DIFFERENTIATING PRIMARY PATHOPHYSIOLOGIC FROM SECONDARY ADAPTATIONAL PROCESSES

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The following manuscript is mainly conceptual in nature. It should be read with reservation since the relevance of its suggestions have yet to be proven. Basically it proposes two rules for the differentiation between primary illness-related pathophysiological vs. secondary adaptational processes. These rules may guide hypotheses generation for further research that is aimed at understanding psychiatric disorders and their shared and unshared mechanisms. For example, in the case of anxiety disorders and depression, it may be of interest to learn if their shared properties are of primary pathophysiological or secondary adaptational significance. We first present some historical observations on the development of the concept of "secondary adaptational processes." We assume such adaptational processes are generated by the organism in order to compensate for primary pathophysiological malfunction or impairment. Next, we propose rules that may enable the dissection of secondary adaptational from primary pathophysiological processes. We also discuss the possible implications of designing studies to sort out these processes, suggesting that the understanding of adaptational processes, may explain the effects of "placebo treatment." Finally we illustrate the application of these rules by two examples: a) amygdala activation, a biological alteration shared by anxiety disorders and major depression and b) elevated plasma soluble interleukin 2 receptor, an unshared property by anxiety disorders and major depression . Also, the first example relates to a biological perturbation associated with a primary pathophysiological mechanism, while the second represents a biological alteration associated with secondary adaptational processes. Depression and Anxiety 14:105–111, 2001. © 2001 Wiley-Liss, Inc.

INTRODUCTION

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ment. Next, we propose rules that may enable the dissection of secondary adaptational from primary pathophysiological processes. We also discuss the possible implications of designing studies to sort out these processes, suggesting that the understanding of adaptational processes may explain the effects of "placebo treatment." Finally we illustrate the application of these rules by two examples: a) amygdala activation, a biological alteration shared by anxiety disorders and major

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depression and b) elevated plasma soluble interleukin 2 receptor, an unshared property by anxiety disorders and major depression. Also, the first example relates to a biological perturbation associated with a primary pathophysiological mechanism, while the second represents a biological alteration associated with secondary adaptational processes.

The existence of adaptational mechanisms within the framework of the human body was first conceived by the Greek physician Hippocrates. Hippocrates (460–377 BC) coined the term that was phrased at a later time in Latin as "*vis medicatrix naturae*," meaning the healing power of the body. According to this principle, Hippocrates stated, nature creates adequate countermeasures enabling the human body to combat disease [Bettmann, 1956]. However it was not until the writing and teaching of Thomas Sydenham (1624–1689) that this general principle gained wide recognition [Bettmann, 1956]. In the nineteenth century, this concept was further refined by the French physiologist Claude Bernard (1813–1878), portraying the human body as a single functional entity, demonstrating a balanced interplay of body fluids. In such a system, Bernard stated that compensatory mechanisms counterbalance any threatening interference, thus retaining the stability of the body's internal physiologic environment or its homeostasis [Wasserstein, 1996].

There are ample data that adaptational compensatory processes operate within the central nervous system and that the uncovering of such processes is crucial for the understanding of neurobiological correlates of neurologic disorders [York and Steinberg, 1995; Kalant, 1998; Barron, 1995; Verbalis, 1998; Scher, 1997]. Similarly, psychotropic drug treatment has also been discussed in the context of adaptational processes [Hyman and Nestler, 1996], although, this article does not focus on drug-induced adaptational processes but rather on adaptational processes associated with psychiatric disease itself. Nevertheless much of the neuropsychiatric literature fails to make a distinction whether a given biological perturbation is related to secondary adaptive processes or to primary pathophysiology.

The following article offers two rules that may elucidate the probable linkage of a given biological perturbation to either secondary adaptive processes or to primary pathophysiology.

