The Potential Role of Serotonin in the Pathogenesis of Neurocardiogenic Syncope and Related Autonomic Disturbances

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Recurrent episodes of autonomic decompensation resulting in hypotension and bradycardia of sufficient severity to result in loss of consciousness (neurocardiogenic syncope), not only offer a diagnostic and therapeutic challenge to the clinician, they also provide an intriguing puzzle for the physiologist who seeks to understand the origin of the disorders [1]. Starting with Sir Thomas Lewis’s initial description of these disorders, a number of investigators have speculated on the pathogenesis of neurocardiogenic syncope [2]. However, these postulates remained quite theoretical, as no way to confirm or deny them was available. This situation changed quite dramatically in 1986, when Kenny and colleagues reported that head upright tilt table testing could reliably provoke episodes of autonomic decompensation in susceptible individuals [3]. The ability to induce these episodes in a controlled laboratory setting has permitted detailed measurements and observations to be made before, during, and after a syncopal episode. As a result, there has been a virtual explosion in research concerning both the pathophysiology and clinical aspects of neurocardiogenic syncope [4–6]. Concomitantly, a significant body of data has accumulated suggesting that alterations of the neurotransmitter serotonin (5-hydroxytryptamine or 5-HT) within the central nervous system may play an important role in the genesis of the hypotension and bradycardia that is characteristic of neurocardiogenic syncope [7].

In 1937, the Italian researcher V. Erspamer and colleagues isolated a compound from the enterochromaffin cells of the mucosa of the gastrointestinal tract that would cause intense uterine contractions. They named this substance “enteramine” [8]. Later, in 1948, the team of Rapport and Page purified a similar vasoconstrictive substance from bovine serum and called it “serotonin” (from a combination of the words serum and tone) [9]. Later, serotonin was chemically determined to be 5-hydroxytryptamine (5-HT). Erspamer’s team then determined that the substance “enteramine” was also 5-hydroxytryptamine [10]. The first isolation of serotonin from neural tissue in the brain occurred in 1953, and over the following decade a brilliant series of studies by Bard et al. [11] and by Dahlstrom and Fuxe [12] mapped out the general pattern and distribution of serotonin containing neurons throughout the entire central nervous system (CNS). These and other investigations have found that the serotonergic neurons of the CNS are densely clustered around the midline raphe nuclei of the midbrain and in the brainstem (or medulla) [13]. These nerves then provide extensive projections throughout the entire brain and spinal cord. The serotonergic neurons appear to be concentrated in the area of the dorsal raphe nucleus and the medial raphe nucleus which then give off projections to the medial forebrain bundle. From this site, nerve fibers are distributed to the limbic system, hypothalamus, cerebral cortex, and striatum. Projections to the spinal cord come from both the raphe obscurus and raphe magnus nuclei, combining with a few projections from the ventrolateral medulla [14].

Two morphologically different types of axon termi-

History and Physiology

A wide variety of neurotransmitters have been found to play an active role in both the regulation and maintenance of normal neural function. These include what are known as the monamine compounds such as seroton, epinephrine, norepinephrine, glutamine, dopamine, substance P, as well as other less well understood substances [1].

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nals in serotonergic neurons have been identified [15]. One group are called “D fibers,” which are quite fine and have multiple small varicosities. They begin in the dorsal raphe nucleus and branch extensively. The other type are called “M fibers.” They are beaded with large spherical varicosities. These start at the median raphe nuclei and have short thin branches with numerous and elaborate synapses. The D fibers are concentrated with the striation of the brain, while the M fibers predominate in the area of the dentate gyrus. Areas such as the cerebral cortex are rich in both M and D fibers.

