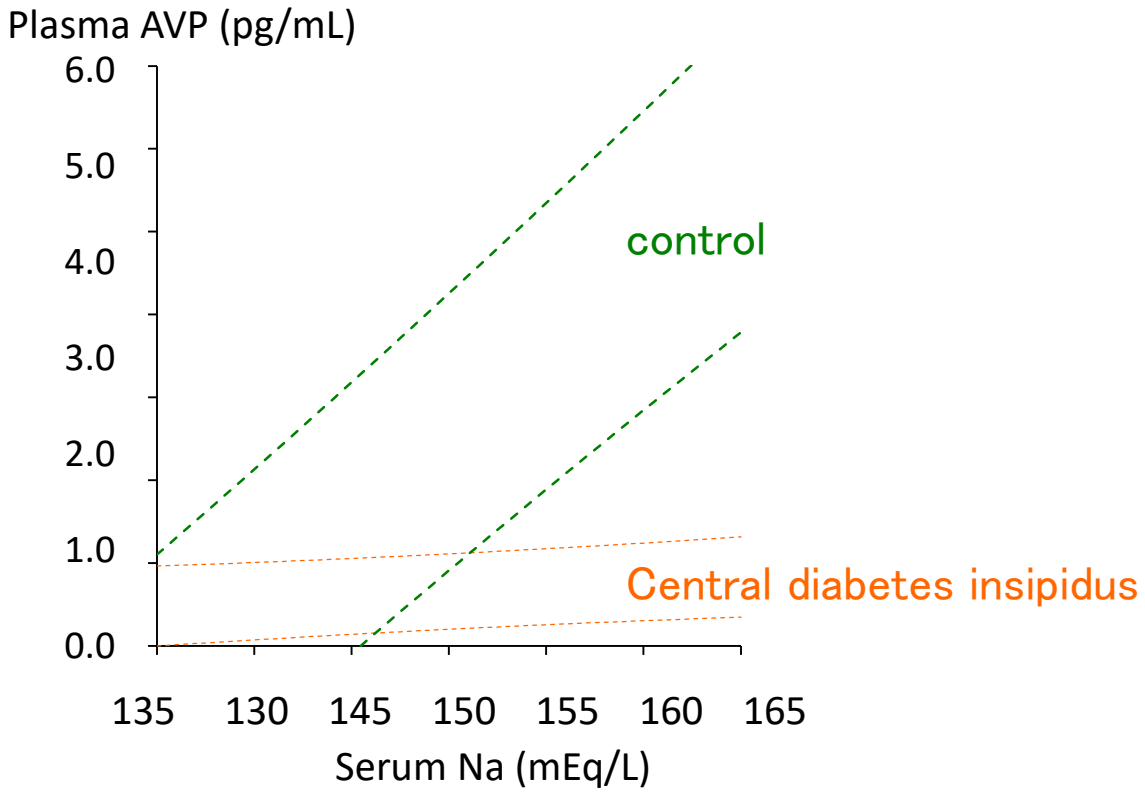
CDI patients

Case	gender	age	After diagnosis	Urine volume		Urine osmolality	etiology
				(mL/day)	(mL/kg/day)	(mOsm/kg)	
1	M	42	0	9,000	124.0	111	idiopathic
2	M	46	0	5,600	87.6	103	idiopathic
3	F	62	0	8,060	155.0	n.d.	angiogranuloma
4	M	53	1	5,000	47.5	n.d.	Pituitary tumor
5	F	40	0	4,000	89.1	n.d.	Pituitary tumor
6	F	38	4	8,400	166.7	n.d.	craniopharyngioma
7	M	56	3	n.d.	n.d.	134	Pituitary tumor
8	F	32	0	5,600	107.7	126	Pituitary tumor
9	M	47	2	2,800	41.1	n.d.	IgG4
10	F	45	9	10,000	108.0	n.d.	idiopathic
11	F	53	0	3,500	53.0	159	Pituitary tumor
12	M	64	27	n.d.	n.d.	n.d.	idiopathic
13	M	73	0	2,740	52.7	n.d.	IgG4

AVP release during hypertonic saline injection

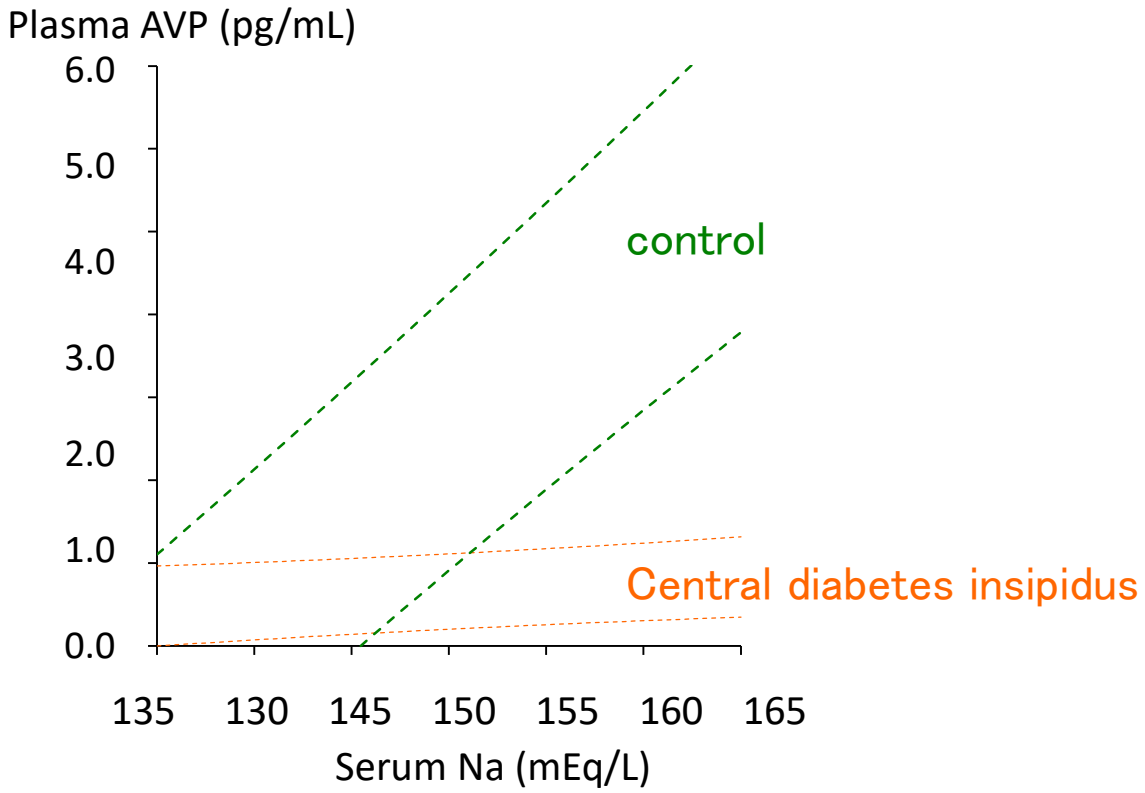


AVP release during hypertonic saline injection



There are no differences in basal values of plasma AVP between control and CDI

AVP release during hypertonic saline injection

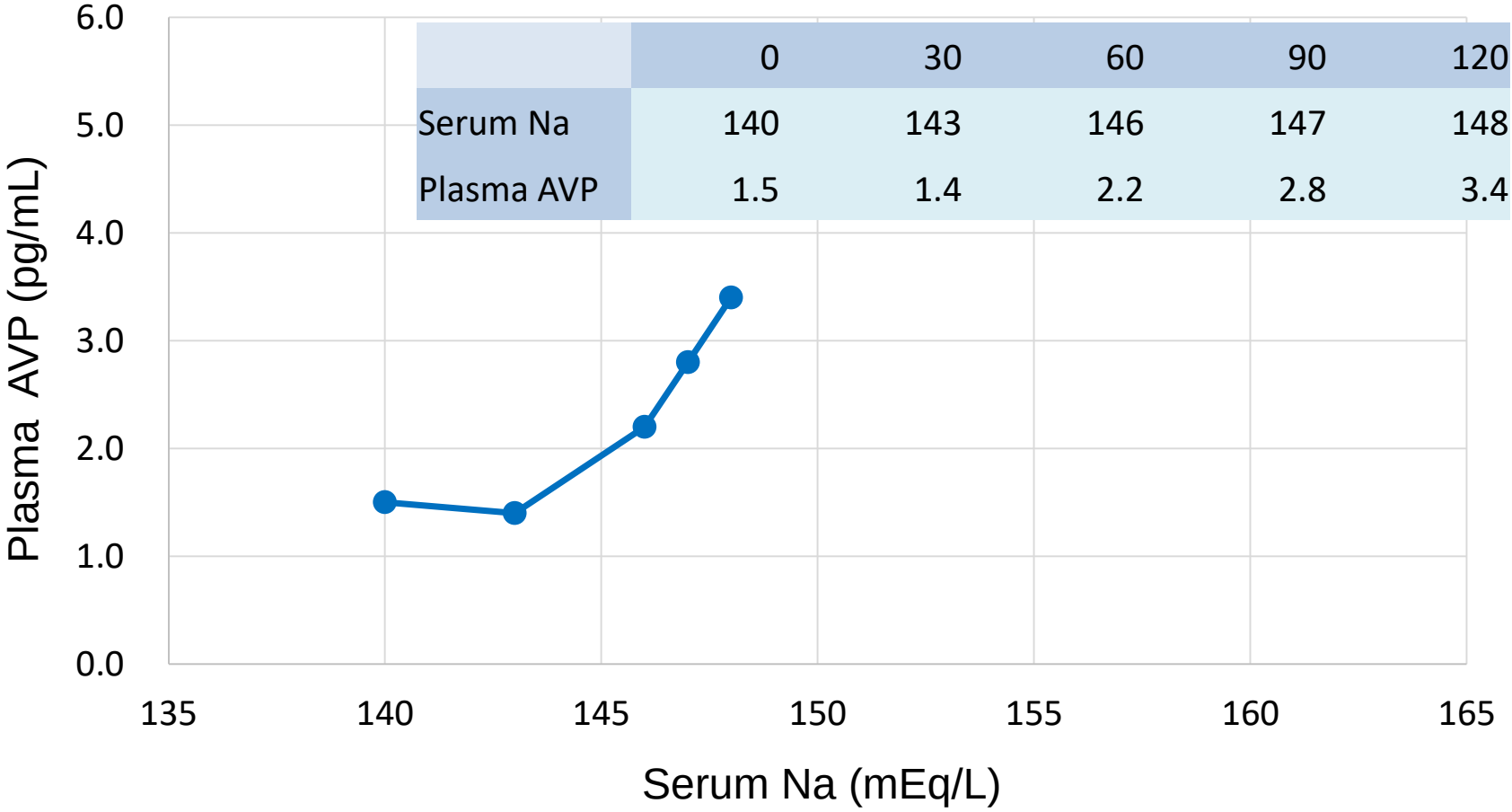


① gradient of regression lines

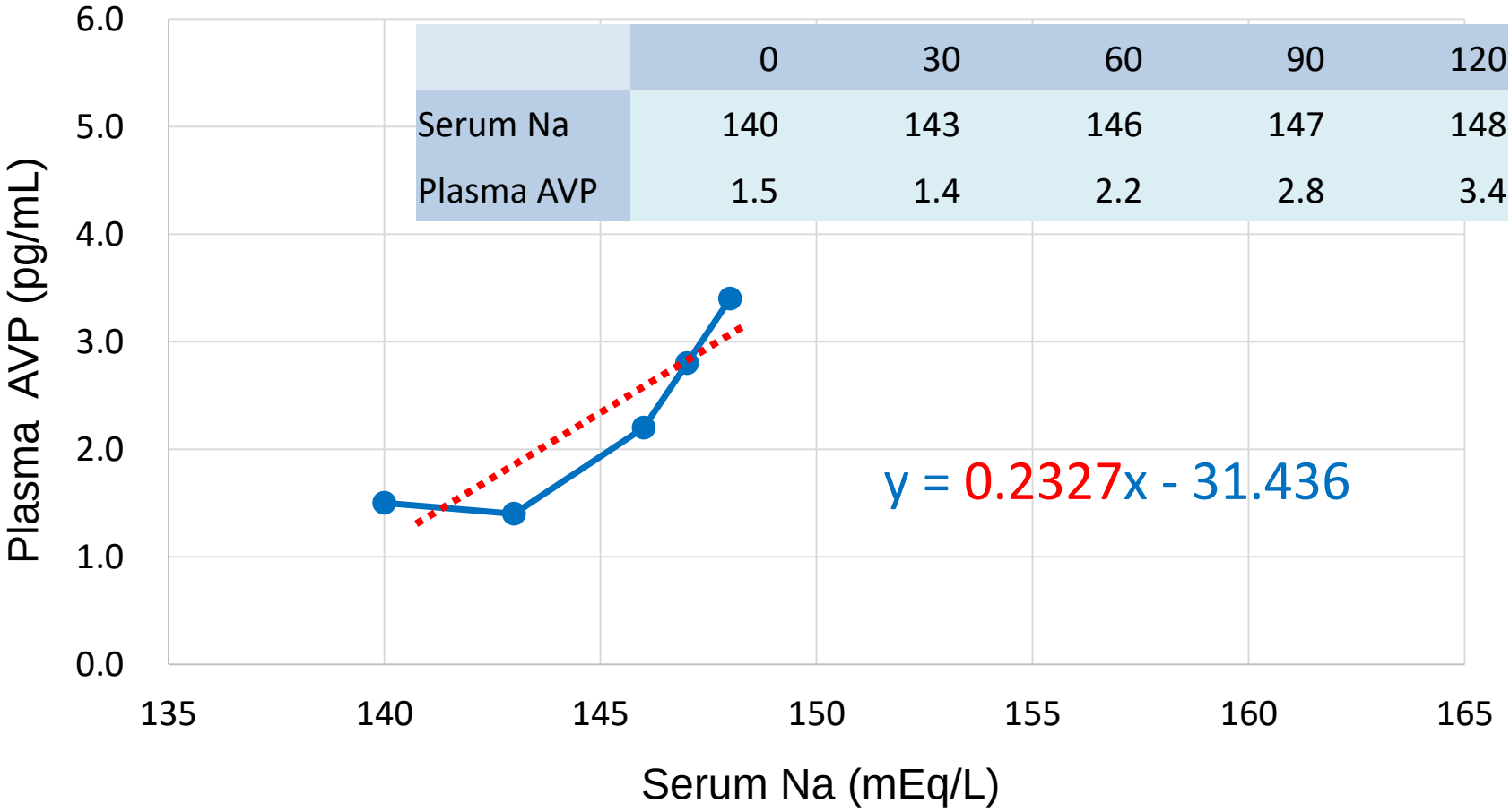
② estimated plasma AVP values at serum Na 149 mEq/L

