Molecular Mechanisms for Heterologous Sensitization of Adenylate Cyclase

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ABSTRACT

The nine membrane-bound isoforms of the enzyme adenylate cyclase (EC 4.6.1.1) are highly regulated by neurotransmitters and drugs acting through G protein-coupled receptors to modulate intracellular cAMP levels. In general, acute activation of G\textsubscript{i/o}-coupled receptors stimulates cAMP accumulation, whereas acute activation of G\textsubscript{q/11}-coupled receptors typically inhibits cAMP accumulation. It is also well established that persistent activation of G-protein coupled receptors will alter subsequent drug-modulated cAMP accumulation. These alterations are thought to represent cellular adaptive responses following prolonged receptor activation. One phenomenon commonly observed, heterologous sensitization of adenylate cyclase, is characterized by an enhanced responsiveness to drug-stimulated cAMP accumulation following persistent activation of G\textsubscript{q/11}-coupled receptors. Heterologous sensitization of adenylate cyclase was originally proposed to explain tolerance and withdrawal following chronic opiate administration and may be a mechanism by which cells adapt to prolonged activation of inhibitory receptors. Such an adaptive mechanism has been suggested to play a role in the processes of addiction to and withdrawal from many drugs of abuse and in psychiatric disorders including schizophrenia and depression. Although the precise mechanisms remain unknown, research over the last decade has led to advances toward understanding the molecular events associated with heterologous sensitization of recombinant and endogenous adenylate cyclases in cellular models. These events include the pertussis toxin-sensitive events that are associated with the development of heterologous sensitization and the more recently identified G\textsubscript{q/11}-dependent events that are involved in the expression of heterologous sensitization.

Historical Perspective

Acute activation of G\textsubscript{q/11}-coupled receptors inhibits cAMP accumulation, whereas prolonged activation enhances drug-stimulated cAMP accumulation. This enhanced responsiveness was first observed following persistent activation of the \(\mu\)-opioid receptor in the laboratory of Dr. Marshall Nirenberg (National Institute of Mental Health, Bethesda, MD), who proposed that the increased responsiveness was a mechanism of opiate tolerance and dependence (Sharma et al., 1975). This phenomenon has since been described using many different names, including cAMP overshoot, supersensitivity, superactivation, supersensitization, and heterologous sensitization of adenylate cyclase (EC 4.6.1.1).

ABBREVIATIONS: AC, adenylate cyclase; PKA, cAMP dependent protein kinase A.
precise role of cAMP inhibition is unknown (Thomas and Hoffman, 1987).

Although the general characteristics of heterologous sensitization proposed by Thomas and Hoffman (1987) are consistent with more recent studies of Gας, coupled receptors, a number of advances have provided additional information regarding the molecular mechanisms of heterologous sensitization using a variety of cellular models. The cloning and biochemical characterization of the nine membrane-bound adenylate cyclase isoforms has revealed that different isoforms have distinct regulatory properties (Taussig and Zimmerman, 1998). Several research groups have sought to exploit the differences among isoforms to identify mechanisms of heterologous sensitization, and the results of their studies suggest that sensitization is isoform-dependent so that the characteristics of heterologous sensitization in a given cell depend on the complement of adenylate cyclase isoforms present in the cell (Thomas and Hoffman, 1996; Watts and Neve, 1996; Avidor-Reiss et al., 1997; Cumbay and Watts, 2001). In the present article, the mechanisms of heterologous sensitization in neuronal and non-neuronal cultured cells will be discussed as they relate to the early (development) and the late (expression) events associated with heterologous sensitization (Fig. 1). The development of heterologous sensitization will refer to events that are more closely associated with the persistent stimulation of the Gας, coupled receptor (e.g., activation of Gας, proteins). The expression of heterologous sensitization will refer to events that influence cAMP accumulation in response to Gας, coupled receptor agonists, forskolin (a direct activator of adenylate cyclase), or selective activators of adenylate cyclase isoforms (Cumbay and Watts, 2001). Studies over the last 15 years have focused on the mechanisms involved in the development of heterologous sensitization, and more recent studies have identified potential mechanisms specifically involved in the expression of heterologous sensitization. Although the present article will often focus on heterologous sensitization following persistent stimulation of the D2 dopamine receptor (Fig. 2), it is likely that the mechanisms associated with one Gας, coupled receptor are similar to those associated with other Gας, coupled receptors, including μ-opioid, CB1 cannabinoid, α2 adrenergic, M2 and M4 muscarinic, A3 adenosine, and 5-hydroxytryptamine1A serotonin receptors (Avidor-Reiss et al., 1995; Hensler et al., 1996; Thomas and Hoffman, 1996; Palmer et al., 1997; Nevo et al., 1998; Rhee et al., 2000).