METHODS
RULE 1: LINKING AN ILLNESS-RELATED BIOLOGICAL PERTURBATION WITH SECONDARY ADAPTIVE MECHANISMS

a) If a given psychiatric disorder is associated with a certain biological alteration and;

b) a certain drug or other mode of biological therapy known to be effective for this disorder augments the magnitude of this biological alteration, then;

c) these alterations are probably due to secondary adaptational processes.

d) This argument may be strengthened in those cases where placebo responders demonstrate similar augmentation.

RULE 2: LINKING AN ILLNESS-RELATED BIOLOGICAL PERTURBATION WITH PRIMARY PATHOPHYSIOLOGIC MECHANISMS

a) If a psychiatric disorder is associated with certain biological alteration and;

b) a certain drug or other mode of biological therapy, known to be effective for this disorder, attenuates or abolishes the magnitude of such alteration, then;

c) this alteration may be due to a disorder-related primary pathophysiologic processes. However, in such a case, one cannot rule out the possibility that these alterations are associated with secondary adaptational processes.

d) The probability for such linkage with primary pathophysiologic processes is strengthened in those cases where placebo treatment responders do not demonstrate such attenuation.

We do not presume that these rules are the only ones that may be used to sort out the existence of secondary adaptive mechanisms. Drevets and Raichle [1998], for example, reported that increased blood flow in certain brain areas (i.e., amygdala, ventral anterior cingulate cortex, and orbital cortex) during emotional tasks is associated with decreased blood flow in other brain areas implicated in higher cognitive tasks (i.e., dorsal anterior cingulate and dorsolateral prefrontal cortex). Correspondingly, during the performance of cognitive tasks this pattern of blood flow change is reversed. Such reciprocity suggests that adaptive changes are occurring in cognitive brain areas during the performance of emotional tasks and vice versa.

Adaptational processes may find particular application in the treatment effects associated with placebo. Per definition, placebo treatment carries no specific effects and thus may affect secondary adaptational processes but would not therefore be expected to involve primary pathophysiological ones. Study of adaptive and secondary compensatory mechanisms may provide a method to evaluate and quantify the effects of placebo.

For instance, if a known biological alteration is considered to be a compensatory or adaptational process in a given disorder, and placebo treatment can potentially modify this alteration, one may evaluate the magnitude of such modification and then relate it to the observed clinical improvement demonstrated by placebo. Such a strategy may be repeated with different biological alterations, all considered to be of secondary adaptational nature. Second, with the accumulation of knowledge as to the various disorder-related adaptive processes, placebo may be replaced by more specific agents affecting these adaptive processes.

RESULTS

EXAMPLE 1: A COMMON BIOLOGICAL ALTERATION REPORTED IN MAJOR DEPRESSION AND SCHIZOPHRENIA, BUT NOT IN ANXIETY DISORDERS HYPOTHESIZED TO BE ASSOCIATED WITH SECONDARY ADAPTATIONAL PROCESS—THE CASE OF ELEVATED PLASMA SOLUBLE INTERLEUKIN 2 RECEPTOR

The cytokine, interleukin 2 (IL-2), is identified in various brain regions, including the hippocampus, neostriatum, and the cortex. Interleukin 2 is produced by cells within the central nervous system including astrocytes and microglial cells. IL-2 appears to play a role in neuroregulatory and neurodevelopmental brain processes [Remick and Friedland, 1997]. In addition to the expression of interleukin 2 receptor (IL-2R) by activated peripheral T blood cells, a soluble form of interleukin 2 receptor (sIL-2R) is released in vitro into the supernatant of activated T cell cultures. This molecule appears to regulate immune function by binding IL-2, and thereby neutralizing and antagonizing its cellular effects. Various authors reported that sIL2R levels probably represent an activation of the immune system that correlates in certain instances with disease activity [Remick and Friedland, 1997; Rubin et al., 1990]. Soluble plasma interleukin 2 receptor was found to be elevated in both major depression [Maes et al., 1995; Seidal et al., 1995] and schizophrenia [Rapaport and Lohr, 1994; Rapaport et al., 1994; Gaughran et al., 1998; Barak et al., 1995; Maes et al., 1995], although there are also a few negative studies [Kim et al., 1996; Rothermundt et al., 1998]. However no alterations in this parameter were reported in anxiety disorders [Spivak et al., 1997; Rapaport and Stein , 1994a,b; Maes et al., 1994a]. Antipsychotic treatment was reported to increase sIL-2R levels [Maes et al., 1994b; Pollmacher et al., 1995, 1996; Muller et al., 1997], although not all studies could replicate this result [Kim et al., 1995; Pollmacher et al., 1997].

