

# Blood glutamate scavenging as a novel glutamate-based therapeutic approach for post-stroke depression

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**Abstract:** Post-stroke depression (PSD) is a major complication of stroke that significantly impacts functional recovery and quality of life. While the exact mechanism of PSD is unknown, recent attention has focused on the association of the glutamatergic system in its etiology and treatment. Minimizing secondary brain damage and neuropsychiatric consequences associated with excess glutamate concentrations is a vital part of stroke management. The blood glutamate scavengers, oxaloacetate and pyruvate, degrade glutamate in the blood to its inactive metabolite, 2-ketoglutarate, by the coenzymes glutamate–oxaloacetate transaminase (GOT) and glutamate–pyruvate transaminase (GPT), respectively. This reduction in blood glutamate concentrations leads to a subsequent shift of glutamate down its concentration gradient from the blood to the brain, thereby decreasing brain glutamate levels. Although there are not yet any human trials that support blood glutamate scavengers for clinical use, there is increasing evidence from animal research of their efficacy as a promising new therapeutic approach for PSD. In this review, we present recent evidence in the literature of the potential therapeutic benefits of blood glutamate scavengers for reducing PSD and other related neuropsychiatric conditions. The evidence reviewed here should be useful in guiding future clinical trials.

**Keywords:** blood glutamate scavenging, glutamate, post-stroke depression, treatment

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## Introduction

Post-stroke depression (PSD) is a major and frequent consequence of stroke, associated with an increase in morbidity and mortality.<sup>1–4</sup> Although the precise prevalence of PSD is hard to ascertain, estimates range from 20% to 60%.<sup>5,6</sup> Despite its debilitating effects on patients' recovery and quality of life, there remains no reliable and universal treatment for PSD. Historically, most antidepressant therapeutics influence serotonergic, adrenergic, and/or dopaminergic systems with the aim of increasing synaptic availability of serotonin, norepinephrine, and dopamine. However, more recent studies have investigated the involvement of the glutamatergic system in the etiology and treatment of depression.

Glutamate is a nonessential amino acid that accounts for approximately 60% of all neuro-mediator activity. During stroke, glutamate

concentrations in the brain's extracerebral fluid and cerebrospinal fluid (CSF) increase 300–400-fold.<sup>7–11</sup> As a result, the glutamate spreads, causing neuronal damage to areas beyond the infarcted tissue.<sup>12</sup> Glutamate receptors are stimulated by the excess glutamate and lead to cell swelling, apoptosis, and neuronal death, with subsequent poor neurological outcomes.<sup>13–15</sup> The glutamatergic system similarly plays a critical role in many mood disorders, such as depression, anxiety, dementia, and other psychiatric diseases.<sup>16–54</sup> Ample evidence in the literature suggests that the next generation of antidepressants will consist of substances centered around the glutamate system.<sup>55</sup> Limiting the secondary brain damage accompanied by excess glutamate concentrations post-brain injury is a vital part of stroke management.

A promising method involves the administration of intravenous pyruvate and oxaloacetate, called

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'blood glutamate scavengers' (BGS) which have demonstrated reductions in brain glutamate concentrations.<sup>56</sup> In recent years, BGS have been gaining attention in the scientific community and have been extensively examined in a wide variety of neurologic and psychiatric animal models. This review discusses recent evidence in the literature for the potential therapeutic benefits of BGS for reducing PSD and other related neuropsychiatric conditions. Although clinical human trials have not yet taken place, the efficacy of BGS in limiting depressive-like symptoms following stroke has been shown in rodents.<sup>57</sup> Unlike existing methods for treating PSD, the ability of BGS to reduce brain glutamate levels can potentially cease PSD development by targeting both the psychiatric and neurologic pathology.

### The impact and burden

Stroke is often a devastating event, suffered by over 16 million people globally each year, and is a leading cause of death and disability.<sup>58–61</sup> One third of cases lead to death, and another third to permanent disability.<sup>62,63</sup> Stroke is a major contributor to acute hospitalizations for neurological conditions.<sup>64</sup> Depression and anxiety disorders are the most common psychiatric conditions that appear post-stroke; however, many experience other psychotic symptoms, including hallucinations, delusions, and manic symptoms.

