COMMENT

Pathophysiology of "Cholinoceptor Supersensitivity" in Affective Disorders

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Phenomenological and physiological variables demonstrate supersensitive changes to cholinergic challenge in affective disorder subjects. Theorists generally assume the primary defect is the postsynaptic muscarinic receptor. However, in addition to defectiveness or up-regulation of this receptor, the appearance of postsynaptic "cholinoceptor supersensitivity" can result from abnormal presynaptic mechanisms, membrane "pathology," derangement of intracystolic mechanisms that amplify effects of receptor–agonist coupling, or aberrant cholinergic–monoaminergic interaction. This article discusses abnormalities of the postsynaptic receptor, regulation of postsynaptic receptor density, the presynaptic muscarinic receptor, and other mechanisms regulating the release of acetylcholine, membrane dynamics, and "cascade" mechanisms—specifically the phosphatidylinositol (PI) cycle, Ca^{2+} mobilization, and cyclic guanosine monophosphate (GMP) generation—as causes of cholinergic system "supersensitivity." It is suggested that an approach to the topic emphasizing site of abnormality will encourage greater clarity of thought in the study of the cholinergic component of the pathophysiology of affective illness.

Introduction

Basic and clinical investigations suggest that cholinergic systems are involved in the pathophysiology of affective disorders, but the nature of cholinergic defects in these diseases is not known. Investigators generally imply that muscarinic receptor supersensitivity is a major factor. This article questions this implication. Evidence for an abnormality in cholinergic systems provides the context for discussion.

Drugs activating cholinergic systems produce depressive symptoms (Grob et al. 1947; Rowntree et al. 1950; Gershon and Shaw 1961; Bowers et al. 1964; Janowsky et al. 1972; El-Yousef et al. 1973; Janowsky et al. 1973a,b; Janowsky et al. 1980; Janowsky

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et al. 1982; Risch et al. 1981a,b,c) and neuroendocrine (Carroll et al. 1980; Risch et al. 1981a,b; 1983a,b; Risch 1982; Doerr and Berger 1983) and polysomnographic (Grob et al. 1947; Sitaram et al. 1976, 1977, 1980, 1982; Hill et al. 1979, 1980; Gillin et al. 1980; McCarley 1982) data typical of major depressive disorder (MDD), endogenous subtype (Spitzer et al. 1975). Systemically and centrally administered anticholinesterases and cholinomimetics cause decreased drive reduction behavior in humans and animals. These drugs may be useful in the development of models of hedonic function (Myers and Yaksh 1961; Grossman 1962; Stark and Boyd 1963; Carlton 1967; Domino and Olds 1968; Olds and Domino 1969; Avery 1971; Russell et al. 1971a,b; Overstreet et al. 1972). Affective disorder patients exhibit supersensitive changes in behavioral (Janowsky et al. 1980; Risch et al. 1981a,b), neuroendocrine (Risch 1982), and polysomnographic (Sitaram et al. 1979; Gillin et al. 1980; Sitaram et al. 1982) variables upon cholinergic challenge, relative to normal and psychiatrically ill control subjects. These data implicate central muscarinic system supersensitivity in some forms of affective illness (Sitaram et al. 1976; Hill et al. 1980; Janowsky et al. 1982, 1983; Risch 1982; Risch et al. 1983b).

Drugs directly blocking postsynaptic central muscarinic receptors have antidepressant effects and produce euphoria (Bolin 1960; Tislow 1970; McVicar 1977; Jellinek 1979; Kasper et al. 1981; Kaminer et al. 1982; Crawshaw and Mullen 1984; Pullen et al. 1984). These agents also produce up-regulation (Takeyasu et al. 1979; Ben-Barak and Dudai 1980; Rehavi et al. 1980; Wise et al. 1980; Nomura et al. 1982; Ehlert et al. 1983; Yamada et al. 1983) and supersensitivity (Domino 1975; Gillin et al. 1979; Sitaram et al. 1979; Dilsaver and Greden 1983; Dilsaver et al. 1983) of cholinergic systems. Their abrupt withdrawal can precipitate depression (Innes and Nickerson 1975; Dilsaver and Greden 1984) and escape of plasma cortisol from suppression by the synthetic corticosteroid dexamethasone (Greden and Dilsaver 1984; Dilsaver and Greden 1985). This is consistent with development of cholinergic overdrive consequent to drug withdrawal. Pharmaceuticals interfering with the release of acetylcholine by presynaptic mechanisms are euphoriants and liable to abuse. Cannabinoids (Layman and Milton 1971; Yoshimura et al. 1974; Kumbarachi and Nastuk 1980; Dilsaver et al. 1984), opiates (Jhamandas et al. 1970; Domino and Wilson 1973; Jhamandas et al. 1973), barbiturates (Wahlström and Ekwall 1976; Norberg and Sundwall 1977; Wahlström 1978; Wahlström and Nordberg 1979), and ethanol (Tabakoff et al. 1979) all produce this effect. Depressed mood and affect, psychic and somatic anxiety, psychomotor retardation, and anorexia and other features of meancholia follow discontinuation of these drugs.

