In the Framingham Offspring Study, higher baseline plasma aldosterone levels within the physiologic range were associated with an increased risk of BP elevation or development of hypertension after 4 years in 1,688 normotensive individuals.[13] The clinical observation suggests that MR overactivation plays a crucial role in not only cardiovascular complications but also a risk of developing hypertension.

ALDOSTERONE ACTION AND MR ACTIVITY

The MR is a member of the nuclear receptor superfamily and is essential for controlling sodium and potassium transport in epithelial cells, most notably in the kidney and colon.[14,15] Aldosterone induces activation of serum- and glucocorticoid-inducible kinase 1 and epithelial sodium channel which is followed by downstream actions that promote both ion transport and inflammation. In the kidney, the upregulation of intercellular adhesion molecule-1, monocyte chemotactic protein-1, interleukin-6, plasminogen activator inhibitor-1, and transforming growth factor-β contributes to vascular injury, tubulointerstitial inflammation and subsequent fibrosis, and glomerular injury. Aldosterone also plays an important role in nonepithelial cells, such as cardiac myocytes and vascular walls.

Nuclear receptor coregulators are composed of both coactivators and corepressors and are defined as nonreceptor proteins which interact with nuclear receptors to potentiate or attenuate transactivation. Among over 300 coregulators, the number of MR-interacting coregulators identified to date is very limited such as p160 family, RHA, ELL, Ubc9, and NF-YC.[16–22] Most of the canonical mechanisms of aldosterone are considered to be mediated by cytosolic/nuclear MR with multiple coregulators which are defined as genomic action. However, it is now generally accepted that aldosterone has acute effects, through rapid, so-called nongenomic signaling pathways.[23,24] Though aldosterone mediates rapid nongenomic effects via both MR-dependent and -independent pathways, the mechanism(s) of this MR-independent effect of aldosterone have remained a focus of controversy. Recent studies implicated that rapid vascular response to aldosterone is dependent on the availability of GPR30, which is originally an orphan G protein-coupled receptor. Functional significance of GPR30 and MR remains to be elucidated.[25–27]

There is one clinical observation that patients with autosomal dominant pseudohypoaldosteronism type 1, in whom plasma renin and aldosterone levels are elevated due to the MR gene mutations, present with no significant cardiovascular diseases or hypertension.[28] These findings suggest that the MR-independent aldosterone action alone may not lead to cardiovascular complications. Since the clinical significance of MR-independent aldosterone action has not been proved yet, the role of aldosterone in cardiovascular function may be mainly mediated by classical MR.

MR ACTIVITY AND HYPERTENSION

Previous reports have demonstrated the antihypertensive efficacy of high doses of spironolactone in subjects with PA and, to a lesser degree, subjects with RHTN.[10–12] Nishizaka et al.[29] showed that low-dose spironolactone provides significant additive BP reduction in African American and white subjects with RHTN with and without PA, indicating that MR is likely to be overactivated in patients with RHTN. Since the MR is activated by its agonistic ligands, elevation of plasma aldosterone levels obviously activate the MR activity in target tissues. In addition, the MR activity can be activated without elevation of plasma aldosterone levels in several diseased states through multiple mechanisms including increased MR expression levels, increased MR sensitivity, or MR overstimulation by other factors. In fact, RHTN frequently includes hypertension whose BP level is effectively controlled by MR antagonists. We therefore designate such MR antagonist–responsive RHTN in a broad sense as MR-associated hypertension. The MR-associated hypertension can be divided into two subtypes, that with high aldosterone and that with normal aldosterone levels (Figure 1, Tables 1 and 2). In the former subtype, plasma aldosterone levels are relatively higher (usually ≥150 pg/ml) in proportion to plasma renin activity. It is reasonable that RHTN with elevated plasma aldosterone levels can be effectively treated with MR antagonists. However, it should be noted that several subsets of patients with RHTN with normal plasma aldosterone levels can also be effectively controlled by add-on therapy with MR antagonist, which we define as MR-associated hypertension in a narrow sense (Table 2).

MR-ASSOCIATED HYPERTENSION WITH ELEVATED PLASMA ALDOSTERONE LEVEL

PA is a typical MR-associated hypertension with elevated plasma aldosterone level. The recommendation of PA clinical practice guideline consists of three consecutive steps: case

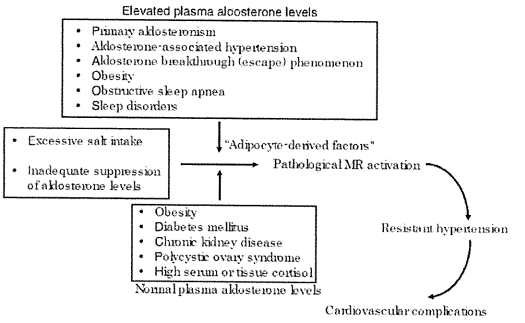

Figure 1 ‖Pathogenesis of MR-associated hypertension.
MR, mineralocorticoid receptor.

Table 1 | MR-associated hypertension with elevated plasma aldosterone levels
Definition
MR antagonist–responsive hypertension
High plasma aldosterone levels (usually greater than 150 pg/ml) in proportion to plasma renin activity
Pathologic state
Primary aldosteronism
Aldosterone-associated hypertension
Aldosterone breakthrough (escape) phenomenon
Obesity
Obstructive sleep apnea
Sleep disorders (insomnia, sleep deprivation, shift working)

MR, mineralocorticoid receptor.