PSD is often overlooked and untreated, though it can have a serious, long-lasting impact on recovery and quality of life. It is estimated that PSD can appear in 30–35% of patients, with a range of 20–60%.<sup>5,6</sup> Recently, it has been found that greater than 50% of rats developed mental and behavioral disorders after stroke and subarachnoid hemorrhage.<sup>65,66</sup> The highest prevalence occurs between six months and two years following stroke,<sup>6</sup> and the condition is accompanied by more acute physical and cognitive impairments, impaired quality of life, and an increased mortality.<sup>67</sup> The rate of anxiety in the first 6 months after stroke varies between 22% and 25%.<sup>68</sup>

Another common neuropsychiatric complication of stroke is delirium, considered a major complication. In clinical studies, delirium in the acute period of stroke occurs 19%<sup>69</sup> to 48%<sup>70</sup> of the time, and the rate of post-stroke dementia is 6–32%. Post-stroke emotional incontinence (PSEI) affects between 11% and 52% of all stroke survivors.<sup>71,72</sup> It is typically observed within a few

weeks following stroke,<sup>73</sup> persists from 1 week to a few years,<sup>73,74</sup> and makes clinical treatment difficult.<sup>75</sup> Most often, patients with PSEI present with bouts of laughter, crying, or both, that are uncontrollable,<sup>76</sup> without any perceivable stimulus or initiated by minor, nonspecific stimuli. PSEI can cause patients distress and embarrassment, as well as social difficulties,<sup>77</sup> and may interfere with the rehabilitation process due to the irritability and impulsiveness of the patients.

All of these deleterious side effects lead to enormous financial burden. Stroke costs the United States and European Union an estimated \$34 billion<sup>78</sup> and €45 billion,<sup>79</sup> respectively, each year. Considering the modest arsenal of medical approaches for the treatment of PSD and behavior-related complications, we believe that the utilization of new therapeutic options in the form of glutamate scavengers may have enormous benefits to improve quality of life for stroke survivors.

### Nonglutamate mechanisms of post-stroke psychiatric complications

The basis of PSD and other psychiatric complications of stroke remain largely unknown, with many theories linking their mechanisms to other, similar mechanisms known to be associated with depressive symptoms. Yet, as will be seen, these models are imperfect, given the specific cause of PSD compared with other depressive conditions.

#### *Monoamine hypothesis*

The monoamine hypothesis suggests that disruption in the synaptic availability of neurotransmitters, including serotonin, dopamine and norepinephrine, are largely responsible for depressive behavior and other psychiatric symptoms.<sup>80–82</sup> Patients with PSD have been found to have significant reductions in levels of both serum and CSF serotonin.<sup>83</sup> A common treatment for depression, including PSD, involves decreasing the reuptake of serotonin through amino-neurotransmitter drugs like selective serotonin reuptake inhibitors (SSRIs), and serotonin and norepinephrine reuptake inhibitors (SNRIs).<sup>4</sup>

#### *Vascular depression theory*

Some evidence suggests that vascular depression caused by cardiovascular disease might contribute to the pathogenesis of PSD.<sup>4,84–89</sup> This theory

suggests that cerebral lesions disrupt critical areas in the brain that lead to symptoms of depression.<sup>90,91</sup> Hypertension after stroke has been shown to result in depressive symptoms,<sup>92</sup> and homocysteine, a risk factor for vascular disease, has also been studied for its possible association with PSD.<sup>93</sup>

#### *Neurogenesis hypothesis*

Alternatively, the neurogenic hypothesis suggests that depression may be related to an impairment in neurogenesis, the brain's capacity to produce new neurons.<sup>4</sup> This hypothesis bases itself on studies of people with depression or animals exhibiting depressive-like symptoms with decreased neurogenesis and hippocampal volume.<sup>94</sup> Furthermore, studies have shown that antidepressants enhance the neurogenesis of hippocampus.<sup>95</sup>

#### *Activation of the hypothalamic–pituitary–adrenal axis*

PSD is associated with increased cortisol levels,<sup>96</sup> yet the specific pathogenesis of hypercortisolism-related depression remains unknown.<sup>4</sup> Like other stressors, the stress from stroke may cause activation of the hypothalamic–pituitary–adrenal axis. There is also evidence, however, that hypercortisolism may be related to cytokine activity<sup>97,98</sup> with or without monoamine dysfunction.<sup>99</sup>

#### *Estrogen and progesterone theory*

The hormone estrogen has been implicated in depressive disorder. Similarities between estrogen and brain-derived neurotrophic factor, which is associated with PSD, suggest that estrogen replacement therapy would be a proper treatment for PSD.<sup>66,100,101</sup>