**G Protein α Subunit Specificity for Heterologous Sensitization**

Pertussis toxin treatment prevents heterologous sensitization of both endogenous and recombinant adenylate cyclases in several cellular models (Watts and Neve, 1996; Palmer et al., 1997; Watts et al., 1998, 1999; Rhee et al., 2000; Rubenzik et al., 2001). Because pertussis toxin prevents receptor coupling to Gα11, Gα12, Gα13, and Gαs in a nondiscriminating fashion, one important question is which pertussis toxin-sensitive G protein is responsible for heterologous sensitization. This question has been investigated for D2L dopamine receptors and several of the opioid receptors (Watts et al., 1998, 1999; Tso and Wong, 2000; Tso and Wong, 2001). The D2L dopamine receptor study used viral-mediated gene delivery of individual genetically engineered pertussis toxin-resistant G proteins (Gαs*) to determine the G protein specificity for heterologous sensitization in NS20Y neuroblastoma cells (Watts et al., 1998). These experiments examined the ability of individual recombinant α subunits Gαs* to rescue heterologous sensitization in pertussis toxin-treated cells. Selective activation of Gαs* by D2L receptors was found to be responsible for heterologous sensitization of forskolin-stimulated cAMP accumulation in NS20Y-D2L cells. In contrast, expression of mutant Gα11*, Gα12*, and Gα13* subunits did not rescue heterologous sensitization in pertussis toxin-treated cells. Similar studies in pertussis toxin-treated human embryonic kidney-D2L cells revealed that heterologous
sensitization is rescued by the expression of either Goα1* or Goα3* (B. L. Wiens, V. J. Watts, and K. A. Neve, unpublished results). The abundant expression of Goα in the central nervous system and recent studies demonstrating that D2 dopamine receptors couple efficiently to Goα in native brain tissue suggest an important role for Goα in heterologous sensitization (Jiang et al., 2001).

Heterologous sensitization may also involve the simultaneous activation of multiple Goα proteins. For example, the magnitude of selective Goα*-induced heterologous sensitization seems to be reduced when compared with sensitization in cells where the entire endogenous Goα pool was available (Watts et al., 1998). In fact, a role for multiple Goα subunits has been proposed for opioid-induced heterologous sensitization because the expression of Goα1* only partially rescues δ-opioid receptor-induced sensitization, whereas expression of Goα3* or a pertussis toxin-insensitive Goα2*/α3* chimera has no effect (Tso and Wong, 2000, 2001). Furthermore, the expression of Goα1*, Goα3*, or a pertussis toxin-insensitive Goα2*/α3* fails to rescue μ- or κ-opioid receptor-induced sensitization (Tso and Wong, 2000, 2001). Although the importance of Goα in opioid receptor-induced heterologous sensitization has not been examined, these results would be consistent with the contribution of multiple Goα subunits to sensitization. In addition, it is also possible that the specificity among Goα subtypes for heterologous sensitization is governed by receptor/G protein coupling. In other words, all pertussis toxin-sensitive G proteins may have the ability to induce heterologous sensitization if activated sufficiently by a receptor.