Table 2 | MR-associated hypertension with normal plasma aldosterone levels
Definition
MR antagonist–responsive hypertension
Normal plasma aldosterone levels
Pathologic state
Obesity
Diabetes mellitus
Chronic kidney disease
Polycystic ovary syndrome
High serum or tissue cortisol levels

MR, mineralocorticoid receptor.

detection, confirmatory, and lateralization tests.[30,31] The case detection of PA should be performed with combination of an increased plasma aldosterone concentration (pg/ml)/plasma renin activity (ng/ml/h) ratio of greater than 200 and a plasma aldosterone concentration of greater than 150 pg/ml.

Among several confirmatory tests, the Keio University Hospital (Tokyo, Japan) mostly relies on oral salt loading test. When 24-h urine aldosterone excretion is greater than 8 μg with a urinary Na excretion greater than 170 mmol, PA can be definitively diagnosed. Inadequately suppressed aldosterone levels under excessive salt intake have been shown to overstimulate the MR transactivation particularly in non-epithelial tissues such as myocardium and vasculature, thus resulting in the development and progression of several cardiovascular diseases.[5–9] Two most common subtypes of PA are aldosterone-producing adenomas (APAs) and idiopathic hyperaldosteronism (IHA) due to bilateral adrenal hyperplasia. The subtype diagnosis of PA is crucial because treatment option is dependent on its subtype; unilateral adrenalectomy for APAs and medical therapy including MR antagonist for IHA. The pathogenesis of APAs is due to autonomous overexpression of CYP11B2 in the tumors[32] or the KCNJ5 potassium channel gene mutation, whereas that of IHA is totally unknown at present.[33]

Doi et al. have recently reported that mice lacking cryptochrome-1 (Cry1) and cryptochrome-2 (Cry2), which are clock genes that produce the circadian rhythm, show salt-sensitive hypertension with high plasma aldosterone and suppressed plasma renin activity levels.[34] Further research revealed that a newly identified steroidogenic enzyme, 3β-hydroxysteroid dehydrogenase type 6 (Hsd3b6) is exclusively overexpressed in the adrenal zona glomerulosa cells of Cry1/Cry2 double-knockout mice, thus resulting in enhanced aldosterone secretion. They also showed that HSD3B1, a human ortholog of mouse Hsd3b6, is enriched in human adrenal zona glomerulosa cells, suggesting a role of this enzyme in aldosterone synthesis. It remains to be elucidated a possible role of HSD3B1 in the pathogenesis of IHA.

Several reports showed that a higher prevalence of metabolic syndrome in a large population of patients with PA compared with patients with essential hypertension.[35,36] Of interest, a recent retrospective study of 100 patients with PA showed that the prevalence of the metabolic syndrome and the body mass index (BMI) value were significantly higher in IHA compared with APA patients.[37] Similarly, in our institute, the BMI and homeostasis model assessment of insulin resistance were significantly correlated with urinary aldosterone excretion in patients with IHA (n = 54), but not with APA (n = 31) (Tables 3 and 4). It is tempting to speculate that the pathogenesis of aldosterone excess in IHA may be related with obesity and insulin resistance. Previous reports showed that secretory products from isolated human adipocytes strongly stimulated aldosterone secretion in human adrenocortical NCI-H295R cells, indicating that human adipocytes secrete aldosterone-releasing factors.[38,39] Several reports showed that plasma aldosterone levels are correlated with BMI and waist circumference in hypertensive subjects,[40,41] suggesting that the adipocyte-derived factors may play an important role in MR-associated hypertension with elevated plasma aldosterone levels particularly including IHA.

Second, high aldosterone level is also involved in RHTN other than PA. Sartoli et al.[42] demonstrated that high levels of plasma aldosterone in hypertensive patients increase the risk of poor BP control, despite the use of combination therapy with multiple antihypertensive agents, even when they do not meet the diagnostic criteria for PA. They designated such RHTN as "aldosterone-associated hypertension", which was defined as hypertension with an elevated aldosterone-to-renin ratio and plasma aldosterone levels, but no PA based on captopril suppression test. In this

Table 3 | Clinical features of two subtypes of primary aldosteronism

	APA	IHA	*P* value
Characteristics	Values (± s.d.)	Values (± s.d.)	
N	31	54	
Age, years	51 ± 11	51 ± 9	0.82
Sex (women)	12/31	30/54	0.14
BMI, kg/m^2	23.6 ± 4.5	24.8 ± 3.7	0.20
Waist circumstance, cm	83 ± 17	84 ± 9	0.84
Systolic BP, mm Hg	136 ± 20	140 ± 14	0.32
Diastolic BP, mm Hg	89 ± 16	86 ± 11	0.43
Diabetes mellitus	3/31	2/54	0.35
Dyslipidemia	1/31	9/45	0.085
Plasma aldosterone, pg/ml	404 ± 203	232 ± 96	<0.001**
Plasma-active renin, pg/ml	3.8 ± 2.6	6.5 ± 6.5	0.017*
Aldosterone-renin ratio	133.5 ± 80.9	55.1 ± 36.1	<0.001**
Urinary aldosterone, μg/day	23.9 ± 15.0	13.1 ± 7.5	0.01**
Serum potassium, mEq/l	3.7 ± 0.6	4.0 ± 0.4	0.009**

APA, aldosterone-producing adenoma; BMI, body mass index; BP, blood pressure; IHA, idiopathic hyperaldosteronism. *P< 0.05, **P< 0.01 between APA and IHA.

