6 Cell Communication by Autacoids and Paracrine Hormones

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6.1 Introduction: Endocrine, Paracrine, and Autocrine Control

Multicellular organisms require mechanisms by which coordination is secured. This coordination is based on one of the following basic principles:

- Cell-to-cell communication by gap junctions
- Neuronal networks and neuronal control
- Hormonal control

Gap Junctions Communication by connexons (gap junctions) is a highly specific type of close communication. Connection by gap junctions leads to a very tight but not absolute coupling (Gleichschaltung). Individual cells are thus coordinated in a functional syncytium. This is discussed explicitly in Chap. 7.

Neuronal Networks The basis of neuronal networks is discussed in Chaps. 24 and 54. Neuronal networks can be characterized by their precise connections from one neuron to another; from one receptor to its sensory pathway; from one α-motoneuron to a muscle fiber, etc. Another typical feature of neuronal communication is the long distance over which the message is transmitted without any loss of information. Consider, for example, long fibers of α-motoneurones running from the spinal cord to the distal muscles of the limbs. This type of coordination is very fast, with conduction velocities of 80–120 m/s. Also, the delays produced by synapses are only in the millisecond range. The degree of coordination achieved by these processes is unmatched by any other mechanism. Physiology, to a large extent, is nothing but the attempt to explore this coordination.

Hormonal Control Hormonal control mechanisms are discussed in Chap. 1 and in several other, more specific, chapters (Chaps. 19–23, 62, 65, 66, 71, 82, 86, 113, 116, 117, 119, 121). The principle is entirely different from that of neuronal control. Specific endocrine glands produce a hormone that is delivered to the blood. Circulation distributes the hormone throughout the body, causing it to reach all cells and act on those that possess receptors and effector mechanisms for the hormone concerned (cf. Chap. 5). Therefore, hormonal coordination is also precise, inasmuch as the reaction is defined by the hormone sensitivity of the tissue. This type of coordination is much slower than neuronal control. Rapidly acting hormones, e.g., adrenaline, still require up to several minutes for the effector mechanisms.

Thyroid Hormone as an Illustration The above-mentioned two regulatory mechanisms are tightly connected: hormone release mechanisms are ultimately controlled by the nervous system (Chaps. 17–19, 82). As an example, consider thyroid hormone (triiodothyronine and thyroxin \(T_3, T_4\); cf. Chap. 22]. The release and the production of the hormone are controlled by thyroid-stimulating hormone (TSH), which in turn is released from the anterior pituitary gland. The release of TSH is controlled by TSH-releasing hormone (TRH), which is produced in the hypothalamus. The release of TSH and TRH is controlled (i) by \(T_3\) and \(T_4\), with negative feedback loops and also (ii) by neuronal control mechanisms.

Transmitter Release In a more mechanistic sense, endocrine and neuronal control share some basic functions. In the nervous system, each message is transmitted electrically in dendrites and axons and con-
nections are made by synapses. In the synapses (cf. Chaps. 15, 16) incoming electrical signals depolarize the presynaptic membrane and trigger transmitter release. This is achieved by the exocytosis of small vesicles containing this transmitter. The transmitter reacts with receptors of the postsynaptic membrane and generates new electrical signals (end-plate potentials, excitatory postsynaptic potentials or inhibitory postsynaptic potentials). In many instances, hormone release mechanisms are very similar. Electrical signals, glandotropic hormones or other factors induce the release, where the hormone acts almost exclusively in the synaptic cleft. The transmitter reacts with receptors of the postsynaptic membrane and generates new electrical signals (end-plate potentials, excitatory postsynaptic potentials or inhibitory postsynaptic potentials). In many instances, hormone release mechanisms are very similar. Electrical signals, glandotropic hormones or other factors induce the exocytosis of the hormone concerned. In fact, as will be discussed later in this book (Chap. 16), transmitter release is frequently tightly coupled with the release of a cotransmitter, which might act as a local hormone.

