Minireview: Potassium Channels and Aldosterone Dysregulation: Is Primary Aldosteronism a Potassium Channelopathy?

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Primary aldosteronism is the most common form of secondary hypertension and has significant cardiovascular consequences. Aldosterone-producing adenomas (APAs) are responsible for half the cases of primary aldosteronism, and about half have mutations of the G protein-activated inward rectifying potassium channel Kir3.4. Under basal conditions, the adrenal zona glomerulosa cells are hyperpolarized with negative resting potentials determined by membrane permeability to $K^+$ mediated through various $K^+$ channels, including the leak $K^+$ channels TASK-1, TASK-3, and Twik-Related Potassium Channel 1, and G protein inward rectifying potassium channel Kir3.4. Angiotensin II decreases the activity of the leak $K^+$ channels and Kir3.4 channel and decreases the expression of the Kir3.4 channel, resulting in membrane depolarization, increased intracellular calcium, calcium-calmodulin pathway activation, and increased expression of cytochrome P450 aldosterone synthase (CYP11B2), the last enzyme for aldosterone production. Somatic mutations of the selectivity filter of the Kir3.4 channel in APA results in loss of selectivity for $K^+$ and entry of sodium, resulting in membrane depolarization, calcium mobilization, increased CYP11B2 expression, and hyperaldosteronism. Germ cell mutations cause familial hyperaldosteronism type 3, which is associated with adrenal zona glomerulosa hyperplasia, rather than adenoma. Less commonly, somatic mutations of the sodium-potassium ATPase, calcium ATPase, or the calcium channel calcium channel voltage-dependent $L$ type alpha 1D have been found in some APAs. The regulation of aldosterone secretion is exerted to a significant degree by activation of membrane $K^+$ and calcium channels or pumps, so it is not surprising that the known causes of disorders of aldosterone secretion in APA have been channelopathies, which activate mechanisms that increase aldosterone synthesis. (Endocrinology 155: 47–55, 2014)
increase in cardiovascular morbidity and mortality compared with patients with essential hypertension with similar levels and duration of their elevated blood pressure (5–8). Most PAs are caused by aldosterone-producing adrenomas (APAs) and bilateral ZG hyperplasia (idiopathic hyperaldosteronism) (5). There are also rare familial causes of PA: type 1 or glucocorticoid-suppressible aldosteronism due to a crossover recombination between the CYP11B2 (cytochrome P450 aldosterone synthase), normally expressed in the ZG, and the CYP11B1 (11b-hydroxylase), normally expressed in the zona fasciculata (ZF), causing a hybrid gene with the promoter region of the CYP11B1 gene and most of the coding region of the CYP11B2 gene. The resulting hybrid gene is expressed in the ZF and regulated by ACTH (9). Type 2 familial hyperaldosteronism is the most common familial form, but the etiology is yet unknown, although many cases are in linkage with chromosome 7p22 (10). Type 3 familial hyperaldosteronism is caused by mutations of the KCNJ5 gene and described in more detail below (11–14).

**Potassium Channels in the Adrenal and Steroid Biosynthesis**

Intracellular recordings from adrenocortical tissue and isolated ZF and ZG cells from multiple species demonstrated that these steroid-producing cells maintain negative resting potentials primarily determined by membrane permeability to K⁺ (15–21). Depolarization of the membrane results in an increase in the transport of calcium (Ca²⁺) into the cells mediated by calcium channels, the most important of which appears to be Ca₉.1.3 and Ca₉.3.2 and to a lesser degree dihydropyridine-inhibited slow calcium channels (22, 23), and mobilization of intracellular Ca²⁺ from endoplasmic reticulum (1, 24). Several voltage-gated K⁺ conductances are also present in adrenal cortex cells, some of which are slowly voltage activating/voltage inactivating or nonactivating in rat and human (18, 19, 21, 25) (Table 1). Others have been described are very slowly voltage activating/nonactivating (26, 27), outward rectifier (26), and Ca²⁺-dependent maxi-K⁺ channels (21, 28, 29). Analyses of these voltage-dependent conductances suggest that ZG cells with hyperpolarized resting membrane voltages are steriogenically inactive (22). The identity of specific channel gene products involved in the maintenance of ZG membrane potential in different species is still uncertain (Table 1) (22). Two background K⁺ currents have been identified in ZG cells, inward rectifying (12, 21) and leak K⁺ currents (29–31). The leak K⁺ channels play a significant role in aldosterone biosynthesis as demonstrated by gene deletion studies (32–35).