Table 4 | **Correlation between urine aldosterone excretion** and metabolic parameters

	APA		IHA	
	R	*P* value	R	*P* value
BMI	0.028	0.894	0.443	0.003**
HbA_{1c}	0.384	0.058	0.279	0.099
Glucose	−0.100	0.643	0.196	0.231
HOMA-R	−0.170	0.530	0.789	<0.001**
HDL-C	−0.109	0.582	−0.116	0.519
LDL-C	−0.027	0.089	0.086	0.613
TG	−0.100	0.605	0.175	0.279

APA, aldosterone-producing adenoma; BMI, body mass index; HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-R, homeostasis model assessment of insulin resistance; IHA, idiopathic hyperaldosteronism; LDL-C, low-density lipoprotein cholesterol; R, correlation coefficient; TG, triglyceride.
**P< 0.01.

type of hypertension, adequate BP control was reached in a lower fraction of patients after a longer treatment period as compared with essential hypertensive patients.

Third, blocking the renin–angiotensin–aldosterone system with angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin II receptor blockers (ARBs) is often associated with an initial decrease in plasma aldosterone followed by a subsequent increase in aldosterone above pretreatment levels during prolonged treatment. This phenomenon is named as "aldosterone escape" or "aldosterone breakthrough" and it may contribute to drug resistance counteracting the antihypertensive actions of the drugs. Bomback and Klemmer[43] showed that an incidence of aldosterone breakthrough is 10–53% in patients with chronic heart or kidney disease on ACE-I or ARB therapy. However, the detailed molecular mechanisms for aldosterone breakthrough have not been elucidated. The add-on therapy of an MR antagonist in this context could result in an improved prognosis through a further and sustained BP reduction.

Obstructive sleep apnea (OSA) is characterized by recurrent episodes of partial or complete upper airway obstruction during sleep. OSA is particularly common in patients with RHTN.[44–48] Stimulation of sympathetic activity by OSA is likely representing the most important effect by which OSA increases BP through elevation of vascular resistance, greater cardiac output, and possibly stimulation of the renin–angiotensin–aldosterone system. Several adipocytokines, such as angiotensinogen, 12, 13-epoxy-9-keto-10(trans)-octadecenoic acid, and adipocyte-derived factors, would also stimulate aldosterone secretion.[44,46,48,49] Treatment of OSA with use of continuous positive airway pressure has generally shown a consistent but modest antihypertensive benefit due to suppression of the sympathetic activation. A positive correlation between OSA severity and aldosterone levels suggests two opposite possibilities[44,46,48]; either untreated OSA is stimulating aldosterone release or aldosterone excess is worsening OSA. Human studies, however, have not shown that treatment of OSA with continuous positive airway pressure to have a substantive effect on aldosterone levels. A preliminary study showed that treatment with a MR antagonist substantially reduces the severity of OSA,[45] suggesting that aldosterone-mediated chronic fluid retention as an important mediator of OSA severity in patients with RHTN.

Besides OSA, sleep disorders such as insomnia, sleep deprivation, and shift working have become common problems in many people. A sleep-inducing hormone, melatonin, rapidly suppresses the neural activity of suprachiasmatic nucleus through the melatonin type 1 receptor to induce sleep. Most sleep disorders are associated with disrupted circadian rhythm by which reduction of melatonin secretion leads to biological clock dysfunction. Based on a report that Cry knockout mice reveal a human-type IHA and salt-sensitive hypertension, a possible link among sleep disorders, melatonin, and elevated plasma aldosterone levels is suggested.[50]

MR-ASSOCIATED HYPERTENSION WITH NORMAL PLASMA ALDOSTERONE LEVEL

The prevalence of obesity is increasing and weight gain is associated with increases in BP. Mechanisms of obesity-related hypertension include insulin resistance, sodium retention, increased sympathetic nervous system activity, activation of the

renin–angiotensin–aldosterone, and altered vascular function. The clinical implications of the role of aldosterone in the metabolic syndrome and RHTN have been strongly suggested (Table 2, Figure 1).[51–55] It is therefore possible to hypothesize that the MR activity is overstimulated in the context of metabolic syndrome even in the absence of elevated plasma aldosterone levels.

Second, patients with diabetes often present with RHTN. ACE-Is or ARBs have become the cornerstone of the management of patients with hypertension plus diabetes and both drugs have been shown to have a beneficial effect on surrogate endpoints such as decreasing microalbuminuria, slowing progression from microalbuminuria to macroalbuminuria, and slowing the decline in renal function.[56,57] MR antagonists can be exceedingly helpful in selected diabetic patients. These drugs have been shown to reduce target organ disease and surrogate endpoints such as microproteinuria and left ventricular hypertrophy. The addition of spironolactone to a regimen that includes maximal ACE-I affords greater renoprotection than the addition of the ARB losartan in diabetic nephropathy, indicating that MR is overactivated in selected diabetic patients even in the absence of high plasma aldosterone levels.[57,58]

Plasma aldosterone levels have been correlated with alterations in kidney function in CKD, suggesting an association between kidney dysfunction and MR activation. ACE-Is or ARBs have become a first-line therapy for the management of patients with proteinuric CKD in a similar manner to diabetes. The use of MR antagonists as an add-on agent in CKD is recommended because of the possible direct MR activation as well as aldosterone breakthrough by ACE-Is or ARBs.[58–60] Beneficial effects of MR antagonists in CKD have been reported in diabetic nephropathy as well as nondiabetic proteinurias.[61–65] It is therefore suggested that direct activation of the MR that can occur in pathological states associated with CKD, even in the absence of increased circulating levels of aldosterone.

PCOS, which is characterized by chronic anovulation, hyperandrogenism, and insulin resistance, is considered metabolic disease associated with long-term health risks including cardiovascular disease and type 2 diabetes mellitus. Women with PCOS appear to have higher aldosterone levels than age- and BMI-matched controls.[66] A putative cause of the increased aldosterone levels, even if within normal limits, observed in PCOS could be the insulin resistance.

