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The Roles of Guanine Nucleotide Binding Proteins in Health and Disease

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Abstract: G-proteins are important mediators of cellular and tissue functions and are characterised by a recognition site for Guanine Triphosphate (GTP), Guanine Diphosphate (GDP) and possess intrinsic GTPase activity. They play important roles in signal transduction responsible for cytoskeletal remodelling, cellular differentiation and vesicular transport. They are made up of three types namely, the small G-proteins, the sensors and the heterotrimeric G-proteins. The G-protein heterotrimers consist of G-alpha (Gα), G-beta (Gβ) and G-gamma (Gγ) subunits. Each heterotrimeric G-protein have different subunits and the combination of these subunits define the specific role of each G-protein. The activation of Gα subunits regulates the activity of effector enzymes and ion channels while Gβγ subunits function in the regulation of mitogen-activated protein kinase (MAP-kinase) pathway. The G-protein-mediated signal transduction is important in the regulation of a cells morphological and physiological response to external stimuli. MAPKs are involved in the phosphorylation of transcription factors that stimulate gene transcription. $G\alpha_s$ stimulates adenylate cyclase, thereby increasing cyclic adenosine monophosphate (cAMP) leading to the phosphorylation and subsequent activation of Ca^{2+} channels. G proteins are involved in disease pathology through several mechanisms which interfere with the G protein activity. Other disease pathologies associated with abnormal mutations in G proteins can interfere with signal transduction pathways which may involve signal transmission that is either excessive, by augmentation of G protein function, or insufficient, via inactivation of G proteins.

Key words: Cyclic adenine monophosphate, effectors, G-protein, guanine diphosphate, guanine triphosphate, mitogen activated protein kinase

INTRODUCTION

Guanine nucleotide binding proteins (G-proteins) are important mediators of cellular functions. They are characterised by a recognition site for guanine nucleotides namely Guanine Triphosphate (GTP) and Guanine Diphosphate (GDP), and possess intrinsic GTPase activity (Siegel *et al*., 1999). The G proteins play a central role in signal transduction and many other cellular processes. They are divided into three distinct groups namely, the switches, the sensors and the clocks (Siegel *et al*., 1999).

The switches are the small G proteins that play important roles in cell function such as cytoskeletal remodelling, cellular differentiation and vesicular transport. The small G proteins, like other G proteins, bind guanine nucleotides; possess intrinsic GTPase activity and cycle through GDP-and GTP-bound forms (Siegel *et al*., 1999; Blaukat *et al*., 2000). The small G proteins function as molecular switches that control several cellular processes and examples include ras, rap, ran and ADP-ribosylation factor 1 (Table 1).

The ras p21 protein plays an important role in the regulation of cell differentiation through the stimulation of receptor tyrosine kinases (Blaukat *et al*., 2000). The binding of a growth factor to a receptor, stimulates the autophosphorylation of tyrosine kinase which assists in the recruitment of exchange factors. These exchange factors stimulate GDP-GTP exchange on the small monomeric G protein ras, leading to the activation of Mitogen-Activated Protein Kinases (MAPKs). MAPKs are involved in the phosphorylation of transcription factors that stimulate gene transcription (Siegel *et al*., 1999; Dhanasekaran and Prasad, 1998; Cabrera-Vera *et al*., 2003).

The sensors are the translation and elongation factors such as Tu and G. The translation factors play a pivotal role in protein synthesis especially in the second step of the three-step translation process (initiation, elongation and termination) (Cabrera-Vera *et al*., 2003). These GTP-binding elongation factors are responsible for two elements of elongation. The elongation factor Tu escorts the tRNA carrying the correct amino acid to the correct

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Table 1: Examples of small G proteins and their cellular functions

Class	Cellular function
Ras	Signal transduction (control of growth factor and MAP-kinase pathways)
Rac, CDC42	Signal transduction (control of cellular stress responses and MAP-kinase*** pathways)
Rab	Localized to synaptic vesicles, where it regulates vesicle trafficking and exocytosis.
Rho	Assembly of cytoskeletal structures (e.g., actin microfilaments)
ARF*	ADP-ribosylation of Gαs; Assembly and function of Golgi complex.
EFTU**	Association with ribosomes, where it regulates protein synthesis.
Ran	Nuclear-cytoplasmic trafficking of RNA and protein