These data suggest that the increase of sIL-2R is probably common to major depression and schizophrenia, and, based upon current knowledge, is not shared by anxiety disorders. Since effective treatment for schizophrenia further increases plasma sIL-2R levels, altered plasma sIL-2R levels found in major depressions and chizophrenia are probably associated with secondary-adaptational mechanisms (at least in schizophrenia). In the case of schizophrenia, it may be postulated that such a mechanism is aimed at neutralizing excessive IL-2 levels [see Licinio et al., 1993] that are hypothesized to be associated with relapse [McAllister et al., 1995]. For instance, IL-2 is hypothesized to activate dopaminergic pathways [Alonso et al. , 1987].

EXAMPLE 2: A COMMON BIOLOGICAL ALTERATION IN MAJOR DEPRESSION AND ANXIETY DISORDERS HYPOTHESIZED TO BE ASSOCIATED WITH UNDERLYING PRIMARY PATHOPHYSIOLOGICAL PROCESS—THE CASE OF AMYGDALAR ACTIVATION

The application of the above rules to findings from imaging studies [Positron emission tomography (PET) and magnetic resonance imaging (MRI)] poses a unique challenge. First, the brain appears to function within the framework of parallel and hierarchical systems. It is thus of more interest to report illness-associated alterations in brain structures and activity within the framework of brain systems or circuits as opposed to discreet findings. Applying such a strategy may enable the integration of findings within a meaningful framework. However defining relevant brain systems is a complex task, and the literature may disagree as to which structures and pathways are involved in such systems.

Second, the application of PET for the measurement of brain activity is based on evidence that shows that alterations in synaptic activity are followed by alterations in regional cerebral blood flow (rCBF) and glucose metabolism to the relevant area [Raichle, 1998]. Positron emission tomography (PET) imaging studies in psychiatric disorders introduce many findings—not all of which are relevant to the disorder being investigated. For example, increased blood flow in certain brain areas in a given disorder, as a rule, is followed by decreased blood flow to other areas [Drevets and Raichle, 1998]. Such reciprocity enables the modulation of neural processing at a given time point. These decreases may have no relevance or specificity to the index disorder. It is thus recommended that corroborative data, from electrophysiological or lesion analysis studies in humans and experimental animals, and from brain mapping studies in healthy humans during induced cognitive, emotional, or behavioral states, should be taken into consideration when interpreting results from functional imaging studies.

Third, the number of subjects in such studies, given the large individual differences between subjects, is usually relatively small. This also poses difficulties as to differentiating relevant from irrelevant findings.

Fourth, technical limitation in the temporal and spatial resolution of neuroimaging studies further complicate the interpretation of experimental results [reviewed in Drevets, 1999].

We will herein examine brain imaging findings mainly from the involvement of the amygdaloid body in depressive and anxiety disorders.