In summary, excessively active central cholinergic networks appear to contribute to the genesis of depressive phenomena and inhibition of these systems with the development of subjectively desirable states.

Amitriptyline (Rehavi et al. 1980; Goldman and Erickson 1983) and desipramine (Nomura et al. 1982) up-regulate muscarinic receptors in the brain and heart of mice and rats, respectively, Desipramine produced a marked increase in the sensitivity of ornithine carboxylase to muscarinic agonists in rat cardiac muscle and increased quinuclidinyl benzilate binding. Tricyclics also cause rapid cycling in bipolar patients (Wehr and Goodwin 1979). In contrast, treatments down-regulating or subsensitizing cholinergic systems, e.g., seizures (Byrne et al. 1980; Dashieff and McNamara 1980; Dashieff et al. 1981, 1982), and lithium (Janowsky et al. 1979; Pestronk et al. 1980; Levy et al. 1982; Dilsaver 1984) often abort rapid cycling. Dilsaver (1984) recently reviewed the effects of tricyclics, lithium, and electroshock (EST) on cholinergic mechanisms and

suggested that the hypotheses "up-regulation or supersensitivity of cholinergic systems is involved in the induction of tricyclic associated rapid-cycling" and "the probability of a bipolar patient who has never exhibited rapid-cycling, developing a rapid-cycling course is a function of an enhanced propensity of critical central cholinergic systems to become supersensitive in response to endogenous or exogenous (e.g., tricyclic treatment) assaults many of us are subjected to without ill effect" are heuristically important.

Anticholinesterases (Janowsky et al. 1973c; Shopsin et al. 1975) and dietary loading with precursors of acetylcholine (Cohen et al. 1980, 1982; Schreier 1982) diminish the intensity of manic symptoms. This may be due to cholinergic inhibition of monoaminergic activity (Muscholl 1973). In any event, the clinical state labeled "mania" may be characterized by a hypocholinergic neurobiological state. The converse would be true of depressive states.

Definitions

The literature pertaining to the topic under discussion often equates "supersensitivity" to muscarinic agonists with "supersensitive muscarinic receptor." This is erroneous. Further, this focus on the muscarinic receptor may be a little bit like a spy listening to the sounds created by pressing the buttons on a Touchtone telephone without attending to the conversation. The consequence is loss of information.

Imprecise usage of "up-regulation" and "supersensitivity" and of "down-regulation" and "subsensitivity" produces confusion in the literature. The concepts of up-regulation and supersensitivity parallel those of down-regulation and subsensitivity. Thus, this discussion is restricted to the former pair. "Up-regulation" means there is a significant increase in the maximum number of ligand binding sites per unit; typically this is expressed in milligrams of protein per milliliter. "Supersensitivity" indicates enhanced receptor-mediated responses to direct or indirect agonists. This phenomenon may be receptor independent, i.e., supersensitive responses to pharmacological agents do not necessarily indicate supersensitivity of the receptor and are not equivalent to up-regulation. Supersensitivity occurs both with and without receptor up-regulation. It can even exist in the presence of receptor down-regulation. For instance, EST produces increased sensitivity to dopaminergic, serotonergic, and noradrenergic agents in the absence of change in receptor binding parameters or even in the presence of receptor down-regulation (Lerer and Belmaker 1982).