Gradient of regression lines

	0	30	60	90	120
Serum Na	140	143	146	147	148
Plasma AVP	1.5	1.4	2.2	2.8	3.4

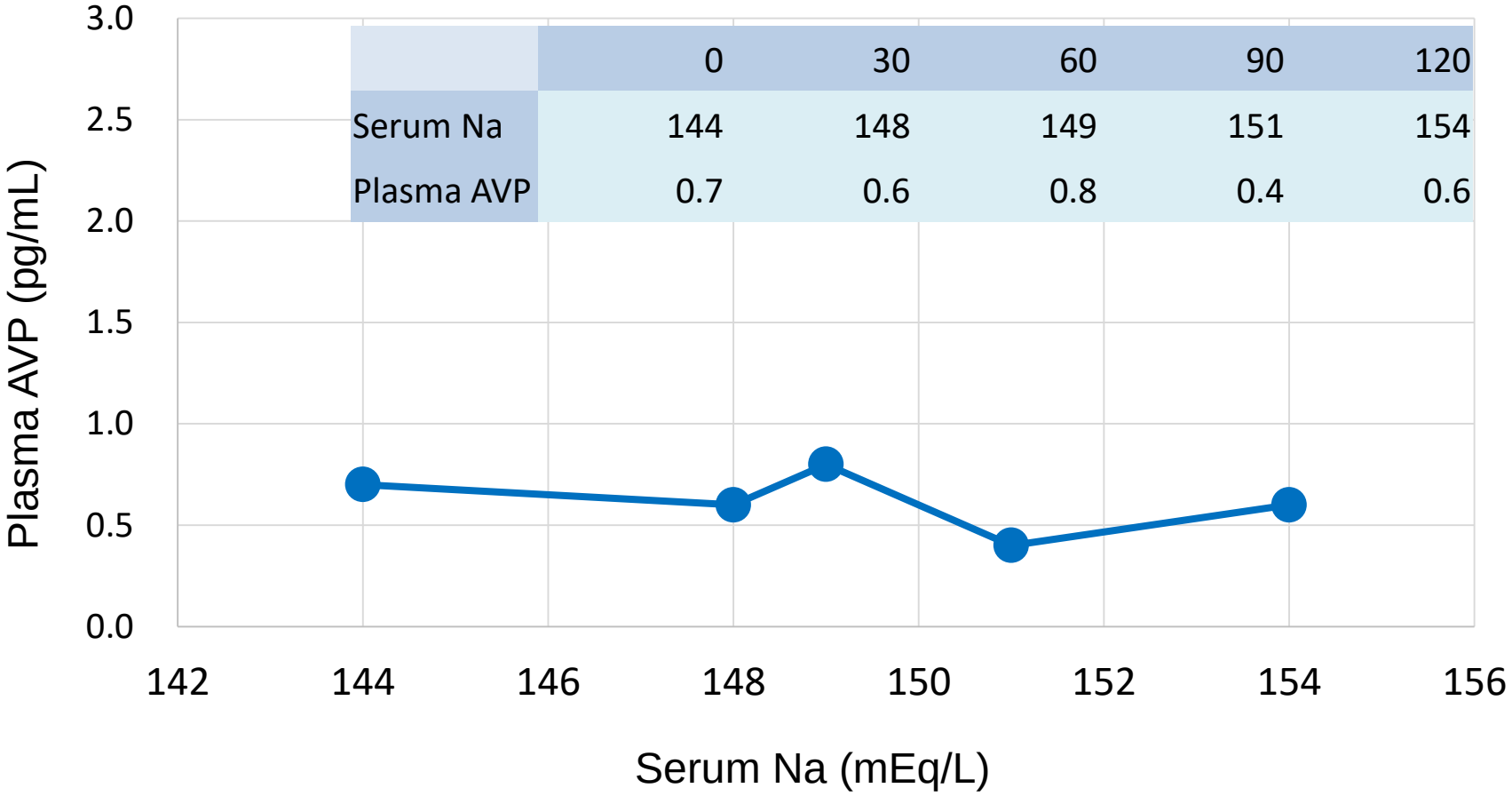


Gradient of regression lines



Gradient of regression lines

	0	30	60	90	120
Serum Na	144	148	149	151	154
Plasma AVP	0.7	0.6	0.8	0.4	0.6



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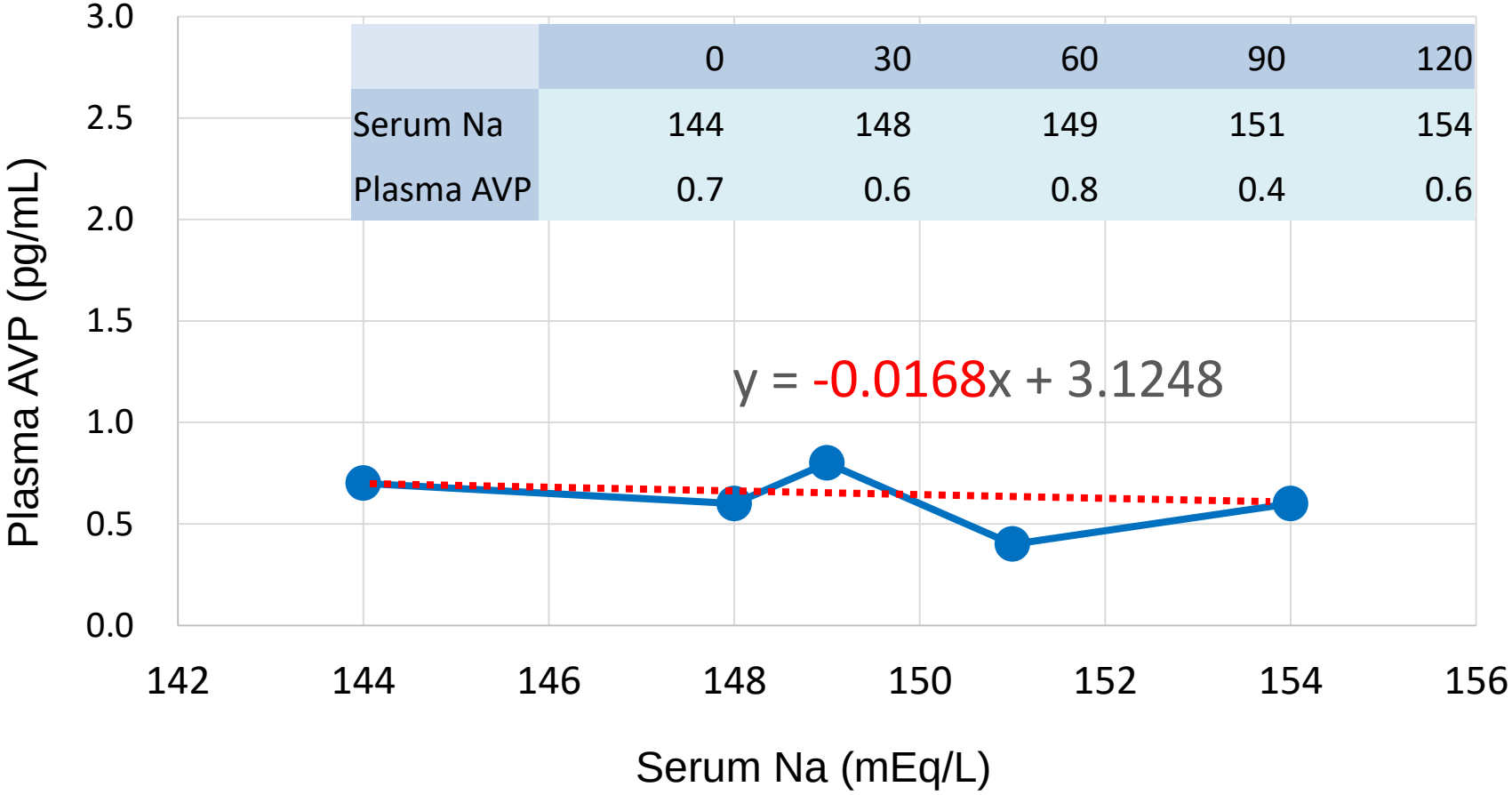
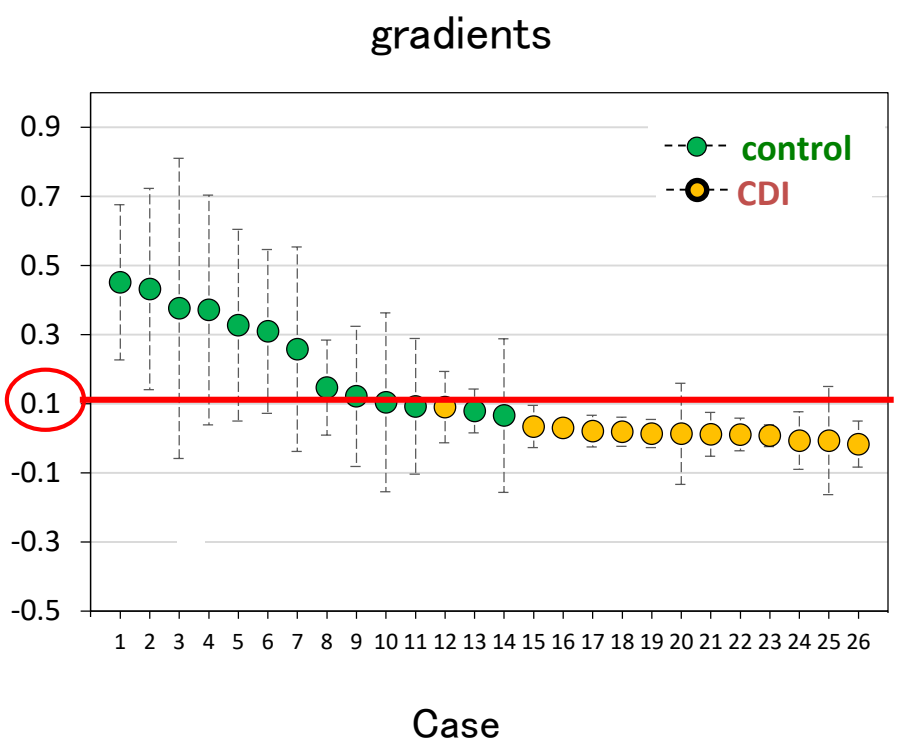
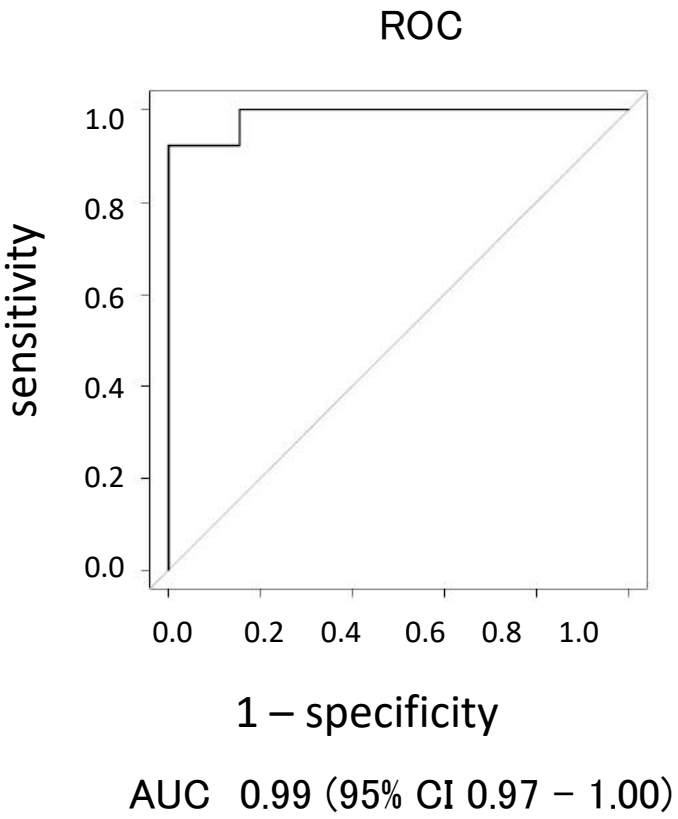


Diagnosis of CDI
using gradients of regression line



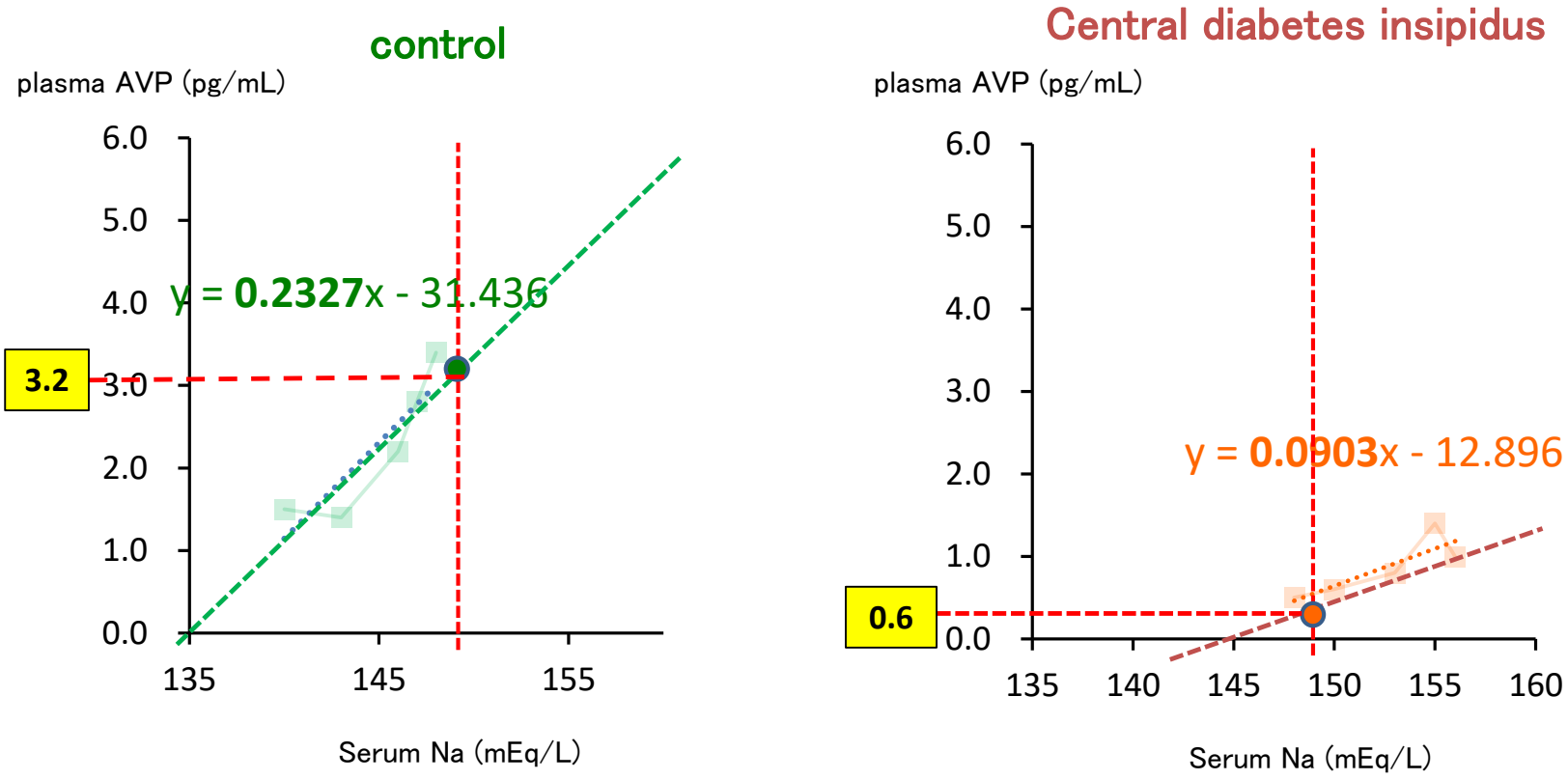


AUC 0.99 (95% CI 0.97 – 1.00)

Gradient 0.1 → sensitivity 100% specificity 77%

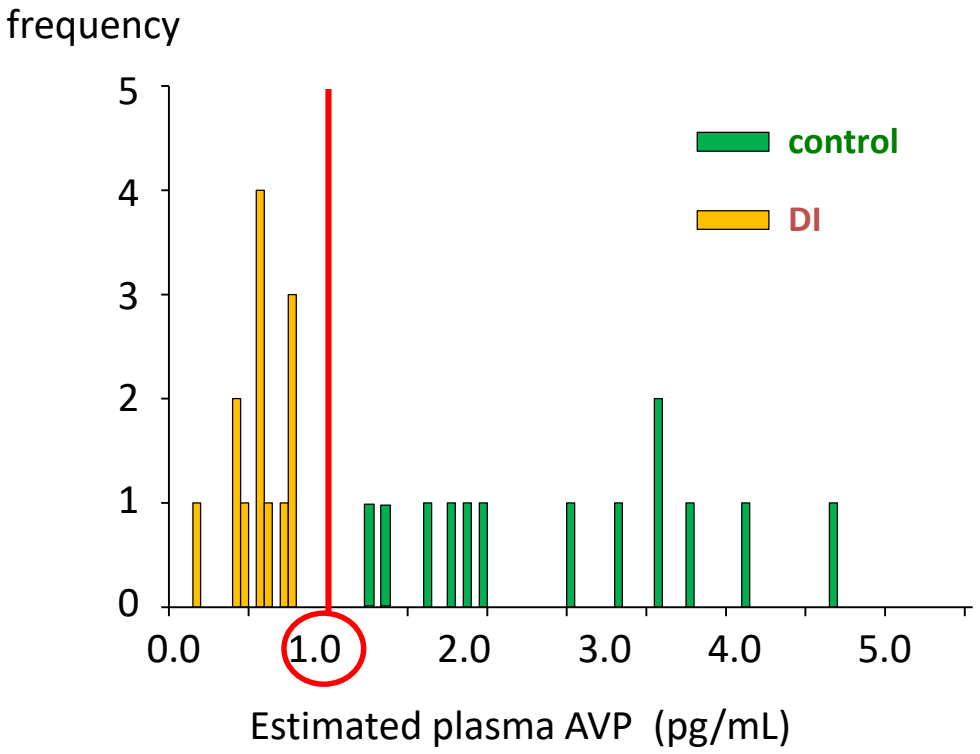
Takagi et al., 2020 **Endocri J**

Diagnosis of central diabetes insipidus using estimated plasma AVP concentrations at serum Na 149 mEq/L



Mean concentrations of serum Na after hypertonic saline injection were 149 mEq/L in control

Diagnosis of central diabetes insipidus using estimated plasma AVP concentrations at serum Na 149 mEq/L



Estimated plasma AVP 1.0 pg/ml at serum Na 149 mEq/L
→ sensitivity 99% specificity 95%

Takagi et al., 2020 **Endocri J**

Research on hypothalamic pituitary disorder Ministry of Health, Labor, and Welfare

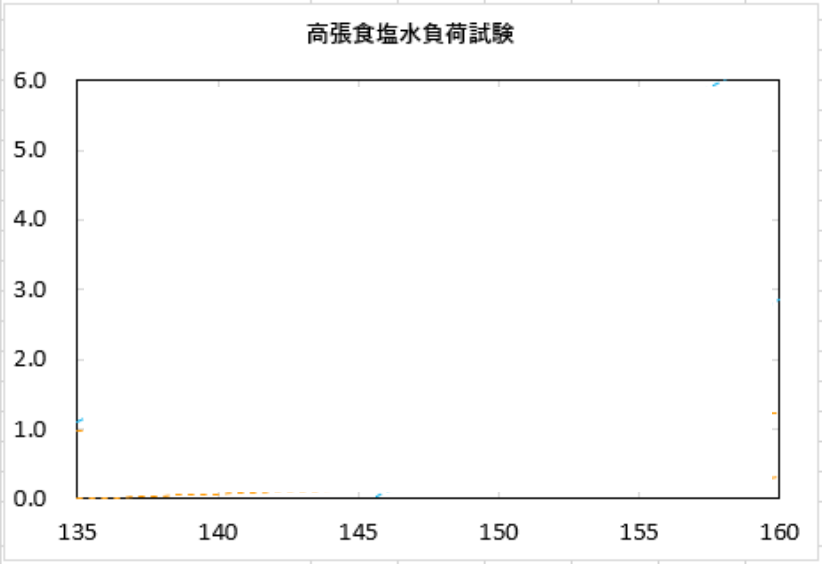
A tool to diagnose CDI

高張食塩水負荷試験 結果解析

	0	30	60	90	120
血清Na濃度（mEq/L）	140	143	146	147	148
血漿AVP濃度(pg/mL)	1.5	1.4	2.2	2.8	3.4

上の表に実際の測定値を入力して下さい。

0.4 pg/mL未満の場合は0.4を入力して下さい。



近似直線の傾き

血清Na149mEq/L時点の推定AVP値

中枢性尿崩症診断基準

＜ 0.1

(感度 100%, 特異度 77%)

＜ 1.0 pg/mL

(感度 99%, 特異度 95%)

参考文献 Endocrine Journal 2019 doi: 10.1507/endocrj.EJ19-0224.

A tool to diagnose CDI

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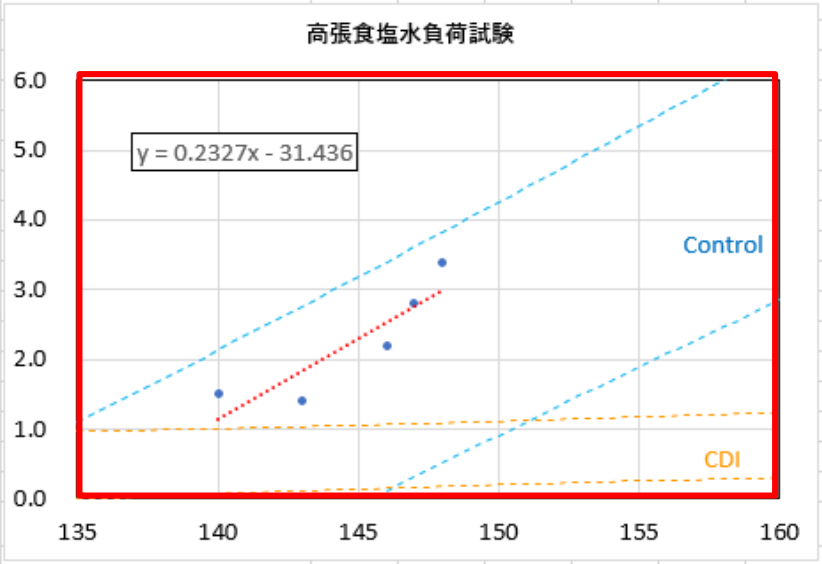

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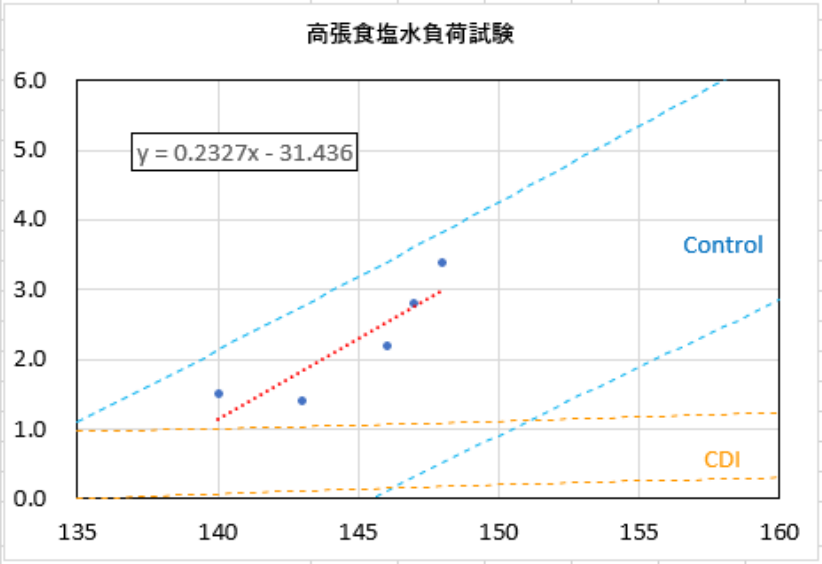

近似直線の傾き	0.233
血清Na149mEq/L時点の推定AVP値	3.237

中枢性尿崩症診断基準

＜ 0.1

(感度 100%, 特異度 77%)

＜ 1.0 pg/mL

(感度 99%, 特異度 95%)

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Diagnosis of central diabetes insipidus

4. Urine osmolality does not exceed 300 mOsm/kg after water is deprived for 6.5 h or BW decreases by 3%.

5. Urine volumes decrease and urine osmolality increases above 300 mOsm/kg after 5 IU vasopressin sc injection after water deprivation.

Case 1：75 years old female

Main symptoms

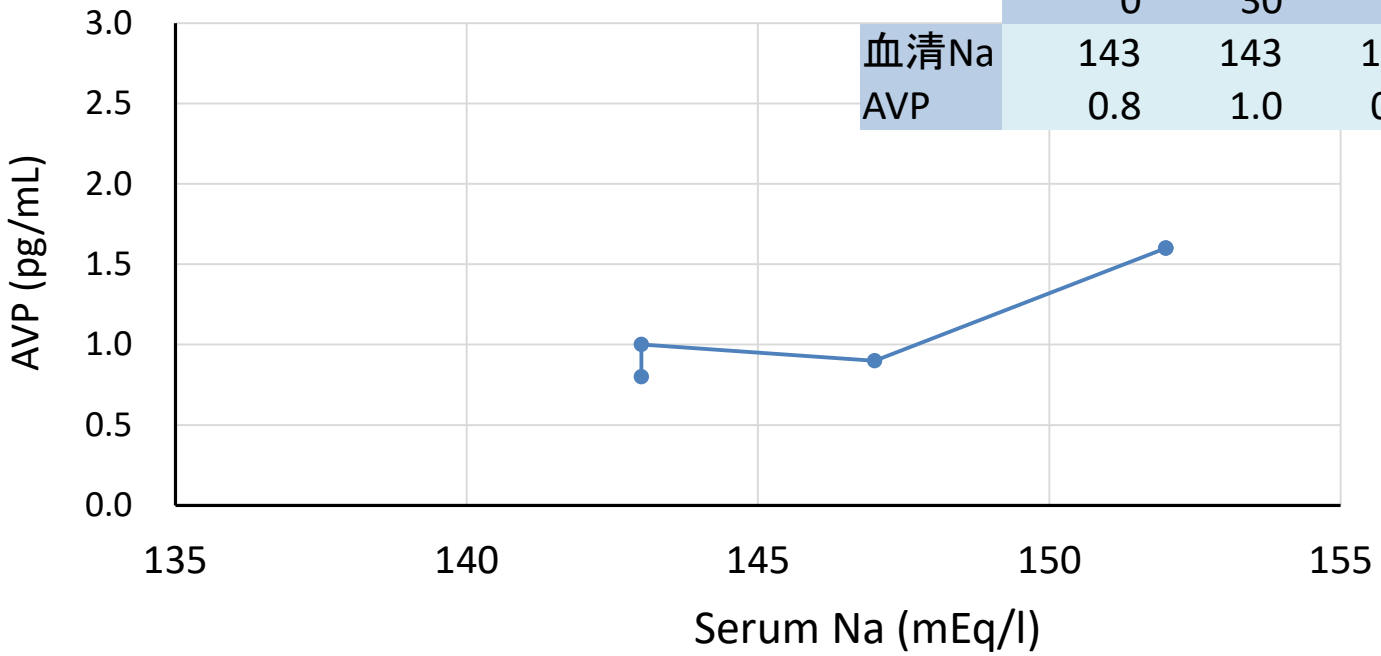
pollakisuria at night

Current medical history

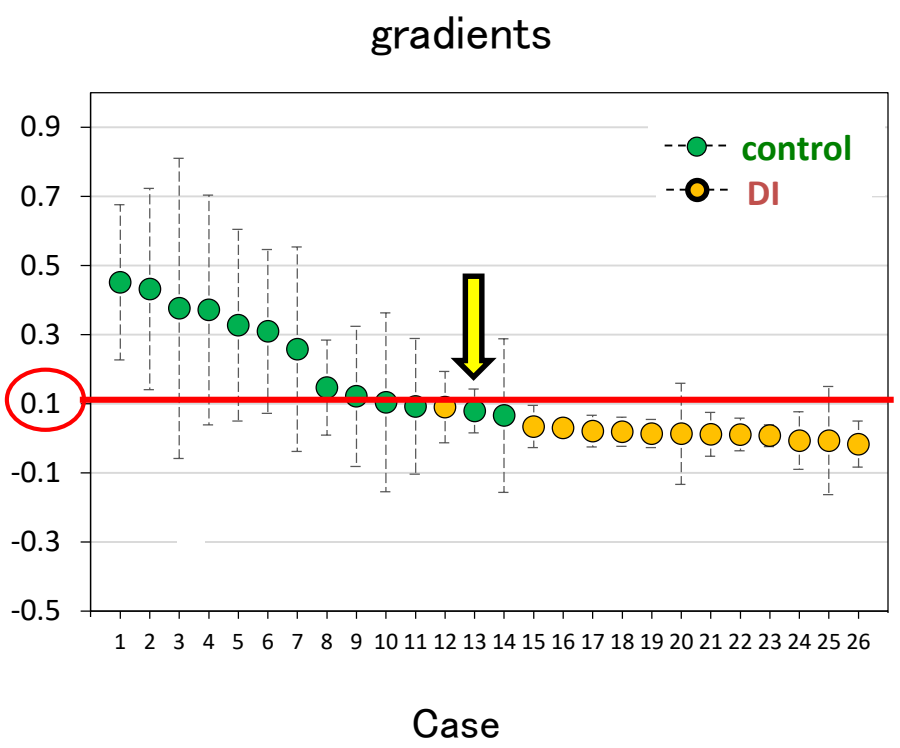
She visited the urology department for pollakisuria. Then, she was introduce to the Endocrinology department to rule out diabetes insipidus.