Adrenal Medulla. One classic example that can highlight the similarity of hormonal and endocrine control is the adrenal medulla. This “gland” consists of ganglia, which, under the control of sympathetic innervation, release adrenaline (epinephrine) (70–80%) and nor-adrenaline (norepinephrine) (20–30%). Adrenaline (epinephrine) acts as a hormone in a variety of organs. Neurotransmission can therefore be looked at as a very specific case of “hormone” release, where the hormone acts almost exclusively in the synaptic cleft. The mechanisms of neurotransmission were discovered in the heart by Loewi. Along these lines, the prospect of looking at individual hormones and transmitters was intriguing. There are several specific substances that act both as hormones, e.g., in the gastrointestinal tract, and as neurotransmitters in the brain. Some well-known examples are listed below, but there are many more:

- Vasoactive intestinal peptide
- Adrenaline (epinephrine)
- Substance P
- Cholecystokinin
- Neurotensin
- Neuropeptide Y
- Histamine
- Serotonin
- Cerulein
- Somatostatin
- Bombesin

It appears that the repertoire of basic substances from which signalling substances can be designed (cf. Chap. 5) is finite, and that the substances are used as elements in a toolbox in a wide variety of settings. The hormone may have certain effects in distal targets, and the same molecule serves an entirely different purpose as a transmitter. Therefore, despite so many and important conceptual differences, hormonal and neuronal coordination appear to be variations on the same theme. The specific chapters dealing with endocrinology will discuss certain groups of hormones and their effects (Chaps. 20–22, 66, 71, 82, 113, 116, 117, 119, 121). In this chapter, the emphasis will be on locally acting hormones. In this area the differences between transmitters and hormones become even more vague. A hormone may act very locally, i.e., on the secreting cell itself (autocrine), on its neighbors (paracrine), or on far distant target cells (endocrine). Locally acting hormones are also called autacoids, which means they act in the area where they are produced (Greek: αυτός = on itself; αύτο = acting) rather than in the rest of the body. It will become apparent that there are no clear distinctions between autacoids and hormones in the general sense.

6.2 Prostaglandins, Thromboxanes (Prostanoids), and Leukotrienes

The name prostaglandin is a misnomer inasmuch as these local hormones are by no means restricted to the prostate gland. Furthermore, they are not systemic hormones. Their discovery relates to experiments performed by Kurzrok and Lieb [38] as early as 1930, in which they found the contracting and/or relaxing effects of semen on uterine muscle. Von Euler, working with lipid extracts from semen, showed the effect on smooth muscle, and he coined the term prostaglandin. This name has been generally accepted since, although it is recognized that prostaglandins are produced by virtually every cell [43].

6.2.1 Metabolism of Arachidonate

These local hormones are all derived from arachidonic acid (Fig. 6.1). At physiologic pH, due to the pKₐ of arachidonic acid, it appears more appropriate to refer to this substance as arachidonate, rather than arachidonic acid. Since arachidonate has 20 carbon atoms, the hormones in this group are also referred to as eicosanoids (from the Greek: εἴκοσιν for 20). Arachidonate can be formed in almost every cell from membrane lipids (Fig. 6.1) [10]:

- By phospholipase A₂.
- By the sequential action of phospholipase C and phospholipase A₂. The former enzyme hydrolyzes phosphatidyl-inositol-(4,5)-diphosphate (PIP₂) to inositol-1,4,5-trisphosphate (IP₃) and diacylglycerol (DAG), while the last enzyme hydrolyzes arachidonate from DAG (also cf. Chap. 5).
- By the sequential action of phospholipase C, DAG kinase, and phospholipase A₂. DAG is converted to phosphatidic acid, and this is hydrolyzed to arachidonate.
- By the sequential action of phospholipase D and phospholipase A₂. The former enzyme cleaves phosphatidic acid from membrane lipids (cf. Chap. 5), while the latter produces arachidonic acid and lysophosphatidic acid.

At this stage it is impossible to trace the sources of arachidonate. It appears likely that a large fraction is not