**G Protein α Subunit Expression and Heterologous Sensitization**

It has been proposed that persistent activation of Goα10 induces heterologous sensitization through changes in the abundance of Goα and Goαo. In some studies, chronic activation of Goα10-coupled receptors results in reduced levels of Goαo or increased levels of Goα (Haddock and Malbon, 1993; Watts et al., 1999), either of which would be predicted to enhance subsequent adenylate cyclase activity. In contrast, other studies have demonstrated that alterations in the abundance of Goα or Goαo are not required for heterologous sensitization of adenylate cyclase (Palmer et al., 1997; Watts et al., 1999; Bayewitch et al., 2000). The ability of agonist treatment to induce changes in Goαo or Goα levels seems to be dependent on the cellular model or cell line under investigation. Furthermore, the magnitude of and time course for changes in Goαo or Goα do not seem to correlate directly with measures of heterologous sensitization. For example, heterologous sensitization can be observed within 15 min of agonist treatment (Thomas and Hoffman, 1996; Watts and Neve, 1996; Jones et al., 1987), and robust sensitization is commonly observed following 2 to 4 h of drug treatment (Avidor-Reiss et al., 1995; Watts and Neve, 1996; Palmer et al., 1997; Nevo et al., 1998; Cumbay and Watts, 2001; Watts et al., 2001). In contrast, agonist-induced changes in Goα levels, which probably involve changes in gene expression, typically require long-term receptor activation (Haddock and Malbon, 1993; Watts et al., 1999). Together, these observations suggest that, although agonist-induced changes in Goαo or Goα levels are not required for the development of heterologous sensitization, they may influence the magnitude or expression of heterologous sensitization.

It is also possible that heterologous sensitization could involve a change in the localization of G proteins, as opposed to a change in overall protein levels. For example, persistent agonist treatment of μ-opioid receptors decreases the detergent solubility (and presumably lipid microdomain localization) of Goα and the β1 subunit (Bayewitch et al., 2000). These changes occur rapidly (<4 h) and correlate with agonist-induced heterologous sensitization of adenylate cyclase. Similar agonist-induced changes in the detergent solubility of Goα and β1 were also observed in cells expressing κ-opioid and M₄ muscarinic receptors. Additional studies are necessary to determine the precise role that these changes play in both the development and expression of heterologous sensitization.

**G Protein βγ Subunits and Heterologous Sensitization**

The activation of Goα10-coupled receptors results in the dissociation of activated Go and βγ subunits. The released βγ subunits directly modulate a number of cellular effectors, including several isoforms of adenylate cyclase (Bayewitch et al., 1998; Taussig and Zimmerman, 1998). That both the release of βγ subunits and heterologous sensitization occur in a pertussis toxin-sensitive manner may suggest a potential relationship. More direct evidence to support a role for βγ subunits in heterologous sensitization was obtained using recombinant proteins capable of binding βγ subunits, such as the C-terminus of GRK2 (pARK-Ct) or Goa, (Avidor-Reiss et al., 1996; Thomas and Hoffman, 1996). This approach is based on the tenet that overexpression of a βγ-binding protein prevents downstream βγ subunit signaling by scavenging free βγ subunits. Expression of these βγ subunit scavenger attenuates or prevents the development of heterologous sensitization following the activation of μ-opioid, CB₁ cannabinoid, and D₂ dopamine receptors in cultured cell systems (Avidor-Reiss et al., 1996; Thomas and Hoffman, 1996; Rhee et al., 2000; Rubenzik et al., 2001).

