

# Angiogenesis in refractory depression: A possible phenotypic target to avoid the blood brain barrier

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## Summary

Major depressive syndrome (so-called depression) is a common but serious mental disease that causes low mood. Most patients are treatable, mainly because of high response rates for medicines such as selective serotonin-reuptake inhibitors (SSRIs). However, there are still a considerable number of patients with refractory or drug-resistant depression. On the other hand, recent findings suggest that angiogenesis, *i.e.*, making new blood vessels, could have an important role in the recovery from depressive disorders, at least in part. It has been reported that the brain capillaries are physiologically capable of undergoing angiogenesis upon stimuli such as exercise and SSRIs seem to accelerate brain angiogenesis. Drugs targeting angiogenesis may possibly be another good concept. In addition, the blood brain barrier (BBB), which is a major obstacle for drug development for the central nervous system, would be circumvented. Here I summarize the reports that relate angiogenesis to a cure for major depression and discuss some of the potential molecular targets.

**Keywords:** BBB, VEGF, pericyte, vasculogenesis, SERT

## 1. Introduction

The brain is filled with blood vessels. The mean distance from the center of the neuronal somata to the closest microvessel is reported to be 15 microns (1) and is of a certain variety (2,3). In the brain, angiogenesis, the process involving the budding and stretching of new brain capillaries from existing vasculatures, has been reported to be induced by physical exercise (4-7) in addition to normal growth in infancy (8).

Major depressive syndrome (so-called depression) is a common (~10%) and serious mental disease with long episodes of low mood, that can sometimes lead to suicide. The response rate for anti-depressants such as selective serotonin-reuptake inhibitors (SSRIs) is relatively high, and, together with good counseling therapy and changing the stressful environment, most patients recover well. However, there are a considerable number of drug-resistant patients. Most refractory

patients stay socially inactive, and their life is heavily dependent on the support of families and social welfare systems. Thus, 'drug discoveries and therapies' are eagerly awaited.

Recent findings suggest that brain angiogenesis may be important in the recovery from depressive disorders, at least in some cases. Thus, here I will summarize these reports and focus on efficient cures.

### 1.1. Mechanism of angiogenesis

Angiogenesis is physiologically necessary for wound healing. It also has been highly studied in cancer development, and anti-angiogenic drugs have become good anti-cancer agents. Metabolically active cells such as growing tumor cells and working neurons should consume oxygen and enter an ischemic state. Ischemia is a trigger for cells to express then secrete an angiogenic factor, vascular endothelial growth factor (VEGF) (6), and this facilitates the growth and motility of endothelial cells for making new vessels. Since nutrients and oxygen supplied by vasculature are critical for neuronal function, angiogenesis is thought to work as the adaptive 'supply on demand system'.

Angiopoietin 2 (Ang-2) secreted by ischemic cells works as the first signal to make new vasculatures. Upon stimulation, the endothelial cells (or another

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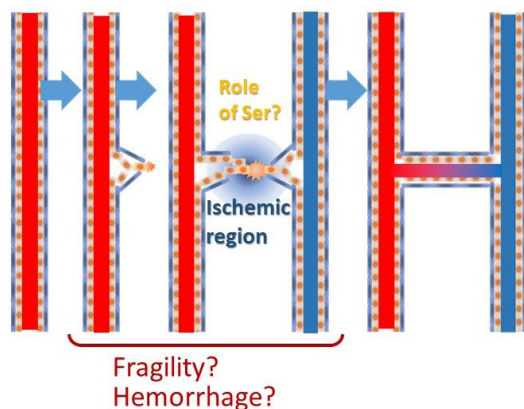
vessel cell, pericytes) secrete a protease and move inside, then, upon further stimulation by VEGF, grow then elongate as a tubule of the immature vessels. A brain capillary has a single endothelial layer folded by pericytes, then these pericytes follow to complete the structure, while pericytes may go faster (9).

The two secreted factors can dominate angiogenesis. Actually, mice treated with a VEGF protein infusion plus Ang-2 expression by a virus vector had significantly increased microvessels in their brains (10), while the mechanism to protect fragile newborns during angiogenesis from blood pressure is yet to be determined (Figure 1).