AMYGDALA AND EMOTIONS

The amygdala plays a major role in the acquisition, retention, and possibly extinction of conditioned fear in animals [Ledoux, 1996] and humans [LaBar et al.,

1998]. Its extensive connectivity to a variety of brain areas suggests that it may be involved in coordinated expression of autonomic, affective, cognitive and motor components of emotions including anxiety and depression [Roy-Byrne and Cowely, 1998; Davis, 1998; Post et al., 1998; McDonald, 1998; Iverson et al., 2000; Ledoux, 1996, 2000]. Data from patients with bilateral amygdala damage demonstrate impairment of declarative memory for emotional material [Adolphs et al., 1997]. Also, the amygdala was demonstrated in human imaging studies to be involved in the processing of negative affective stimuli [Liberzon I et al., 1998], including that of fearful and sad facial expressions [Morris et al., 1996; Blair et al., 1999].

EFFECTS OF ANTIDEPRESSANTS/ ANTIANXIETY AGENTS ON AMYGDALA FUNCTIONING

There are animal data that demonstrate that effective treatment for anxiety and depressive disorders induces changes in amygdala function. Horowitz et al. [1966] observed that injection of an antidepressant medication directly into the centromedial nucleus of the amygdala had a effect similar to the inducement of lesions in this area and suggested that antidepressants are "amygdaloid depressants." Gerber et al. [1983] reported decreased 2-deoxyglucose uptake after chronic desipramine administration. Also, the antidepressant reboxetine, at 10 and 30 mg/kg, attenuated increased serotonin turnover in the amygdala and this was associated with behavioral immobility [Leonard, 1998]. Aubry et al. [1999] reported that chronic treatment with the antidepressant amitryptiline decreases CRF-R1 receptor mRNA in the rat amygdala, whereas Morelli et al. [1999] reported induction of Fos-like-immunoreactivity in the central amygdala by citalopram and imipramine. Finally, Daws et al. [1998] reported that desipramine and phenelzine but not fluoxetine down-regulate beta-adrenoreceptors in the amygdala. These animal data suggest that antidepressants decrease or down-regulate amygdala neurotransmitter and neuroreceptor systems. Similarly, biological treatments for human depression seem to be associated with deceased amygdala activity. Wu et al. [1992] reported that successful sleep deprivation treatment in humans seems to be associated with decreased amygdala metabolism. Drevets [Drevets,1992; Drevets and Raichle, 1999] reported that antidepressant treatment that results in and maintains symptom remission in depressed patients is also associated with normalization of amygdala activity.

AMYGDALA INVOLVEMENT IN ANXIETY DISORDERS

Experiments in animals indicate that the amygdala plays a major role in fear conditioning [Ledoux, 2000]. Sajdyk et al. [1999] suggested that CRF and urcortin, a cloned peptide related to CRF, generate anxiety and panic-like responses when microinjected into the basolateral nucleus of the amygdala. File et al. [1998] studied an animal model for phobic anxiety and reported data that suggests that the basolateral amygdala plays a crucial role in the consolidation of information needed for the formation of specific phobias. Kalin et al. [1999] also showed that the amygdala mediates acute fear responses in nonhuman primates.

There are indications that the amygdala may be involved in the pathogenesis of post traumatic stress disorder (PTSD). Fear conditioning to visual and auditory stimuli is hypothesized to be of relevance to some of the core symptoms of PTSD [Davis et al., 1997; Charney et al., 1993] and this phenomenon involves thalamic-amygdaloid pathways. Failure of extinction for traumatic experiences may exist in PTSD [Charney et al., 1993], possibly implicating some abnormality in prefrontal-amygdaloid body pathways. Recently, Shin et al. [1997], using PET, reported that unlike control subjects, subjects with PTSD had increased rCBF in ventral anterior cingulate gyrus and the right amygdala when generating mental images of combat-related pictures.

The amygdala was also suggested to be involved in panic disorder. Shekhar et al. [1999] reported that repeated activation of the basolateral amygdala in rats by GABA$_A$ receptor blockade produced long-term synaptic changes, resulting in chronic anxiety and reactivity to peripheral lactate infusions, similar to patients with panic disorder. PET studies that used fluorodeoxyglucose-examining metabolic activity in patients with panic disorder exhibited increased metabolism in hippocampal and para-hippocampal regions [Roy-Byrne et al., 1998; Reiman et al., 1986; Nordhal et al., 1990; Bissaga et al., 1998], areas to which the amygdala has extensive connectivity.