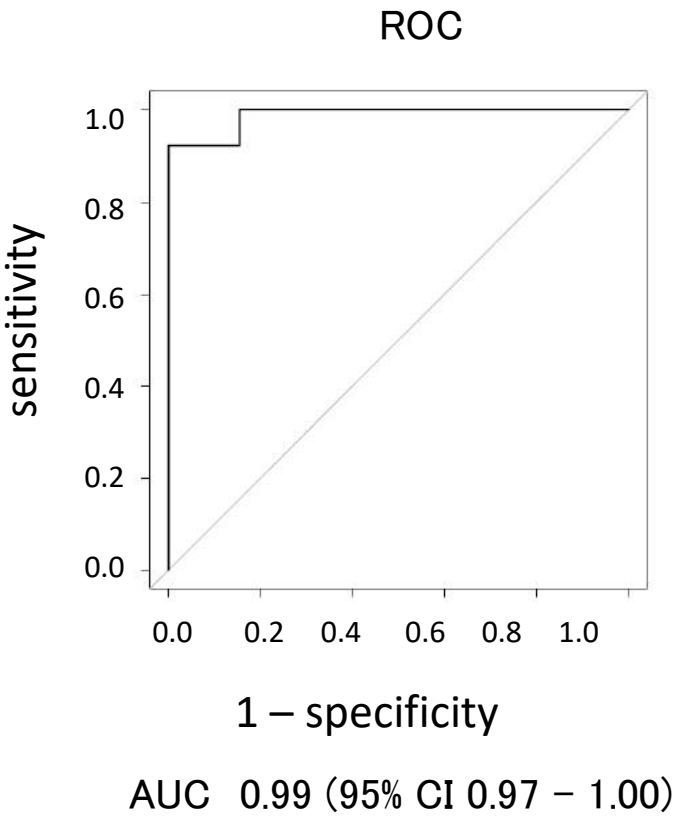
Case 1：75 years old female

	0	30	60	90	120
血清Na	143	143	147	152	152
AVP	0.8	1.0	0.9	1.6	1.6



Diagnosis of central diabetes insipidus using gradients of regression line





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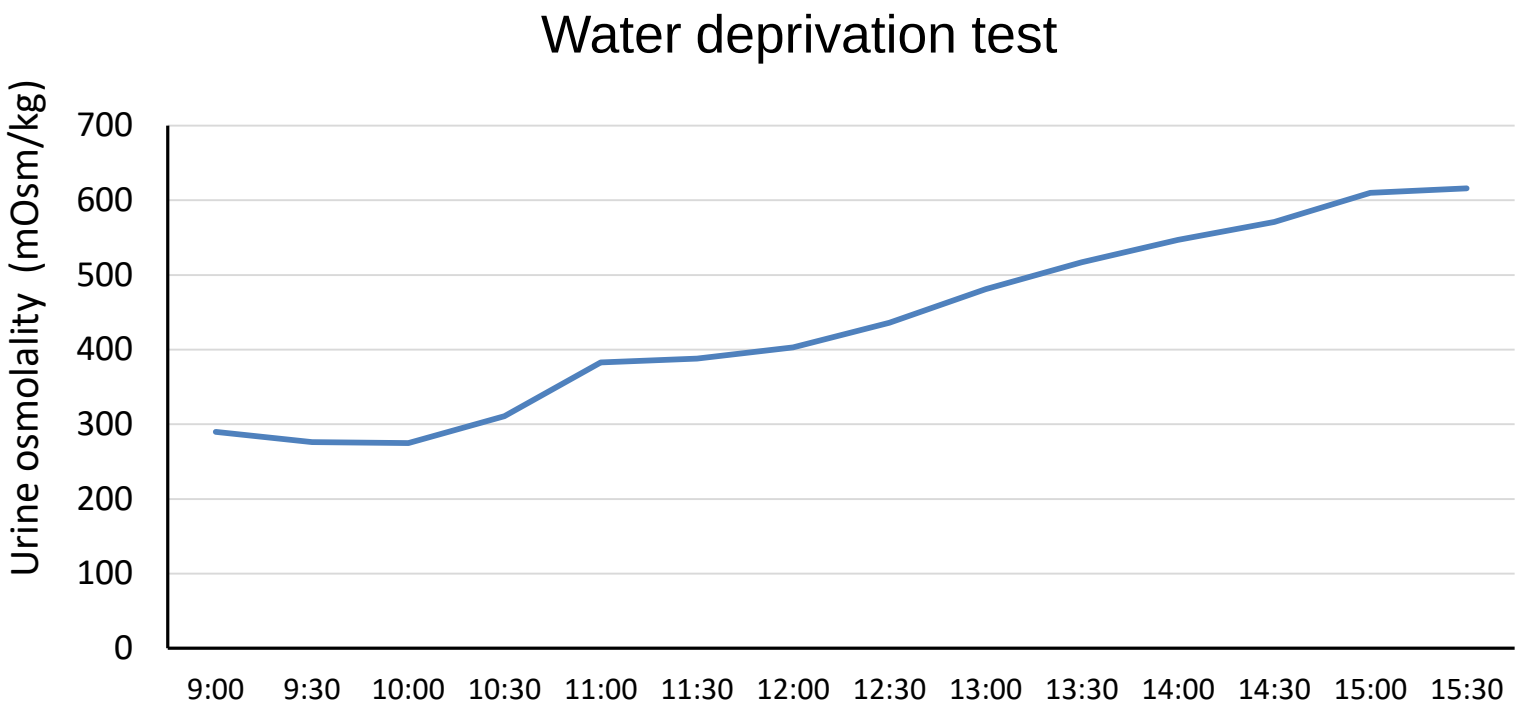


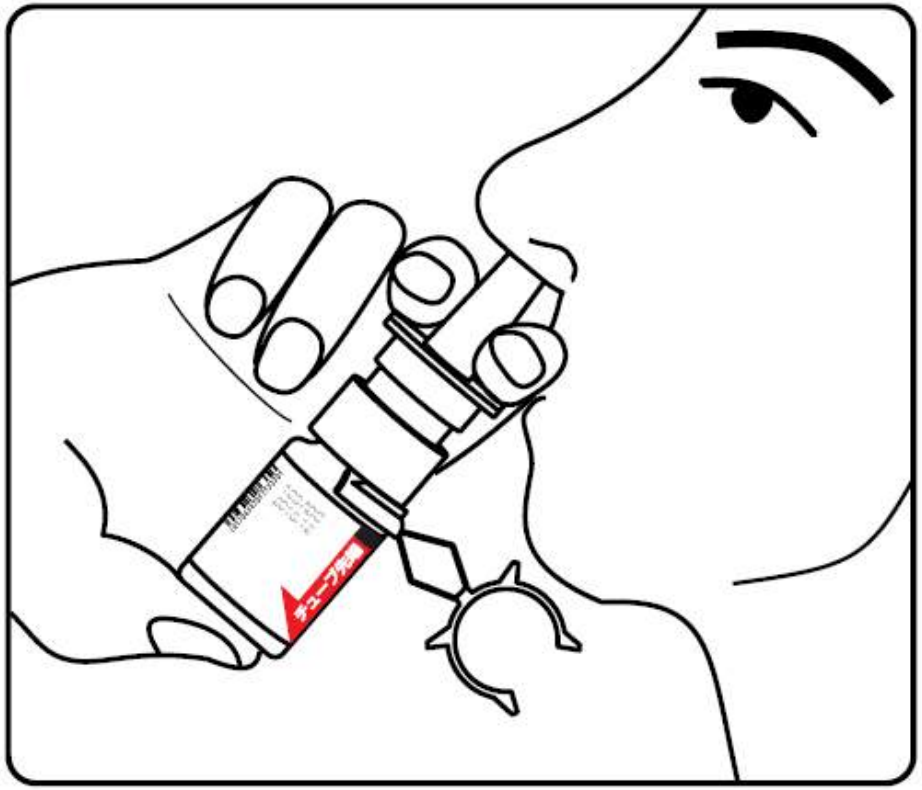
CDI is unlikely

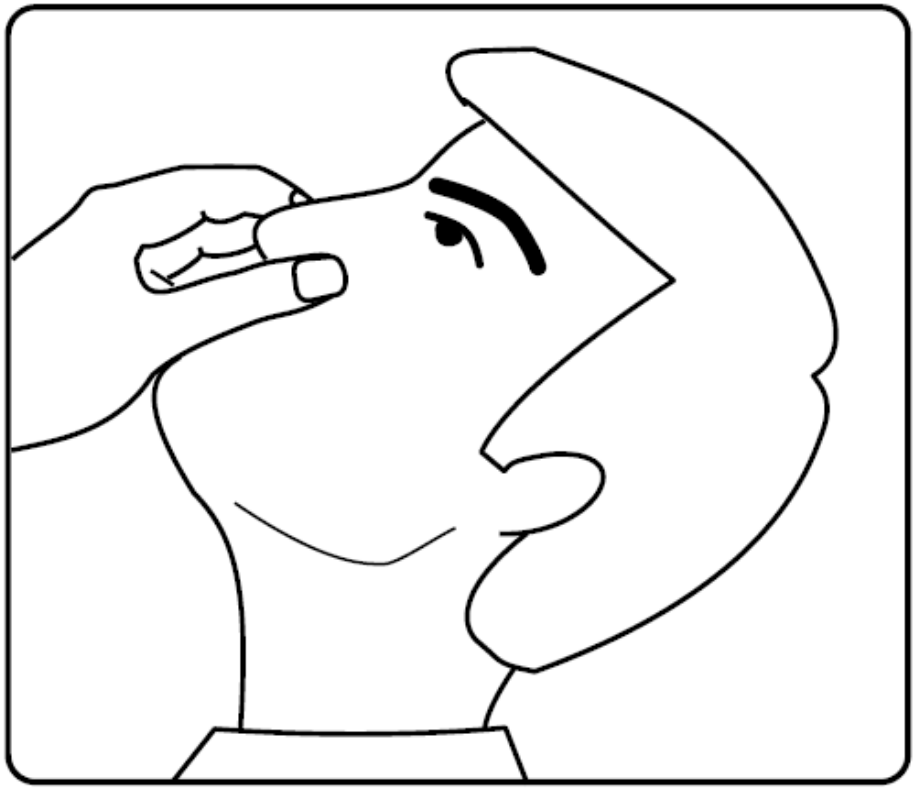
- Water balance
- Diagnosis of central diabetes insipidus (CDI)
- Treatment of CDI
- Adipsic CDI
- Familial neurohypophysial diabetes insipidus

Desmopressin formulation

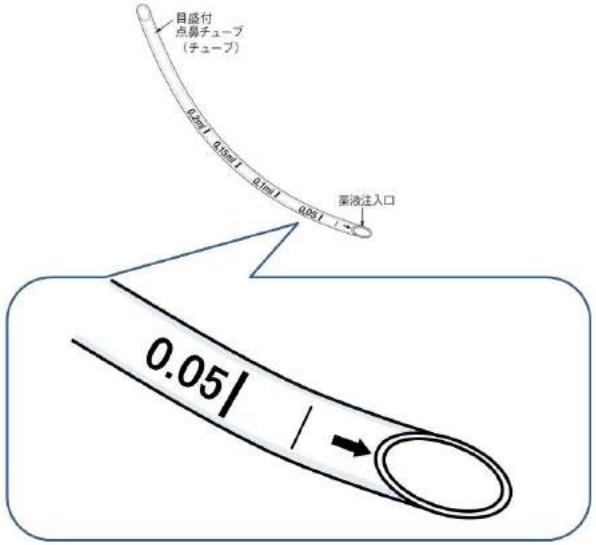
デスモプレシンOD錠			デスモプレシン経鼻薬	
OD錠 60μg	OD錠 120μg	OD錠 240μg	スプレー2.5	点鼻液0.01%
				

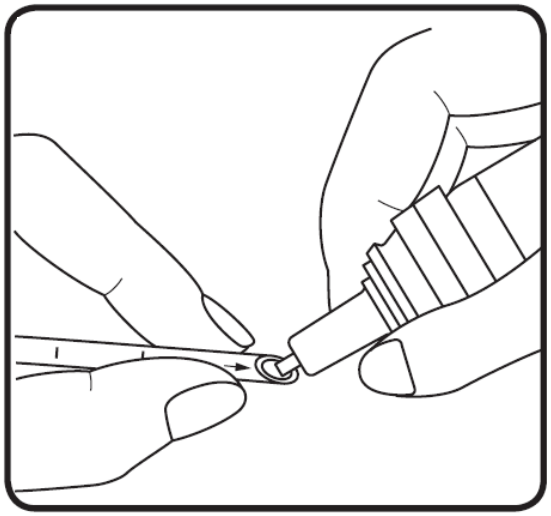
Desmopressin・spray

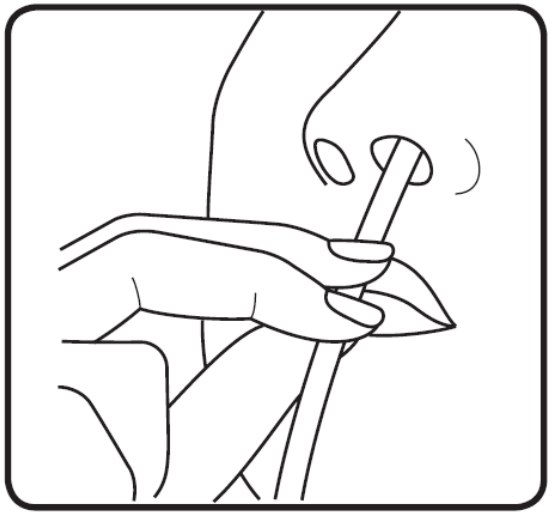


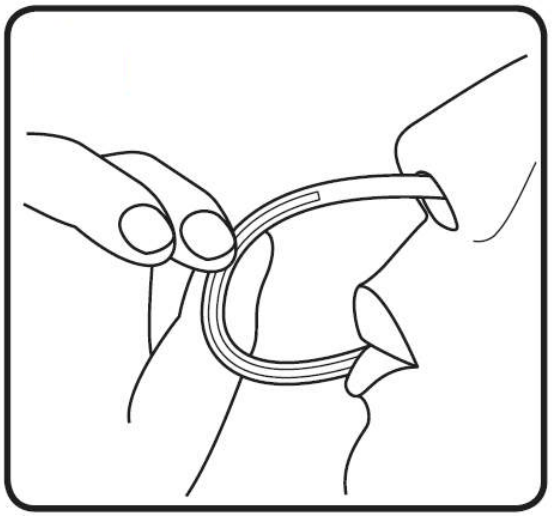


Desmopressin・nasal solution



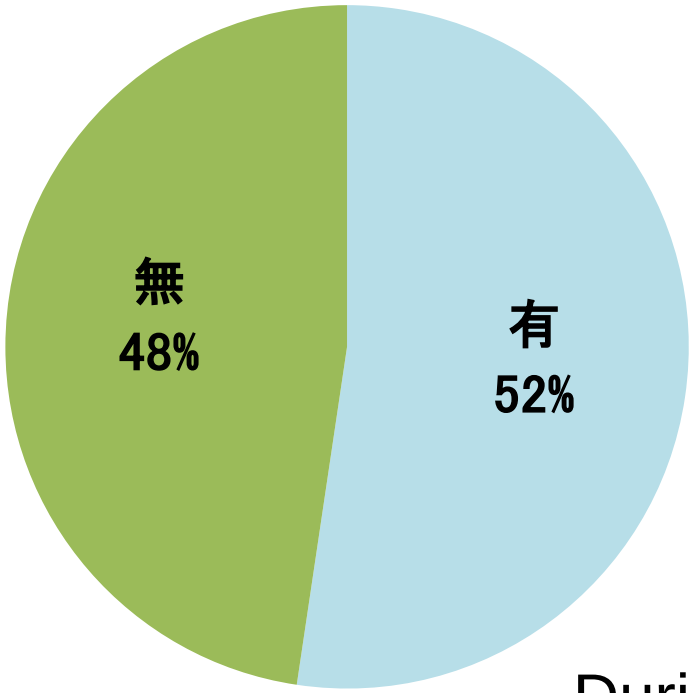




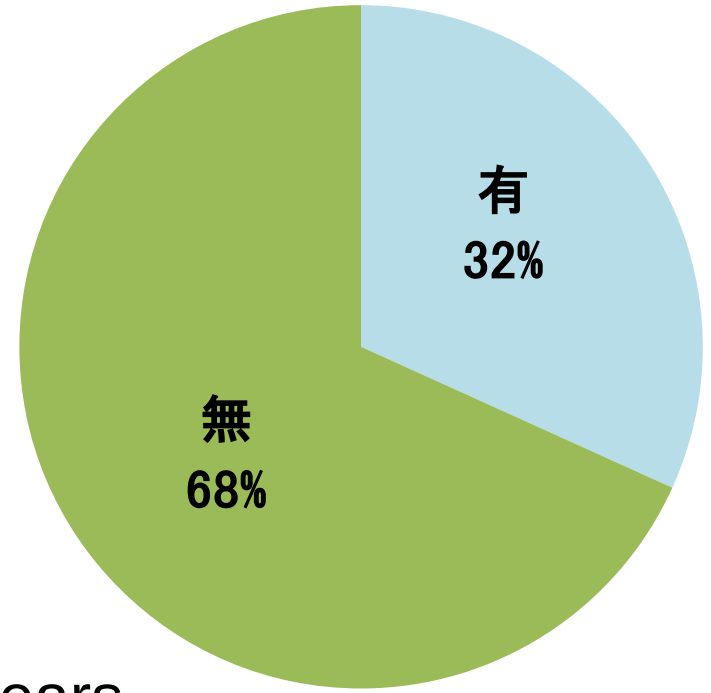


Hyponatremia in CDI patients treated with DDAVP (spray or nasal solution)

< 135 mEq/l

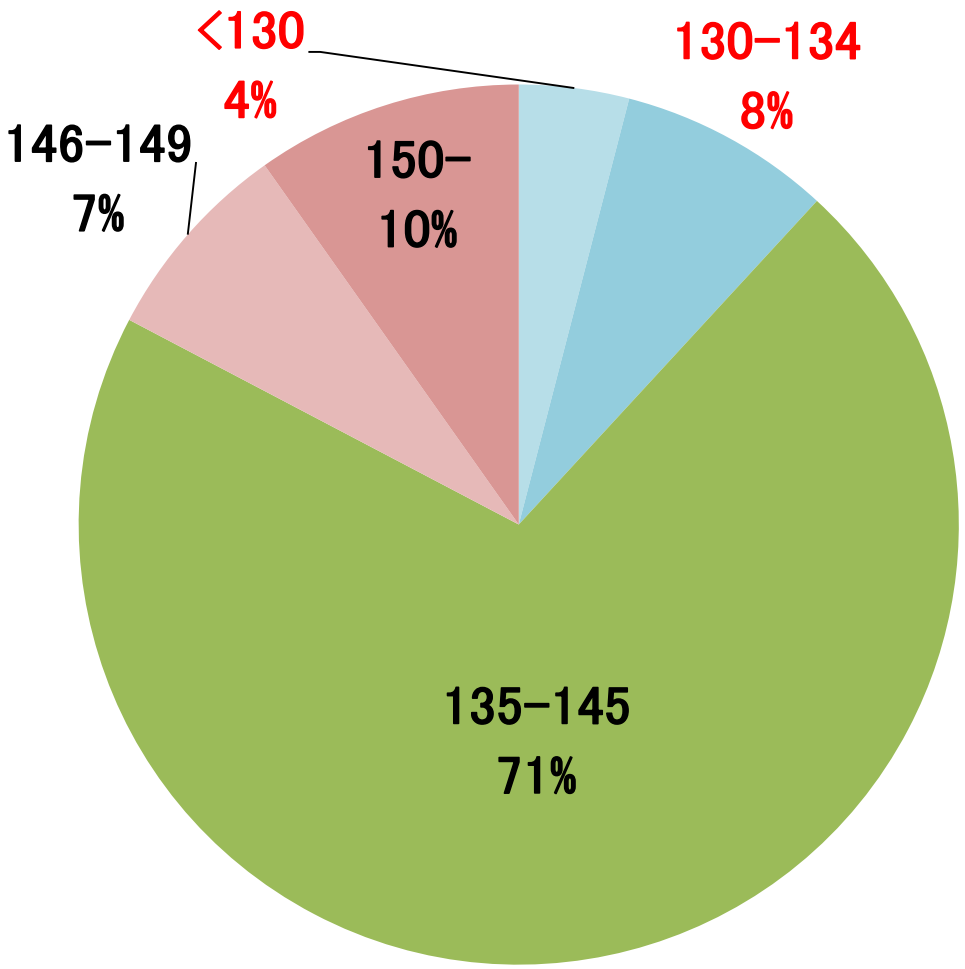


< 130 mEq/l



During 5 years

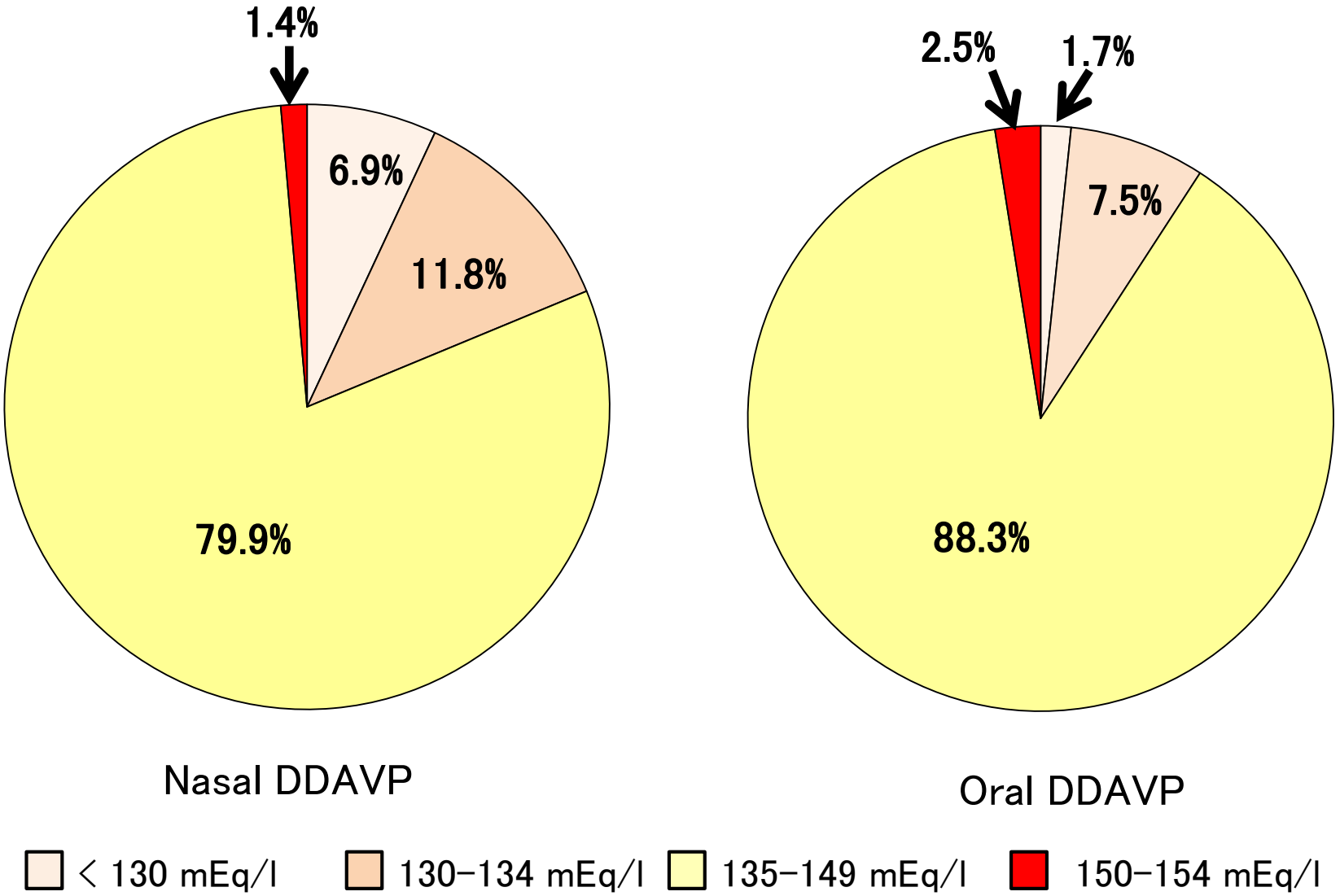
Hyponatremia in CDI patients treated with DDAVP (spray or nasal solution)