The simplest explanation for these results is that prolonged activation of Goα10 liberates βγ subunits that directly activate and sensitize adenylate cyclase. However, this mechanism is unlikely for several reasons. First, the persistence of the sensitized response following removal of the Goα10-coupled receptor agonist (≥1 h) is inconsistent with a transient increase in free βγ subunits (Watts and Neve, 1996). Second, adenylate cyclase isoforms capable of undergoing heterologous sensitization (Table 1) show markedly different patterns of regulation by βγ subunits (Watts and Neve, 1996). This approach is based on the tenet that overexpression of a βγ-binding protein prevents downstream βγ subunit signaling by scavenging free βγ subunits. Expression of these βγ subunit scavenger attenuates or prevents the development of heterologous sensitization following the activation of μ-opioid, CB₁ cannabinoid, and D₂ dopamine receptors in cultured cell systems (Avidor-Reiss et al., 1996; Thomas and Hoffman, 1996; Rhee et al., 2000; Rubenzik et al., 2001).
drug-stimulated activity of AC5 but prevents the development of agonist-induced sensitization of both AC5 and AC6 (Avidor-Reiss et al., 1996; Thomas and Hoffman, 1996; Bayewitch et al., 1998; Rhee et al., 2000; Rubenzik et al., 2000). These observations suggest that the effects of βγ subunits on the expression of heterologous sensitization are complex and may be isoform-dependent. Nevertheless, the data demonstrating that both βγ subunit scavengers and pertussis toxin treatment prevent heterologous sensitization provide evidence of an important role for the liberation of βγ subunits in the development of sensitization.

**Role of cAMP Accumulation and PKA in Heterologous Sensitization**

Although acute activation of Gαo-coupled receptors can modulate a number of signaling pathways, inhibition of drug-stimulated cAMP accumulation is often considered the defining physiological response. Inhibition of cAMP formation decreases PKA activity and inhibits subsequent PKA-mediated phosphorylation events. The role of PKA inhibition in Gαo-coupled receptor-induced sensitization has been addressed by manipulating both intracellular cAMP levels and PKA activity, with results suggesting that inhibition of cAMP and PKA is not generally required for heterologous sensitization (Thomas and Hoffman, 1992; Avidor-Reiss et al., 1995; Watts and Neve, 1996; Watts et al., 1999; Johnston et al., 2001). In contrast, a role for PKA in heterologous sensitization was observed in one study in which somatostatin treatment induced sensitization in wild-type S49 cells but not in the PKA-deficient kin− S49 cells (Thomas and Hoffman, 1989).

Another study showed that PKA activators prevent A1 adenosine receptor-induced heterologous sensitization in DDT1-MF-2 cells (Port et al., 1992). Results from recent studies in our laboratory demonstrated that chronic inhibition of PKA induced heterologous sensitization in a novel neuronal cell line, Cath.a. differentiated (CAD)-D21 cells, and that activators of PKA attenuated sensitization (Johnston et al., 2002). Thus, although inhibition of cAMP and PKA is not generally required for the development or expression of heterologous sensitization, inhibition of PKA may contribute to the development of sensitization in select cellular models.