### 1.2. SSRI

SSRIs, the selective serotonin-reuptake inhibitors such as Fluoxetine and Paloxetine, are the major antidepressants currently used. Actually, whether patients show any signs of recovery by taking these drugs is the main branch point to 'drug-resistance'. The SSRIs inhibit the action of a molecule called serotonin transporter (SERT) and increase local concentrations of serotonin. Serotonin (Ser) is an amino acid that can be synthesized from tryptophan in serotonergic neurons in the brain, and works as a neurotransmitter/neuromodulator that regulates mood. SERT at the presynaptic terminal of neurons reuptake the released Ser, thus the SSRI enhances the action of Ser through inhibiting SERT and increasing Ser concentration in the synapses.

However, SSRIs are mysterious drugs. Their effects as antidepressants take a few to several weeks to become



**Figure 1. Diagram of the mechanism of angiogenesis in general.** Blue arrow indicates progression of angiogenesis steps. Angiogenesis was induced by ischemia around the vessel. It evokes secretion of protease from the vessel cells, then the some of endothelial cells move into the tissue. They form tubules and grows till the tip cells from artery and vein meet. The detailed feature in the brain including the mechanism to protect fragile newborn vessels (bracket) from blood circulation is not well understood. Especially, in the brain, there should be multiple mechanisms for that, because the risk of hemorrhage (bleeding in the brain) should be avoided. SERT, the target of SSRI, might have some roles because it is expressed in the smallest of brain capillaries (13) and Ser can act as a vasoconstrictor (12).

evident, even though the action on the SERT molecule is rapid. Furthermore, the mechanism of how SSRIs go through the blood brain barrier into the brain is not well known.

Ser has many other functions in the body. It accelerates angiogenesis *in-vivo* via a receptor on endothelial cells (11). The intriguing thing is its role in hemostasis as a vasoconstrictor (12). Ser is released from activated platelets. Vasoconstriction activity stops or slows blood flow by this activity and generally protects injured vessel walls. SERT, the target of SSRIs has been found in the smallest of brain capillaries (13), while the role at the loci is not well understood. There is a possibility that Ser increased by SERT contracts the vessel to protect the site of angiogenesis in progress.

### 2. Angiogenesis might act as a cure for depression via neurogenesis

The hippocampal dentate gyrus is a particular place where many neuronal progenitors reside, and they keep on generating new neurons even in adults. This generation of neurons is called neurogenesis, and this has attracted attention as the target for SSRIs, because chronic administration of antidepressants up-regulates neurogenesis (14) and this cellular response is required for the effects of the drugs (15). I studied circuit generation by newly-born hippocampal granule cells (16) and considered that neurogenesis promotes the formation of novel neuronal circuits. The newly formed circuits would provide a curative effect for depression probably by supporting a different way of thinking.

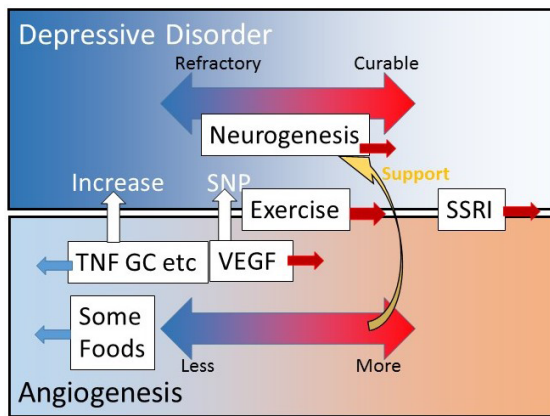
On the other hand, there are some reports describing that angiogenesis acts on the SSRI-induced upregulation of neurogenesis (17-19). If this is true, angiogenesis may be a more promising phenotypic target for future drugs, because blood vessels are on the accessible side of the blood brain barrier (BBB). In addition, the action of angiogenesis will widely affect whole regions of the brain.

Another factor in the support for the role of neurogenesis in anti-depressive effects is in the treatment for drug-resistant depression, electric stimulation which stimulated neurogenesis. Also in this case, angiogenesis is accelerated (20).