Twik-Related Potassium Channel 1 (TREK1) is the major K⁺ channel in bovine ZG and ZF and also is present in the rat and human adrenals (36–38). TREK1 current is inhibited by ACTH and angiotensin II (A-II), and its relevance is demonstrated by the inhibition of A-II-induced membrane depolarization and aldosterone production by a specific inhibitor of TREK1, cinnamyl 3,4-dihydroxy-α-cyanocinamate (36). The bovine adrenal is unique in that it has only one CYP11B enzyme that synthesizes aldosterone only in the ZG, and cortisol only in the ZF (39). The importance of TREK1 in other species is unclear, but it is expressed in the human adrenal carcinoma cell line H295R (40). The inward rectifying channels will be addressed below.

**Animal Models of Hyperaldosteronism and Potassium Channels**

The KCNK 2-pore domain family “leak” K⁺ channels are encoded by 15 genes belonging to 7 subfamilies. They show little or no voltage dependence and generate background K⁺ currents responsible for setting the adrenal negative resting membrane voltages (30). They are assembled as homo- or heterodimers to form 2-pore, 4 transmembrane domain channels in the membrane. Two family members are represented from the TWIK-related acid-sensitive K⁺ channels TASK-1 and TASK-3 in the adrenal (30, 31, 41). TASK-1 and TASK-3 are expressed in mouse, rat, and human ZG cells (30, 31, 40, 42), although in the normal human adrenal and in APAs, TASK-1 predomnates (42). Based on the observation that A-II inhibits TASK-1 and TASK-3 and stimulates aldosterone secretion (43), several potassium channel deletions (TASK-1, TASK-3, and TASK-1 and TASK-3 double deletion) models have been produced in mice (32–35).

TASK-1⁻/⁻ deletion mice have a sexually dimorphic hyperaldosteronism independent of salt intake and hypertension and low plasma renin (34). In TASK-1⁻/⁻ transgenic mice, the CYP11B2 enzyme crucial for aldosterone biosynthesis is expressed in the ZF of young animals and in mature female animals, but not in mature males who do not develop hyperaldosteronism. The hyperaldosteronism was suppressed by inhibition of ACTH by dexamethasone, and the hypertension was normalized by the administration of mineralocorticoid receptor antagonists. Castration of male mice resulted in hyperaldosteronism, whereas administration of testosterone to female mice produced a suppression of the phenotype (34). The nature of the androgen-dependent compensatory mechanism was
proposed to be due to TASK-3 homodimers or heterodimers with other 2-pore domain potassium channels (44). TASK-1<sup>−/−</sup>/TASK-3<sup>−/−</sup> double knockout mice also have hyperaldosteronism, but the expression of the CYP11B2 is in the ZG, not in the ZF. However, in this report, only males were studied, so the issue of androgen-dependent abnormality in the ZF as in the single TASK<sup>−/−</sup> mice cannot be resolved (32).

The TASK-1<sup>−/−</sup>/TASK-3<sup>−/−</sup> double knockout mice exhibited no TASK-like current and depolarization of the cell membrane of ZG cells. It was of interest that although these animals had a profound degree of depolarization of the membrane, the alterations of aldosterone excretion were relatively mild and statistically significant, whereas the animals were on a low- or high-sodium diet but not on a normal-sodium diet (32). Plasma aldosterone was increased by a low-sodium diet but not suppressed by high-salt intake. The increase was partially suppressed with candesartan, an A-II receptor blocker revealing that aldosterone production in the TASK-1<sup>−/−</sup>/TASK-3<sup>−/−</sup> mice ZG was partially regulated. Other potassium channels must be compensating for the loss of TASK-1 and TASK-3 to preserve the ZG distribution and partial regulation of aldosterone production in these mice.