**Adenylylate Cyclase Isoform Specificity and Heterologous Sensitization**

A number of studies have provided evidence that agonist-induced sensitization is influenced by the complement of endogenous or recombinant adenylylate cyclase isoforms present within the cell (Thomas and Hoffman, 1996; Watts and Neve, 1996; Avidor-Reiss et al., 1997; Rhee et al., 2000; Cumbay and Watts, 2001). The basic features associated with heterologous sensitization of the recombinant isoforms of adenylylate cyclase parallel those characteristics described for studies of the endogenous isoforms of adenylylate cyclase. In addition, a few distinct patterns have been observed for the recombinant adenylylate cycrases (Table 1). For example, both of the Ca2+-inhibited isoforms of adenylylate cyclase, AC5 and AC6, show a marked degree of heterologous sensitization to Gαo- and forskolin-stimulated cAMP accumulation (Thom- as and Hoffman, 1996; Avidor-Reiss et al., 1997; Nevo et al., 1998, 2000; Rhee et al., 2000; Cumbay and Watts, 2001;
Persistent agonist treatment also causes sensitization of Ca\(^{2+}\)-stimulated AC1 and AC8 activity (Avidor-Reiss et al., 1997; Nevo et al., 1998; Cumbay and Watts, 2001). In contrast to AC1 and AC8, the remaining Ca\(^{2+}\)-stimulated isoform AC3 does not show robust sensitization to calcium ionophores or G\(_{\alpha_i}\) (Avidor-Reiss et al., 1997; Nevo et al., 1998), although sensitization to forskolin has been reported (Rhee et al., 2000). AC2, AC4, and AC7, which are conditionally activated by \(\beta\gamma\) subunits, show a unique pattern of heterologous sensitization. Specifically, it was observed that these isoforms of adenylate cyclase either show no sensitization or have a reduced responsiveness to G\(_{\alpha_i}\)-stimulated cAMP accumulation following agonist treatment (Thomas and Hoffman, 1996; Avidor-Reiss et al., 1997; Nevo et al., 1998; Nevo et al., 2000; Rhee et al., 2000; Cumbay and Watts, 2001). In contrast, protein kinase C-stimulated AC2 activity is robustly sensitized by persistent activation of D\(_2\) dopamine receptors (Watts and Neve, 1996; Cumbay and Watts, 2001). At present, the reasons for the small disparities between laboratories are unclear but may be due to differences in the G\(_{\alpha_{i0}}\)-coupled receptors, the cell type, transfection methodology (stable versus transient), the method used to assess adenylate cyclase activity, or other variations in laboratory procedures (Table 1). Although the preponderance of evidence indicates that most isoforms are capable of undergoing sensitization, that each isoform (or family of isoforms) shows distinctive patterns of G\(_{\alpha_i}\) activation in the presence of other adenylate cyclase regulators is an important factor in the observed cAMP response (Harry et al., 1997; Taussig and Zimmerman, 1998). Moreover, the response to G\(_{\alpha_i}\) and the unique regulatory properties of each isoform are likely to influence the expression, but not the development, of heterologous sensitization of each adenylate cyclase isoform following persistent G\(_{\alpha_{i0}}\)-coupled receptor activation.

### Role of G\(_{\alpha_i}\) in Heterologous Sensitization

In spite of their differential regulation, all isoforms of adenylate cyclase are activated by G\(_{\alpha_i}\) (Tausig and Zimmerman, 1998), and several observations support the hypothesis that the mechanisms underlying heterologous sensitization involve enhanced G\(_{\alpha_i}\) activity or enhanced G\(_{\alpha_i}/\alpha_{i0}\)/adenylate cyclase interactions. Jones and Bylund (1990) demonstrated that sensitization of adenylate cyclase is associated with an increase in [\(^{3}H\)]forskolin binding that may represent the formation of G\(_{\alpha_i}\)-adenylate cyclase complexes. Studies in C6 gloma cells expressing the D\(_{2}\) dopamine receptor revealed that agonist treatment increases the potency of forskolin and enhances the maximal responsiveness of adenylate cyclase to the \(\beta\)-adrenergic receptor agonist isoproterenol, consistent with the effects of increased G\(_{\alpha_i}\) activity on adenylate cyclase (Watts and Neve, 1996). Furthermore, isoforms of adenylate cyclase that are activated synergistically by G\(_{\alpha_i}\) together with isoform-selective activators (i.e., AC1, Ca\(^{2+}\); AC2, phorbol esters; AC5, 100 nM forskolin) also show a marked degree of short-term (2 h) sensitization (Watts and Neve, 1996; Tausig and Zimmerman, 1998; Cumbay and Watts, 2001; Watts et al., 2001). These findings suggest that AC1, AC2, and AC5 may share an overlapping mechanism of heterologous sensitization that seems to be dependent upon a synergistic response to selective activators and G\(_{\alpha_i}\). Although these observations provide important evidence that G\(_{\alpha_i}\) is involved in heterologous sensitization of adenylate cyclase, the precise role for G\(_{\alpha_i}\) is unknown.