Under high serum or tissue cortisol levels such as Cushing's syndrome or inhibition of 11β-hydroxysteroid dehydrogenase type 2 by glycyrrhizin, clinical benefit of MR antagonists depends on displacement of cortisol from the cardiac as well as renal MR.[67,68]

PATHOGENESIS OF MR-ASSOCIATED HYPERTENSION

The MR action is principally activated by elevation of aldosterone levels and by alterations of MR status. The pathogenesis of MR-associated hypertension in a narrow sense is recognized to be overstimulation of MR independent of elevated plasma aldosterone levels (Figures 1 and 2). At present, putative molecular mechanisms of MR-associated hypertension are considered to include five mechanisms: increased MR gene transcription, increased MR sensitivity, MR stabilization, MR overstimulation by other factors, and activating mutation of the MR gene (Table 5).

Increased MR gene transcription

There are several pathological states in which MR gene transcription is increased. First, we have previously shown that MR expression and superoxide production was concomitantly increased in astrocytes of the striatum in the mouse 20-min middle cerebral artery occlusion model.[69] Treatment with spironolactone markedly stimulated the expression of neuroprotective or angiogenic factors, such as basic fibroblast growth factor and vascular endothelial growth factor, thus resulting in reduction of infarct size. These data indicate that increased MR transcripts play a pathological role in cerebral infarction in vivo and that MR antagonist therapy may thus provide a new therapeutic neuroprotective effects in the ischemic brain after stroke.

Second, rodent models of types 1 (streptozotocin-treated rat) and 2 (db/db mouse) diabetes mellitus developed albuminuria and histopathological evidence of renal injury as well as increased renal cortical levels of MR protein, MR messenger RNA (mRNA), transforming growth factor-β mRNA, and osteopontin mRNA. All of these changes were significantly reduced by treatment with eplerenone except for the elevated MR levels.[70] The beneficial effects of eplerenone were not

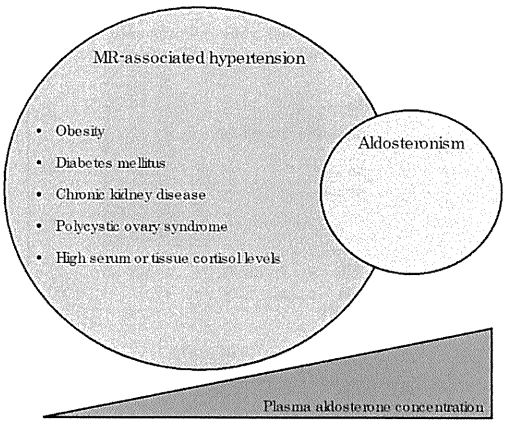

Figure 2 MR-associated hypertension and putative diseases.
MR, mineralocorticoid receptor.

attributable to changes in BP or glycemia. It is possible that increased intrarenal expression of MR may be one mechanism contributing to increased MR activity in diabetic kidneys.

Third, another study also showed increased MR mRNA levels in kidney biopsies from patients with chronic renal failure and heavy albuminuria, most of whom did not have diabetes.[71] Taken together with the above studies, increased expression of MR may be attributable to several pathological conditions, such as cerebral infarction, diabetes mellitus, and CKD.

Increased MR sensitivity

The MR activity is shown to be enhanced by post-translational modification, such as sumoylation, ubiquitylation, phosphorylation, and glycosylation.[15,18,72-74] First, treatment with H_2O_2 leads to global protein desumoylation including MR, thus resulting in enhancement of aldosterone-mediated MR transactivation by several fold in vitro.[18] Further analyses revealed that reduction of the MR sumoylation levels by overexpression of sumoylation-defective MR mutant, K89R/K399R/K494R/K953R significantly enhances MR transactivation by several fold in vitro (Figure 3). It is therefore speculated that oxidative stress enhances MR sensitivity through desumoylation of MR protein.

Second, cyclin-dependent kinase 5 (CDK5), a member of the CDK family of serine/threonine kinases, is essential for neuronal morphogenesis, function, and survival. Recent evidence suggests that aberrant CDK5 activation plays a role in the pathogenesis of neurodegenerative disorders, such as Alzheimer's disease. CDK5 phosphorylates MR, thus resulting in enhanced expression of brain-derived neurotrophic factor in rat cortical neuronal cells.[73] Therefore, increased MR sensitivity by CDK5-mediated phosphorylation of MR may reflect neuronal viability, synaptic plasticity, consolidation of memory, and emotional changes in vivo.

MR stabilization

There are several pathological states in which MR transcripts or proteins are stabilized. First, the MR expression is tightly regulated by osmotic stress through alteration of MR transcript stabilization.[75] Hypertonic conditions leads to a severe reduction in MR transcript and protein levels through induction of tonicity-induced expression of Tis11b, a mRNA-destabilizing protein, which may favor hypertonicity-dependent degradation of labile MR transcripts. Osmotic stress-regulated MR expression may explain an important molecular determinant for physiological abundant localization of MR at renal cortical collecting duct cells.