**Table 1.** Type of Potassium Channel Identified in the Various Species, Their Function, and Pathophysiology

<table>
<thead>
<tr>
<th>Channel (gene)</th>
<th>Adrenal Expression</th>
<th>Species</th>
<th>Function</th>
<th>Pathophysiology</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TASK-1 (&lt;KCNK3&gt;)</td>
<td>ZG&gt;ZF&gt;ZR</td>
<td>Rat, mouse, human</td>
<td>Contribute to resting membrane potential; acid and A-II inhibited</td>
<td>TASK-1&lt;sup&gt;−/−&lt;/sup&gt;: sexual dimorphic hyperaldosteronism and ZF CYP11B2 expression. Highly expressed in the human</td>
<td>34, 42</td>
</tr>
<tr>
<td>TASK-2 (&lt;KCNK5&gt;)</td>
<td>ZR</td>
<td>Mouse, human</td>
<td>Unknown</td>
<td>Unknown</td>
<td>31, 44</td>
</tr>
<tr>
<td>TASK-3 (&lt;KCNK9&gt;)</td>
<td>ZG</td>
<td>Mouse, rat, human?</td>
<td>Probably forms heterodimers with TASK-1 to set membrane potential</td>
<td>TASK-3&lt;sup&gt;−/−&lt;/sup&gt;: neonate-high adrenal renin, severe hyperaldosteronism. Adults-mild hyperaldosteronism or low-renin hypertension. TASK-1&lt;sup&gt;−/−&lt;/sup&gt; + TASK-3&lt;sup&gt;−/−&lt;/sup&gt;: hyperaldosteronism</td>
<td>31, 33, 35</td>
</tr>
<tr>
<td>TASK-4 (&lt;KCNK17&gt;)</td>
<td>Adrenal gland</td>
<td>Human</td>
<td>Unknown</td>
<td>Unknown</td>
<td>72</td>
</tr>
<tr>
<td>TASK-5 (&lt;KCNK15&gt;)</td>
<td>Adrenal gland</td>
<td>Mouse, rat, human, bovine</td>
<td>Unknown</td>
<td>Inhibited by A-II and ACTH</td>
<td>73</td>
</tr>
<tr>
<td>TREK1 (&lt;KCNK2&gt;)</td>
<td>Adrenal cortex</td>
<td>Human</td>
<td>Unknown</td>
<td>Unknown</td>
<td>38, 74</td>
</tr>
<tr>
<td>KvLQT1/Isk (&lt;KCNQ1/KCN1&gt;)</td>
<td>ZG APA</td>
<td>Mouse</td>
<td>Membrane potential repolarization</td>
<td>KCNE1&lt;sup&gt;−/−&lt;/sup&gt;: K&lt;sup&gt;+&lt;/sup&gt; induced hyperaldosteronism</td>
<td>27, 75</td>
</tr>
<tr>
<td>maxiK (&lt;KCNMA1/KCNMB1&gt;)</td>
<td>ZG&gt;ZF&gt;ZR</td>
<td>Mouse, human</td>
<td>K&lt;sup&gt;+&lt;/sup&gt; conductance stimulated by ANP (reduces aldo)</td>
<td>MaxiK&lt;sup&gt;−/−&lt;/sup&gt;: hyperaldosteronism + unaltered renin response</td>
<td>76, 77</td>
</tr>
<tr>
<td>Kir3.4 (&lt;KCNJ5&gt;)</td>
<td>ZG</td>
<td>Human</td>
<td>Inhibited by A-II. Overexpression suppresses aldo synthesis</td>
<td>Mutations of selectivity filter sequence in some human APAs and familial hyperaldosteronism III</td>
<td>12, 47–49, 63</td>
</tr>
<tr>
<td>KCNK1 (&lt;KCNK1&gt;)</td>
<td>APA</td>
<td>Human</td>
<td>Unknown function in adrenal</td>
<td>Overexpressed in APA by microarray. Increased in Ca&lt;sub&gt;1.3&lt;/sub&gt;=&lt;sup&gt;−/−&lt;/sup&gt;/KCNJ5 mut</td>
<td>69, 78</td>
</tr>
<tr>
<td>KCNK12 (&lt;KCNK12&gt;)</td>
<td>APA</td>
<td>Human</td>
<td>Unknown function in adrenal</td>
<td>Overexpressed in APA by microarray, but not by qPCR</td>
<td>78</td>
</tr>
<tr>
<td>KCNH3 (&lt;KCNH3&gt;)</td>
<td>APA</td>
<td>Human</td>
<td>Unknown function in adrenal</td>
<td>Overexpressed in APA by microarray, but not by qPCR</td>
<td>78</td>
</tr>
</tbody>
</table>

