Angiotensin II Type 2 Receptor Agonists as Therapies for Ischemic Stroke

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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 (AT$_2$R) agonists may be useful therapies for acute cerebral ischemia. The authors show that CGP42112, the peptide agonist of the AT$_2$R, 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 AT$_2$R activation could also improve neurorecovery. The likely multifaceted beneficial effects of AT$_2$R activation make this an exciting and potentially fruitful area of research. It is also worth noting that AT$_2$R activation has been proposed as a potential therapeutic target for several other neurological diseases, including Alzheimer disease and cognitive decline.

The idea that AT$_2$R activation has beneficial effects on the outcome of cerebral ischemia is not entirely new. In 2004, Iwai et al suggested that the AT$_2$R has protective effects because AT$_2$R knockout mice had larger cerebral infarcts after middle cerebral artery occlusion than control mice. The authors attributed the negative effect of AT$_2$R 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 (AT$_1$R) expression is increased in AT$_2$R knockout mice, and this could enhance the detrimental effects of the AT$_1$R activation. Other studies focusing on AT$_1$R antagonism have provided hints that AT$_2$R activation is beneficial. It is widely accepted that some of the beneficial effects of AT$_1$R antagonism are the result of increased AT$_2$R activation. This is true for cerebral ischemia; AT$_2$R antagonism with PD123319 prevented the beneficial effects of AT$_1$R 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 AT$_2$R 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 AT$_2$R activation were observed without the concomitant inhibition of the AT$_1$R, suggesting that AT$_2$R agonists can overcome the powerful detrimental effects of AT$_1$R 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 AT$_2$R after the induction of ischemia; this dramatically increases the clinical relevance of the studies presented. Beneficial effects of AT$_2$R 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 AT$_2$R 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 AT$_2$R 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. 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 $AT_2R$ activation improves blood flow, 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, it is not clear whether CGP42112 can improve cerebral blood flow when administered intracerebroventricularly. It is also not clear how important an effect on blood flow would be in this particular situation. The first dose of CGP42112 was given at 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 $AT_2R$ 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 perplexing, it does not necessarily detract from the importance of the studies presented. The effects of cerebral ischemia on $AT_2R$ expression are also controversial. One study using the filament occlusion model of ischemic stroke suggests that $AT_2R$ expression is increased after the induction of cerebral ischemia; these receptors were expressed only in neurons and appeared to promote neurite outgrowth. Conversely, in the previous study from McCarthy et al, it appears that $AT_2R$ expression is reduced after cerebral ischemia. The reason for this disparity in the results observed could be many fold and include the method of the induction of ischemia, the region of the brain studied, and the strain of rat used.

From the studies presented, it seems that activation of the $AT_2R$ 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 therapeutically useful in rats but have failed to transition to clinical 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 useful therapy for stroke.

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None.

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