Second, the MR activation seems to involve the epidermal growth factor receptor (EGFR) for the development of fibrosis and vascular dysfunction.[76-79] The activated MR can rapidly transactivate the EGFR probably via the cytosolic tyrosine kinase, cSrc, resulting in extracellular signal-regulated kinase 1/2 (ERK1/2) activation. Furthermore, activated MR can enhance EGFR expression by a genomic mechanism. Increasing the number of EGFR makes a cell more sensitive for transactivating activity of other pathophysiological relevant stimuli, like angiotensin II, endothelin-1, or reactive oxygen species. Besides, our preliminary data showed that EGFR activation enhanced aldosterone-mediated MR transactivation via increased MR protein levels. The EGFR activation, coupling with activation of EGFR–tyrosine kinase and ERK, resulted in deubiquitylation and MR protein stabilization (Y. Mitsuishi,

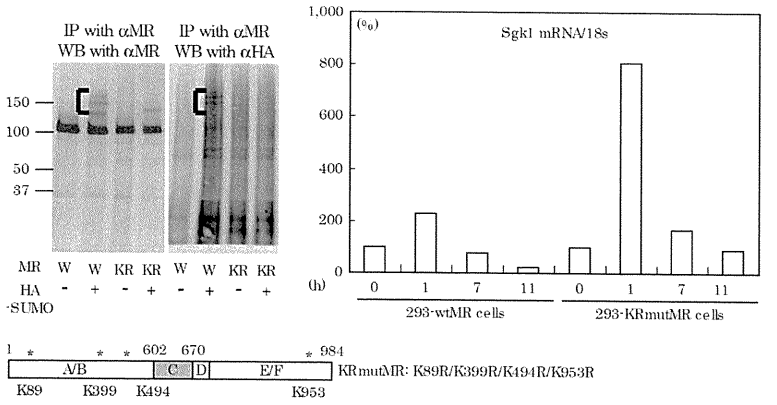

Figure 3 | Induction of endogenous Sgk1 mRNA levels was enhanced in stable transformants of sumoylation-inactivate MR mutant (KRmutMR). *Indicate four-K residues (K89, K399, K494, and K953) which were mutated to R. αHA, anti-HA antibody; αMR, anti-MR antibody; HA, hemagglutinin; HA-SUMO, HA-tagged SUMO; IP, immunoprecipitation; mRNA, messenger RNA; MR, mineralocorticoid receptor; SUMO, small ubiquitin-related modifier; WB, western blot.

H. Shibata, I. Kurihara, H. Itoh, unpublished data). Activation of EGFR either activated by its peptide ligand or transactivated by factors such as reactive oxygen species, angiotensin II, or leptin may elicit vasconstriction and renal sodium retention.[80]

Third, it is believed that hyperglycemia is one of the most important metabolic factors in the development of both micro- and macrovascular complications in diabetic patients. One of the adverse effects of hyperglycemia is the chronic activation of protein kinase C (PKC).[81–84] Clinical trials using a PKCβ isoform inhibitor, ruboxistaurin, in diabetic patients showed 40% risk reduction in vision loss and decrease in urinary albumin excretion for diabetic nephropathy.[85,86] Our preliminary data showed that high glucose condition activate several PKC isoforms including PKCβ, thus resulting in enhancement of aldosterone-mediated MR transactivation via MR protein stabilization in vitro (T. Hayashi, H. Shibata, I. Kurihara, H. Itoh, unpublished data). These data suggest that some of the beneficial effects of PKCβ inhibitor are attributable to destabilization of MR proteins.

Fourth, another adverse effect of hyperglycemia is a O-linked N-acetylglucosamine (O-GlcNAc) glycosylation. The O-GlcNAc modification now appears to play a major role in glucotoxicity and participates in diabetic complications in various tissues.[72,87,88] Our preliminary data showed that high glucose condition enhances aldosterone-mediated MR transactivation by several fold via increased O-GlcNAc modification of MR and MR protein stabilization in vitro (R. Ob, H. Shibata, I. Kurihara, H. Itoh, unpublished data). The in vitro data may partially explain that add-on therapy with MR antagonist to maximum dose ACE-I further reduce albuminuria in diabetic nephropathy in a BP-independent manner.[57]

Table 5 | Putative molecular mechanisms of MR-associated hypertension

Molecular mechanisms	Pathological states
Increased MR gene transcription	
Unknown	Cerebral ischemia
Unknown	Diabetes mellitus
Unknown	Chronic kidney disease
Increased MR sensitivity	
Desumoylation	Oxidative stress
Phosphorylation by cyclin-dependent kinase 5	Neurodegenerative diseases
MR stabilization	
MR mRNA stabilization through reduction of Tis11b	Osmotic hypotonicity
Deubiquitylation	Hypercytokinemia (EGF, angiotensin II, leptin etc.)
Phosphorylation by PKCβ	High glucose
O-linked-β-N-acetylglucosamine modification	High glucose
MR overstimulation by other factors	
Rac1-mediated MR nuclear translocation	Excessive salt intake
Activating mutation of the MR gene (S810L)	Pregnancy-induced hypertension

EGF, epidermal growth factor; MR, mineralocorticoid receptor; mRNA, messenger RNA; PKCβ, protein kinase Cβ.

MR overstimulation by other factors

Excessive salt intake induced renal injury, such as heavy proteinuria, mesangial proliferation, and tubulointerstitial inflammation and fibrosis. Salt-induced renal injury was shown to be ameliorated by administration of MR antagonist, suggesting that the renal MR is pathologically activated even when plasma aldosterone level is suppressed. Recent reports showed a novel signaling crosstalk between MR and the small GTPase Rac1 that modulates MR function.[89] Salt excess increased expression levels of Rac1 in Dahl salt-sensitive, but not salt-insensitive rats.[90] Rac1 is shown to increase nuclear translocation of MR, thus resulting in enhanced MR activity. Elevation of Rac1 levels may therefore explain one mechanism of salt-sensitive hypertension. As shown before, alterations of abundance and/or MR affinity of coactivators and corepressors,[16–22] such as Ubc9, ELL, RHA, PGC-1α, PIAS1, and NF-YC play crucial roles in MR activation.