The species for which the pathophysiology is described is in bold.
with salt (33, 35). The adrenal cells from this model were also profoundly depolarized. However, the aldosterone phenotype was mild (35). One would expect that a better correlation between the degree of depolarization should result in a greater increase in calcium mobilization and aldosterone secretion. However, the reason for this relative dissociation is not clear. The adrenal phenotype of the TASK-3−/− mice is severe in neonatal mice (45) and becomes mild in the adult (33, 35). The age-related phenotype appears to be induced by abnormal expression of renin in TASK-3−/− newborn mice (45). The expression of TASK-3 in the ZG and the consequences of its decreased activity have led to the hypothesis that human idiopathic hyperaldosteronism or low-renin hypertension with normal aldosterone might represent graded deficiencies in TASK-3 expression within the human adrenal (46). However, TASK-3 expression in the normal human adrenal or in APAs is very low compared with TASK-1 (42).

Somatic and Germinal Cell Mutations of the Selectivity Filter Inward Rectifying Potassium Channel (Kir) 3.4 Producing Hyperaldosteronism

About half the patients with PA have APAs; 30%–60% of APA have somatic mutations of the selectivity filter of the G protein-activated inward rectifying potassium channel Kir3.4 coded by the KCNJ5 gene (12–14, 47–51). The selectivity filter is a conserved region within this family of channels that allows the selective transport of potassium over other cations (52). Four Kir3 channel genes have been identified coded by the KCNJ genes. Kir proteins have 2 putative membrane-spanning domains and form tetrameric complexes linked by an extracellular pore-forming region and amino and carboxy-terminal domains (52). Kir3.4 can form homotetramers or more common heterotetramers with Kir3.1 (KCNJ3), less often by Kir3.2 (KCNJ6) or Kir3.3 (KCNJ9) (52–55). Kir3.4 is expressed in the ZG and Kir3.1 throughout the human adrenal (Gomez-Sanchez, C. E., unpublished data) (12). Kir3x channels hyperpolarize the membrane of excitable cells, such as cardiomyocytes and neurons, as well as of nonexcitable neuroendocrine cells (52, 56). Dopamine and somatostatin activate Kir3.1 and Kir3.4. Kir3.1 and Kir3.4 in pituitary thyrotrophs are located in the membranes of intracellular dense core vesicles that contain TSH. Stimulation with TRH causes these vesicles to fuse with the plasma membrane, releasing TSH and intercalating the Kir3.1/Kir3.4 heterotetramers into the plasma membrane (55). The increased number of Kir3.1/Kir3.4 in the membrane enhances K+ currents stimulated by dopamine or somatostatin, thus suppressing TSH release (55, 57). Similarly, dopamine inhibits prolactin release from lactotropes by increasing the activity of the Kir3.4/Kir3.1 and hyperpolarizing the membrane (57) and are likely to inhibit aldosterone release by activating Kir3.4/Kir3.1 in adrenal ZG cells (12). Selectivity for K+ by the Kir3.4 homo- or heterotetramer channels resides in the selectivity filter and a highly conserved glycine-tyrosine-glycine (GYG) motif. The GYG sequence is present in all the Kir3x channels in the pore loop of the K+ channels and in the Kir3.1/Kir3.4 heterotetramer presents backbone carbonyls that are oriented to form a narrow pore allowing the coordinated passage of a column of dehydrated K+ ions intercalated by water molecules in single file through the channel (58). Larger ions are excluded and smaller ions like sodium are not effectively coordinated and dehydrated, so their entry is energetically unfavorable (52, 58). Mutations of the GYG motif result in loss of this selectivity (12). Similarly, mutations in adjacent amino acids affect crucial salt bridges around the pore (59). Somatic mutations altering the selectivity function of Kir 3.4 are associated with APA, whereas a germinal mutation in the area is the cause of familial hyperaldosteronism type 3 (12, 13, 60).