hyponatremia 12%

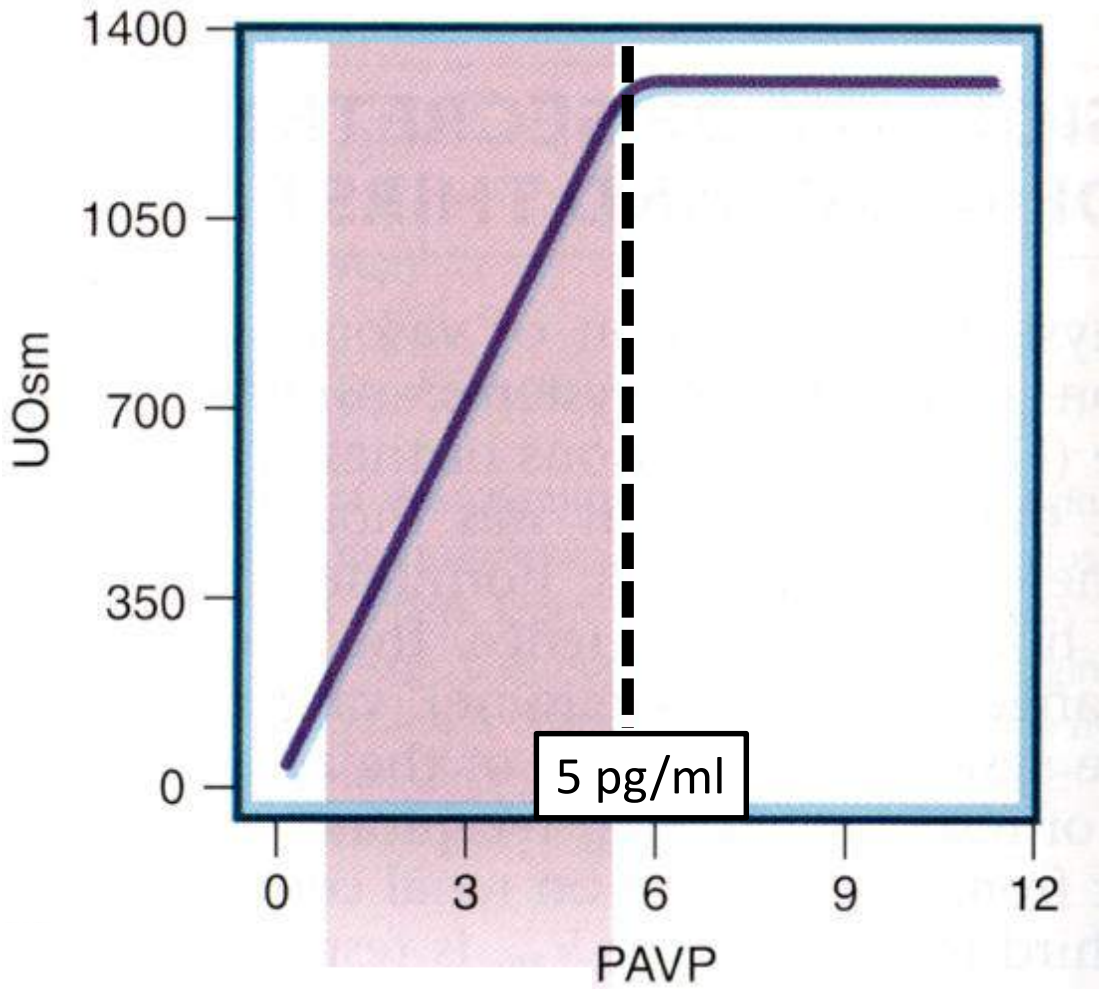
6,439 times measurement

DDAVP formula and hyponatremia



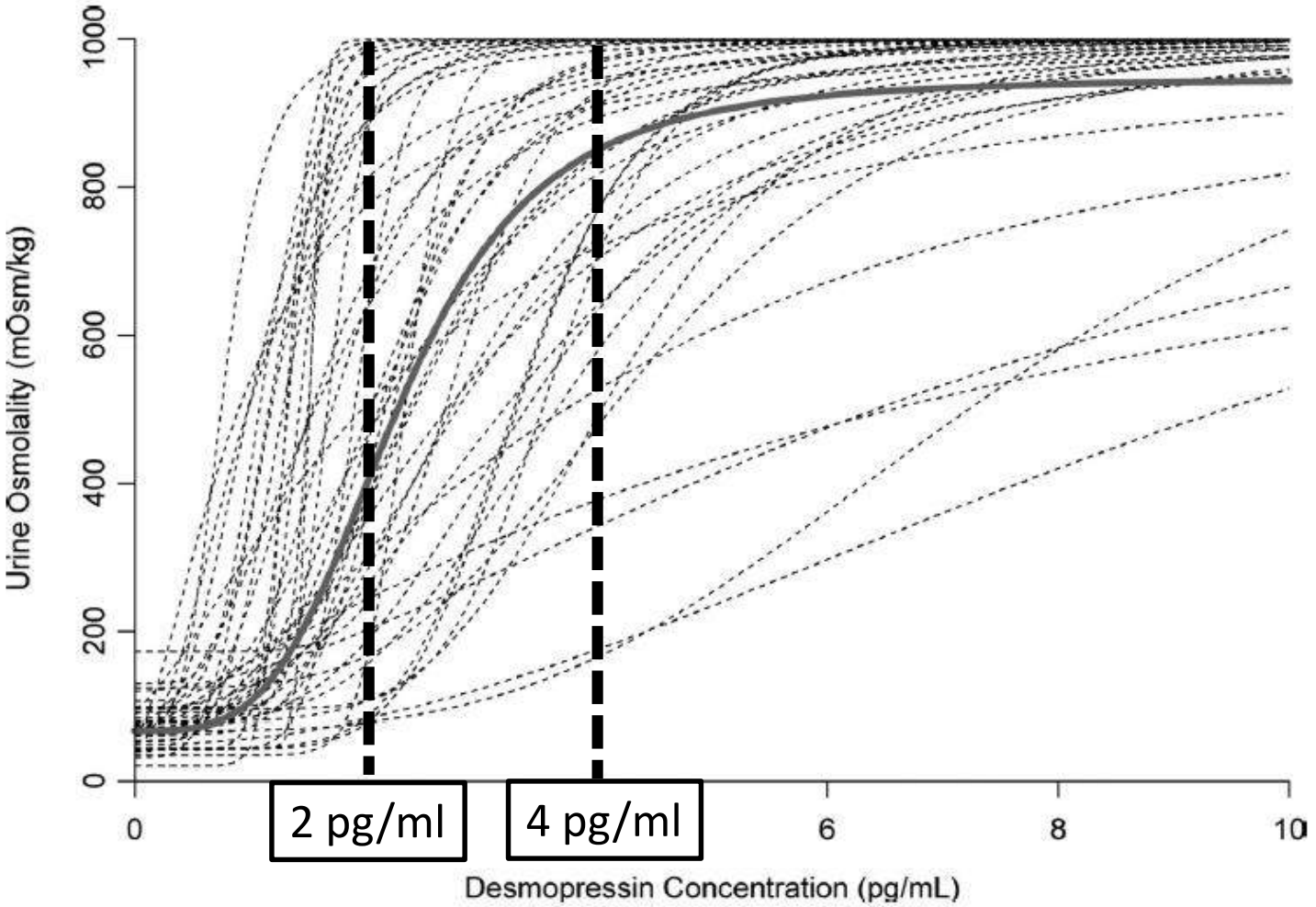
Kataoka et al., 2014 **Endocr J**

Relationship between plasma AVP and urine osmolality



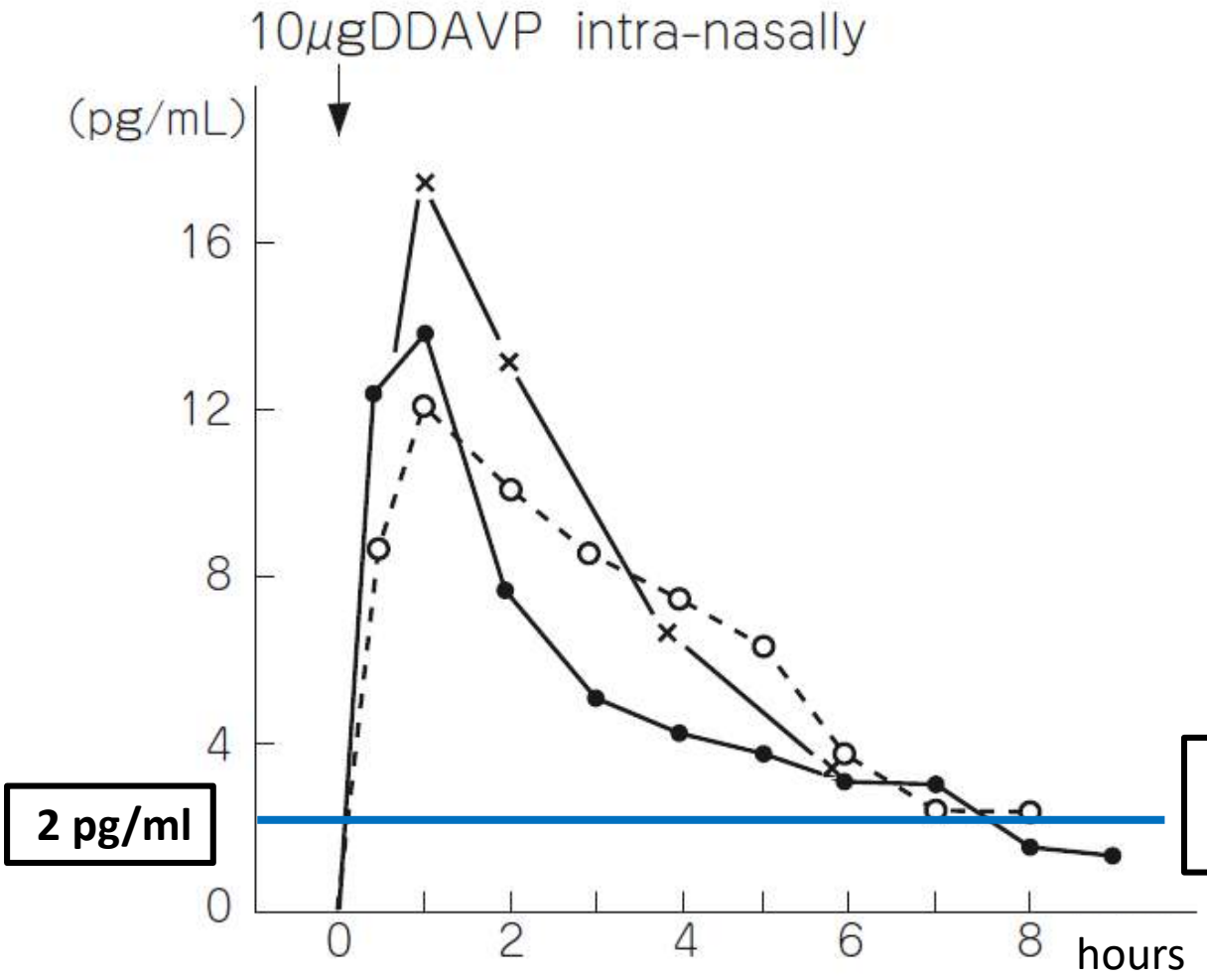
Robinson AG et al., Williams Textbook

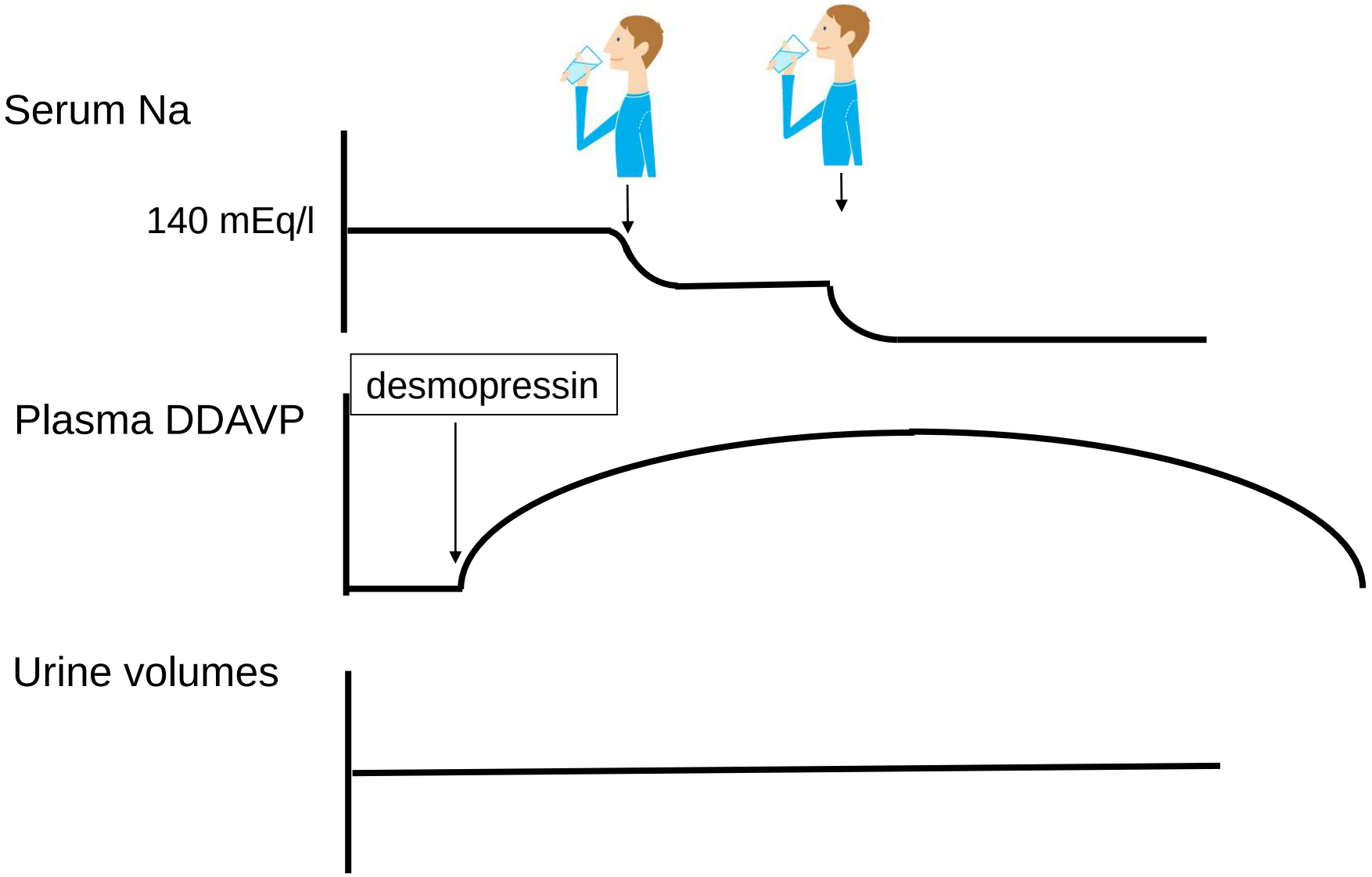
Relationship between DDAVP and urine osmolality