Activating mutation of the *MR* gene

The MR S810L mutation has been shown to be an activating mutation and it plays a crucial role in pregnancy-induced hypertension, since high progesterone levels during pregnancy act as an agonist for the mutant MR.[91]

CLINICAL MANAGEMENT OF MR-ASSOCIATED HYPERTENSION

Since MR-associated hypertension is a salt-sensitive RHTN, reduction of dietary salt intake is very effective to control BP. As a therapeutic approach for RHTN with high plasma aldosterone levels, MR antagonists, such as spironolactone and eplerenone,

Table 6 | Clinical management of MR-associated hypertension

Resistant hypertension with high plasma aldosterone levels
MR antagonist (first-line)
Resistant hypertension with normal plasma aldosterone levels in the presence of obesity, diabetes mellitus, or CKD
ARB or ACEI plus MR antagonist (add-on)

ARB, angiotensin II receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; CKD, chronic kidney disease; MR, mineralocorticoid receptor.

should be used as a first-line drug (Table 6). In contrast, ARBs or ACE-Is is frequently used as a first-line drug to control hypertension in patients with MR-associated hypertension, including obesity, diabetes mellitus, CKD, and POCS.[59,60] Based on the pathogenesis of MR-associated hypertension, low dose of MR antagonists should be given as an add-on agent for the treatment of RHTN with normal plasma aldosterone levels. However, given that patients with diabetes plus hypertension are prone to hyperkalemia due to hyporeninemic hypoaldosteronism, renal impairment, and/or ACE-I/ARB treatment, these drugs should be used cautiously and in low doses only. Serum potassium and creatinine levels will have to be monitored frequently.

Recently, dihydropyridine-type calcium channel blockers, such as nifedipine and amlodipine, are shown to have inhibitory effects on the MR transcriptional activity when they are given at higher doses.[92–94] Our preliminary data in patients with PA showed that switching from a nondihydropyridine-type calcium channel blocker, diltiazem to either amlodipine or nifedipine significantly reduced a transtubular potassium gradient, indicating that dihydopyridine-type calcium channel blockers have MR antagonistic activity in humans (I. Kurihara, H. Shibata, H. Itoh, unpublished data). Since clinical evidence of efficacy of MR antagonist in MR-associated hypertension is lacking, randomized and controlled clinical trial should be expected.

SUMMARY

In conclusion, we propose a clinical subtype of RHTN or organ damage which is effectively controlled by MR antagonists as "MR-associated hypertension" in a broad sense. The MR-associated hypertension is classified into two subtypes, one with elevated plasma aldosterone levels and the other with normal plasma aldosterone levels. This clinical entity includes a variety of pathological states, such as PA, obesity, OSA, diabetes mellitus, and CKD, in which plasma aldosterone levels are elevated in some but normal in others. The MR action is overactivated by elevated plasma aldosterone levels due to activation of sympathetic nerve activity, the renin–angiotensin–aldosterone system, and putative adipocyte-derived aldosterone-releasing factors, and also by several pathways other than elevated aldosterone levels, such as increased MR levels, increased MR sensitivity, and MR-interacting factors. Since the MR antagonist therapy as a first-line or add-on agent is effective, it is important to recognize this type of RHTN.

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Ⅴ 調査資料

調査資料　1

PHEOレジストリー

厚生労働省科学研究費補助金難治性疾患克服研究事業　「褐色細胞腫の診断及び治療法の推進に関する研究」班

Pheo レジストリー

Step

1 **症例の確認**

平成22年以降の未登録例

2 **事務局に連絡**

※調査票が足りない場合はお送りいたします。
※お持ちの場合は3へ。

3 **調査票の記入・対応表作成**

施設患者番号を付与し、
“匿名化”して提出

施設患者番号を記載。

例）良性-1

施設における対応表

記載者ご氏名　　年　月　日

施設患者番号	カルテ番号	患者氏名	イニシャル	性　別	生年月日（西暦）
良性-1	AAA-11111	褐色　細胞腫	S・K	M	1950. 01. 01
			・	M・F	
			・	M・F	

施設で保管

4 **事務局に郵送**

事務局：WEB代行入力

希望者にはＩＤ・ＰＷ発行

厚生労働省科学研究費補助金難治性疾患克服研究事業 「褐色細胞腫の診断及び治療法の推進に関する研究」班

病理組織集中解析

Step

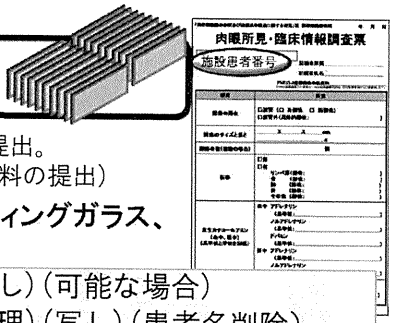
1 対象症例の確認

⚠ ・クロモグラニンＡの免疫染色：陽性であることが必須です。

2 **事務局に連絡**

まずは事務局にご連絡ください。
※送付物などを改めてご案内致します（連絡先は下記）。

3 **標本作製・書類の準備**



⚠ 施設患者番号にて標本を提出。
（連結可能匿名化による試料の提出）

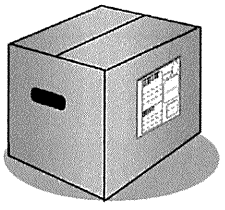
各症例毎に未染標本20枚（コーティングガラス、病理番号のみ記載）

書類
1. 肉眼写真・切り出し図（写し）（可能な場合）
2. 病理診断依頼書（術者→病理）（写し）（患者名削除）
3. 病理診断書（写し）（患者名削除、年齢・性別要）
4. 肉眼所見・臨床情報調査票

4 事務局に郵送日をメールで連絡

⚠ 事務局に送付日をご連絡ください。

5 **事務局に郵送**



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研究代表者　成瀬　光栄　（事務　梅垣）
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解　析