ARF*: ADP-ribosylation factor; EFTU**: eukaryotic elongation factor; MAP-kinase***: Mitogen activated protein kinase

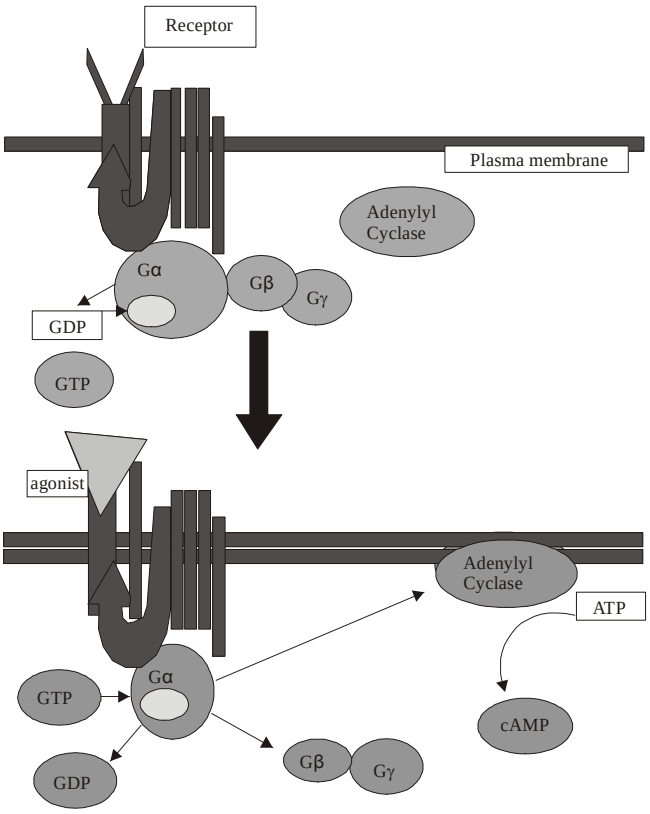

Fig.1: Activation of G proteins by agonists results in the use of GTP to release GDP and AC phosphorylating ATP to yield cAMP

site on the mRNA, where GTP-GDP exchange takes place. The elongation factor G is involved in the translocation of tRNA from the aminoacyl site to the peptidyl site on the ribosome which also involves GTP hydrolysis (Siegel *et al*., 1999). The clocks are the heterotrimeric G proteins present within the cytoplasm and are linked with GPCRs in the cell membrane. The present paper reviews the roles of G protein in health and disease.

Heterotrimeric G proteins: The heterotrimeric G proteins is important in signal transduction and are located at the cytoplasmic face of the plasma membrane, where they interact with the membrane-spanning GPCRs and effector molecules (Siegel *et al*., 2006). The G protein heterotrimers consist of Gα, Gβ and Gγ subunits. Lipid modification of Gα and Gγ subunits help to anchor the G protein heterotrimer to the plasma membrane (Cabrera-Vera *et al*., 2003). The Gα subunits bind guanine nucleotides with high affinity and contain an intrinsic GTPase activity (Siegel *et al*., 1999). The ability of Gα subunits to bind guanine nucleotides arises from their homology with other members of the GTP binding protein super family, including small proteins such as p21, Ras, Rab, ran, Ral, rac, Rho, and EF-Tu (Siegel *et al*., 1999; Cabrera-Vera *et al*., 2003; Fromm *et al*., 1997; Oldham and Hamm, 2006). The Gβ and Gγ subunits form a very tight, non covalent heterodimer and function as a single unit (the Gβγ complex) throughout the G protein signalling cycle (Dolphin,1996). Each heterotrimeric G protein has been shown to have different subunits and the combination of these subunits define the specific role of each G protein, however not all combinations are functional (Siegel *et al*., 1999) (Fig. 1).

