Angiotensin II Type 2 Receptor Agonists as Therapies for Ischemic Stroke

Anne M. Dorrance

See related article, pp 1531–1537

Stroke is the third leading cause of death in the United States and a leading cause of disability, yet the available treatments are limited. Tissue plasminogen activator, the only US Food and Drug Administration-approved pharmacotherapy for cerebral ischemia, was approved for use in 1996. Although tissue plasminogen activator is an effective therapy, tight time restrictions govern its use; it must be administered within 4.5 hours of the onset of ischemia. This small therapeutic window severely limits the number of patients eligible to receive this treatment. Since 1996, many potential neuroprotective agents have been studied, but none have shown improved outcome in phase III clinical trials. The search for stroke therapies falls into 2 categories, neuroprotective agents, which act in the early stages after a stroke to prevent neuronal death, and neurorecovery agents, which facilitate the repair of neural networks in the chronic phase of the stroke. The study presented by McCarthy et al in this issue of Hypertension suggests that angiotensin II type 2 receptor (AT2R) agonists may be useful therapies for acute cerebral ischemia. The authors show that CGP42112, the peptide agonist of the AT2R, reduces the area of infarct after an ischemic stroke and improves motor function. The results are remarkable, with CGP42112 producing a 75% reduction in the poststroke infarct. Although the studies focused on neuroprotection, the current literature suggests that AT2R activation could also improve neurorecovery. The likely multifaceted beneficial effects of AT2R activation make this an exciting and potentially fruitful area of research. It is also worth noting that AT2R activation has been proposed as a potential therapeutic target for several other neurological diseases, including Alzheimer disease and cognitive decline.

The idea that AT2R activation has beneficial effects on the outcome of cerebral ischemia is not entirely new. In 2004, Iwai et al suggested that the AT2R has protective effects because AT2R knockout mice had larger cerebral infarcts after middle cerebral artery occlusion than control mice. The authors attributed the negative effect of AT2R knockout to a reduction in cerebral blood flow and an increase in superoxide generation. Interestingly, this effect appears to be limited to male mice. However, care should be taken in interpreting these results as angiotensin II type 1 receptor (AT1R) expression is increased in AT2R knockout mice, and this could enhance the detrimental effects of the AT1R activation. Other studies focusing on AT1R antagonism have provided hints that AT2R activation is beneficial. It is widely accepted that some of the beneficial effects of AT1R antagonism are the result of increased AT2R effects of AT1R antagonism are the result of increased AT2R activation. This is true for cerebral ischemia; AT1R antagonism with PD123199 prevented the beneficial effects of AT1R blockade with a subpressor dose of irbesartan. Candesartan has a similar effect, although it lowers blood pressure, making it difficult to separate the effects of the drug from the beneficial effects of lowering blood pressure. Positive effects of AT1R activation have been shown previously by the authors of the current study, and in 2009 McCarthy et al showed that CGP42112 reduces the damage caused by cerebral ischemia when administered 5 days before the ischemic insult. Importantly, as with the current study, the beneficial effects of AT1R activation were observed without the concomitant inhibition of the AT2R, suggesting that AT2R agonists can overcome the powerful detrimental effects of AT1R activation.

The current study from McCarthy et al is worthy of comment because of the clinical relevance of the studies. This appears to be the first study using a pharmaceutical agent to activate the AT1R after the induction of ischemia; this dramatically increases the clinical relevance of the studies presented. Beneficial effects of AT1R activation were observed with a first administration of CGP42112 six hours after the induction of cerebral ischemia. This suggests that the therapeutic window for CGP42112 may be significantly longer than that for tissue plasminogen activator; thus, if proven effective, a greater percentage of stroke patients could receive AT2R agonists. An additional positive aspect of this study was the use of a rat model with an appropriate comorbidity for stroke. Hypertension is a leading stroke risk factor; thus, the use of spontaneously hypertensive rats is a significant benefit. The studies were also conducted in conscious rats, removing any confounding effects of anesthesia on the outcome of cerebral ischemia.