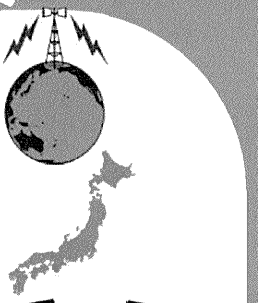
・国立病院機構 函館病院 臨床研究部病因病態研究室
・山梨大学　人体病理学講座

調査資料　2

研究の概要

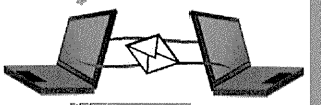
PHEO-J 研究活動の概要

2008- **PHEO Symposium** 計６回（約750人）
（公開シンポジウム）



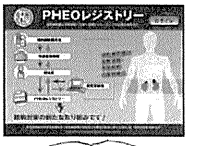
2009- **PHEO Survey** 推定患者2920名（悪性320名）
（全国疫学調査）

PHEO Net 医師110名登録（情報交換約300回）
（医師の全国情報交換メーリングリスト）



2010- **PHEO Guideline・ Criteria**
（診療指針・診断基準） 2010年版出版 全国配布1500部 2011年版改訂中

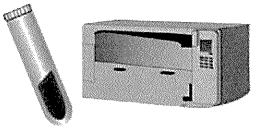
PHEO Registry 約850例登録（悪性11%）
（WEB疾患登録）



PHEO International
（国際連携事業）日中米シンポ開催
国際組織PRESSORとの連携
国際シンポジウム2014（開催予定）

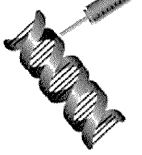
2011- **PHEO Pathology** 約９０例
（病理組織集中解析）

PHEO Bio Bank
（資源バンク）血液収集開始 医薬基盤研との共同
（Pheoを含む難治性副腎疾患約５０名）

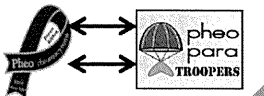


PHEO Treatments
（治療の開発） 「医療上の必要性の高い未承認薬・適応外薬」要望書提出 ６件

2012- **PHEO Genetics** （予定）



PHEO Patient Group
（患者会） 共同シンポ開催、パネル討論、日米パートナーシップ宣言



In Japan In USA

厚生労働省科学研究費補助金　難治性疾患克服研究事業

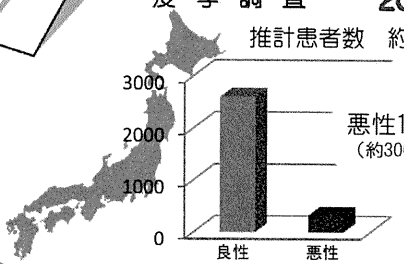
①「褐色細胞腫の実態調査と診療指針の作成」研究班
②「褐色細胞腫の診断及び治療法の推進に関する研究」研究班

（平成21年度から開始した稀少難治性内分泌疾患　褐色細胞腫研究班の活動成果）

目的：①原因解明②診断・治療法の開発③診療水準の向上④患者QOL改善⑤医療費低減⑥患者会支援

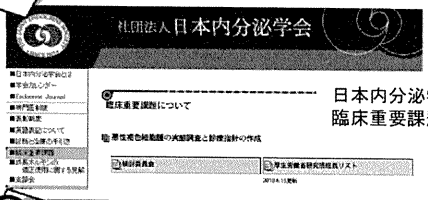
疫学調査　2009年

推計患者数　約3,000人



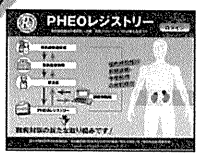
悪性11%
（約300人）

情報提供（学会ホームページ）2007年

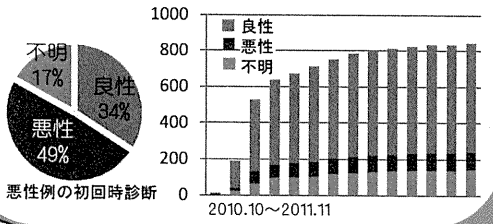


日本内分泌学会
臨床重要課題

疾患レジストリー　2010年



協力医師　約300人
登録数　約900人

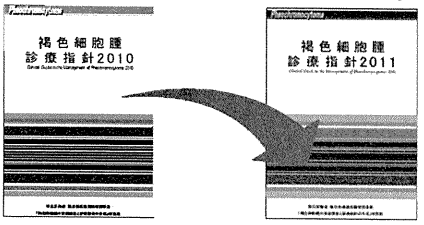


PHEONET　2009年

国立病院機構
京都医療センター

褐色細胞腫の診療水準向上を
目的とする情報交換メーリング
リスト
約８０施設
約１１０名参加（2012.1現在）

診療指針の作成　2010年

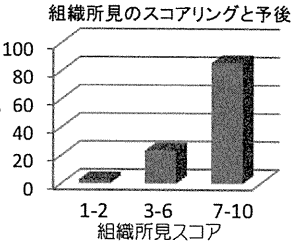


（診療指針2011改訂中）

病理組織集中解析　2011年

組織所見のスコアリングと予後

転移・
再発率（%）



協力施設：関西医科大学、京都大学、聖マリアンナ医科大学、東京医科歯科大学 、京都医療センター、滋賀医科大学、島根大学、社会保険中京病院、市立岸和田市民病院、高岡市民病院、館林厚生病院、勤医協中央病院、函館五稜郭病院、広島大学、福井県済生会病院、新潟県立中央病院、日本大学、浜松赤十字病院、東京慈恵会柏病院、高槻赤十字病院、福井県立病院、杏林大学、大津市民病院、宮城県立がんセンター 他