#### *Immune dysfunction hypothesis*

A substantial volume of evidence shows that depression may be partly attributable to dysfunction of the immune system.<sup>102,103</sup> While the specific mechanisms on the molecular and cellular level remains unclear, this theory proposes that PSD may be related to an overly activated inflammatory response<sup>104</sup> leading to inflammation-bound cell death in areas of the brain involved in mood.<sup>105</sup> During PSD, there is an increase in numerous inflammatory markers, pro-inflammatory cytokines, and pre-inflammatory/anti-inflammatory ratios with reduced complementary expression.<sup>4,106</sup>

### **Glutamate mechanisms of post-stroke psychiatric complications**

There is increasing evidence from the past few years that the glutamatergic system plays a crucial role in the development of mental disorders.<sup>26–54</sup> Glutamate levels have been shown to contribute to depression,<sup>16–19</sup> anxiety,<sup>20–22</sup> and dementia<sup>23–25</sup> among other psychiatric diseases.

Alterations in glutamate levels have been described in the blood<sup>38</sup> and CSF<sup>37</sup> of patients with major depression disorder (MDD). Plasma glutamate levels are associated with the severity of depressive symptoms.<sup>39</sup> Frontal cortex postmortem human tissue has been shown to have increased glutamate levels in those with a history of depression-compared controls.<sup>36</sup> Magnetic resonance spectroscopy (MRS) facilitates simultaneous *in vivo* glutamate measurements, and the observed regional changes in glutamate provide the most promising evidence of an association between glutamate and depression. These studies have revealed increased levels of brain glutamate of patients with MDD<sup>107,108</sup> and patients with PSD.<sup>109</sup>

### **Current approaches for the treatment of PSD**

The previous section demonstrated mechanisms of PSD which often parallel other depressive conditions. Since PSD remains difficult to manage and treatment often fails, current therapeutic approaches for this condition have been of great interest (Table 1). While historically, treatment for PSD targeted the  $\gamma$ -aminobutyric acid or serotonergic neurotransmitter systems, recent therapeutic modalities have focused on the role of the glutamatergic system.

#### *Nonglutamate-based antidepressants*

Treatments that target the  $\gamma$ -aminobutyric acid or serotonergic system, such as benzodiazepines and SSRIs, respectively, are the most commonly utilized therapy for anxiety, depression, stress, and trauma-related disorders. However, only 50–60% of patients treated for depression and anxiety with antidepressants respond to this therapy.<sup>110,111</sup>

PSD can often be treated with SSRIs, SNRIs, monoamine-oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), norepinephrine and dopamine reuptake inhibitors, other serotonergic antidepressants, as well as stimulants

**Table 1.** Therapeutic targets for poststroke depression.

Therapeutic targets	Advantages	Disadvantages
$\gamma$ -aminobutyric acid or serotonergic system (SSRI, SNRI, MAOIs, TCAs, NDRIs)	Antidepressive effects Most widely used	Not universally effective Does not address neurologic pathology of stroke Unpleasant side effects Risk of drug interactions May take more time for effect
NMDA-receptor antagonists (ketamine, esketamine, Ro25-6981, CP-101,606, memantine, magnesium, MK-0657, AZD6765, traxoprodil, NRX-1047, GLYX-13, D-cycloserine, zinc, MK-801, CGP37849)	Antidepressive effects Associated with positive neurological outcome in animal models	Associated with poor neurological outcome, cardiovascular disease, and mortality in clinical studies Decreases normal glutamate activity within and outside of the brain
AMPA-receptor antagonists (aniracetam, piracetam, ampakines, CX614, LY392098, LY451646)	Antidepressive effects	Decreases normal glutamate activity within and outside of the brain Limited clinical trials
BGS (pyruvate, oxaloacetate)	Antidepressive effects Maintains neuronal integrity Associated with positive neurological outcome Inexpensive Ability to maintain functional glutamate levels	Lacking clinical studies
Other (glutamate-transporter mediated, mGluRs antagonists, minocycline, riluzole)	Antidepressive effects	Decreases normal glutamate activity within and outside of the brain Limited clinical trials

AMPA,  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BGS, blood glutamate scavengers; MAOIs, monoamine-oxidase inhibitors; mGluRs, metabotropic glutamate receptors; NDRIs, norepinephrine and dopamine reuptake inhibitors; NMDA, N-methyl-D-aspartate receptor; SNRIs, serotonin and norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

and even electroconvulsive therapy.<sup>112–115</sup> These treatments are not universally effective. A recent randomized controlled trial showed that the SSRI, sertraline (Zoloft), was no more effective than placebo in treating people with depression following traumatic brain injury (TBI).<sup>116</sup> Due to the high prevalence of post-TBI and PSD, finding a solution that specifically targets these neuropsychiatric conditions is optimal.