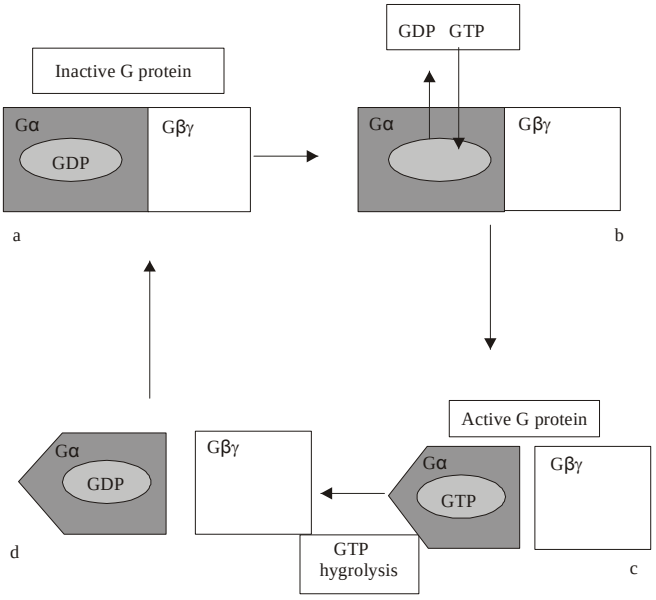

Fig. 2: G protein cycles between active and inactive states involving
a) Gα binds to guanosine diphosphate (GDP) in inactive state
b) Stimulation of the receptor by the agonist, leads to the release of the GDP, of which the GTP then binds to the empty site because its concentration is higher than the GDP
c) The dissociation of βγ subunits due to low affinity of GTP-bound Gα
d) GTP is hydrolysed to GDP due to GTPase activity of Gα

The G protein α subunit contains a binding site for a guanine nucleotide, which allows the binding of GDP in its non-activated state (Siegel *et al*., 2006, Walter *et al*., 2003). The G protein activation results in the exchange of GDP for GTP on the Gα subunit. When the Gα subunit is activated, it facilitates its dissociation from the Gβ and γ subunits (Dolphin 1996; Durchánková *et al*., 2008). These activated Gα subunits then regulate the activity of effector enzymes such as phospholipase C, phospholipase A_2, and ion channels like K^+ or Ca^2 (Flavahan and Vanhoutte, 1990; Durchánková *et al*., 2008). Although the Gα subunit interacts with different effector domains according to each G protein, the Gβ and Gγ subunits appear to be interchangeable (Siegel *et al*., 1999). Other G proteins have distinct Gβ and Gγ subunit differences and these subunits may play a role in signal production and transduction (Levitzki, 1990; Wang, 1999; Zhong, 2003; Walter *et al*., 2004). The dissociation of Gα subunit and the effector is regulated by the intrinsic GTPase activity of the Gα subunit (Sprang, 1997). G proteins may be activated many more times before desensitisation of the receptor and consequently the reassociation of the G protein components together (Levitzki, 1990; Siegel *et al*., 1999; Durchánková *et al*., 2008) (Fig. 2).

The different types of G protein contain distinct α subtypes, which in part, confer the specificity of their functional activity. The types of G protein α subunit are categorized based on their structural and functional homologies (Siegel *et al*.,1999; Sprang, 1997; Durchánková *et al*., 2008). The molecular weight (Mr) of these proteins varies between 38,000-52,000. Multiple subtypes of β and γ subunits include five β subunits of Mr 35,000-36,000 and seven γ subunits of Mr 6,000-9,000. These proteins show distinct cellular distributions and differences in their functional properties (Siegel *et al*., 2006; Morris and Malbon, 2000; Oldham and Hamm, 2006). Multiple forms of heterotrimeric G proteins have been shown to exist in the nervous system (Siegel *et al*., 1999; Oldham and Hamm, 2006). Three types of heterotrimeric G protein have been identified according to Siegel *et al*., (1999). $G_{t,}$ or transducin, was identified as the G protein that couples rhodopsin to regulate photoreceptor cell function, and G_s and G_i were identified as G proteins that couple plasma membrane receptors to the stimulation and inhibition of adenylyl cyclase, the enzyme that catalyzes the synthesis of cAMP (Siegel *et al*., 1999; Benians *et al*., 2005). Since the early 1990s, over 35 heterotrimeric G protein subunits have been identified by a combination of biochemical and molecular cloning techniques (Siegel *et al*., 2006; Mullaney, 1999; Oldham and Hamm, 2006; Dignard *et al*., 2008). In addition to G_t, G_s and G_i, the other types of G protein in the brain are designated as G_o, G_{olf}, G_{gust}, G_z, G_q and $G_{11\text{-}16}$. Moreover, for some of these G proteins, multiple subtypes show unique distributions

