DEVELOPMENT OF A PYRROLIDINONE DERIVATIVE (CYCLIC GABA) FOR MODULATING BRAIN GLUTAMATE TRANSMISSION

Kenji Matsuyama, Choichiro Miyazaki and Masataka Ichikawa

Department of Hospital Pharmacy, Nagasaki University Hospital
7-1 Sakamoto-machi, Nagasaki 852, Japan

INTRODUCTION

Senile Dementia of Alzheimer Type (SDAT) is a debilitating neurological disease that affects about one in six persons past the age of sixty (1,2). In spite of numerous hypotheses concerning the etiology of SDAT, e.g., abnormal blood aluminum levels (3), viral agents (4), genetic factors (5) and selective vulnerability of specific neuronal systems (6,7), its precise cause or causes remain unknown.

In 1976, Davies and Maloney (8) reported the selective loss of choline acetyltransferase (CAT), the synthesizing enzyme for acetylcholine, in the cortex of patients with SDAT. Since then, neurochemical studies have increased tremendously in scope and number. Alterations in the cholinergic (9,10), serotonergic (11), noradrenergic (12) and glutamatergic systems (13,14) have been reported. Recently, the potential roles of gamma-aminobutyric acid (GABA), glutamate (Glu) and aspartate (Asp) in neural functions have become an additional center of attraction in this disease process.

The amino acids Glu and Asp are major excitatory transmitters in the central neurons system. When present in high concentration, they are neurotoxic and could play a role in ischemic damage in the brain, suggesting their potential participation in vascular dementia. Furthermore, Greenamyre et al. (14) proposed that high levels of Glu are closely involved in the development of SDAT from the observation that neurofibrillary tangles, senile plaques and granulovacuolar degeneration selectively occurred in the hippocampal CA1 region to which Glu neurons project.

As illustrated in Fig. 1, the release of glutamate can be modulated at several distinct sites. Receptors for GABA (15) and adenosine (16) have been localized in the presynaptic glutamate terminal, and have been shown to modulate Glu release (17,18). Furthermore, GABA has been reported to enhance acetylcholine release from hippocampal nerve endings (19). From that point of view, we developed GABAergic derivatives in the form of prodrugs for the transmitter. The use of prodrug therapy is discussed in detail in other chapters of this book.

Shashoua et al. (20) has demonstrated increased permeability of GABA derivatives into the brain in the form of various aliphatic and steroidal esters. Each ester was taken into the brain faster than GABA itself after peripheral administration; however, only the cholesteryl ester of GABA exerted a pharmacological response. This observation demonstrates that the rate of hydrolysis in the brain can be another important factor for prodrug-potency.

With these observations in mind, three kinds of aromatic acids, isonicotinic acid, nicotinic acid and anisic acid, were used for the pro-moieties of GABA because these groups attributed different electron states on amido bonds formed between these acids and the amino group of GABA. In the present study, we determined the GABA levels in the mouse whole brain after the intraperitoneal administration of the same dose of isonicotinoyl-GABA (IG), nicotinoyl-GABA (NG), anisoyl-GABA (AG), isonicotinoyl-2-pyrrolidinone (IP), nicotinoyl-2-pyrrolidinone (NP), and anisoyl-2-pyrrolidinone (AG) to determine if the brain GABA-elevating effect of GABAergic derivatives reflected the difference in the electron state of the amido bond of IG, NG, AG, IP, NP and AP. The structures of these compounds are shown in Fig. 2.

![Fig 1 Schematic diagram for pre- and postsynaptic glutamate neuron.](image)

(1) Synthesis of neurotransmitter pool of glutamate. (2) Presynaptic GABA and adenosine receptors. (3) Glutamate autoreceptors. (4) Antagonists of postsynaptic receptors (represented by solid symbols). (5) Receptor ion channel blockers. GLU indicates glutamate; GLN glutamine; ADP, adenosine diphosphate; ATP, adenosine triphosphate; and Na, sodium.

From Greenamyre (14).

![Fig. 2 The structures of IG, NG, AG, IP, NP, AP, 2-P and GABA](image)