Physical exercise has been known to have good effects on mental health (22), and it also has anti-depressant effects. At least in animals, angiogenesis seems to be indispensable, because an injection of an inhibitor for angiogenesis, not directly of neurogenesis, halted neurogenesis and deteriorated the action of exercise (5).

### 3. Relationship of angiogenesis-deficiency and refractive depression

The patients' status related to angiogenesis is summarized as follows.



**Figure 2. Accordance in action of factors on angiogenesis and on depressive disorder.** There seems to be a good accordance in factors for angiogenesis and cure for depressive disorder, as if angiogenesis accompanies with the remedy of this disease. In this figure, red and blue arrows show the orientation of the effect of boxed factors for the included phenotypes.

### 3.1. Angiogenesis deficiency in patients suffering from depression

One of the signs of angiogenesis is said to be circulating endothelial progenitor cells (EPC). There is a report on decreased numbers of circulating EPCs in patients with a current episode of major depression with a significant inverse relationship between EPC levels and the severity of their depressive symptoms (21). A group of patients with major depressive disorders in general had a significantly higher VEGF level in serum concentration, while patients who had attempted suicide had a lower VEGF serum level compared to patients who had not attempted suicide (22). Further correlation analysis would be required for the patients. The accumulation of data on VEGF-related drugs may become clues in linking angiogenesis to the disease.

### 3.2. Genetically different VEGF in a portion of the patients

There are reports on genetics. One is VEGF polymorphism associated with treatment-resistant depression (23,24).

The other is on VEGF receptor gene polymorphism. It is in patients with a recurrent depressive disorder, not exactly matched for the refractory one, that distribution of the polymorphism differs significantly in patients compared to that of healthy subjects (7).

### 3.3. Increased anti-angiogenic factors in refractory depression

As above, genetically different patients would show insufficient angiogenesis that may lead to drug resistance. In addition, there may be a possible contribution of anti-angiogenic factors. Corticosterone or glucocorticoid

(GC) is the so-called 'stress hormone', and is released from the adrenal gland upon mental and physical stress. It is reported to inhibit angiogenesis induced by electric shocks (25) and to damage pericytes forming brain capillaries (26).

Post stroke depression is a type of refractory depression seen in 20-60% of survivors of brain stroke. In these patients having depressive symptoms, serum interleukin (IL)-18 on day 7 was independently associated with incident post-stroke depression (27). IL-18 has been known to suppress angiogenesis (28), probably *via* interferon- $\gamma$  (29). There is also a report on tumor necrosis factor (TNF)-alpha, showing a significant inverse correlation between TNF-alpha and EPC levels (21).

If there are obstacles for angiogenesis in the patients of refractory depression, removal of them might be a good concept for drug-development. Since anti TNF-alpha drugs are already on the market, research on the patients' mood may reveal a causal relationship.

## 4. Angiogenic regulators that might be future clues for remedy

As endogenous angiogenic regulators, the major ones are angiopoietin 2 and VEGF (10). Leptin, a satiety factor that suppresses appetite, also works as an angiogenic factor (30,31), while serum levels of leptin were independently associated with post-stroke depression (32). Brain-specific angiogenesis inhibitor 2 (BAI2), that correlate with anti-angiogenesis in the brain, might be a candidate target protein, because BAI2 gene disruption in deficient mice showed significant antidepressant-like behavior (33).

In foods, there are reports of anti-angiogenic materials. For example, resveratrol in wine (34,35) curcumin in turmeric (36,37) and 6-gingerol in ginger (38,39) have all been reported to inhibit angiogenesis, even though they are seemingly good for the body. Ingesting too much of these foods would inhibit angiogenesis and might worsen depressive disorders.

More extensive research on these effectors would provide clues for the remedy of depressive symptoms.

## 5. Conclusion

There seems to be good reasons to think about angiogenesis as a therapeutic target for refractory depression, because there seems to be an accordance in roles of factors for angiogenesis and for depressive disorders (Figure 2). Extensive research on the above mentioned effectors should be further performed in light of angiogenesis and recovery from depression.

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