There are also significant negative aspects to the studies presented. Although the time of drug delivery is considered a plus, the intracerebroventricular route of administration limits its therapeutic usefulness. Clearly, studies need to be conducted to test the effects of systemic CGP42112 administration. CGP42112 is a peptide, so in a healthy brain it is unlikely to cross the blood-brain barrier, but cerebral ischemia causes blood-brain barrier breakdown, and thus CGP42112 could potentially enter the brain in the region of the infarct to have direct neuroprotective effects. It is also possible that the nonpeptide AT2R agonist, compound 21, could be...
effective with systemic administration. The second concern is
the choice of model of ischemia. There are many good models
of stroke, but none of them are perfect.10 The authors chose
to use the endothelin-1 model of ischemia; endothelin-1 is
injected into the brain, this constricts the cerebral arteries and
produces ischemia that generally lasts for <1 hour, after which
the arteries relax and cerebral perfusion is restored. Relatively
speaking, this is a short duration of ischemia and it will be
important to show that CGP42112 has similar effects in longer
durations of ischemia that better mimic the population that
would be ineligible for tissue plasminogen activator treatment.
The strength of the endothelin-1 model is that it can be done
in conscious rats. That said, this technique is used in a tiny
percentage of the studies; thus, there is a dearth of historical
data to help with the interpretation of the studies presented.
The use of conscious rats also prevents the measurement of
blood flow during the ischemic insult. This limits our ability
to evaluate the potential mechanisms of the effects of CGP42112.
Other studies suggest that AT2R activation improves blood
flow,9 and the authors suggest in their concluding statements
that they believe that increased cerebral blood flow is an
important component of the effects of CGP42112. That said,
mentioned earlier, it is not clear whether CGP42112 can improve cerebral blood
flow when administered intracerebroventricularly. It is also
true that it is not clear how important an effect on blood flow would be
in this particular situation. The first dose of CGP42112 was
administered 6 hours after the initial endothelin-1 insult; this means
that most rats will have had cerebral blood flow restored for 5
hours before the agonist is delivered.

The authors also observed an interesting effect of
PD123199; this AT2R antagonist was used to show that the
effects of CGP42112 were receptor specific. In most of
the studies, PD123199 inhibited the effects of CGP42112.
Interestingly, motor function and apoptosis were improved by
both receptor activation and inactivation. Although this is per-
plexing, it does not necessarily detract from the importance of
the studies presented.

The effects of cerebral ischemia on AT2R expression are also
controversial. One study using the filament occlusion model
of ischemic stroke suggests that AT2R expression is increased
after the induction of cerebral ischemia; these receptors were
expressed only in neurons and appeared to promote neurite out-
growth.7 Conversely, in the previous study from McCarthy et al,9
it appears that AT2R expression is reduced after cerebral isch-
emia. The reason for this disparity in the results observed could
be many fold and include the method of the induction of isch-
emia, the region of the brain studied, and the strain of rat used.

From the studies presented, it seems that activation of the
AT2R has the potential to be a viable therapy for ischemic
stroke. That said, the stroke field has been in this position
many times before; countless compounds have appeared ther-
apeutically useful in rats but have failed to transition to clini-
cal use. This does not limit the enthusiasm for pursuing this
line of research, but only suggests that we should be cautious
and diligent in conducting the additional studies required to
prove that this increasingly interesting class of drugs is a use-
ful therapy for stroke.

Sources of Funding
This work was funded by grants from the American Heart Association
(0130364N) and the Vice President’s office at Michigan State
University.

Disclosures
None.

References
1. Zivin JA. Acute stroke therapy with tissue plasminogen activator (tPA)
since it was approved by the U.S. Food and Drug Administration (FDA).
2. Del Zoppo GJ, Saver JL, Jauch EC, Adams HP Jr; American Heart
Association Stroke Council. Expansion of the time window for treatment
of acute ischemic stroke with intravenous tissue plasminogen activator:
a science advisory from the American Heart Association/American Stroke
RE. Angiotensin II type 2 receptor stimulation initiated after stroke causes
4. Mogi M, Horiuchi M. Effect of angiotensin II type 2 receptor on stroke,
cognitive impairment and neurodegenerative diseases. Geriatr Gerontol
Int. 2012; In press.
T, Horiuchi M. Possible inhibition of focal cerebral ischemia by angioten-
14–23.
tors protect against cerebral ischemia-induced neuronal injury. FASEB J.
8. Lu Q, Zhu YZ, Wong PT. Neuroprotective effects of candesartan against
cerebral ischemia in spontaneously hypertensive rats. Neuroreport.
receptor stimulation causes neuroprotection in a conscious rat model of
10. Howells DW, Porritt MJ, Rewell SS, O’Collins V, Sena ES, van der Worp
HB, Traysman RJ, Macleod MR. Different strokes for different folks: the
rich diversity of animal models of focal cerebral ischemia. J Cereb Blood
Angiotensin II Type 2 Receptor Agonists as Therapies for Ischemic Stroke
Anne M. Dorrance

Hypertension. 2012;60:1391-1392; originally published online October 22, 2012;
doi: 10.1161/HYPERTENSIONAHA.112.200956

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/60/6/1391

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial
Office. Once the online version of the published article for which permission is being requested is located,
click Request Permissions in the middle column of the Web page under Services. Further information about
this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/