Table 2: Heterotrimeric G protein α-subunits in the brain

Family	Molecular weight (Mr)	Effector protein(s)
Gs		
G αs_1	52,000	Adenylyl cyclase (activation)
$G\alpha s_2$	52,000	
$G\alpha s_3$	45,000	
$G\alpha_4$	45,000	
Gαolf	45,000	
Gi		
$G\alpha i_1$	41,000	Adenylyl cyclase (inhibition)
$G\alpha i_2$	40,000	K^+ channel (activation)
$G\alpha i_3$	41,000	Ca^{2+} (inhibition)
	PI-Phospholipase C (activation)	
	Phospholipase A_2	
$G\alpha o_1$	39,000	K^+ channel (activation)
$G\alpha o_2$	39,000	Ca^{2+} channel (inhibition)
$G\alpha t_1$	39,000	Phosphodiesterase (Activation) in rods and cones.
$G\alpha t_2$	40,000	
Gαgust	41,000	Phosphodiesterase (activation) in taste epithelium
Gαz	41,000	Adenylyl cyclase (inhibition)
Gq	41,000-43,000	
Gαq		PI-Phospholipase C (activation)
$G\alpha_{11}$		
$G\alpha_{14}$		
$G\alpha_{15}$		
$G\alpha_{16}$		
G_{12}	44,000	Unknown
$G\alpha_{12}$		
$G\alpha_{13}$		

in the brain and peripheral tissues (Mullaney, 1999; Siegel *et al*., 2006; Neer, 1995; Kitanaka *et al*., 2008) (Table 2).

The Gα subunit: The Gα subunits are divided into four classes ($G\alpha_s$, $G\alpha_i$, $G\alpha_q$ and $G\alpha_{12}$), based on their amino acid sequences (Table 2). Each of these classes has at least two subtypes. The $G\alpha_s$ class includes subtypes $G\alpha_s$ and $G\alpha_{olf}$. $G\alpha_{olf}$ is located in chemosensory neurons only (Novotny and Svoboda, 1998; Kitanaka *et al*., 2008). $G\alpha_s$ stimulates Adenylate Cyclase (AC) 1-6, thereby increasing cAMP, leading to the phosphorylation and subsequent activation of Ca^{2+} channels (Dolphin, 1996). This G protein is also associated with the inactivation of cardiac Na^+ channels and may be directly coupled to intracellular Ca^{2+} channels (Novotny and Svoboda, 1998; Dolphin, 1996; Straiker *et al*., 2002). ADP-ribosylation of the $G\alpha_s$ subunit which is catalysed by cholera toxin, causes an increase in AC by slowing the 'off' phase of GTPase reaction (Levitzki, 1990; Oldham and Hamm, 2006).

Two variants of $G\alpha_s$ have been shown in both humans and animals- the short (~44kDa) and the long (~46kDa) (Milligan *et al*., 1999; Oldham and Hamm, 2006). The majority of $G\alpha_s$ variants located in the kidney, placenta, cortex, cerebellum and adrenal medulla are $G\alpha_{s\text{-}L}$, however $G\alpha_{s\text{-}S}$ predominates in the heart, liver, neostriatum and platelets (Novotny and Svoboda, 1998). Both variants of these G proteins are functionally similar, however a measurable difference in the rate of GDP dissociation is observed. $G\alpha_{s\text{-}S}$ may have a higher efficacy

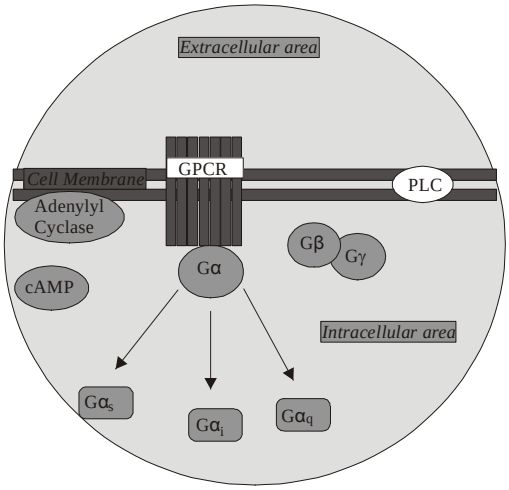

Fig. 3: The G protein alpha subunits activation through G protein coupled receptors present on the cell membrane

