NEUROTRANSMITTERS IN THE CAROTID BODY

Nanduri R. Prabhakar

Department of Medicine,
Case Western Reserve University School of Medicine
Cleveland, Ohio 44106 U.S.A.

INTRODUCTION

One of the most fundamental physiological stimuli is oxygen, or more appropriately the lack of oxygen, i.e., hypoxia. The discovery that the carotid bodies are the principal sensory organs for monitoring the arterial oxygen opened new perspectives in respiratory physiology. The chemoreceptor organ morphologically resembles a miniaturized brain. It is comprised of type I (also called glomus) cells that are of neural crest origin and contain neurotransmitters. Glomus cells are in functional contact with afferent nerve endings; whereas the type II (or sustentacular) cells resemble glia. Currently, it is believed that the type I cells are the initial transducers of the hypoxic stimuli. Transduction mechanism(s) may involve biochemical or biophysical processes (Acker, 1989, Biscoe & Duchen, 1990, Fidone & Gonzalez, 1986). Neurochemical(s), on the other hand, are essential for sensory transmission in the carotid body (Fidone & Gonzalez, 1986; Prabhakar, 1992). The general consensus is that in response to low O₂ glomus cells release neurochemical(s), which act on the nearby afferent nerve ending to increase the sensory discharge (Biscoe & Duchen, 1990, Fidone & Gonzalez, 1986, Prabhakar, 1992). Glomus cells are endowed with several types of chemicals that function as transmitters or modulators elsewhere in the nervous system. These include biogenic amines, neuropeptides and nitric oxide (NO) and carbon monoxide (CO). Some of these neurochemicals co-exist within the same glomus cell (Wang et al., 1992b), and perhaps co-released during hypoxia. In view of this, the notion that hypoxia releases a "single" neurochemical, perhaps is no longer tenable.

In addition to type I cells, some of these chemicals are localized to the nerve fibers that regulate carotid body activity (Fidone & Gonzalez, 1986). So far, no neurotransmitters have been demonstrated within the type II cells. The purpose of this article is to review the possible roles of neurotransmitters in the initiation and maintenance of carotid body sensory activity by hypoxia.

ACETYLCHOLINE (ACh)

Schweitzer and Wright (1938) were the first to note the stimulatory effects of ACh on
Subsequently, for more than two decades, i.e., from 1940 to 1970, several studies examined the role of ACh in the carotid body response to hypoxia. Evidence for and against the role of ACh as the mediator of the carotid body response to hypoxia has been reviewed extensively (Fidone & Gonzalez, 1986).

There is little doubt with regards to the presence of ACh in the carotid bodies. Chemoreceptor tissue contains the enzymatic machinery necessary for its synthesis and degradation, and hypoxia may release ACh-like material from mammalian carotid bodies (Fidone & Gonzalez, 1986). Furthermore, the presence of cholinergic receptors (muscarinic and nicotinic types) has been reported in rabbit and cat carotid bodies (Dinger et al., 1985, 1986). The problem with ACh as the mediator of the hypoxic response, however, stems from the following studies. The stimulatory actions of ACh vary with species. For instance, in cats, ACh stimulates, whereas in rabbits, it inhibits, the carotid bodies (Monti-Bloch et al., 1980). Moreover, cholinergic antagonists which block the actions of exogenous ACh have little influence on the chemosensory response to hypoxia (Fidone & Gonzalez, 1986). Species variations and the lack of effect of cholinergic blockers on hypoxic excitation cast serious doubts on its role as the principal mediator of the sensory response to low PO2.

Recently Fitzgerald and his associates (Fitzgerald & Shirahata, 1992) re-examined the role of ACh in the carotid body. They tested the effects of cocktail of cholinergic receptor blockers (i.e., α-bungarotoxin + atropine + mecamylamine) on the carotid body response to hypoxia in anesthetized cats. This combination of cholinergic blockers attenuated the carotid body response to hypoxia. Based on these findings, it was concluded that ACh is an excitatory transmitter that is necessary for the hypoxic response. Interestingly, cholinergic blockers also attenuated the carotid body response to CO2. Given the possibility that ACh may mediate the ventilatory response to CO2 acting on the medulla oblongata (Dev & Loescheke, 1979), it is likely that it plays a prominent role in the carotid body response to hypercapnia. If this is true, then the attenuation of hypoxic response by cholinergic blockers could conceivably be secondary to an attenuation of the carotid body response to CO2. Nonetheless, these studies by Fitzgerald (Fitzgerald & Shirahata, 1992) are not only interesting but also point to the complexity of cholinergic receptors especially the muscarinic (M1, M2, M3) and nicotinic (neuronal and non-neuronal) subtypes. Future studies using specific agonists and antagonists to cholinergic receptor subtypes may provide important information as to the role of ACh in the carotid body.

**CATECHOLAMINES**

While ACh was the focus of interest between 1940 and 1970, catecholamines, especially dopamine, became the center of attention in the 70's in carotid body research. Lever and Boyd (Lever & Boyd, 1957, Lever et al., 1959) were the first to report catecholamines in rabbit and cat carotid bodies. It is clear from subsequent studies that the chemoreceptor organ resembles chromaffin tissues containing catecholamines. In fact, it has now become a common practice to identify glomus cells by catecholamine fluorescence. There is a good deal of confusion with regard to catecholamine content in mammalian carotid bodies. Much of this is due to (a) different techniques used for measurements of catecholamines and (b) expressing the amine content per carotid body (which varies considerably) without normalizing the data either per milligram of protein or weight of the carotid bodies. Fidone and Gonzalez in their elegant review (Fidone & Gonzalez, 1986), tabulated results from different laboratories including variations in methodological approaches and species differences. It is evident from their review that dopamine (DA) is the major catecholamine in the carotid body in many species, followed by norepinephrine (NE). However, epinephrine (E) content is either negligible or is even absent in some species.