Consider this sentence, "Antimuscarinic agents induce up-regulation and supersensitivity of cholinergic systems" (Dilsaver, in press). "Up-regulation" indicates that the density of cholinoceptors is significantly increased due to antimuscarinic treatment. The statement also suggests that measurement of behavioral, physiological, or biochemical variables during and/or after antimuscarinic treatment, relative to before (baseline), indicates that a given quantum of cholinergic stimulation now produces an exaggerated change in the value of these variables. That is, the dose–response curve is shifted to the left. This use of terms promotes accuracy of expression and (as highlighted by the material following) focuses attention on the array of factors that may produce an observation compatible with postsynaptic "receptor supersensitivity." It may simultaneously encourage intellectual movement away from the postsynaptic receptor. This may not be bad! Finally, accurate definitions can promote clarity of thought in considering factors involved in the pathophysiology of the affective disorders.

Organization of Discussion

We will consider the theme, "pathophysiology of cholinergic system supersensitivity in the affective disorders" according to possible loci of defect. These include the postsynaptic receptor, regulation of muscarinic receptor density, the membrane, intracytosolic mechanisms and modes of signal transductance, and abnormalities of cholinergic–monoaminergic interaction. The thrust is conceptual, and the discussion is not intended to be exhaustive. Methods of studying events at these sites will be highlighted where appropriate.

Abnormalities of the Muscarinic Cholinergic Receptor

Affective disorder patients could inherit an abnormal muscarinic cholinergic receptor. Perhaps this receptor possesses greater affinity for acetylcholine than does the receptor of normal subjects. Measurement of the affinity of the human muscarinic receptor for acetylcholine in vivo is not possible now. However, imaging strategies, e.g., positron emission tomography (PET), may allow estimation of the in vivo affinity of muscarinic receptors for an exogenously administered ligand in the near future.

Frey and associates (Frey 1984; Frey et al. 1985a,b,c) have performed much of the preclinical work required before PET studies using a muscarinic receptor ligand can be undertaken in humans. This strategy involves the use of a muscarinic receptor radioantagonist, e.g., [^{3}H]scopolamine, a ligand that binds to the muscarinic receptor with high affinity and specificity. The agent is infused into the living animal; thus, the binding to the receptor occurs in vivo. The animal is sacrificed shortly after infusion, and brain slices are prepared for autoradiographic measurement of binding variables. Unfortunately, [^{3}H]scopolamine is not suitable for studies in humans, owing to its long halflife of 12.5 years and the resulting high dose of radiation subjects would receive per study. A radioisotope with a sufficiently short halflife and that stably binds scopolamine might allow in vivo experiments in humans. In the interim, [^{3}H]scopolamine continues to be used in preclinical studies.

It is possible to address the question of whether or not the nicotinic muscarinic receptor is a mutant now (Stevens 1985). The amino acid sequence of all four units of the receptor is known (Devillers-Thiery et al. 1983; Claudio et al. 1983; Nadi et al. 1984). The same principles used in these studies apply to the muscarinic receptor. However, study of the muscarinic receptor is hindered by lack of a source of a high concentration of receptors. The nicotinic receptor was recently crystallized, and crystallographic studies promise to inform us of its dynamic properties. It should also be possible to crystallize the muscarinic receptor if it were available in a high enough concentration. The muscarinic receptor can be isolated and reconstituted into a membrane now (Shreeve et al. 1984). This may have value in studying the functional properties of the receptor, devoid of confounding influences. In conclusion, the question of whether or not the muscarinic receptor is abnormal in the affective disorders is answerable in principle, but technical problems are currently limiting.

Regulation of Muscarinic Receptor Density

Affective disorder subjects may have an increased density of postsynaptic central muscarinic receptors. If so, a quantum of acetylcholine might have a greater effect than in normal subjects. This abnormality has not, however, been shown to mark affective

disorder subjects. Nadi et al. (1984) reported that fibroblasts cultured from affective disorder subjects and their ill relatives demonstrated an increased density of muscarinic receptor binding sites relative to controls, but this finding was not replicated (Kelsoe et al., 1984; Lennox et al. 1985).

Imaging techniques can in principle address this question. The [^{3}H]scopolamine technique developed by Frey et al. (Frey 1984; Frey et al. 1985a,b,c) allows estimation of B_{max}. The appropriate ligand would allow estimation of receptor density in humans. In conclusion, this is an open question.

