2.3 | GABA, Homocarnosine, and β-Alanine

Erwin E.W. Jansen, Cornelis Jakobs, K. Michael Gibson

2.3.1 Introduction

γ-Aminobutyric acid (4-aminobutyric acid, GABA), β-alanine (2-aminopropanoic acid), and homocarnosine (γ-aminobutyryl-L-histidine) represent bioactive amines with diverse roles in intermediary metabolism and central neurotransmission. In adults, GABA is the primary central inhibitory neurotransmitter derived from excitatory glutamate in a reaction that is catalyzed by glutamic acid decarboxylase. Its neuronal disposal is mediated by GABA transaminase (GABA-T) and succinate semialdehyde dehydrogenase (SSADH) [8]. In the transamination step, 2-oxoglutarate serves as a nitrogen acceptor to generate glutamate, thus forming what is historically referred to as the “GABA shunt” pathway. Perhaps one-third of mammalian synapses employ GABA as neurotransmitter, but it also has a pronounced role in nonneural tissues [22]. In the developing central nervous system (CNS), GABA acts trophically in an excitatory fashion, with important roles in synapse formation, dendritic outgrowth and maturation, and synaptic developmental roles [18].

β-alanine is derived from uracil and the decarboxylation of aspartic acid, and is a precursor of acetyl-CoA [7]. It may also be found as the β-alanyl-L-histidine conjugate carnosine (an antiglycation agent), in analogy to the GABA-histidine conjugate homocarnosine (see below) [16]. A preponderance of data (presynaptic localization, calcium-dependent release and/or transmitter-induced release, and postsynaptic receptors) suggest that β-alanine is also a neurotransmitter in mammals, but it is present in much lower concentrations in the brain than is GABA [7]. Recent evidence indicates that quantities of β-alanine are modulated by the stress response, with a resultant downstream effect on excitotoxic and antiapoptotic responses [16].

Homocarnosine is a brain-specific dipeptide that is synthesized by carnosine synthetase in glial cells and hydrolyzed by carnosinase. In some brain regions, concentrations exceed 1 mM, and there is evidence that specific neuronal tracts employ homocarnosine as a storage form of GABA [7]. The specific function of homocarnosine in brain has been widely explored, and the predominance of data suggest a role as an osmoregulator [23]. However, other studies have suggested that homocarnosine is neuroprotective (e.g., similar to β-alanine), especially with respect to ischemic damage, antioxidant damage, and protection from carbonyl toxicity [9]. The mechanism(s) by which these functions occur remain largely undefined.
2.3.2 Analyte Properties and Formulae

The analytes quantified in this chapter (Fig. 2.3.1) are bifunctional, with both amine and carboxyl moieties, which lend themselves to derivatization with several compounds. The physiological fluid of choice for determination is cerebrospinal fluid (CSF) although all species can be quantified in plasma, sera, urine, and even tissue extracts when necessary [9]. It is still unclear as to whether GABA and β-alanine share the same transaminase and nitrogen acceptor (2-oxoglutarate, pyruvate, etc), or if there are different enzymes with distinct specificities [7]. However, arguing in favor of only a single transaminase is the observation that body fluids from a documented patient with GABA-T deficiency had significantly increased β-alanine in addition to GABA [10].

GABA is significantly increased in both GABA-T and SSADH deficiencies; thus, quantitation in CSF has diagnostic importance [8, 11]. GABA levels in CSF derived from SSADH-deficient individuals may also have therapeutic ramifications in gauging the biochemical response to treatment [6]. Quantitation of β-alanine in CSF has diagnostic value for detecting GABA-T deficiency, but this disorder is rare. Isolated homocarnosinem/homocarnosinosis has been detected in two families, a rare disorder linked to serum carnosinase deficiency [7, 14]. Homocarnosine is also increased in CSF derived from SSADH-deficient individuals (see below).

![Fig. 2.3.1 Structures of the metabolites γ-aminobutyric acid (GABA), β-alanine, and homocarnosine](image-url)