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# Tyramine: From octopamine precursor to neuroactive chemical in insects

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ABSTRACT

It is well acknowledged that tyramine acts as the biosynthetic intermediate precursor for octopamine. This fact has biased the interpretation of biological effects of tyramine towards an artifact of it being a partial agonist on octopamine receptors. Over recent years there has been an accumulation of evidence to show that tyramine is in fact a neuroactive chemical in its own right, with diverse physiological/behavioral roles. In addition, tyramine plays a unique role in a non-neuronal tissue, namely the Malpighian tubules. This review examines this evidence, taking into account the criteria that need to be satisfied in order to claim neuroactive chemical status. Thus, the evidence points to tyramine being synthesized by, and present in, neurons; capable of being released from neurons; removed by high affinity plasma membrane transporters; acting upon specific tyramine receptors; and producing physiological/behavioral effects that can be blocked by antagonists. This composite evidence is strong, although the final proof still awaits analysis on a uniquely identifiable tyraminergic neuron as has been possible with octopamine.



## 1. Introduction

Nervous systems of animals use a variety of neuroactive chemicals in order to produce integrated and coordinated behaviors. Acting as neurotransmitters, neurohormones, or neuromodulators these neuroactive chemicals ultimately enable flexibility in communication associated with the privacy of the message (confined to synaptic sites or accessible by many tissues as a neurohormone), speed of delivery of the message (speed of synaptic transmission or via the circulatory system as a neurohormone), and duration of the message (Orchard, 1982; Orchard et al., 2001). One family of neuroactive chemicals includes the biogenic amines. Biogenic amines represent a small, but very important group of neuroactive chemicals derived through decarboxylation of amino acids. Two biogenic amines, the catecholamines noradrenaline and adrenaline, are predominantly important in the vertebrates, whereas another two, the monoamines tyramine and octopamine, are predominantly important in the invertebrates. Others, for example dopamine and 5-hydroxytryptamine (5-HT), are important in both vertebrates and invertebrates. Interestingly, tyramine was originally recognized as a trace amine in the vertebrate nervous system, associated with the dopaminergic system (see Boulton, 1984; Wu et al., 1980). In the invertebrates tyramine occurs in larger concentrations than found in the vertebrates but, influenced by the vertebrate literature, was originally considered only as a biosynthetic intermediate of octopamine and not as a neuroactive chemical in its own right (see Downer et al., 1993; Hiripi et al., 1994). Work over the last decade, however, has led to a reconsideration of tyramine as a true neuroactive chemical in both the vertebrates and the invertebrates (see Blenau and Baumann, 2003; Roeder, 2005). For example, specific tyraminergic effects on physiological processes have been described (see Downer et al., 1993; Donini and Lange, 2004), specific neurons have been shown to express tyramine in the absence of octopamine (Nagaya et al., 2002), and cDNA receptor clones have been isolated from insect species and from mammals, which show specificity for tyramine (Cazzamali et al., 2005; Evans and Maqueira, 2005; Borowsky et al., 2001). Thus, tyramine appears to be a legitimate neurochemical in at least the invertebrates, especially insects, where it may participate in a variety of physiological processes.

In this review, the evidence for tyramine acting as a neuroactive chemical in insects will be reviewed, making reference to octopamine where appropriate. Evidence for tyramine as a neuroactive chemical is also strong in some other invertebrates, such as *Caenorhabditis elegans* (Wragg et al., 2007). Particular attention will be paid to the criteria that must be satisfied to support the true classification of a chemical as a neuroactive chemical. These criteria have been reviewed and updated recently (Cowan et al., 2001) and include the following: (1) the neurochemical must be present, and therefores synthesized, in the cell, (2) stimulation of the cell must result in the release of the neurochemical, (3) mechanisms for inactivation or removal of the neurochemical must be present, (4) the neurochemical must act on specific receptors on the target cell, (5) application of the neurochemical must mimic the natural

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effect of the signaling cell, and (6) blocking the receptor via blocking agents must stop the activity of the neurochemical.