Juul KV et al., 2013 Am **J Physiol Renal Physiol**

Plasma DDAVP concentration after nasal injection

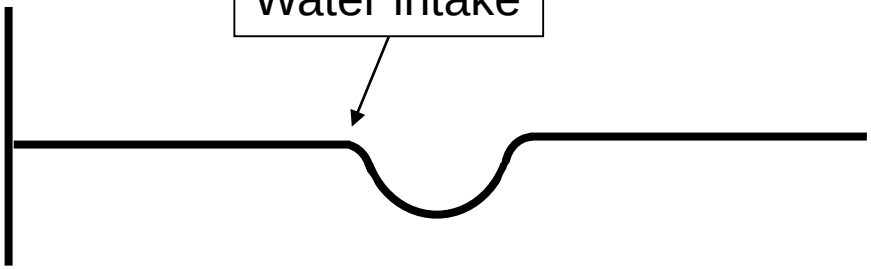



Serum Na
140 mEq/l
desmopressin
Plasma DDAVP
Urine volumes

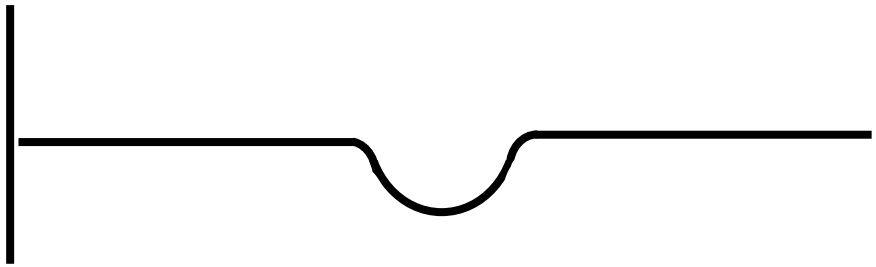
Serum Na

Water intake

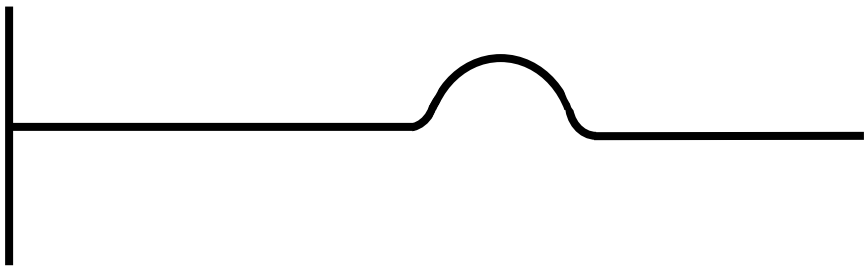
140 mEq/l



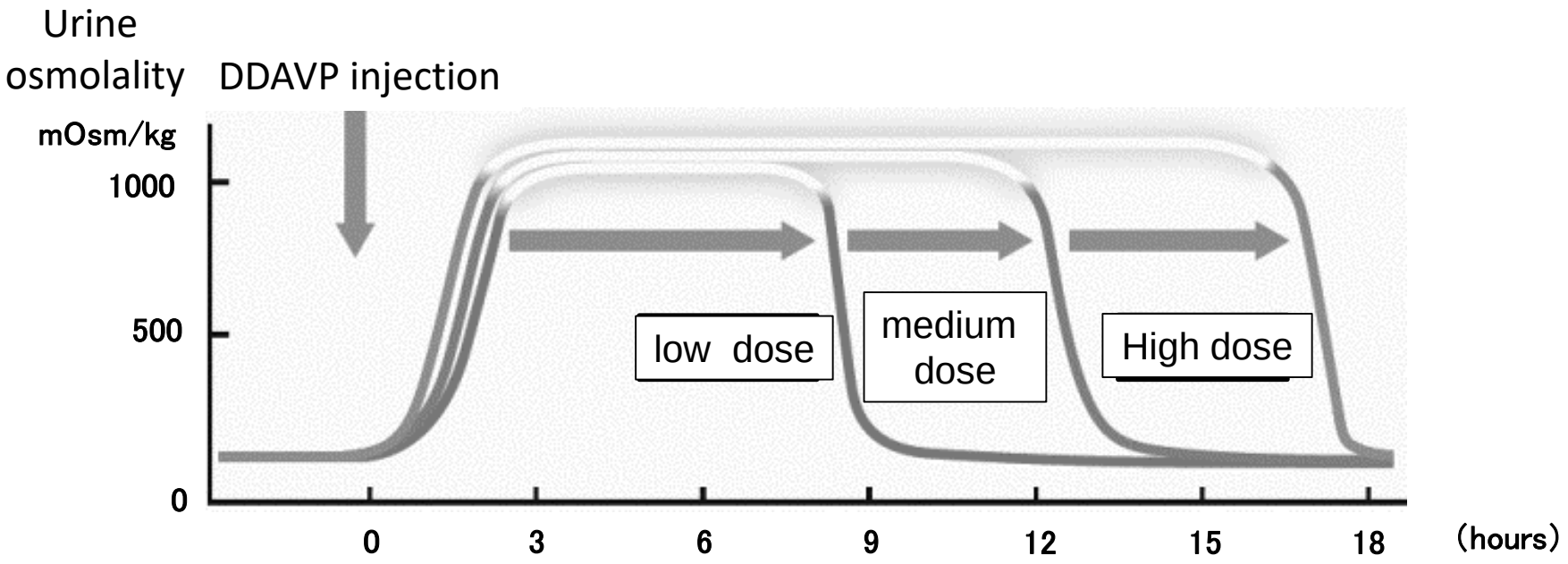
Plasma AVP



Urine output



Relationship between doses of DDAVP and antidiuretic effects



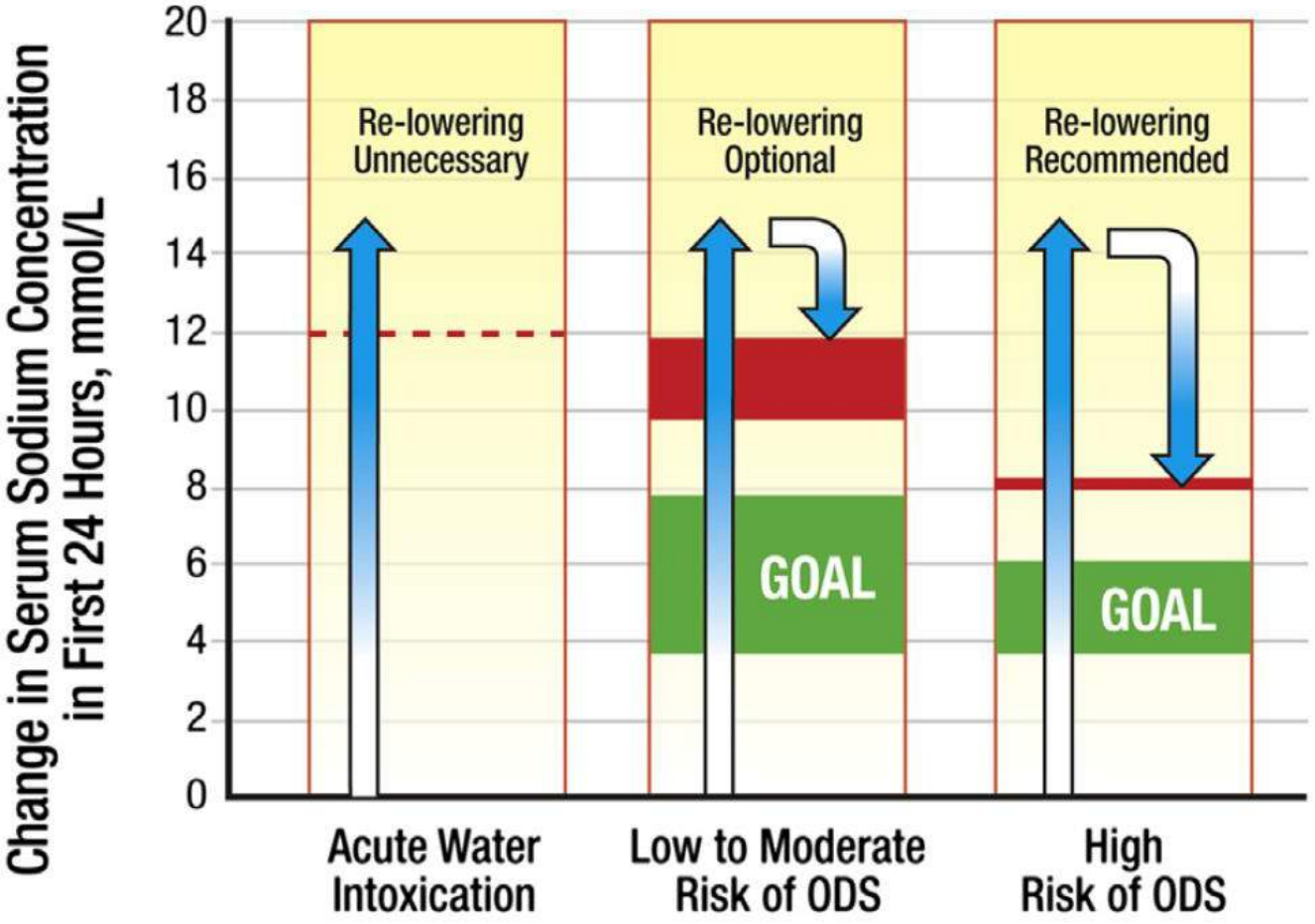
Yokoya S, 1993 Syonishinryo; 9:1799

Case 2: 70 years old female treated with DDAVP

day	5/9	5/13	5/14	5/15
time		9:30	18:00	6:00
Serum Na	120	121	117 →	128

Δ Na : 11 mEq/L/12 h

Serum Na concentrations should be lowered when they rise more than expected



2013 Verbalis JG et al., **Am J Med** 126:S1

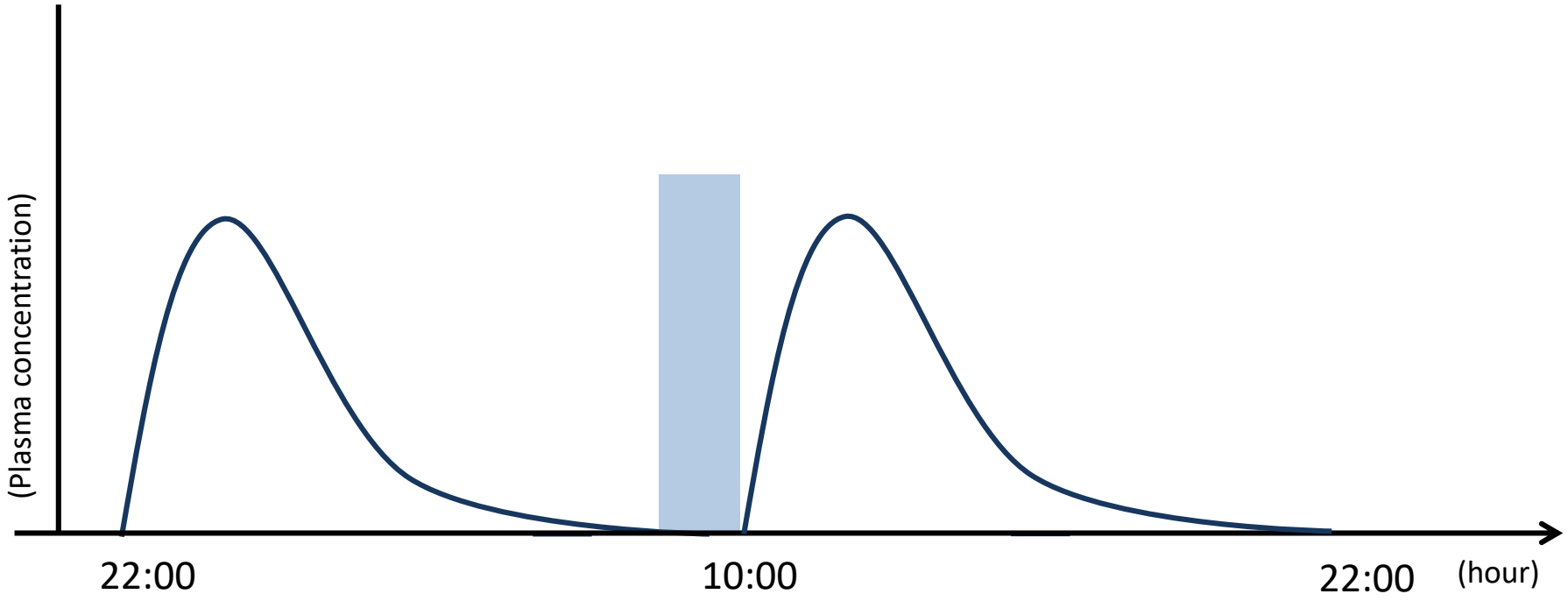
Case 2: 70 years old female treated with DDAVP

time	8:00	10:00	12:00	14:00	16:00	18:00
Urine volume	448	421	109	186	892	504
Serum Na	128		129			131
5% glucose						
DDAVP	60 μg					60 μg

Case 2: 70 years old female treated with DDAVP

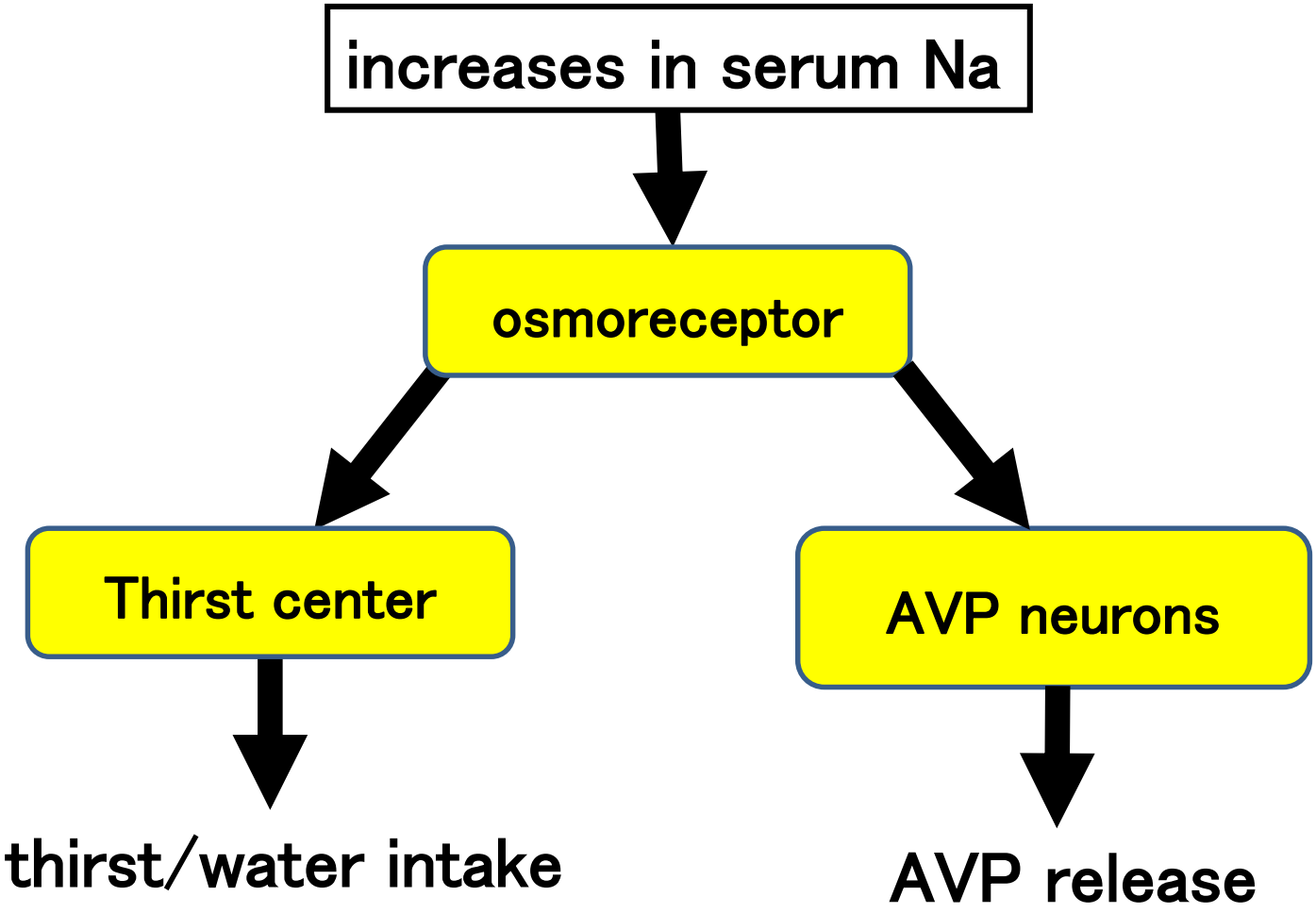
time	8:00	10:00	12:00	14:00	16:00	18:00
Urine volume	448	421	109	186	892	504
Serum Na	128		129			131
5% glucose						
DDAVP	60 μg					60 μg

Changes in plasma DDAVP concentrations

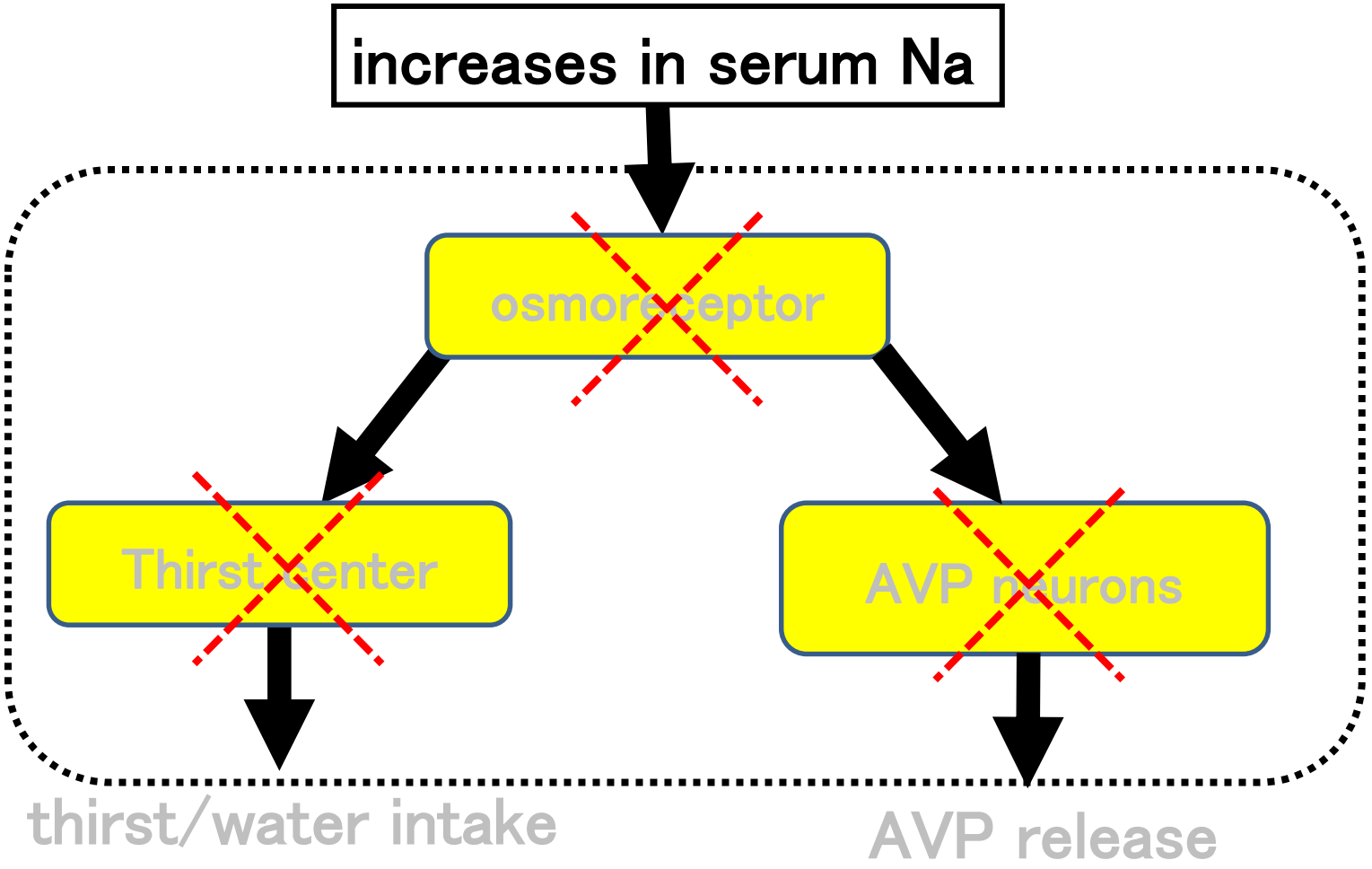


- Water balance
- Diagnosis of central diabetes insipidus (CDI)
- Treatment of CDI
- Adipsic CDI
- Familial neurohypophysial diabetes insipidus

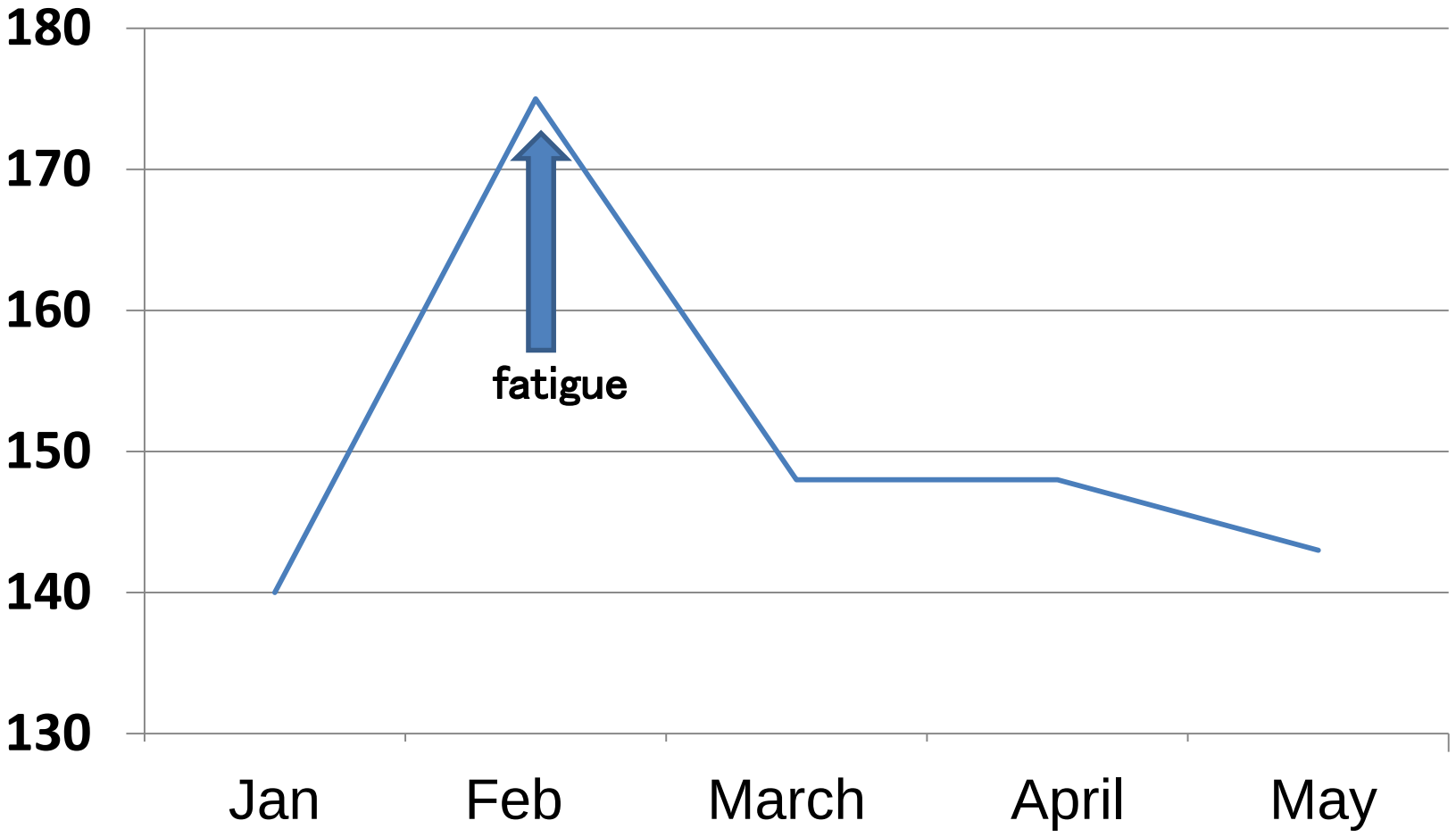
AVP release and water intake



AVP release and water intake



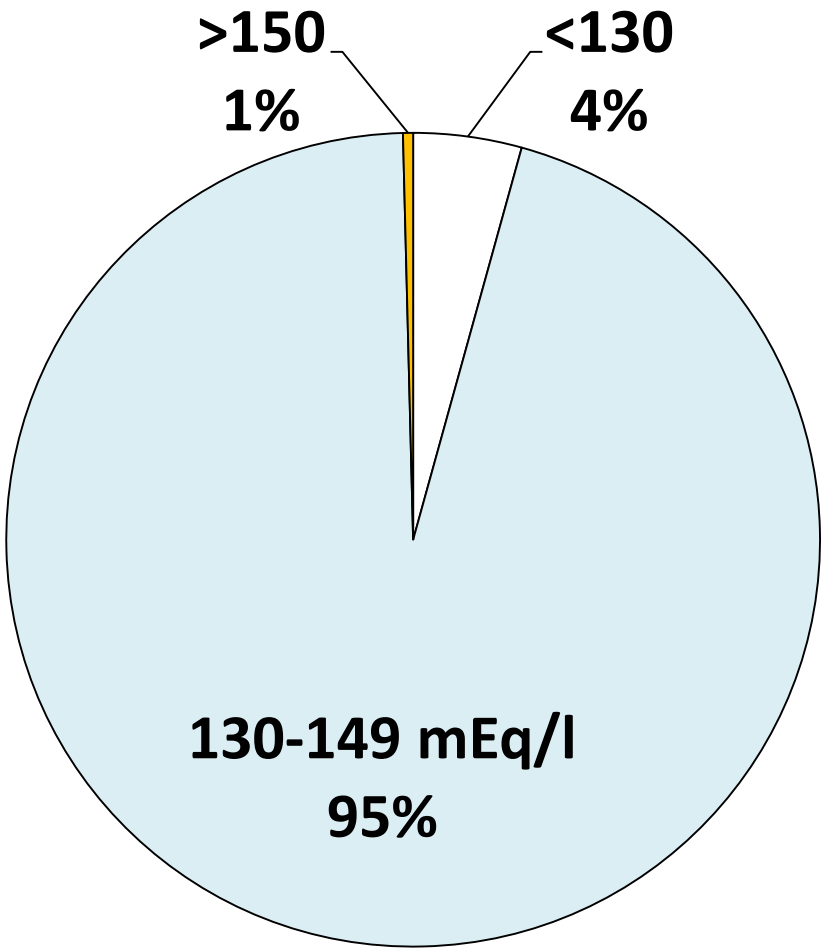
Case 3: 15 years old boy diagnosed CDI due to germ cell tumor