#### *Glutamate-based antidepressants*

The antidepressant-like effects of glutamatergic agents have recently become more widely studied and applied to the treatment of various mood disorders. Recent clinical studies have illustrated the effectiveness of glutamatergic agents for the treatment of PSD,<sup>16,19,117,118</sup> obsessive-compulsive

disorder,<sup>119</sup> post-traumatic stress disorder,<sup>120,121</sup> generalized anxiety disorder,<sup>120–124</sup> and social phobia.<sup>125</sup> It is thought that the efficacy of these drugs reflects the impact of glutamate in the development of mental disorders.<sup>18–21,117,126–130</sup> Here, we summarize the known antidepressant properties of various therapeutic agents that act on the glutamatergic system.

#### *N-methyl-D-aspartate receptor antagonists*

There are many clinical studies that have revealed antidepressive effects of drugs that antagonize the N-methyl-D-aspartate receptor (NMDA) receptor. Recent evidence has determined the rapid antidepressive effects of ketamine, which interferes with glutamate receptor activation in patients with treatment-resistant MDD.<sup>131,132</sup>

The robust and now widely accepted antidepressant effects of NMDA receptor antagonists have led to the development of other agents targeting the same receptor, including Ro25-6981,<sup>133</sup> CP-101,606,<sup>134</sup> memantine,<sup>135</sup> magnesium,<sup>136</sup> MK-0657,<sup>137</sup> AZD6765,<sup>138</sup> traxoprodil,<sup>139</sup> NRX-1047,<sup>139</sup> GLYX-13,<sup>140</sup> D-cycloserine,<sup>141</sup> zinc,<sup>142</sup> MK-801,<sup>143</sup> and CGP37849.<sup>144</sup> Recently, the US Food and Drug Administration has approved the NMDA receptor antagonist esketamine for patients with treatment-resistant depression.<sup>145</sup>

#### *α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonists*

At least six agents that target α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors have been observed as potential therapies for depression: aniracetam,<sup>146</sup> piracetam,<sup>147</sup> ampakines,<sup>147</sup> CX614,<sup>148</sup> LY392098,<sup>149</sup> and LY451646.<sup>150</sup>

#### *Metabotropic glutamate receptors*

Glutamatergic transmission is controlled by ionotropic and by metabotropic glutamate receptors (mGluRs). Recent studies have shown that antagonism of mGluRs lead to antidepressant action in mGluR1<sup>151</sup> and mGluR5<sup>152</sup> (group I); mGluR2<sup>153</sup> and mGluR3<sup>154</sup> (group II); and mGluR4,<sup>155</sup> mGluR6,<sup>156</sup> mGluR7,<sup>157</sup> and mGluR8<sup>156</sup> (group III).

#### *Glutamate transporters*

Antidepressant activity has been demonstrated not only from agents that modulate the glutamatergic synapse, but also in those that modify glutamate transporters responsible for extracellular glutamate uptake. There is evidence for the roles of glutamate transporter 1<sup>158,159</sup> and excitatory amino acid transporter 2 on depression.<sup>128,160</sup>

#### *Other*

Other glutamatergic drugs have antidepressant-like effects, including minocycline and riluzole. Minocycline is a metabolic pathway of the essential amino acid L-tryptophan, which may cause NMDA-receptor activity in the brain.<sup>127</sup> Riluzole is an NMDA, AMPA, and kainate receptor antagonist that prevents the emission of presynaptic glutamate and facilitates the uptake of glial glutamate at relatively high concentrations.<sup>161</sup>

#### *Problems*

Although glutamate receptor antagonists have been shown effective for treatment of depressive symptoms in both preclinical and clinical studies, their efficacy in preclinical studies to improve neurologic outcomes after stroke and other neurological insults has not been replicated in human trials.<sup>162</sup> Following stroke and TBI, clinical studies of NMDA receptor antagonists led to an increase in the neurological severity outcomes and mortality rate.<sup>163-165</sup> Complications of these studies included premature death, cardiovascular issues, and development of psychoses, likely due to the harmful impact on the function of normal physiologic glutamate receptors in both healthy brain tissue and areas at risk of stroke-related injury.<sup>162</sup> At normal levels, glutamate plays a crucial role in maintaining neuronal function and communication through the activation of NMDA-receptor signal pathways. Agents that block NMDA receptors do not differentiate between the positive and negative consequences of NMDA signal dysfunction.<sup>165,166</sup> In addition, glutamate antagonists target glutamate transporters that are found in other areas of the body outside the brain, such as in the pancreas,<sup>167-171</sup> that are important for the metabolic regulation of glutamate. It is likely that NMDA-receptor antagonists have a negative effect on metabolic processes throughout the body.