in stimulating AC in some cells and the cellular distribution of the two variants also varies (Novotny and Svoboda, 1998; Durchánková *et al*., 2008). $G\alpha_i$ class includes $G\alpha_i$, $G\alpha_t$, $G\alpha_o$ $G\alpha_{gust}$ and $G\alpha_z$. $G\alpha_i$ inhibits AC, decreases cAMP and activates K^+ channels. The $G\alpha_o$ with molecular weight of 39kDa, inhibits Ca^{2+} channels, is present in brain tissues and is believed to be involved in neuronal responses (Milligan *et al*., 1990, Kaziro *et al*., 1991; Hepler and Gilman, 1992; Durchánková *et al*., 2008). The $G\alpha_q$ activation stimulates

PLC-β leading to increased Ca^{2+} and subsequent activation of PKC which respectively activates AC1 and AC2 leading to increased cAMP production and finally the activation of PKA (Dolphin, 1996; Murray and Shewan, 2008) (Fig. 3).

The Gβγ dimer: The tightly bound Gβγ dimer has been shown to regulate many effectors and may be involved in GPCR kinase recruitment and hence involved in the activation of second messengers (Hamm and Gilchrist, 1996; Dignard *et al*., 2008). The Gβ subunit is approximately 36kDa and comprises subtypes that are highly homologous. The Gγ subtypes about 6-9kDa are more divergent and are thought to account for the functional differences in Gβγ (Hamm and Gilchrist, 1996). The Gβγ dimer has been demonstrated to have several roles in signal transduction. The Gβγ subunits are membrane associated, due to the isoprenylation of the Gγ subunit, which is also necessary for the effective interaction of Gβγ with Gα (Muller and Lohse, 1995).

When GTP is bound to the Gα subunit, the heterotrimeric complex becomes activated and the subsequent dissociation of Gα from Gβγ allows the Gβγ subunit to interact with effectors. Although little is known about the specific sites on the Gβ or Gγ subunit that interact with effector systems, it is now known that Gβγ dimer is important in effector activation (Hamm and Gilchrist, 1996; Blackmer *et al*., 2001). Some forms of AC such as 1, 2 and 4 are stimulated or inhibited by interactions with Gβγ (Muller and Lohse, 1995). These subunits can also influence GRK transportation to the cell membrane, K^+ channel opening frequency and other effectors such as phospholipase A_2 (PLA_2). The Gβγ is also involved in the inhibition of unidentified Ca^{2+} currents, possibly by facilitating alterations in the closed state of the ion channel, making the ion channel less willing to open (Clapham, 1996; Blackmer *et al*., 2001).

The function of G protein βγ subunits: It has been demonstrated that one group of protein kinase, the G protein receptor kinases (GRKs), can bind to βγ subunits. These kinases phosphorylate G protein-coupled receptors that are occupied by ligand and thereby mediate one form of receptor desensitization (Siegel *et al*., 2006). It is now known that βγ play a very important role in receptor desensitisation and the GRK is normally a cytoplasmic protein that does not come in appreciable contact with the plasma membrane receptor under basal conditions (Siegel *et al*., 2006). Ligand binding to the receptor activates the associated G protein, which results in the generation of free α and βγ subunits. The βγ subunits, which remain membrane-bound, are now free to bind to the C-terminal domain of GRK. This draws the GRK into close physical proximity with the receptor and enables receptor phosphorylation. In this way, the βγ subunits target GRKs, which have constitutive catalytic activity to those receptors that are ligand-bound (Hamm and Gilchrist, 1996; Siegel *et al*., 2006; Dignard *et al*., 2008).

Another important role of βγ subunits is the regulation of the mitogen-activated protein kinase (MAP-kinase) pathway (Siegel *et al*., 1999). MAP-kinases are the major effector pathway for growth factor receptors however, signals that act through GPCRs, particularly those coupled to G_i, can modulate growth factor activation of MAP-kinase pathway. This is mediated via βγ subunits (Siegel *et al*., 2006). Activation of receptors leads to the generation of free βγ subunits which then activate the MAP-kinase pathway at some early step in the cascade (Siegel *et al*., 2006). Some possibilities are by direct action of the βγ subunits on Ras or on one of several linker proteins between the growth factor receptor itself and activation of Ras (Hamm and Gilchrist, 1996; Siegel *et al*., 2006; Dignard *et al*., 2008).