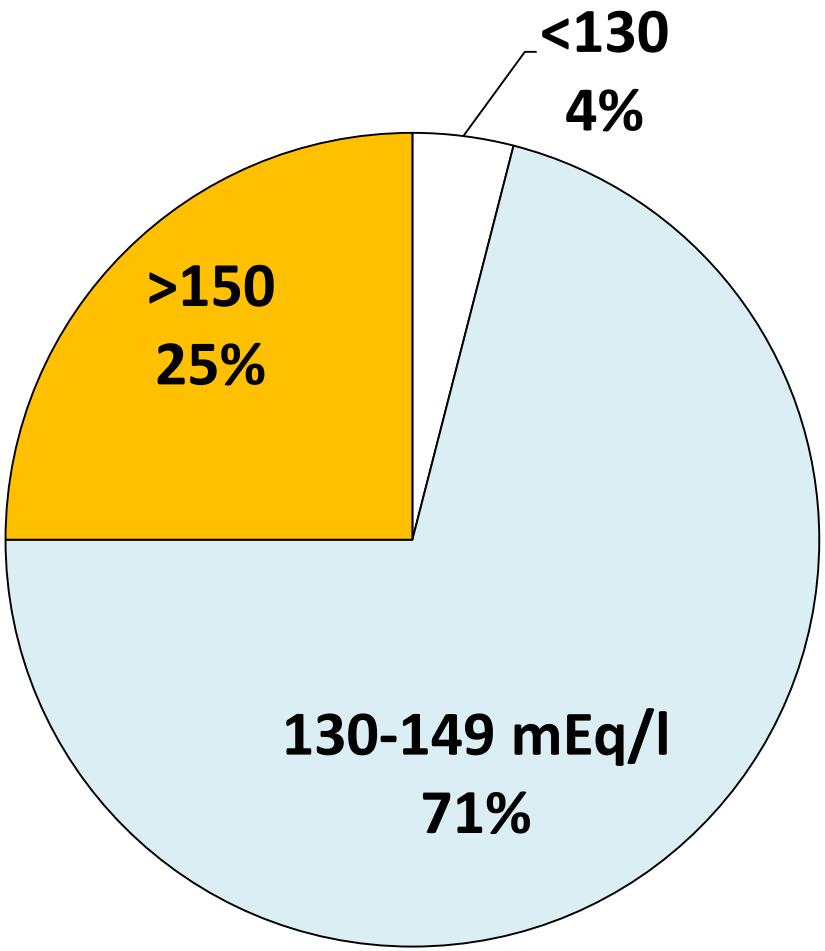
CDI patients with/without adipsia

		Non-adipsia	adipsia
Number of patients		126	23
Age of onset	<65 years	89%	91%
	<65years	11%	9%
gender	M	56%	52%
	F	44%	48%
hypopituitarism	(−)	37%	13%
	(+)	63%	87%

Serum Na concentrations

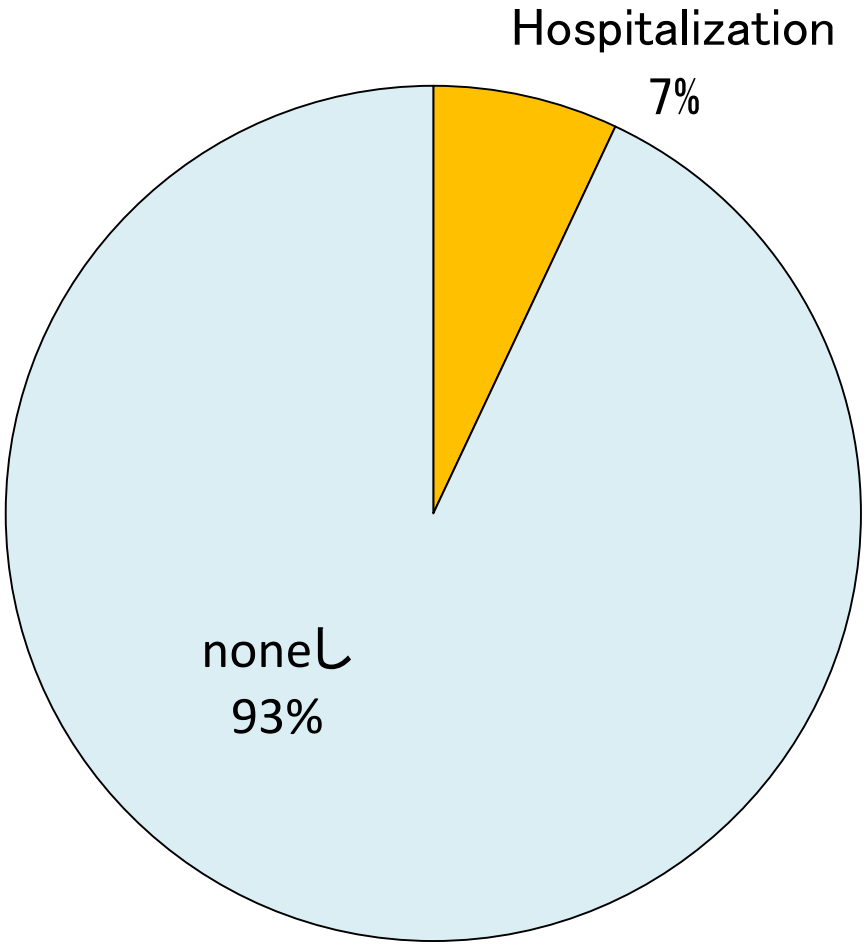


non-adipsia

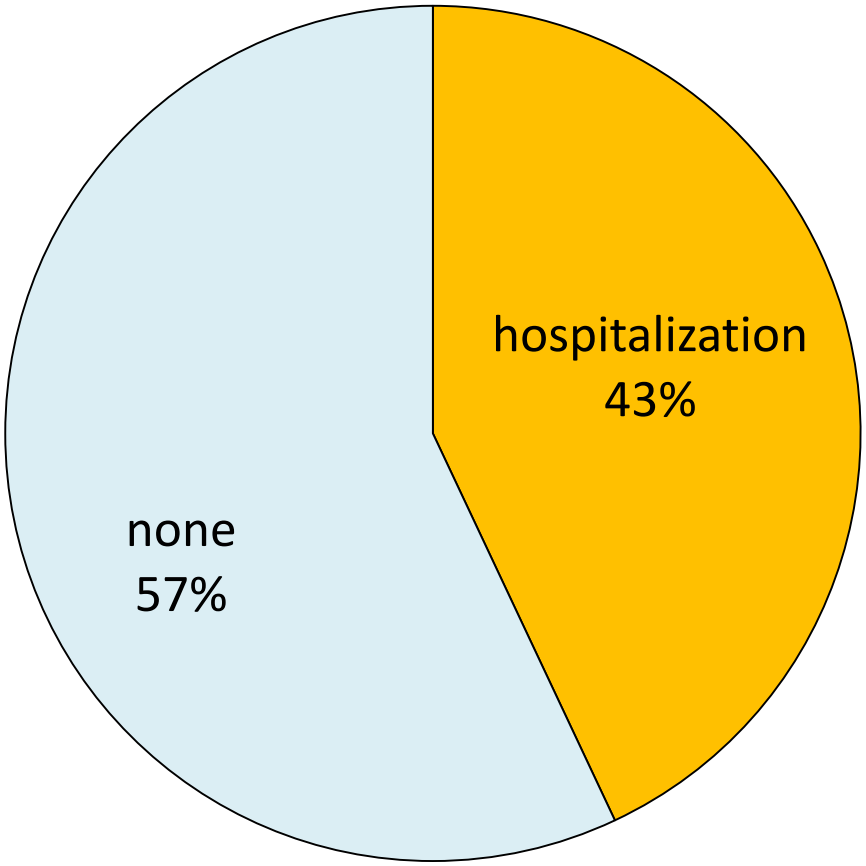


adipsia

Hospitalization due to injection



non-adipsia

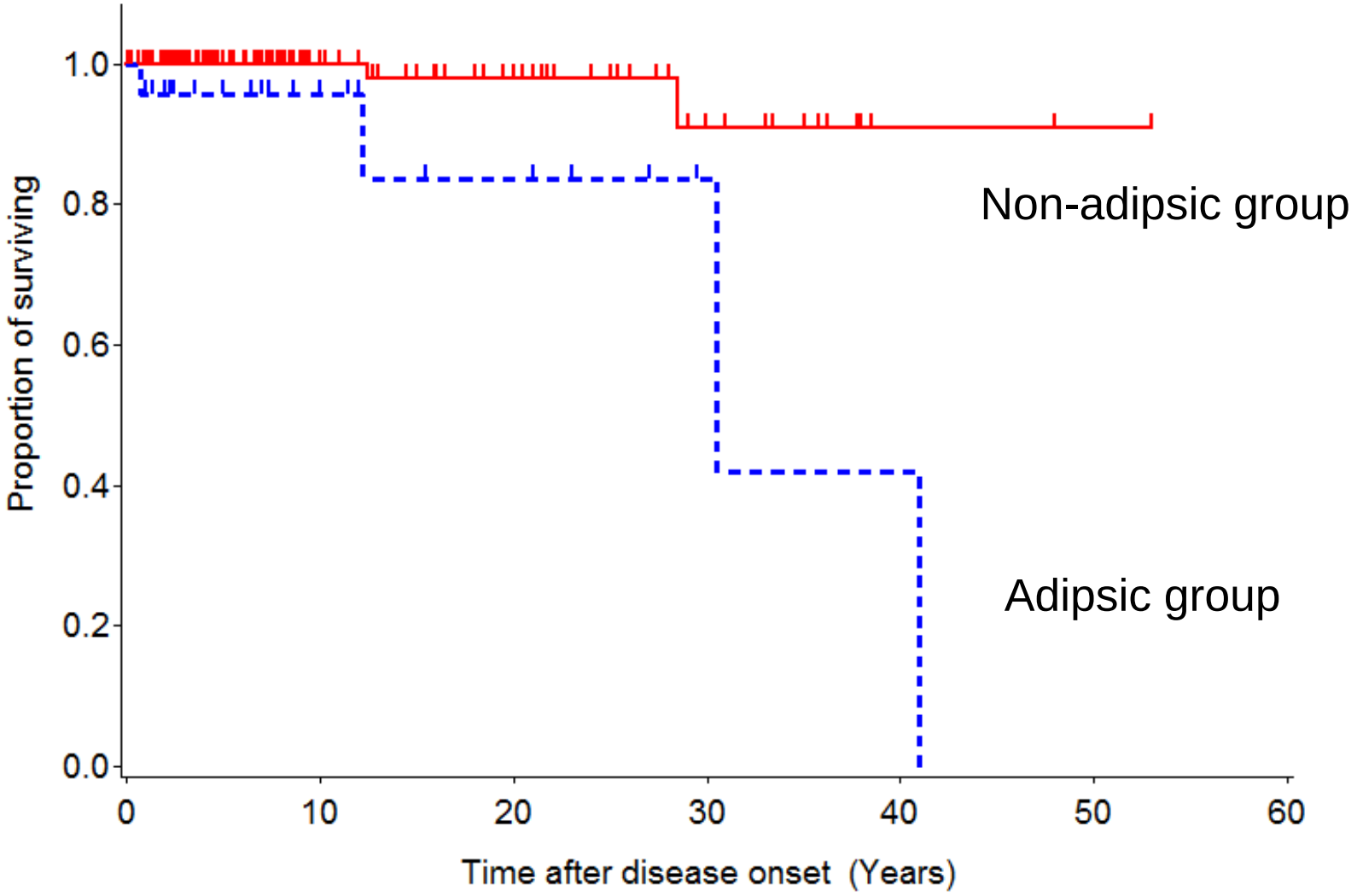


adipsia

Characteristics of patients who died during follow-up

patient	Adipsic/ non-adipsicn	Age of CDI onset	etiology	Age of death	Cause of death
1	adipsic	25	inflammation	37	Sudden death
2	adipsic	12	malformation	42	pneurmonia
3	adipsic	10	Germ cell tumor	51	cholecystitis
4	adipsic	77	inflammation	78	sepsis
5	Non-adipsic	21	Empty sella	49	influenza
6	Non-adipsic	66	Rathoke's cleft cyst	78	Renal failure

Kaplan-Meier Curves for OS of patients with or without adipsia



Arima et al., 2014 **Endocr J**

Treatment of adipsic patients

- The ideal BW for water balance should be determined based on serum Na concentrations (e.g.60 kg)
- The basal water intake should be determined (e.g. 1L/day)
- The dose of DDAVP are determined so that daily urine volumes are around basal water intake (e.g. 1L/day)
- Daily water intake＝Basal water intake＋（ideal BW—BW）

However, it is not practical to advise adipsic patients to take a high volume of water (e.g., 3L/day). So, just advise to take more water than 1L/day when the BW is decreased.

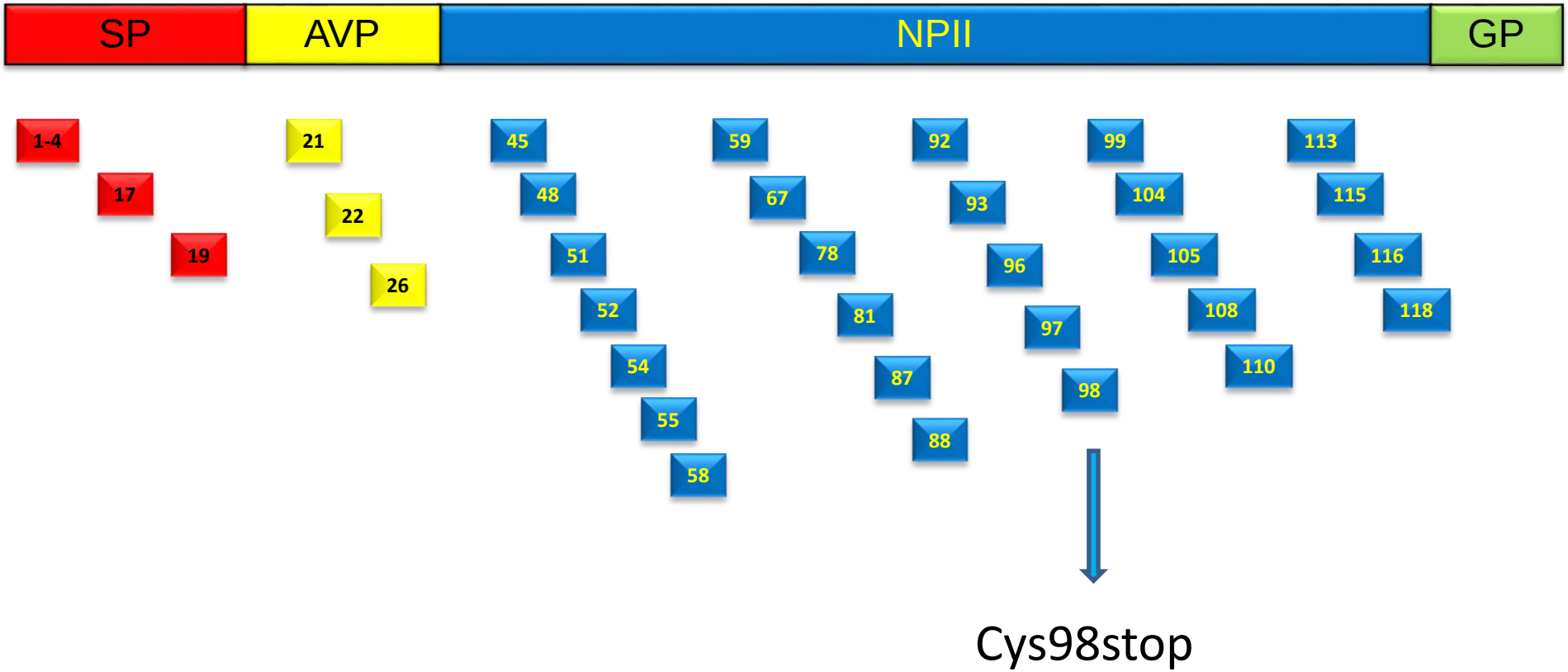
Arima H et al., 2016 **Nagoya J Med Sci**

- Water balance
- Diagnosis of central diabetes insipidus (CDI)
- Treatment of CDI
- Adipsic CDI
- Familial neurohypophysial diabetes insipidus

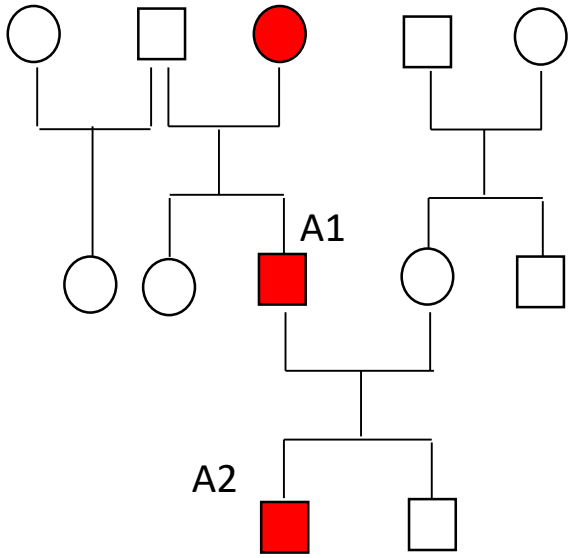
Familial neurohypophysial diabetes insipidus (FNDI)

- Autosomal dominant disease.
- Polyuria appears several months or years after birth.
- Mutations exist mainly in the region of NPII rather than AVP gene.
- Mutant AVP precursors are accumulated in the ER of AVP neurons.
- Autopsy studies show AVP neuronal loss in patients with FNDI.

Mutations causing FNDI



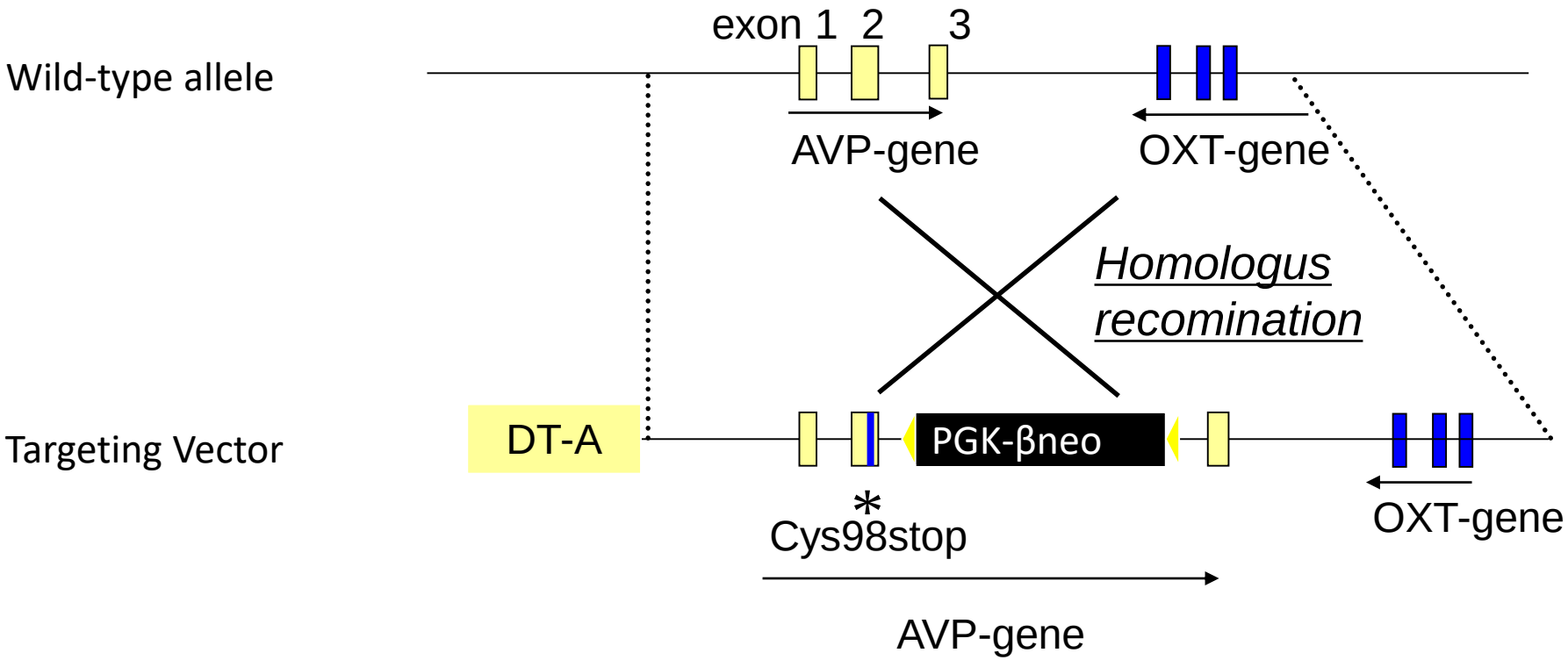
Pedigree of FNDI patients with Cys98 Stop