Abnormal Presynaptic Mechanisms

Presynaptic muscarinic receptors (Sharma and Banerjee 1978; Nordstrom and Bartfai 1981; Wamsley et al., 1981; Briggs and Cooper 1982; Ehlert et al. 1983; Mantione et al. 1983; Reiteri et al. 1983) are localized on both muscarinic (Sharma and Banerjee 1978; Briggs and Cooper 1982; Reiteri et al. 1983) and adrenergic neurons (Ehlert et al. 1983). Activation of presynaptic muscarinic receptors on adrenergic neurons can facilitate the release of norepinephrine in the periphery, but when situated on muscarinic neurons, it decreases the release of acetylcholine (Sorscher and Dilsaver in press). Thus, supersensitivity to cholinergic agonists might result from subsensitivity or down-regulation of muscarinic autoreceptors—the organism would tend to a spontaneous "cholinergic overdrive" state or have an inability to properly compensate in the face of pharmacologically induced cholinergic overdrive. It is possible that in laying emphasis on the postsynaptic neuron, we have been focusing attention at the wrong end of the synapse all along.

A Normal Receptor in an Abnormal Membrane

Abnormalities of membranes receive little attention in psychiatric circles. This may stem from our inability to study membrane pathology and from the lack of training psychiatrists have in membrane biology. However, this is a potentially important subject. Possible membrane and membrane-related abnormalities include distrubances in the regulation of lipid metabolism and fatty acid biosynthesis, abnormalities in the physical properties of membranes due to disturbances of membrane composition, peculiarities in ionic or cyclic nucleotide concentrations, degree of phosphorylation, as well as other factors.

Adult-onset diabetes mellitus with obesity is an example of a disorder marked by a membrane abnormality. In this disorder, the density of insulin receptors (Cuatrecasas 1973) on adipocytes and hepatocytes is decreased, though the absolute number of receptors per cell may be normal. Binding of the receptor by insulin causes changes in intracellular cyclic neucleotide concentration (cyclic GMP, cyclic AMP), and thence, other effects. In the liver, for instance, insulin decreases the intrahepatocyte cyclic AMP concentration. This deactivates protein kinases, which are enzymes capable of phosphorylating a number of other enzymes. The effectiveness of insulin in decreasing cyclic AMP is contingent upon the density of bound receptors. Thus, as the area of the cell surface is increased, the effectiveness of a given number of molecules is diminished.

Baron and asssociates (1984) recently discovered that the incorporation of certain fatty acids into the cell membrane enhanced the sensitivity of muscarinic receptors. An issue is specificity. Fatty acids are detergents and can have nonspecific effects on membranes. However, the hypothesis that abnormalities of membrane constitution or function produce cholinoceptor supersensitivity in affective disorder patients is quite viable.

Abnormal Intracytosolic Mechanisms

Phosphatidylinositol Cycle and Cyclic GMP Formation

The binding of an agonist to a receptor triggers a number of events, e.g., opening of ion channels, alteration of adenosine triphosphatase (ATPase) activity, mobilization of intracellular calcium stores, and stimulation of phospholipid turnover, which may increase the release of calcium from intracellular sites, have an ionophore effect, or increase the activity of cyclases. The issue is "case mechanisms" or "second messengers." Cell surface receptors are coupled to mechanisms translating agonist–receptor coupling into physiological events. Figure 1 illustrates this.

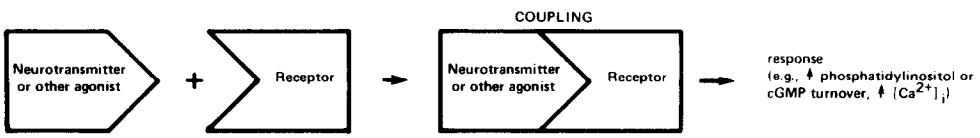
Cholinergic systems employ at least two cascade mechanisms—the phosphatidylinositol cycle and activation of guanylate cyclase. In the periphery, muscarinic receptor-mediated activation of the phosphatidylinositol cycle is associated with generation of polyphosphatidylinositides and a rise in cytosolic Ca^{2+} concentration (Downs 1983). The polyphosphatidylinositides are a number of phospholipids that include a sugar, inositol. The lipid contains fatty acids esterified to a glycerol backbone that also contains arachidonic acid. The resulting compound (phosphatidylinositol) can be phosphorylated at one or more hydroxyl sites located on the inositol moiety. Figure 2 illustrates the molecule and the points of kinase activity.

