CHAPTER 11
Neuropeptides, Signal Transduction and Small Cell Lung Cancer

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Introduction

Small cell lung carcinoma (SCLC) constitutes 25% of all lung cancers and despite initial sensitivity to chemotherapy and radiotherapy has a 5 year survival of less than 5%. Consequently there is an urgent need to develop new therapies and this is most likely to arise from a better understanding of the biology of the disease. There is increasing evidence that multiple neuropeptides including bombesin/GRP, vasopressin, galanin, gastrin, bradykinin and neurotensin can act as autocrine/paracrine growth factors for SCLC cell lines. Therefore, elucidation of the signalling pathways that lead from neuropeptide receptors to the nucleus where mitogenesis is induced may provide important clues for developing new therapeutic strategies.

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Many studies to identify the molecular pathways by which neuropeptide mitogens elicit cellular growth have exploited cultured murine Swiss 3T3 cells as a model system [1, 2]. These cells cease to proliferate when they deplete the medium of its growth-promoting activity, and can be stimulated to reinitiate DNA synthesis and cell division by the addition of various growth factors in serum-free medium [12]. In particular, bombesin [14], vasopressin [15], bradykinin [16], vasoactive intestinal peptide [17], endothelin [18] and vasoactive intestinal contractor [19] can act as growth factors for cultured 3T3 cells. An important feature of mitogenic signalling which has emerged from these and other studies is that cell proliferation can be stimulated through multiple, independent signal transduction pathways which act in a synergistic and combinatorial fashion. In what follows, some fundamental features of the mechanism of action of bombesin and other neuropeptides as growth factors in 3T3 cells will be discussed and subsequently the evidence for multiple neuropeptide growth factor action in SCLC will be considered. The review will then focus on the development of substance SP analogue broad spectrum neuropeptide antagonists as a novel SCLC therapy.

2. Early Signaling Events Induced by Bombesin

The early cellular and molecular responses elicited by bombesin and structurally related peptides have been elucidated in detail in Swiss 3T3 cells (Figure 1). Bombesin is a 14 amino acid peptide first isolated from the skin of the frog *Bombina bombina* [3]. Many bombesin-related peptides have subsequently been isolated from various species and classified into the three subfamilies bombesin, ranatensin and litorin according to their C terminal hexapeptide sequence homology. The principal mammalian counterparts are GRP and neuromedin B, members of the bombesin and ranatensin subfamilies, respectively.

2.1 Inositol Phosphatidyl Turnover, Ca\(^{2+}\) Mobilization and Activation of Protein Kinase C

Binding of neuropeptides such as bombesin/GRP to their receptors initiates a cascade of intracellular signals culminating in DNA synthesis 10 to 15 hours later. The bombesin/GRP receptor like many other neuropeptide receptors [4, 5] belongs to the superfamily of heterotrimeric G protein-coupled receptors. These are characterized by seven transmembrane domains which are thought to cluster to form a ligand binding pocket [4–7]. One of the earliest events to occur after the binding of bombesin to its specific receptor is the activation of the heterotrimeric G protein \(G_\alpha_q\), which in turn stimulates the phospholipase \(C_\beta (PLC_\beta)\) isoform of PLC. This catalyses the hydrolysis of phosphatidyl inositol 4,5-bisphosphate