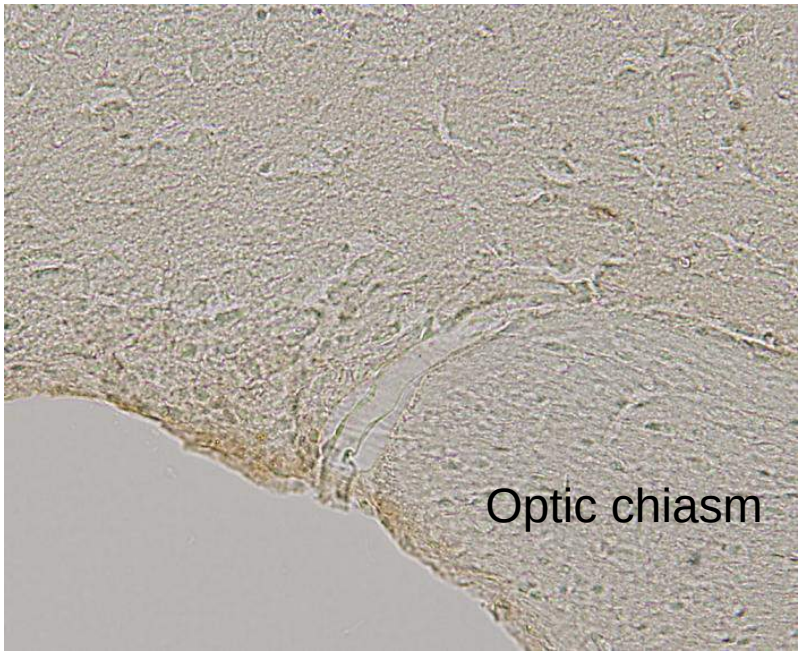
patients	age	onset	urine (l/day)
A1	49	4	10
A2	19	4	10

Nagasaki et al., 1995 **J Clin Endo Metab**

Knock-in mice expressing Cys98stop

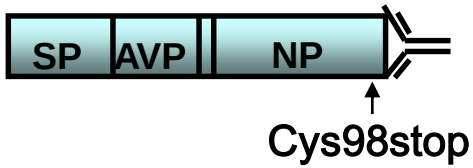


Expression of mutant NPII



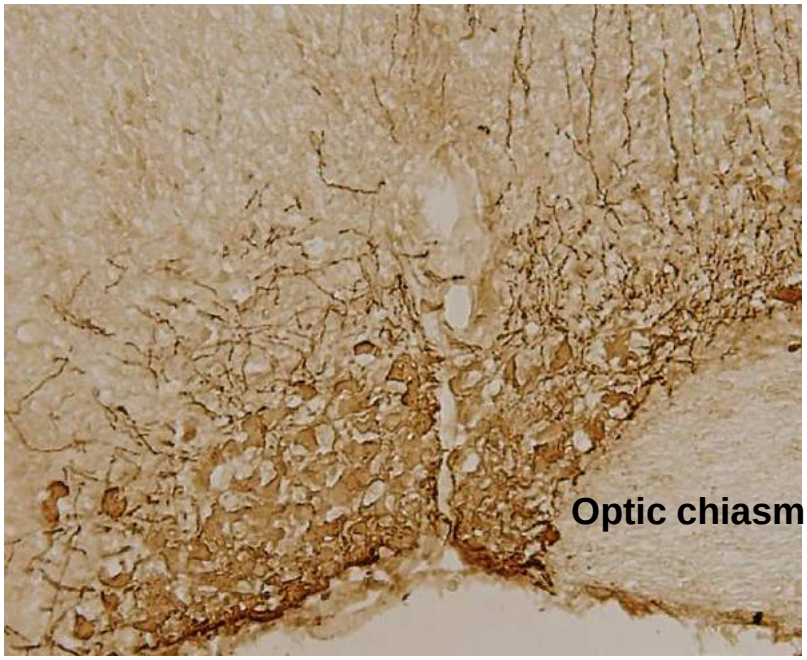
WT mice

FNDI mice

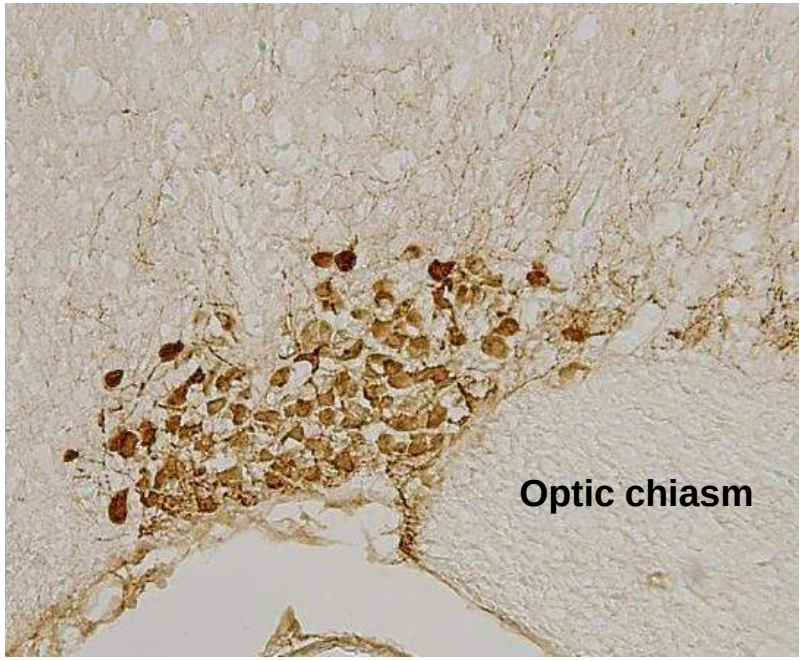


Antibody for mutant NPII

Expression of normal NPII



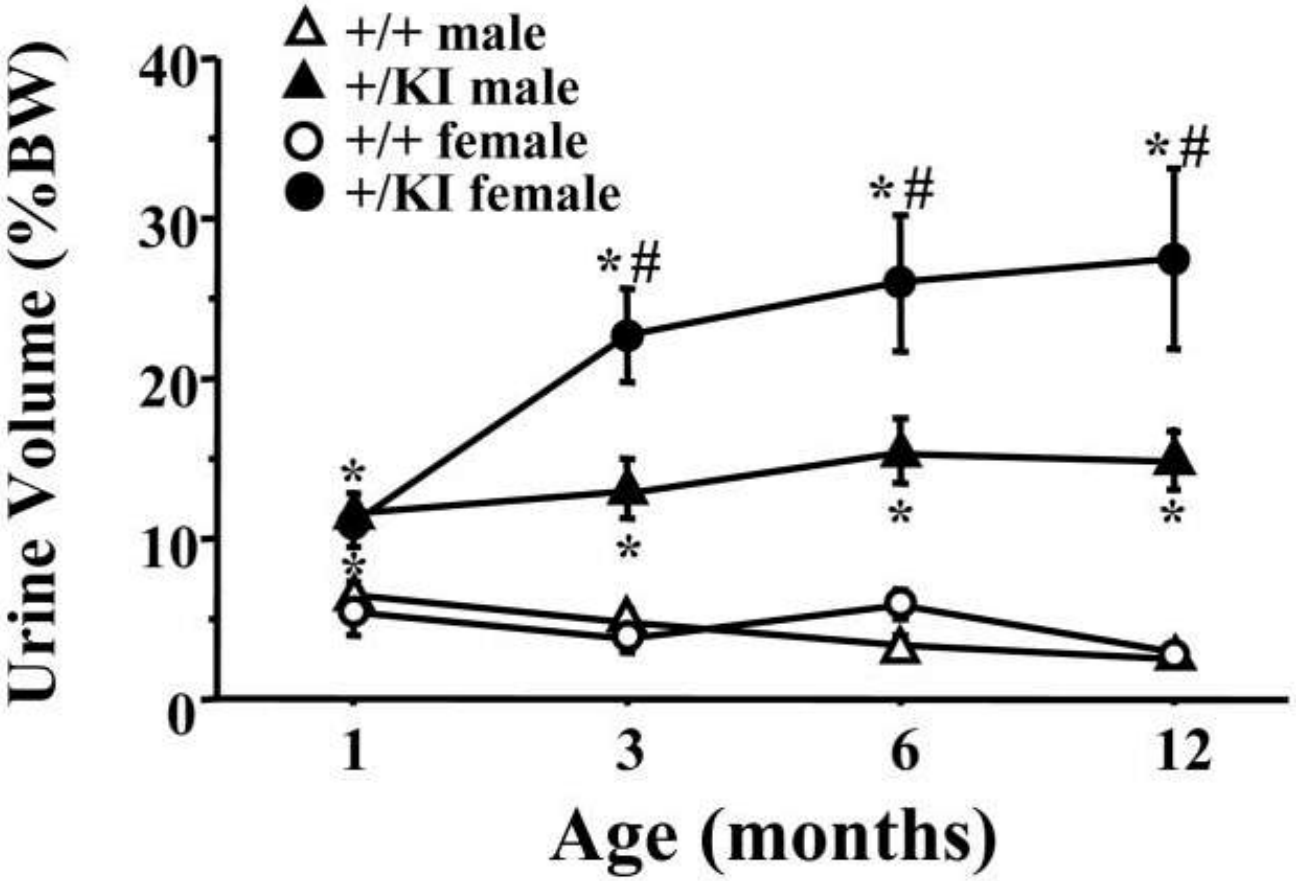
WT mice



FNDI mice

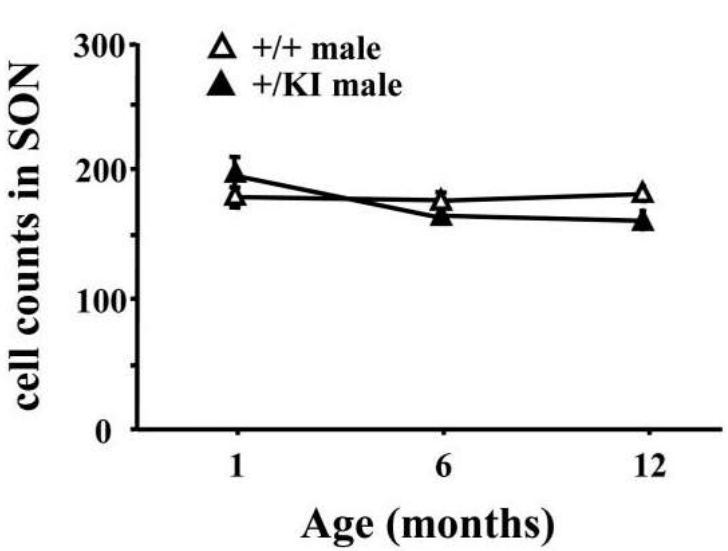
Antibodies for normal NPII

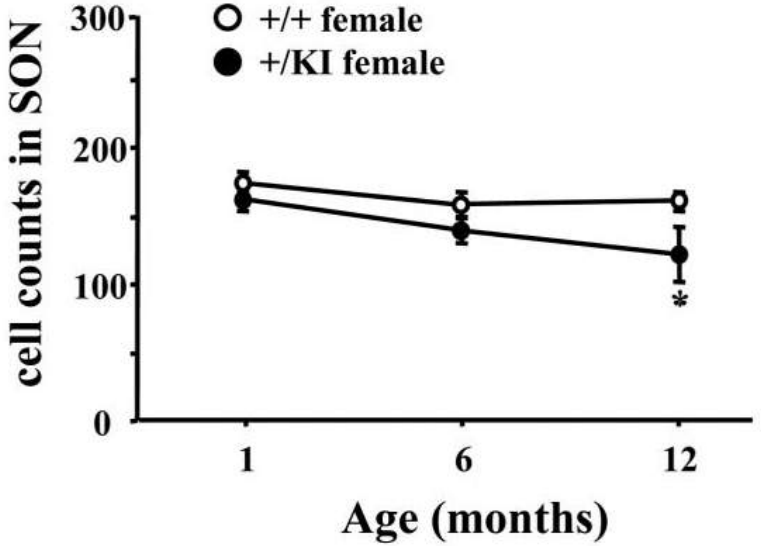
Changes in urine volumes



Hayashi et al., 2009 **Am J Physiol**

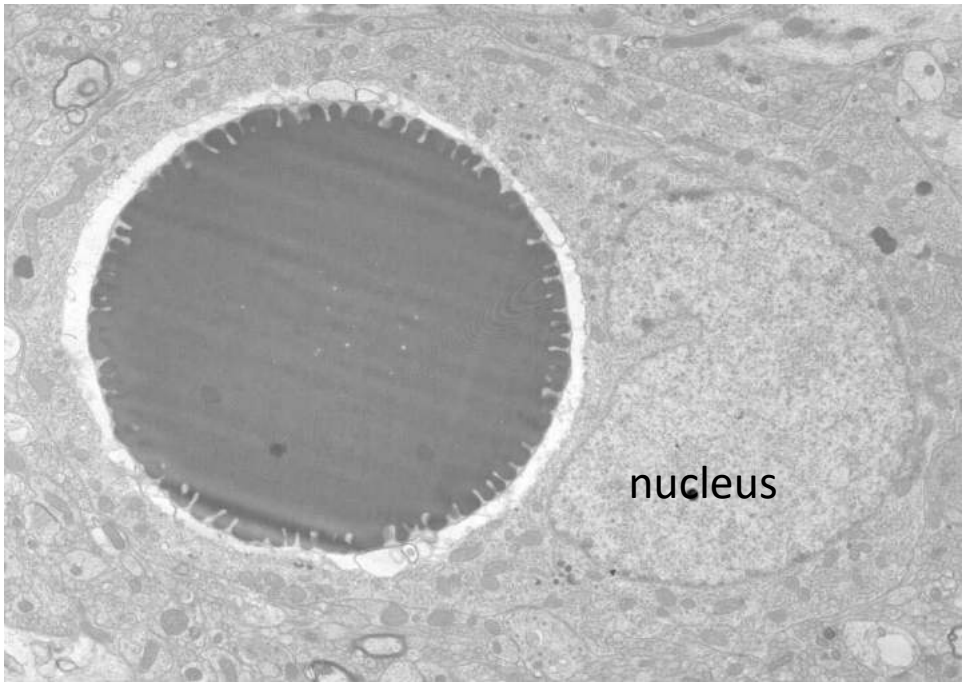
Changes in numbers of AVP neurons

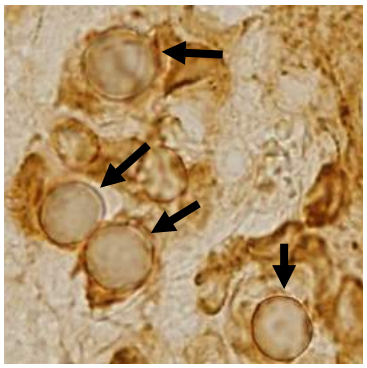




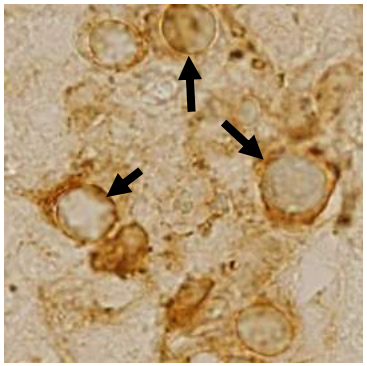
Hayashi et al., 2009 **Am J Physiol**

Analysis with electron microscopy

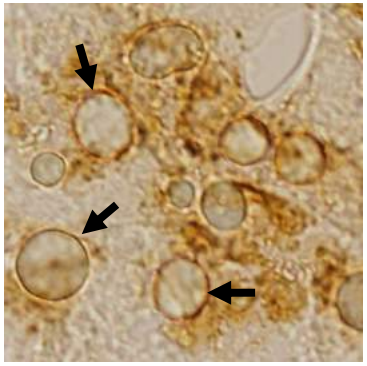




Mutant NPII

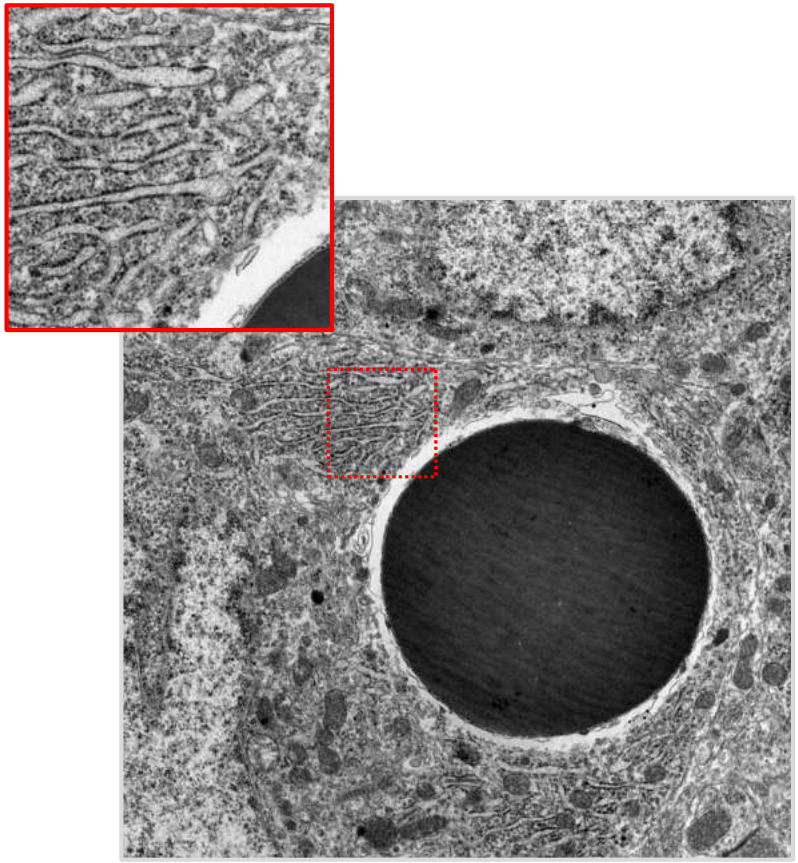


Normal NPII



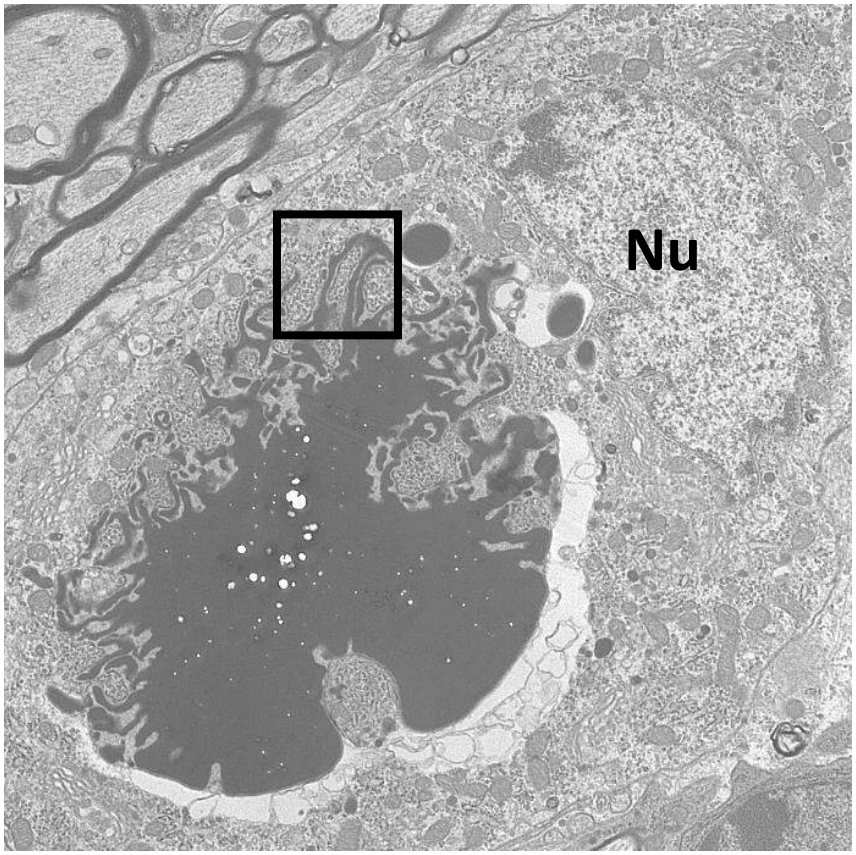
AVP

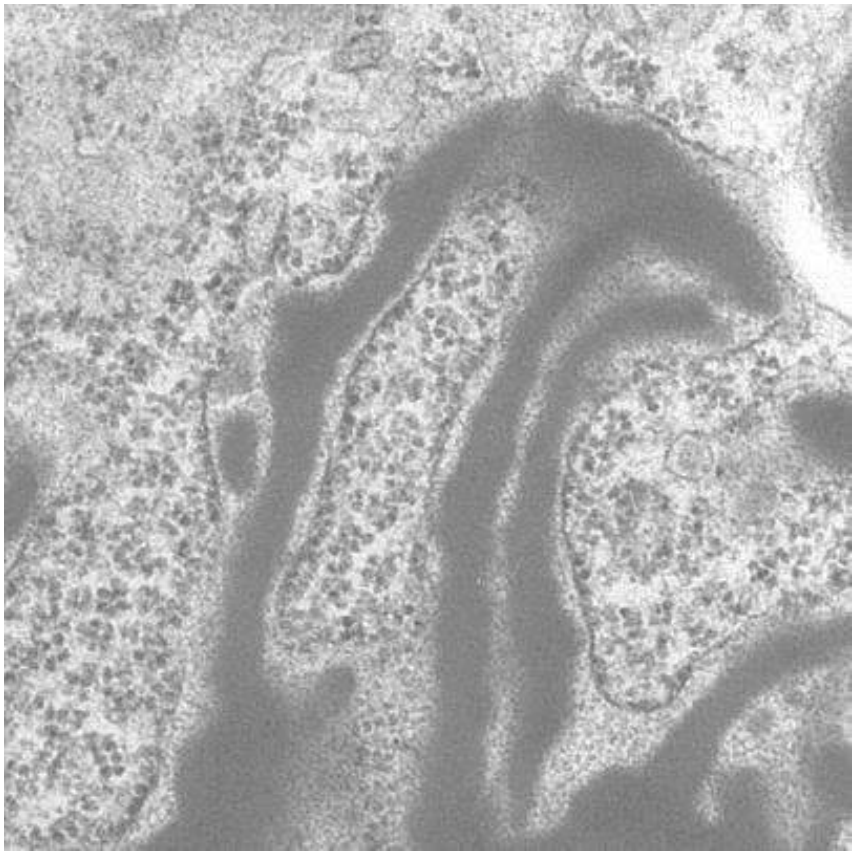
Aggregates are confined to a compartment of ER lumen of AVP neurons in FNDI mice



ERAC
(Endoplasmic Reticulum-Associated Compartment)