In assays, the level of phosphorylation in response to muscarinic receptor stimulation is the variable measured. Phosphatidylinositol replenishes the polyphosphoinositide pool via the actions of specific kinases, enzymes that phosphorylate the hydroxyl groups of the inositol component of phosphatidylinositol. Constant replenishing of polyphosphoinositides allows mobilization of intra- and extracellular calcium ions, presumably via the generation of inositol trisphosphate, which is triphosphorylated inositol in isolation.

Nervous tissue is sensitive to small changes in cytosolic calcium ion concentration (Ca^{2+}). These changes can be translated into a variety of responses via, for example, alteration of calmodulun, a regulatory protein that binds calcium ions in the micromolar concentration range. Calmodulun plays an unusually important role in the regulation of neural function. The calcium-activated form of the enzyme activates several enzymes, such as a protein kinase, another one of the most important regulatory proteins known.

Activation of muscarinic receptors can also increase production of cyclic GMP. Snider et al. (1984) studied this phenomenon in murine neuroblastoma. The process begins with receptor-mediated activation of phospholipase C. The primary substrates for this enzyme are the polyphosphoinositides. Inositol phosphates (e.g., inositol trisphosphate) and diacylglycerol are products of the activity of phospholipase C. Diacylglycerol reacts with

Figure 1. Agonists sterospecifically bind to receptors, thereby producing secondary effects of agonist-receptor coupling, such as increased phosphatidylinositol, cyclic GMP, or cyclic AMP turnover, increases in $[Ca^{2+}]_i$ phosphorylation of regulatory proteins, or activation of other mechanisms. These secondary events can amplify or magnify the effects of receptor activation. Thus, activation of the receptor is only one event determining sensitivity to an endogenous or another agonist.



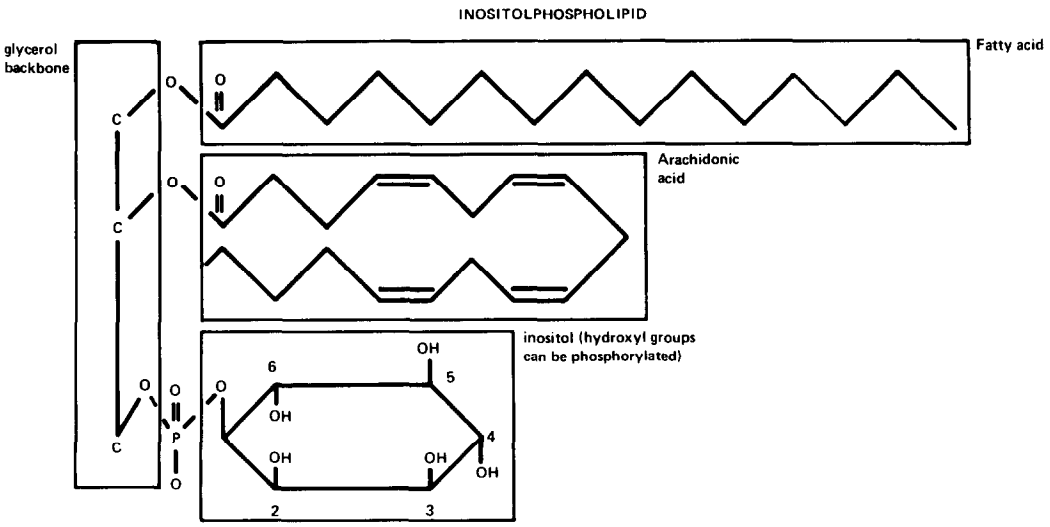


Figure 2. Inositolphospholipid consists of a glycerol backbone esterified to a fatty acid, aracidonic acid, and inositol, a 6-carbon sugar. The sugar moiety can be phosphorylated, generally at positions 4 and 5, while in the form of inositols. The resulting compounds are phosphatidylinositol or the polyphosphatidylinositols.

cytosine triphosphate to yield phosphatidic acid. The latter then reacts with inositol to reform phosphatidylinositol. Hence, the cyclical process of phosphatidylinositol breakdown and regeneration, etc. Incidentally, various intermediates in this cycle other than inositol trisphosphate may be metabolically active, i.e., directly amplify effects of muscarinic receptor activation. For example, phosphatidic acid may act as a Ca^{2+} ionophore.