Role of Kir3.4/Kir3.1 Heterotetramers in ZG Cell Function

We have described the role of Kir3.4 on aldosterone regulation using the human adrenal carcinoma cell line HAC15 (61). A-II stimulation of HAC15 cells down-regulates expression of Kir3.4 mRNA (~41.2%) and protein (~52.7%) associated with a decrease in membrane potential, increase in intracellular calcium, and increased expression of several of the enzymes required for aldosterone biosynthesis (Figure 1) (61). The decrease in the expression of Kir3.4 is due to an increase in intracellular calcium as the calcium ionophore A23187 had the same effect. Naringin activates the Kir3.4/Kir3.1 channel and partially inhibits the effect of A-II on aldosterone secretion (61, 62). A-II also inhibits the activity of TREK1 that also leads to depolarization (36), which might explain that the effect of naringin inhibition on A-II stimulation is limited. Overexpression of Kir3.4 in HAC15 cells decreases calcium mobilization, hyperpolarizes the cell, and inhibits the expression of the CYP11B2 enzyme and aldosterone biosynthesis. This data suggest that Kir3.4 channel transfers K+ from inside to outside the cell continuously.
and that interruption by A-II results in membrane depolarization, mobilization of calcium, and activation of signals to increase expression of the CYP11B2 enzyme (61).

**APAs and KCNJ5 Mutations**

The Lifton laboratory performed pioneering exon sequencing studies of a select group of APAs and found 2 recurring somatic mutations in or around the GYG motif in the KCNJ5 gene resulting in a marked change in selectivity for $K^+$ in comparison with sodium of the Kir3.4 channel in 8 of 22 patients studied. The most common mutations confirmed in subsequent studies by multiple labs in different patient populations around the world are G151R in the narrow point of the filter and L168R, which might disrupt local salt bridge formation through the introduction of a positive charged amino acid (13, 14, 47–51, 59). Additional mutations in or surrounding the selectivity filter have been found, including G151E, T158A, E141Q, I157S, and dell157 (12–14, 47, 59, 60). The T158A mutation was found in the germinal line of a family with hyperaldosteronism type 3 with a very severe hyperaldosteronism and hypertension requiring bilateral adrenalectomy for control of the hypertension and was associated with bilateral hyperplasia, not adenoma (11, 12). The somatic mutation T158A was also found in 1 case of APA (13). Transfection of mutated of Kir3.4 (G151R, L168R, and T158A) into HEK293 cells with or without Kir3.1 resulted in loss of channel selectivity with increase in intracellular sodium, membrane depolarization, and increase in intracellular calcium.

![Figure 1](https://doi.org/10.1210/en.2013-1733)

*Figure 1.* Proposed mechanism for the action of A-II and Kir3.4 mutations affecting the selectivity filter function on aldosterone secretion. A, Baseline. Adrenal ZG cells are hyperpolarized primarily through the activity of the TASK-1 and/or TASK-3 potassium channel and Kir3.4 channels. B, A-II stimulation. A-II depolarizes the ZG cell by blocking the activity of the TASK-1 and/or TASK-3 and Kir3.4 channels. This results in opening of calcium channels, stimulating the calcium calmodulin pathway, resulting in increased expression of the CYP11B2 and decreased expression of the Kir3.4 channel at the mRNA and protein level. C, Kir3.4 mutation. Presence of a copy of a mutated Kir3.4 potassium channel at the selectivity filter results in an increase in intracellular sodium, membrane depolarization, and mobilization of calcium, resulting an increase in the expression of the CYP11B2 enzyme and synthesis of aldosterone.
KCNJ5 T158A transduction of the HAC15 cells

Because HEK293 is not a steroidogenic cell line, we used lentiviruses for the transduction of the Kir3.4 T158A into HAC15 cells (63) a subclone of the human adrenal carcinoma cell line H295R (64). Transduction of the pLX203-T158A lentivirus resulted in a 530% increase in basal aldosterone secretion, approximately 40% increase in A-II-stimulated and approximately 50% in forskolin-stimulated aldosterone secretion in comparison with cells transduced with the empty plasmid (63). Cortisol production was only mildly increased in cells expressing T158A. However, 18-oxocortisol secretion was markedly increased in A-II-stimulated and approximately 50% in forskolin-stimulated aldosterone secretion in comparison with cells transduced with the empty plasmid (63). 18-Oxocortisol is the most abnormal steroid secreted in patients with familial hyperaldosteronism 3 (11) and is also abnormal in many patients with APA (65).