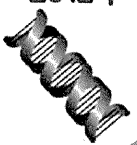
国際連携　2010年

海外研究者との連携による
疾患対策及び情報公開

2010 Japan-China-USA Pheo forum
2014 4th International Pheo Symposium

遺伝子集中解析（予定）2012年

既報遺伝子（10種）
SDHB・SDHD・SDHC・VHL・RET・
NF1・TMEM127・SDHAF2・ DHA・MAX



未知遺伝子の解析

副腎資源バンク　2011年

研究班施設

血清・血漿・組織収集

試料供与契約

（独）医薬基盤研究所

調査資料　3

OPEN－PHEONET

2012年1月現在

PHEO-J NET

褐色細胞腫疾患メーリングリスト

◆Pheo-J　netとは？
　褐色細胞腫に関する情報交換を目的としたメーリングリスト
◆目的・機能は？
　検討委員会の活動の広報・情報提供、医師同士の情報交換、
　臨床研究の提案、学会・研究会の情報、症例の相談など
◆現在の参加者は？
　77施設、110名の先生方がご参加中
◆参加登録するには？
　研究班事務局
　E-mail:keumegak@kyotolan.hosp.go.jpまで
　氏名、所属、e-mail addressをご連絡ください

参加医師の所属施設一覧　（掲載順不同）

NTT東日本関東病院、自治医科大学、筑波大学、愛媛大学、杏林大学、医療法人　豊見城中央病院、横浜市立大学、横浜労災病院、関西医科大学、岐阜大学、宮崎大学医京都大学、金沢大学、九州大学、熊本大学、群馬大学、慶應義塾大学、虎の門病院、広島大学、甲南病院、香川大学、高知大学、国立がんセンター中央病院、国立病院機構　京都医療センター、国立国際医療センター研究所、国立病院機構　小倉医療センター、国立病院機構　函館病院、佐賀大学、済生会福岡総合病院、財団法人癌研究会有明病院、国立病院機構　埼玉病院、山形県立中央病院、山口県立総合医療センター、鹿児島大学、社会保険中京病院、手稲渓仁会病院、順天堂医科大学、信州大学、神戸大学、神奈川県立こども医療センター

（上記続き）聖マリアンナ医科大学、聖路加国際病院、青梅市立総合病院、石心会狭山病院、千葉大学医学部附属病院、大阪警察病院、大阪大学、大阪府立急性期・総合医療センター、大津市民病院、朝比奈診療所、長野市民病院、鳥取大学、土浦協同病院、島根大学、東京医科歯科大学、東京慈恵会医科大学、東京女子医科大学、東京大学、東京都立多摩総合医療センター、東北大学、独立法人労働者健康福祉機構東北労災病院、日本医科大学、日本赤十字社医療センター、日本大学、浜松医科大学、福井県済生会病院、福井県立病院、福井大学、福岡赤十字病院、福島県立医科大学、兵庫県立大学、北海道大学、名古屋医療センター、名古屋大学、名古屋第二赤十字病院、藍野大学、琉球大学

作成：厚生労働省科学研究費補助金難治性疾患克服研究事業「褐色細胞腫の診断及び治療法の推進に関する」研究班

Ⅵ　班会議
打ち合せ会
シンポジウム

平成23年度厚生労働科学研究費補助金難治性疾患克服研究事業

褐色細胞腫の診断及び治療法の推進に関する研究

第３回班会議

日時: 2011年7月2日(土)
11:30～12:30
会場: 東京国際フォーラム G409

議題: 本年度の活動について

1. 平成22年度事業報告
2. 平成23年度の研究事業の概要と組織及び役割分担
   1)疾患レジストリー(PHEO-J)
   2)病理集中解析体制
   3)診療指針2010の改訂
   4)難治性副腎疾患シンポジウムの開催(7/2)
   5)副腎資源バンク
3. 事務連絡事項

※ 昼食を準備致します。

研究代表者 成瀬 光栄 国立病院機構京都医療センター 内分泌代謝高血圧研究部 部長

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中尾 一和	京都大学 内分泌代謝内科 教授
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新保 卓郎	国立国際医療研究センター 医療情報解析研究部 部長
吉本 貴宣	東京医科歯科大学医学部附属病院 内分泌代謝内科 助 教
柳瀬 敏彦	福岡大学医学部 内分泌･糖尿病内科 教授
東條 克能	東京慈恵会医科大学 内科学講座 糖尿病･代謝･内分泌内科 教 授

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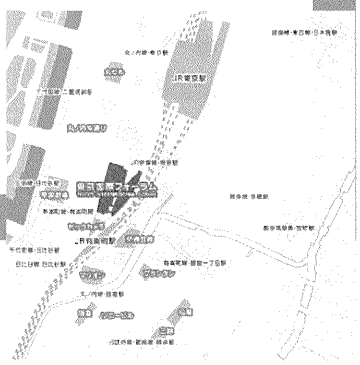
齋藤 淳	横浜労災病院 内分泌･代謝内科 部長
鈴木 知子	国立国際医療研究センター 医療情報解析研究部

研究アドバイザー

増井 徹	独立行政法人 医薬基盤研究所 難病･疾患資源研究部 部長 政策･倫理研究室リーダー

顧 問

三浦 幸雄	独立行政法人労働者健康福祉機構 東北労災病院 院長
平田 結喜緒	東京医科歯科大学 内分泌代謝内科 名誉教授



問い合わせ先
「褐色細胞腫の診断及び治療法の推進に関する研究」研究班 事務局
京都医療センター 内分泌代謝高血圧研究部内 担当 梅垣
〒612-8555 京都市伏見区深草向畑町1-1
TEL：075-641-9161（内線6137）FAX：075-645-8409