## 2. Localization and content of tyramine in the nervous system

One criterion required for defining a neuroactive chemical is that it must be present and synthesized within neurons. Tyramine is synthesized from tyrosine by the enzyme tyrosine decarboxylase. Confounding the study of tyramine, however, is the fact that tyramine is the precursor for octopamine, the substrate being converted by tyramine β-hydroxylase (see Fig. 1). Thus, octopaminergic neurons will contain tyramine as a precursor and therefore even for an octopaminergic neuron, there is the potential for both tyramine and octopamine being released from the same neuron as co-transmitters. On the other hand, tyraminergic neurons should not contain octopamine. Downer et al. (1993) using high performance liquid chromatography coupled to electrochemical detection (HPLC-EC), found that the distribution of tyramine did not parallel that of octopamine in the central nervous system (CNS) of locusts. In particular, the tyramine/octopamine ratio varied in different regions of the CNS and between the CNS and skeletal muscle. Within the CNS, the tyramine content is 3–7 times lower than that of octopamine, whereas in skeletal muscle tyramine content is 2–9 times greater than that of octopamine. An examination by Donini and Lange (2004) and da Silva and Lange (2008) of reproductive visceral muscle tissue in locust found the ratio of tyramine to octopamine was similar to that reported by Downer et al. (1993) for skeletal muscle. Supporting the original suggestion of Downer et al. (1993) that tyramine might serve a specific physiological role independent of octopamine, was the discovery that a specific anti-tyramine antiserum stains a set of larval neurons in *Drosophila* that are distinct from octopaminergic neurons (Nagaya et al., 2002, Fig. 2). Thus, tyramine-like immunoreactivity is found in neurons of the brain, sub-oesophageal ganglion and thoracico-abdominal ganglia. In particular, immunoreactivity is evident in three ventral unpaired median (VUM) neurons of each segment in the sub-oesophageal, thoracic and abdominal ganglia (A1–A7), and in a pair of small dorsal lateral neurons in A1–A7. These VUM neurons project to peripheral muscles. In the terminal, abdominal ganglion (A8) tyramine-like immunoreactivity is present in dorsal unpaired median (DUM) neurons. Of note, is the fact that there are no octopamine-positive neurons in the brain or in thoracic VUM neurons, or in small lateral neurons in the abdominal ganglia (Monastirioti et al., 1995) and so these may be tyramine-specific (Fig. 2). More recent studies indicate an extensive distribution of tyramine-like immunoreactive processes associated with locust oviduct and spermatheca and tyramine-like immunoreactive neurons in VIIth and VIIIth abdominal ganglia of the locust (Donini and Lange, 2004; Lange and da Silva, 2007; da Silva and Lange, 2008), although it is likely that some of these neurons also contain octopamine. Within the VIIth abdominal ganglion, tyramine-like immunoreactive lateral cells are evident that do not appear to contain octopamine (Donini and Lange, 2004; Stevenson et al., 1994; Bräunig and Pflüger, 2001; Clark and Lange, 2003). Similarly, there appear to be some laterally located tyramine-like immunoreactive cells within the VIIIth abdominal ganglion that do not appear to contain octopamine (da Silva and Lange, 2008).

In addition to the information on content and localization of tyramine within neurons of the CNS, the genes for the synthetic enzymes tyrosine decarboxylase (Cole et al., 2005) and tyramine β-hydroxylase (Monastirioti et al., 1996) have been cloned in *Drosophila*. Tyramine β-hydroxylase is expressed in cells that resemble those that are believed to contain octopamine (Monastirioti et al., 1995). Interestingly, while expression of tyrosine decarboxylase also matches these cells, some cells are positive for tyrosine decarboxylase but apparently not for tyramine β-hydroxylase—suggestive of tyramine—specific neurons (Cole et al., 2005). Interestingly there are two genes coding for tyrosine decarboxylase

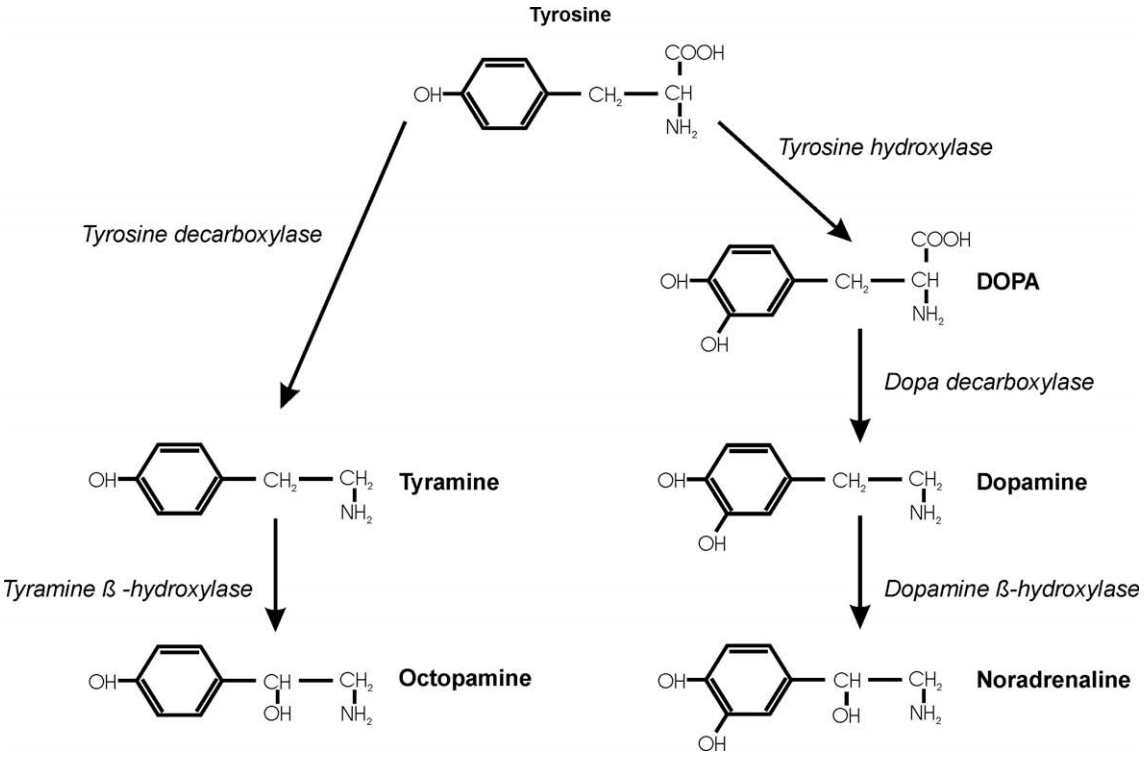


**Fig. 1.** The biosynthetic pathway from tyrosine leads to the production of different biogenic amines. Tyrosine can be hydroxylated by tyrosine hydroxylase to produce DOPA. Both DOPA and tyrosine can be decarboxylated to produce dopamine and tyramine, respectively. These may then be further hydroxylated to produce noradrenaline and octopamine, respectively. Note the similarities in these two pathways.