Confirmation of a direct role for G\(_{\alpha_i}\) in heterologous sensitization is a difficult task because biochemical and molecular reagents specifically inhibiting G\(_{\alpha_i}\) function are not readily available. In light of such limitations, a novel approach to examine the role of G\(_{\alpha_i}\) in heterologous sensitization has recently been developed (Watts et al., 2001). We hypothesized that if G\(_{\alpha_i}\) is required for expression of sensitization, mutants of adenylate cyclase that are not activated by G\(_{\alpha_i}\) should not be sensitized following G\(_{\alpha_{i0}}\)-receptor activation. This hypothesis was tested using viral-mediated gene delivery of G\(_{\alpha_i}\)-insensitive mutants of AC5 to examine D\(_{2}\) dopamine receptor-induced heterologous sensitization (Watts et al., 2001). We observed that persistent activation of the D\(_2\) dopamine receptor failed to sensitize each of the three G\(_{\alpha_i}\)-insensitive mutants of AC5, whereas, the wild-type AC5 showed a marked degree of heterologous sensitization. These results indicate that activation of adenylate cyclase by G\(_{\alpha_i}\) is required for the expression of heterologous sensitization of adenylate cyclase.

The mechanisms responsible for the altered activity of G\(_{\alpha_i}\) or an enhanced interaction between G\(_{\alpha_i}\) and adenylate cyclase that contribute to heterologous sensitization remain unclear. One possibility is that heterologous sensitization may involve a post-translational modification of G\(_{\alpha_i}\) that alters membrane localization. For example, morphine-induced heterologous sensitization has been associated with a reduction in the amount of palmitoylated G\(_{\alpha_i}\) and presumably membrane-associated G\(_{\alpha_i}\), which may, in turn, enhance the interaction of G\(_{\alpha_i}\) with adenylate cyclase (Ammer and Schulz, 1997). Enhanced interactions of G\(_{\alpha_i}\) and adenylate cyclase have been associated with an increase in the proportion of G\(_{\alpha_i}\) that can be extracted from the membranes with Triton X-100 and a decrease in the abundance of G\(_{\alpha_i}\) in caveolin-enriched domains (Toki et al., 1999; Miura et al., 2001). In contrast, colocalization of both G\(_{\alpha_i}\)-coupled receptors and AC6 to caveolin-enriched domains enhances coupling efficiency and drug-stimulated cAMP accumulation (Ostrom et al., 2001). Although a role for caveolae in heterologous sensitization has not been established, future studies should explore the effects of persistent activation of G\(_{\alpha_{i0}}\)-coupled receptors on the subcellular localization of G\(_{\alpha_i}\) and adenylate cyclases. The observations described above implicating a role for G\(_{\alpha_i}\) in heterologous sensitization in cellular models; however, recent studies have suggested that an additional stimulatory G protein, G\(_{\alpha_{i0}}\), is also an important regulator of adenylate cyclase activity (Corvol et al., 2001).