Turnover of phosphatidylinositol involves a transmembrane event catalyzed by calcium bound to intramembrane sites. Initiation of this process, i.e., activation of the phosphatidylinositol cycle, may involve a shift of this bound Ca^{2+} to other bound sites, e.g., phospholipase A_2. Thus, $[Ca^{2+}]_i$ would not change, as it remains compartmentalized. Alternatively, Ca^{2+} phospholipid complexes could induce confirmational changes in membrane proteins, thus activating them. Extracellular calcium is obligatory for muscarinic receptor-mediated cyclic GMP formation to occur, but its formation is not contingent on an increase in $[Ca^{2+}]_i$. This is consistent with shifts of $[Ca^{2+}]_i$ from given sites or locations to others.

In conclusion, muscarinic agonist–muscarinic receptor coupling can produce changes in the phospholipid pool consequent to activation of phospholipase C in murine neuroblastoma. This lipase may have a Ca^{2+} receiving site essential to the neurotransmitter–receptor–cyclic GMP transduction process and/or it may participate in the production of products (lipid metabolites) that activate the cyclase.

Mutations at any point in the model proposed by Snider et al. (1984) might produce a supersensitive response to cholinomimetic challenge or a functionally supersensitive cholinergic system at baseline. Such a defect in humans could predispose to affective disorders. The correctness of the model is not essential to our purposes. There are many conceivable transduction mechanisms, but the same principles apply to all. Currently available models foster understanding of the nature of possible mechanisms producing the appearance of postsynaptic "cholinoceptor supersensitivity" in the affective disorders.

Cholinergic–Monoaminergic Interaction

Cholinergic agents can indirectly mobilize adrenergic systems. This is manifested by increased release, synthesis, and turnover of norepinephrine. Kazic (1973) reported physostigmine produced a significant decrease in hypothalamic and brain stem norepinephrine levels within 15 min of administration. This could be due to massive release and inadequate replacement of this neurotransmitter. An increase in synthesis and turnover of ^{14}C-tyrosine, the precursor of norepinephrine, occurred simultaneously. Seven days of treatment with physostigmine increased tyrosine hydroxylase (the enzyme governing the rate-limited step in catecholamine synthesis) activity in the hypothalamus and brain stem. Increased preganglionic cholinergic activity increases tyrosine hydroxylase synthesis in noradrenergic neurons of peripheral nervous tissue. Cholinergic overdrive, lasting only 60 min, caused a measurable increase in the activity of tyrosine hydroxylase 48 hr later (Thoenen et al. 1973). Richardson and colleagues (1973, 1976) reported that the immediate effect of an anticholinesterase is reduced tyrosine hydroxylase activity. This may be due to a toxic effect on the enzyme. However, the distal or "rebound" effect is increased tyrosine hydroxylase activity. Thus, cholinergic overdrive may contribute to development of a monoaminergic overdrive state, should there be compensatory diminution in the activity of cholionergic systems concomitant with a cholinergically mediated increase in activity of monoaminergic systems (Dilsaver and Greden 1984).

Acetylcholine can also decrease the release of norepinephrine from adrenergic neurons in both brain (Westfall 1973; Hobson 1974; Hobson et al. 1975) and the periphery (Muscholl, 1973). Muscarinic agonists reduced the release of norepinephrine, where as nicotinic agents increased it in rat hypothalamus (Westfall 1973). The net effect of acetylcholine was to decrease the release of norepinephrine unless a calcium-kelating agent or muscarinic antagonist was employed.

Flicker and Geyer (1982b) reported that carbachol produced profound hyperactivity 10–40 min after ionophoretic infusion into the dentate gyrus of rats. Strength of response and lag time were a function of dose. These findings are not compatible with nonspecific effects of the agonist producing behavioral activation. The lag contrasts with immediate effects of norepinephrine, dopamine, and dopamine agonists and potentiating agents applied to the dentate gyrus or other limbic regions (Beani et al. 1968; Pijninburg et al. 1973; Anders and Jackson 1975; Costal and Naylor 1975; Jackson et al. 1975; Dolphine et al. 1977; Jones et al. 1981; Flicker and Geyer 1982a,b,c,d). The latency is consistent with the hypothesis that carbachol activates the animal by mobilizing dopaminergic or other monoaminergic systems.