ERAC is connected to the rest of ER





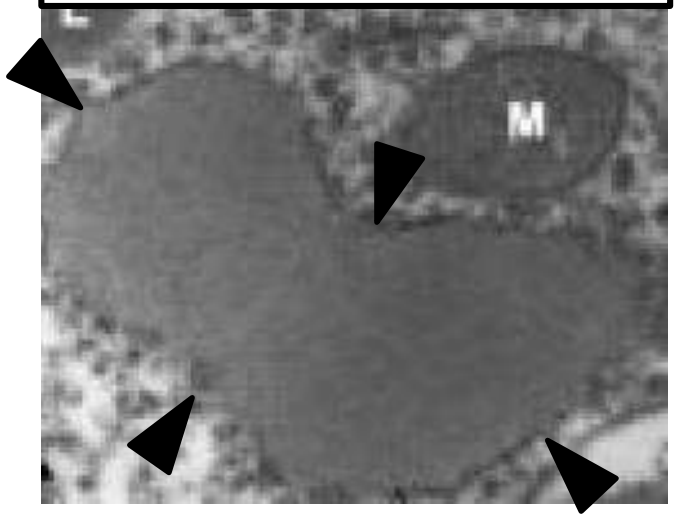
ERAC：ER-associated compartment

The formation of ERAC is also reported in other diseases in which ER stress has been implicated in the pathophysiology.

cystic fibrosis

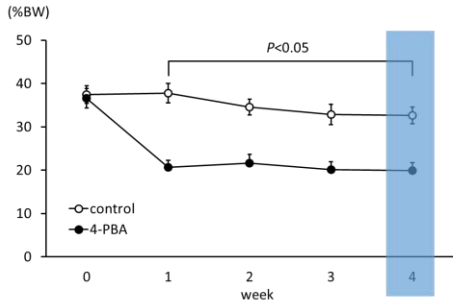
Huyer G et al. 2004 **Mol Biol Cell**

familial encephalopathy with neuroserpin inclusion bodies

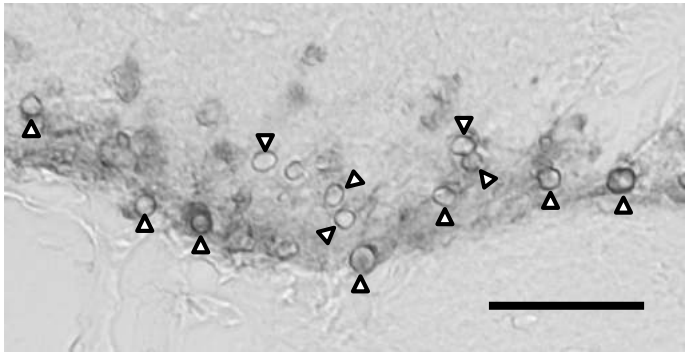


Granell S et al., 2008 **Mol Biol Cell**

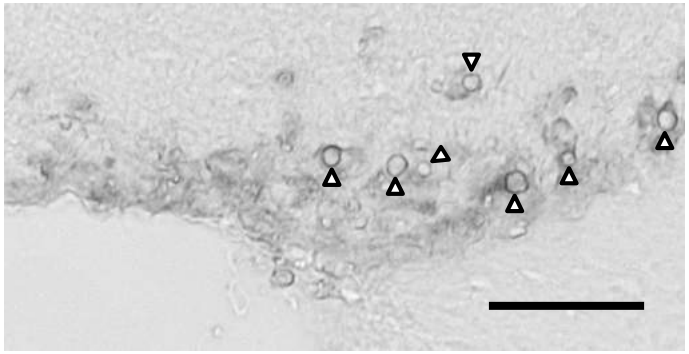
4-PBA reduces the number of ERAC



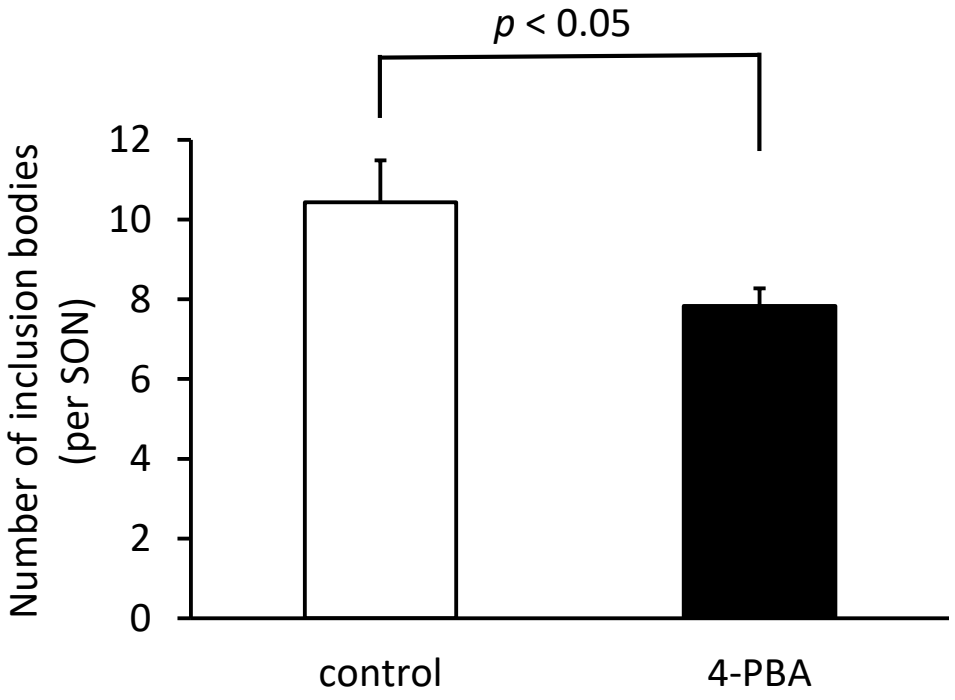
control



4-PBA 28days



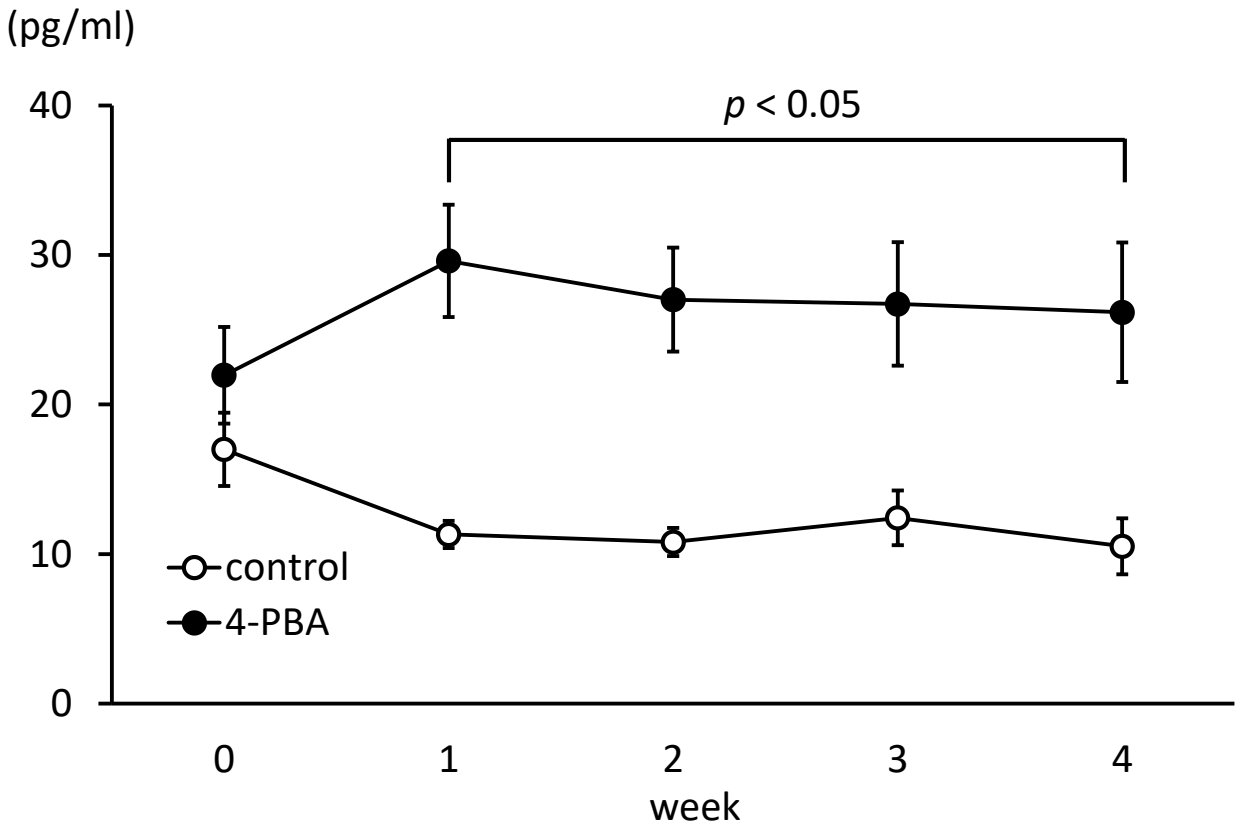
Scale bar, 50 μm



Tochiya et al., 2018 **Neurosci Lett**

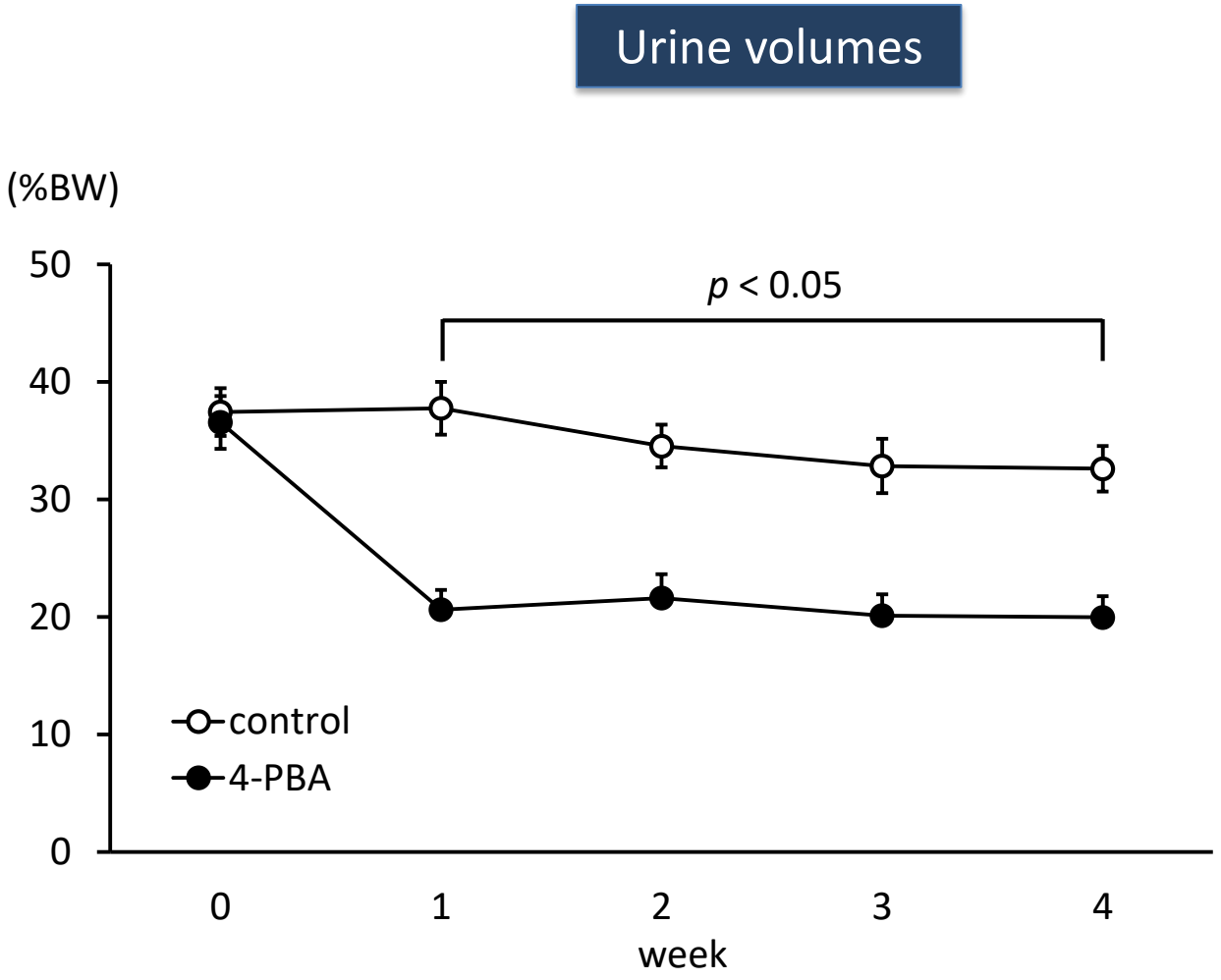
4-PBA reduced urine volumes in FNDI mice

Urine AVP



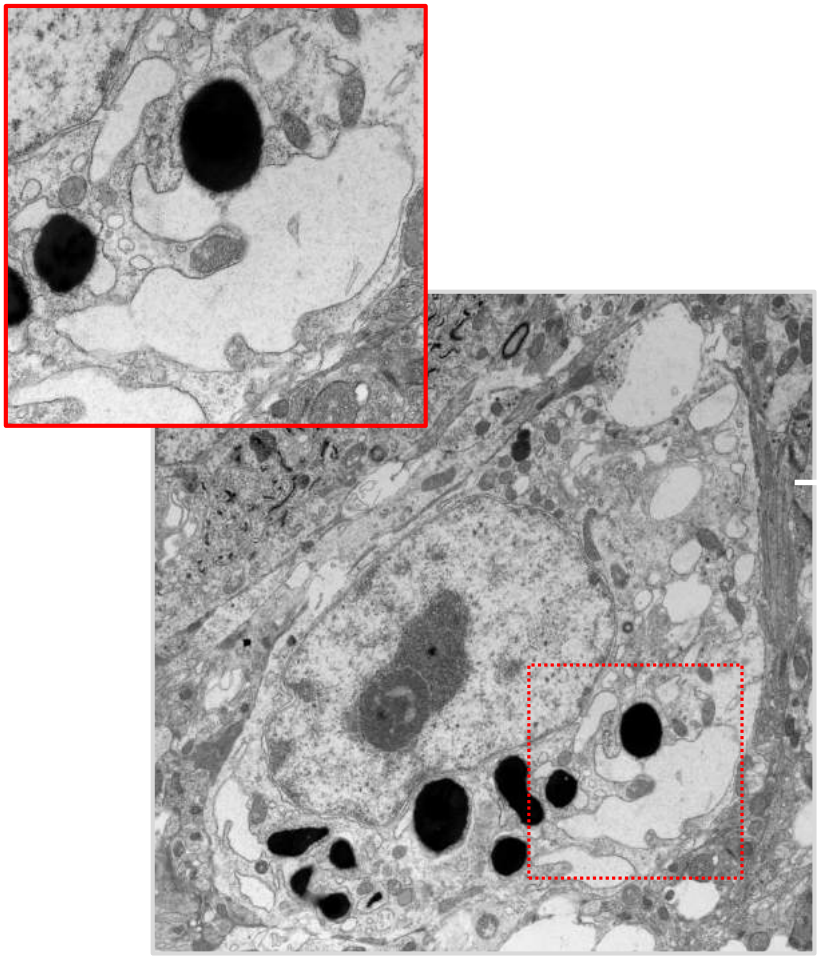
Tochiya et al., 2018 **Neurosci Lett**

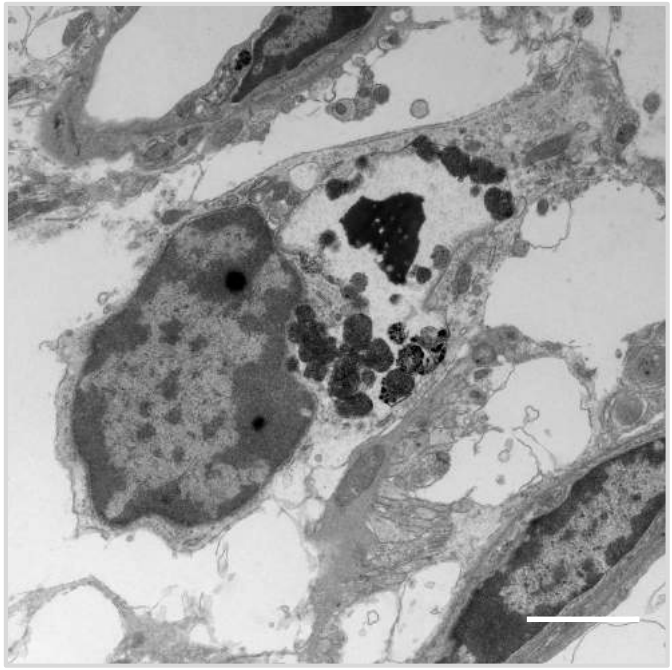
4-PBA reduced urine volumes in FNDI mice



Tochiya et al., 2018 **Neurosci Lett**

AVP neurons are finally lost by mechanism of autophagy-associated cell death

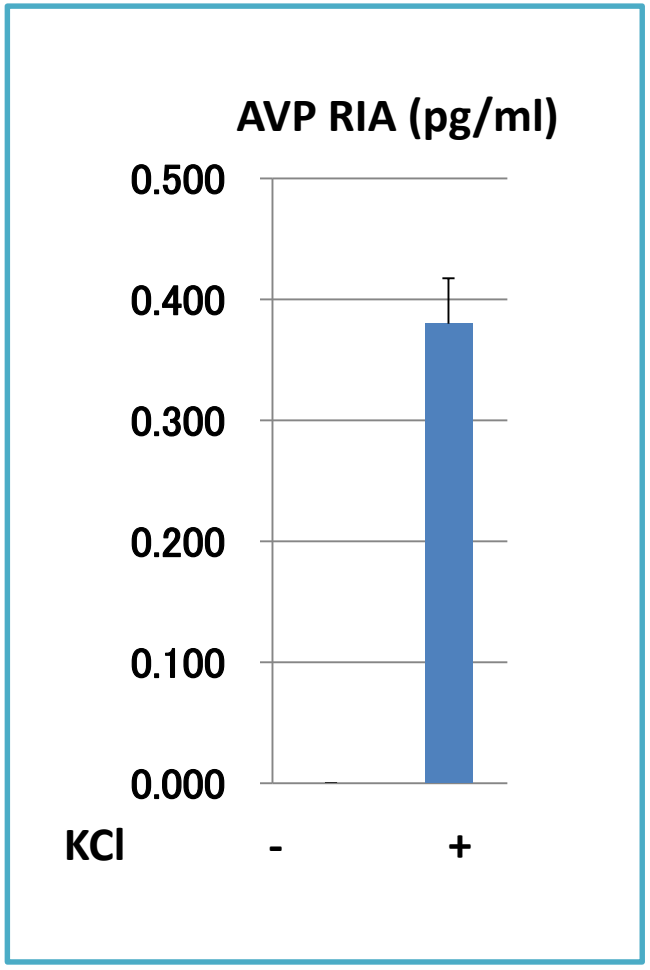


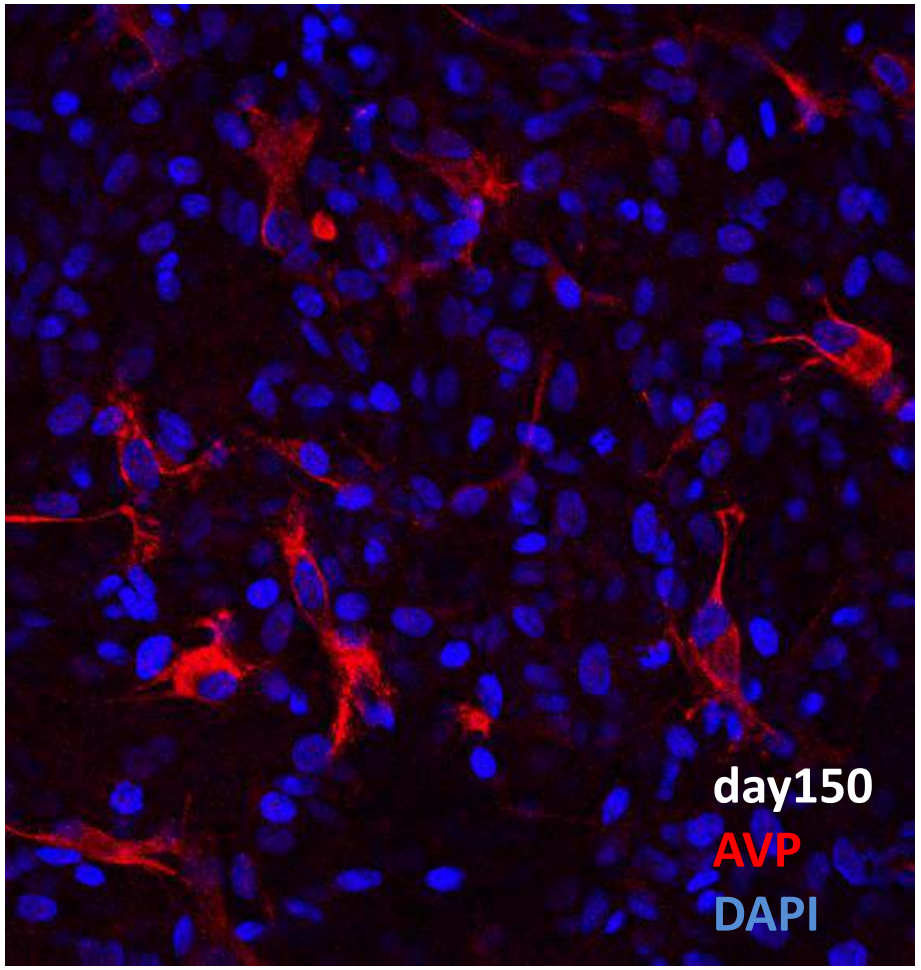


Hagiwara et al., 2013 **Cell Death & Dis**

hES

AVP neurons differentiated from human ES cells





Ogawa et al., 2018 **Sci Rep**

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Thank you for your attention