Transduction of the KCNJ5 T158A increased Na\(^+\) influx as measured using the CoroNa Green cell-impermeant dye showing a 1.2-fold higher fluorescence than control cells. They also showed a 2.3-fold increased accumulation of DiSBAC\(_2\), an indicator of higher plasma membrane voltage compared with control cells. The cells showed a 1.6-fold increase in Fluo-4 AM, an indicator of intracellular calcium concentration compared with control cells (63). mRNA for CYP11B2, the last enzyme in the biosynthesis of aldosterone, increased by 17.7-fold; that for CYP11B1, the last enzyme in the biosynthesis of cortisol, also increased by 5.8-fold, but message for the other enzymes of the steroidogenic cascade did not change or, in the case of the CYP17A1, significantly decreased (63). Measurement by a reporter gene using the CYP11B2 promoter and the gaussia luciferase gene reporter confirmed that transduction with the KCNJ5 T158A virus increased the transcription of the CYP11B2. Inhibition of the slow calcium channel by nifedipine and of calmodulin kinase by W-7 produced a 75% and 18% inhibition of aldosterone secretion in cells transduced by the T158A virus, respectively (63). Similar to the wild type, the aldosterone secretion was only mildly increased in cells expressing T158A, in contrast to the wild type (23, 69).

Additional mutations resulting in increased intracellular calcium

Further exome sequencing in APAs that did not have a KCNJ5 mutation resulted in the identification of loss-of-function somatic mutations of the sodium/potassium ATPase gene ATP1A1 and calcium-ATPase gene ATP2B3 in 5.2% and 1.6% of patients (68, 69) and gain-of-function somatic mutations of the CACNA1D gene, coding for the voltage-gated calcium channel (Ca\(_{1.3}\)), in 4.9%–7.8% of APAs (23, 69). The loss-of-function α1-Na\(^+\)/K\(^+\)-ATPase mutants caused a marked ouabain-sensitive and voltage-dependent inward current (69), and which ions carry the currents depends on the mutation, because in the most common Leu104Arg, it appears that protons are the main carriers of the current. In the del100–104 mutant, it appears to be Na\(^+\) (69). Ouabain, an inhibitor of the sodium/potassium ATPase, stimulates aldosterone secretion in the rat adrenal (70). However, it inhibits aldosterone secretion in human ZG cells (71), and human cells are very sensitive to the toxic effects of ouabain. Functional studies of the ATP1A1 mutants were done with the rat enzyme cDNA, and they demonstrated a loss of pump activity and strong reduced affinity for potassium, resulting in increased intracellular calcium in the H293 transected cells and stimulation of aldosterone secretion in the H295R cell (68, 69). The loss-of-function mutation of the mutated ATP1A1 (68, 69) does not resemble the effects of inhibitor ouabain in the steroidogenic response in H295R cells (71), and currently, the mechanism of action of the mutation on steroidogenesis is unclear. The ATP2B3 pumps calcium out of the cell, so loss-of-function results in increased intracellular calcium concentration that activates the calcium/calmodulin pathway and aldosterone secretion (68). Gain-of-function somatic mutations of the voltage-gated calcium channel (Ca\(_{1.3}\)) result in channels that require less depolarization of the membrane for activation leading to increased aldosterone production compared with the wild type (23, 69).
Perspectives

The membrane voltage in adrenal ZG cells responsible for activation of the signal cascade and gene expression of enzymes responsible for aldosterone synthesis is maintained by the controlled influx of potassium (Figure 1). Membrane depolarization by secretagogues leads to the opening of calcium channels, increased intracellular calcium, and activation of the calcium-calmodulin pathway, resulting in increased CYP11B2 gene (and others) expression required for aldosterone secretion. Every molecular mechanism identified in patients with APAs so far involves mutations of potassium, calcium channels, or ion pumps, resulting in either membrane depolarization and/or increase in intracellular calcium. Studies of abnormalities of potassium or calcium channels in cortisol- or other steroid-producing adrenal adenomas have not been reported, but it is likely that similar abnormalities of channels or pumps that are specific for each cell type might be found, because the regulation of their production also requires depolarization of the cell membrane and mobilization of calcium.

Acknowledgments

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