#### **BGS with oxaloacetate and pyruvate as an alternative method**

BGS likely does not display the same detrimental effects of the other receptor antagonists, which would make it a better treatment option for the same conditions (Table 1). Over the past two decades, studies have shown a link between the mechanisms of depression and disruptions to the glutamatergic system, and determined that this system provides a central focal point from which to develop new antidepressant treatments.

The brain uses several techniques to rid itself of excess glutamate. Initial studies on potential therapeutic modalities focused on antagonizing glutamate receptors, as described above. However, a novel approach consists of removing only excess glutamate in the brain by utilization of BGS in the form of oxaloacetate and pyruvate. This is achieved through facilitating the body's natural brain-to-blood glutamate efflux down its concentration gradient. Glutamate is metabolized in the blood to its inactive metabolite, 2-ketoglutarate, by the enzymes



GOT and GPT in the presence of their cosubstrates, oxaloacetate and pyruvate, respectively.<sup>56</sup> By administering oxaloacetate and pyruvate peripherally, blood-glutamate scavenging can occur through several processes, such as catalyzation of enzymes responsible for glutamate metabolism, glutamate redistribution into tissue, and the acute stress response.<sup>172–174</sup> This approach has been validated by several animal studies.<sup>172,173,175,176</sup>

Unlike NMDA-receptor antagonists, BGS do not interfere with glutamate receptors or glutamate-mediated synaptic activity. Rather, BGS eradicate only the pathologically elevated levels of glutamate in cerebral fluid without eliminating glutamate levels entirely.<sup>172–174</sup> This process of glutamate efflux is self-limiting, slowing and eventually stopping when glutamate concentrations are decreased enough to no longer support glutamate transportation.

The reduction of blood glutamate levels leads to the formation of a concentration gradient of glutamate between the brain and blood that favors glutamate efflux, thereby prompting the transport of excess glutamate from the brain's extracellular fluid (ECF) to the blood. Thus, lowering glutamate levels restricts secondary brain injury associated with glutamate neurotoxicity.<sup>177,178</sup> Moreover, the reduction of glutamate in the blood circulation assists with neurological outcome after TBI<sup>179–182</sup> and stroke.<sup>175,183–187</sup>

Clinical studies have demonstrated an association between low GOT levels and poor neurological outcome post-stroke; while high GOT levels are associated with better neurological outcome.<sup>183,184</sup> GOT and GPT cause a reduction in glutamate levels both in the brain ECF and in the blood,<sup>176</sup> and both have been used for successful treatment in animal models of TBI and stroke.<sup>175,179,180,185</sup>

Due to its ability to limit secondary effects of stroke, BGS potentially provide a treatment option for PSD by targeting both the effects of stroke on neurological function and on resultant depression. Recent support for the role of BGS as a therapeutic modality in PSD was demonstrated in a rodent model showing that administration of pyruvate lowered glutamate levels, and improved neurological outcome and post-stroke depressive behavior.<sup>57</sup> In this study, 80 rats were randomly separated into one of three groups: middle cerebral artery occlusion (MCAO) plus pyruvate treatment, MCAO and treatment with placebo, and a control

group. The rats in the first group showed significant reduction of lesion volume, brain edema and blood-brain barrier breakdown compared with rats who had MCAO with placebo, and displayed fewer depressive-like behaviors.<sup>57</sup>

Therefore, there is growing evidence that BGS may be advantageous as a therapeutic option for PSD due to their ability to maintain the physiological effects of glutamate, allowing for its continued preservation of the metabolic and electrolyte balance, and neuronal function, and its benefits for neurological recovery after brain injury.<sup>188</sup> BGS possess the ability to maintain equilibrium between minimizing the negative effects of excess glutamate and keeping its positive effects that are essential for life.<sup>178</sup>

### Conclusion

Stroke itself has debilitating effects on neurological function, and additional complications such as PSD make treatment of stroke challenging. Current treatment for PSD is often insufficient, but the therapeutic role of glutamatergic agents has been encouraging. Collectively, experimental evidence with BGS has shown much promise in the treatment of PSD. Clinical trials are a requisite future action to studying the clinical effects of BGS for the treatment of PSD in humans. A better understanding of the relationship between glutamate and BGS will produce critical insights that will be indispensable for the advancement of the clinical diagnosis, prognosis, and treatment of PSD.

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