The hypothesis that a hypercholinergic state produces partial denervation of postsynaptic noradrenergic and dopaminergic neurons is supported by an extensive body of data. Chemical or pharmacological denervation is the process whereby exogenously applied chemicals or endogenously generated biochemical events result in a functionally significant blockade of receptors or a decrease in the release of neurotransmitter. There is evidence that this occurs. First, muscarinic agonists modulate the release of monoamines and up-regulate and supersensitize monoaminergic systems, and conversely (Beani et al., 1968; Anderson et al. 1981; Ehlert et al. 1981; Blosser 1983; Dilsaver and Greden 1984). Secondly, muscarinic agonists and antagonists decrease and increase the quantal release of acetylcholine by cholinergic neurons, and down-regulate, up-regulate, subsensitize, and supersensitize muscarinic cholinergic systems, respectively (Gazit et al. 1974; Ben-Barak et al. 1980; Luqmanc et al. 1979; Overstreet and Yamamura 1979; Russell et al.

1979a,b; Schiller 1979; Siman and Klein 1979; Taylor et al. 1979; Naid 1984; Shifrin and Klein 1980; Rehavi et al. 1980; Creese and Sibley 1981; Russell et al. 1981; Goldman and Erickson 1983).

Endogenously arising surges in cholinergic activity create the prospect of major compensatory cholinergic and monoaminergic changes occurring spontaneously in vivo. These surges are "endogenous drug effects," i.e., causally significant biochemical changes in the functional state of an organism consequent to factors internal to it. Thus, muscarinic cholinergic systems mobilize monoaminergic systems and vice versa. This suggests a mechanism accounting for oscillations between hypercholinergic–hypomonoaminergic and hypocholinergic–hypermonoaminergic states. These oscillations would correspond to states of depression and hypomania or mania. These principles suggest that depression of monoaminergic systems by endogenously generated, cholinergic assaults (endogenous pharmacological assaults) on these networks increases the probability of a compensatory monoaminergic overdrive state developing. Supersensitivity of muscarinic cholinergic systems could be due to disturbed cholinergic–monoaminergic interaction (Janowsky et al. 1972a,b, 1973b).

Dilsaver and Greden (1984) and Dilsaver (1984, 1986) have proposed a cholinergic–monoaminergic interaction theory (CMIT) of bipolar disorder. This is a dynamic account of the mutual inter- and intraregulation of cholinergic, noradrenergic, dopaminergic, and serotonergic systems in the pathophysiology of affective disorders. The CMIT maintains that virtually everything pertinent to the neurobiology of bipolar disorder is carefully regulated. In principle, these variables include receptor density and sensitivity, membrane properties, cytosolic Ca^{2+}, Mg^{4+}, Na^{+} and other ionic concentrations, ATPase activities, etc. The inclusiveness of the factors controlled stems from the assumption that the brain is a unified or purposeful dynamism.

A distinction of the theory is the positing of homeostatic mechanisms that preserve the direction of this dynamism. According to the CMIT, the propensity to oscillate between manic and depressed phases is not primarily a function of the severity or magnitude of the alternating cholinergic and monoaminergic overdrive states, though this is an important variable. The theory attributes primary etiological significance to the defectiveness of mechanisms designed to render neural systems resistant to forces potentially inducing pathogenic perturbation. The function of these mechanisms is prevention of significant deviation once a system is sufficiently perturbed to create a potentially pathogenic neurophysiological state. The basic etiological principle is "faulty mechanisms allow 'restorative' monoaminergic system receptor up-regulation and supersensitivity and muscarinic cholinergic system overdrive states, respectively."

Summary

The concept of a muscarinic cholinergic component to the pathophysiology of the affective disorders derives from naturalistic observations and clinical research. This type of study can carry us only so far. Basic knowledge regarding the function of central muscarinic cholinergic systems allows proposal of hypotheses regarding the cause of this phenomenon. The origin of cholinergic system supersensitivity may indeed be the postsynaptic "cholinoceptor." However, presynaptic mechanisms integral to the regulation of acetylcholine release may also be amiss in affective disorder subjects. Alternatively, both pre- and postsynaptic receptors may be normal but embedded in abnormal membranes or coupled to aberrant cascade mechanisms. Whatever the actual case, a dissection of cho-

linergic systems into components cannot help but encourage careful thinking in this exciting and important area of research. The site of "etiology" may be other than we ever expected!

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