### Relevance of Heterologous Sensitization to Drug Abuse

It is well established that chronic administration of opiates and other drugs of abuse induces an up-regulation of the cAMP signaling pathway in several brain regions (Nestler, 2001). Although abused drugs have a variety of acute mechanisms of action, many of the drugs ultimately lead to persistent activation of G\(_{\alpha_{i0}}\)-coupled receptors. For example, morphine acts directly on G\(_{\alpha_{i0}}\)-coupled \(\mu\)-opioid receptors in the locus coeruleus, with chronic treatment leading to enhanced (sensitized) adenylate cyclase activity (Nestler,
Similarly, chronic cocaine treatment increases adenylate cyclase activity in the nucleus accumbens, presumably through its actions on dopamine release in the mesolimbic reward pathway, which would be expected to increase activation of D2-like dopamine receptors (Nestler and Aghajanian, 1997; Self et al., 1998). Such observations are consistent with the in vitro cellular models previously described and support the hypothesis that chronic activation of Gao/o-coupled receptors by abused drugs in vivo induces heterologous sensitization of adenylate cyclase. Furthermore, cellular models of heterologous sensitization indicate that Gao/o-coupled receptor desensitization or tolerance is not responsible for sensitization (Watts and Neve, 1996; Thomas and Hoffman, 1987). In support of in vitro models, Bohn et al. (2000) used a β-arrestin-2 knockout mouse model to demonstrate that opioid receptor desensitization and subsequent tolerance were not required for morphine-induced sensitization of adenylate cyclase. This study showed that β-arrestin-2-deficient (nondesensitizing) mice develop marked physical dependence, as measured by naloxone-precipitated withdrawal, but they did not develop tolerance to the antinociceptive effects of morphine. These findings are consistent with the hypothesized role of cAMP up-regulation in withdrawal following chronic drug abuse.

The mechanisms for the development and expression of heterologous sensitization following chronic treatment with drugs of abuse will vary across brain regions. For example, chronic morphine treatment increases adenylate cyclase activity in the locus coeruleus through an increase in the expression of AC1 and AC8 (Lane-Ladd et al., 1997). Chronic morphine treatment also increases the activity and expression of PKA in the locus coeruleus (Lane-Ladd et al., 1997). A consequence of drug removal would be that activation of the adenylate cyclase (AC1 and AC8) pathway would produce a dramatic increase in PKA-mediated signaling events when compared with drug naive animals. The effects of chronic opiate treatment on the cAMP-PKA pathway, however, would differ in brain areas with high expression of AC5, such as the nucleus accumbens, the ventral tegmental area, and the neostriatum (Lane-Ladd et al., 1997; Nestler and Aghajanian, 1997). Because AC5 is negatively regulated by PKA (Taussig and Zimmerman, 1998), a drug-induced increase in the expression of PKA would dampen the subsequent cAMP-PKA signaling in those particular brain regions. In addition to these examples, chronic opiate administration has also been shown to alter a number cellular signaling proteins that may directly and indirectly contribute to heterologous sensitization (Taylor and Fleming, 2001). These observations highlight the importance of identifying the components involved in heterologous sensitization in the elucidation of the molecular mechanisms in both in vitro and in vivo models.

Summary and Conclusions

Persistent activation of Gao/o-coupled receptors results in an enhanced response to drug-stimulated cAMP accumulation. This heterologous sensitization is a cellular adaptive response that occurs following the persistent activation of a number of Gao/o-coupled receptors including D2-like dopamine, M2 and M4 muscarinic, μ-, δ-, and κ-opioid, CB, cannabinoi, A1 and A3 adenosine, α2 adrenergic, 5-hydroxytryptamine1A serotonin, and somatostatin receptors. The characteristics of this enhanced responsiveness are dependent upon the cellular model used and may ultimately reflect the expression profile of adenylate cyclase isoforms and the agent used to stimulate cAMP accumulation.

The studies discussed in this article support the hypothesis that persistent activation of a Gao/o-coupled receptor promotes the dissociation of Gao and βγ subunits in a pertussis toxin-sensitive matter, which in turn, induces sensitization through a Gao-dependent mechanism (Fig. 2). The signaling events that follow the activation of the Gao/o subunits and the release of the βγ subunits are thought to produce an enhanced interaction between Gao and adenylate cyclase. These signaling events are still undefined but may lead to changes in the activity or the subcellular localization of Gao (Watts et al., 2001). In this model, the pertussis toxin-sensitive events contribute to the development of heterologous sensitization, whereas the Gao-dependent events that regulate the isoforms of adenylate cyclase contribute to the expression of heterologous sensitization. The last 15 years of research have provided additional insight into the mechanisms involved in heterologous sensitization; however, the specific signaling events leading to Gao-dependent heterologous sensitization remain to be elucidated.

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References


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