Modulation of heterotrimeric G proteins: The functioning of heterotrimeric G proteins is modulated by several other proteins. One major class of modulator protein binds to G protein α subunits and stimulates their intrinsic GTPase activity. These are called GTPase-activating proteins (GAPs). The GAPs had been known to exist for small G proteins but have been identified for heterotrimeric G proteins (Siegel *et al*., 1999). The GAPs have been termed regulators of G protein-signalling (RGS) proteins. It has been shown that activation of α subunit, GTPase activity hastens the hydrolysis of GTP to GDP, more rapidly restores the inactive heterotrimer and, hence, the RGS proteins inhibit the biological activity of G proteins (Siegel *et al*., 1999). Nunn *et al*. (2006) and Siegel *et al*. (2006) have shown that some 20 forms of mammalian RGS protein are now known and most are expressed in the brain with highly region-specific patterns. It is also thought that different families of G protein α subunits are likely to be modulated by different forms of RGS protein (Siegel *et al*., 2006; Nunn *et al*., 2006).

Another protein modulator of G protein function is phosducin, a cytosolic protein enriched in the retina and pineal gland but also expressed in the brain and other tissues of humans and other mammals (Danner and Lohse, 1996; Schröder and Lohse, 1996). Phosducin binds to G protein βγ subunits with high affinity and this results in the prevention of βγ subunit reassociation with the α subunit. In this way, phosducin may sequester βγ subunits which initially may prolong the biological activity of the α subunit (Hamm and Gilchrist, 1996), which eventually may inhibit G protein activity by preventing the direct biological effects of the βγ subunits as well as regeneration of the functional G protein heterotrimer (Siegel *et al*., 2006).

Jiang *et al*. (1998), have shown that G_o is the most abundant G protein in neurons, where it constitutes up to 2% of membrane protein, and is also expressed in endocrine cells and the heart. Jiang *et al*. (1998), showed that G_o is activated not only by the same class of seven-transmembrane receptors that activate the inhibitory G proteins, but also by at least two proteins that do not belong to the rhodopsin-like family of G protein-coupled receptors and the Alzheimer amyloid protein precursor protein responsible for familial forms of the disease.

All G protein α subunits have been shown to be modified in their N-terminal domains by palmitoylation or myristoylation (Dohlman and Thorner, 1997). These modifications may regulate the affinity of the α subunit for its βγ subunits and, thereby the likelihood of dissociation or reassociation of the heterotrimer. The modifications also may help determine whether the α subunit, released upon ligand-receptor interaction, remains associated with the plasma membrane or diffuses into the cytoplasm. This could have important consequences on the types of effector proteins regulated. G protein γ subunits are modified on their C- terminal cysteine residues by isoprenylation (Jiang *et al*., 1998). There is evidence that this modification plays a key role in anchoring the γ subunit and its associated β subunit to the plasma membrane (Cabrera-Vera *et al*., 2003; Slessareva *et al*., 2003). The importance of this anchoring shows the ability of βγ- subunits to target GRKs to ligand-bound receptors depends on this membrane localization (Siegel *et al*., 1999; Cabrera-Vera *et al*., 2003).