Production and Regulation of Serotonin

The biosynthesis of serotonin in both nerve fibers and enterochromaffin cells begins with the amino acid L-tryptophan [16]. It is first hydrolyzed to 5-hydroxytryptophan (5-HTp). It appears that the availability of tryptophan is the rate limiting factor in serotonin (suggesting the possibility that dietary levels of tryptophan may affect serotonin levels). 5-HTp then undergoes decarboxylation to 5-HT via the enzymatic activity of aromatic L-amino acid decarboxylase. In nerve fibers, the newly synthesized serotonin is taken up into secretory granules and stored. Following serotonin’s release during nerve stimulation, its actions on post synaptic receptors is ended by its reuptake into presynaptic vesicles by a compound known as the 5-HT transporter. Serotonin is oxidatively deaminated by extracellular monamine oxidase (MAO) forming 5-hydroxindoleacetaldehyde. This in turn is rapidly degraded by aldehyde dehydrogenase to 5-hydroxyindol acetic acid (5-HIAA), the major metabolite of serotonin [17].

Serotonin Receptors

Beginning in the early 1960’s it was found that there were at least three principal groups of serotonin receptors. Initially these were characterized based on their pharmacologic properties; however, over the last decade using radioligand binding techniques, the presence of multiple different serotonin receptors has been made [8,15]. More recent technical advances have made cloning of these receptors possible, allowing for detailed analysis to be performed. At present, it is felt that there are at least three major groups of serotonin receptors [19,20]. These have been identified as: (1) guanine nucleotide binding G protein coupled receptors; (2) ligand-gated ion channels; and (3) transporters. A recent fascinating finding has been that these receptors appear to vary considerably in their sensitivity to serotonin. In addition, it has been observed that some serotonin receptors can be linked to different second messenger systems and that more than one second messenger may be coupled to the same receptor area. Recent studies have determined that other neurotransmitters co-exist with serotonin on the same nerve terminal (such as the neuropeptides, enkephalin, somatostatin, substance P, and galanin) and can profoundly alter the effects of a given receptor subtype.

A variety of different studies have demonstrated serotonin is critical in the regulation of a variety of different bodily functions, such as mood, body temperature, heart rate, blood pressure, appetite, aggressiveness, sleep, pain, and endocrinologic functions [15]. Investigators are presently attempting to determine whether a single receptor or a combination of various receptor subtypes control a particular function (it appears to be both) [14].

Serotonin’s Role in Cardiovascular Regulation

One of the more important developments in modern psychiatry has been the discovery of serotonin’s role in the pathogenesis of depression and in obsessive compulsive disorders. At the same time, neurologists have elaborated serotonin’s role in the production of migraines. Almost simultaneously, serotonin’s role in cardiovascular regulation has become increasingly evident. At the beginning of these investigations it was realized that tryptophan exerted little or no effect on blood pressure, whereas 5-hydroxytryptophan does [21]. The direct intravenous or intracerebral ventricular injection of 5-HTp in animals will cause an abrupt decline in heart rate, blood pressure, and sympathetic activity [22,23]. Later animal studies (in the cat) found that following pretreatment with a decarboxylase inhibitor, these depressor effects of 5-HTp could be blocked [24]. Antonacco and associates reported that when 5-HT alone was given in a dog model there was no significant pressor effect; however, if the subject was pretreated with an MAO inhibitor, 5-HT caused marked depressor effects [25]. Kuhn and colleagues have shown that the central conversion of 5-HTp to 5-HT (serotonin) seems to be the mechanism by which 5-HTp exerts its vasodilatory effects [21].

In regards to neurocardiogenic syncope, a number of investigators have reported that the principal action that leads to hypotension and bradycardia appears to be sudden and profound sympathetic withdrawal [1,26–28]. This appears quite similar to the sudden hypotension and bradycardia that is seen with acute hemorrhage (a phenomenon that can be more easily reproduced in an animal model) [29,30]. Morgan and colleagues have shown that serotonin plays an important role in the renal sympathetic inhibition that can be seen during acute hemorrhage in rats [31]. Using this model it was found that after controlled blood loss there would be a sudden fall in renal sympathetic nerve activity [30]. A completely different result was seen after the animals were pretreated with an inhibitor of serotonin synthesis (P-chlorophenylalanine or PCPA) or a serotonin blocking agent such as methysergide. PCPA could block the reflex hypotensive effects of