G protein and ion channels: Many G proteins are linked to fluctuations in intracellular ion concentrations, which is due to both direct activation of ion channels by G proteins and indirect second messenger-mediated responses (Berridge *et al*., 2003; Lowes *et al*., 2002). AC is stimulated by the activation of G_s which results in the elevation of intracellular cAMP levels. This increase in cAMP can directly open Ca^{2+} channels or, alternatively, can activate Ca^{2+} and K^+ channels via cAMP-dependent phosphorylation of the channel. Protein kinase C (PKC) is involved in the phosphorylation of several Ca^{2+} channels in various cell populations including neurons. PKC is also involved in the inhibition of other ion currents including K^+, Ca^{2+}-dependent K^+, and Na^+ channels. Other second messenger components also influence ion channel activation and inhibition including phospholipase A_2 (PLA_2) and intracellular Ca^{2+} levels (Berridge *et al*., 2003; Berridge, 2006; Burgoyne, 2007). G proteins are involved in direct activation and inhibition of several ion channels. The stimulation of Ca^{2+} current has been associated with the direct interaction with G proteins and similarly the receptor-mediated inhibition of Ca^{2+} channels is also linked to G proteins (Dolphin, 1990; Berridge *et al*., 2003, Walter *et al*., 2003). G proteins couple some neurotransmitter receptors directly to ion channels and one of the best examples of this mechanism in the brain is the coupling of many types of receptors including μ-opioid, α_2-adrenergic, D_2-dopaminergic, muscarinic cholinergic, 5HT1a-serotonergic and $GABA_B$ receptors, to the activation of an inward rectifying K^+ channel (GIRK) via pertussis toxin-sensitive mechanisms (Wickman and Clapham, 1995: Schneider *et al*., 1997). It has been shown that binding of the G protein subunits to the Ca^{2+} channels, reduces their probability of opening in response to membrane depolarization. This mechanism is best seen in L-type Ca^{2+} channels, which are inhibited by the dihydropyridine antihypertensive drugs such as verapamil but may also operate for other types of voltage-gated Ca^{2+} channel (Berridge *et al*., 2003). Another example of direct regulation of ion channels by G proteins is the stimulation L-type Ca^{2+} channels by G_s. In this case, free α subunits appear to bind to the channel and increase their probability of opening in response to membrane depolarization (Wickman and Clapham, 1995; Berridge *et al*., 2003).

G proteins and MAPK: Several G protein-coupled receptors are capable of activating the MAPK pathway (Luttrell *et al*., 1997; Lowes *et al*., 2002). Research has shown the involvement of a ras-dependent mechanism and MAPK was found to induce mitogenesis in cultured fibroblasts after stimulation of GPCRs by naturally occurring phospholipids (Howe and Marshall, 1993). MAPKs are localised in both the cytoplasm and nucleus and are suspected to be involved in the phosphorylation of nuclear transcription factors which regulate gene transcription (Luttrell *et al*., 1997). Activation of PKC and phospholipase C beta (PLCβ) has also been linked to MAPK activation (Kolch *et al*., 1993). Thus, G proteins are linked to pathways that influence not only membrane conductance but also cell proliferation and growth, implicating a possible role of G proteins in disease pathology (Luttrell *et al*., 1997; Berridge, 2006; Cabrera-Vera, *et al*., 2003).

CONCLUSION

G Protein-mediated signal transduction is important in the regulation of a cell's morphological and physiological response to external factors (Wettschureck and Offermanns, 2005; Ohkubo and Nakahata, 2007). G proteins have been demonstrated to be involved in disease pathology through several mechanisms (Ohkubo and Nakahata, 2007). Among them are the exotoxins such as cholera or pertussis toxins which interfere with the G protein activity. Other disease pathologies associated with abnormal mutations in G proteins can interfere with signal transduction pathways and disease pathogenesis may also

involve signal transmission that is either excessive, by augmentation of G protein function, or insufficient, via inactivation of G proteins (Wettschureck and Offermanns, 2005).

Specific mutations may affect the ability of a G protein to hydrolyze GTP which may interfere with signal initiation, transmission and termination (Ohkubo and Nakahata, 2007). Other mutations alter levels of a specific G protein or produce unstable G proteins, leading to changes in the response to a stimulus. Mutations may also alter the rate of GDP release and GTP binding, resulting in modifications to downstream signalling (Farfel *et al*., 1999; Xie and Palmer, 2007).

It has been shown that the regulators of G protein signalling (RGS) proteins may play a role in disease pathology, since the RGS proteins have been found to reduce termination times by accelerating GTP hydrolysis, and are important in mediating slowing of heart rate, photon detection in the retina and the contraction of smooth muscle cells (Berman and Gilman, 1998). Mutations of these RGS proteins may play a role in prolonged stimulation of effectors associated with these proteins (Farfel *et al*., 1999; Lorenz *et al*., 2007).

Genetic variations and defects can also cause the inactivation of G proteins. Pseudohypoparathyroidism type 1 is caused by the null response of cells to parathyroid hormone and other hormones that are mediated by G_s. This may be due to either decreased levels of the active $G\alpha_s$ subunit or the production of inactive $G\alpha_s$ subunits (Farfel *et al*., 1999). Pseudohypoparathyroidism type 1b may also be caused by a genetic defect in $G\alpha_s$ (Farfel *et al*., 1999: Lorenz *et al*., 2007).

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