In obsessive-compulsive disorder (OCD), baseline and symptom provocation studies of patients by using PET, single photon emission computerized tomography (SPECT), and functional MRI showed relative activation in amygdala as well as in caudate, thalamus, and paralimbic structures including the anterior cingulate and orbitofrontal cortex [Barchas and Altemus, 1999]. These areas were suggested to be part of circuits which appear to be hyperactive in OCD [Insel, 1992]. Also, the amygdala is extensively connected with areas reported to be involved in OCD. Thus, the amygdala has extensive connections with the ventromedial striatum, and the magnocellular division of the basal amygdala nucleus projects to the body and tail of caudate [Amaral et al., 1992].

Finally, nonhuman primates after amygdalectomy demonstrate a decrease in social affiliative behavior [Kling and Brothers, 1992]. Nutt [1999] designed a pilot study in which social phobics were exposed to pre-recorded scripts of their own personal anxiety experience. Under such exposure these patients showed deactivation of the amygdala and the hippocampus. However no comparison group was included. These data may indicate the possible involvement of the amygdala in social phobia.

AMYGDALOID BODY INVOLVEMENT IN DEPRESSIVE DISORDERS

Connor et al. [1997] demonstrated that forced swim test exposure, a putative animal model for depression, is associated with increased serotoninergic activity in the amygdala and frontal cortex. Dunchan et al. [1986] showed that some antidepressant drugs injected into the amygdala produce behavioral responses similar to intra-peritoneal injection of these drugs during forced swim stress. Hrdina et al. [1993] conducted a post-mortem study that reported that the ratio between presynaptic 5-HT uptake sites and postsynaptic 5-HT2 receptors in the amygdala was significantly lower in suicidal depressives compared to controls. Drevets and Rachaile [1992], summarizing the literature regarding neuroreceptor and neuro-transmitter amygdala systems, reported that many of these, including beta-adrenergic receptors, dopamine-1, and several 5-HT neuroreceptors, may be involved in the pathogenesis of depression.

Sheline et al. [1998a,b] conducted an MRI study that reported that early onset major depression is associated with volume loss in hippocampus and amygdala core nuclei [Sheline et al., 1998a,b], while others could not find amygdaloid body volume reduction in depressed patients [Bremner et al., 1998].

Also, areas in prefrontal cortex extensively connected with the amygdala were reported to be associated with transient sadness in normal subjects [Beauregard et al., 1998], with minor depression [Kumar et al., 1998], and major depression [Beauregard et al., 1998; Garcia-Sevilla et al., 1999; Drevets, 1992; Drevets et al, 1997].

Horing et al. [1997], using -99m Technetium-hexamethylpropanolamine oxime- single photon emission computed tomography, reported increased hippocampus-amygdala activity in a small group of treatment-resistant depressed patients. However, Wu et al. [1992] showed that elevated amygdala and cingulate regional metabolism in depressive patients predicted successful antidepressant response to sleep deprivation.

Other authors also reported amygdala involvement in depression, Drevets [1999] reported prefrontal cortical amygdalar metabolism alterations in major depression. This author also reported that the amygdala metabolism in major depressive disorder and bipolar disorder is positively correlated with both depression severity and "stressed" plasma cortisol levels measured during scanning. These authors demonstrated that successful antidepressant treatment decreases mean amygdala metabolism, whereas persistence of elevated amygdala metabolism during remission is associated with high risk for relapse. Finally, Drevets [1999] reported a significant mean 5HTIA receptor binding potential decrease (27%) in the mesiotemporal cortex (hippocampus-amygdala) of depressed patients compared with controls.

Interestingly, Altschuler et al. [1998] and Strakowski et al. [1999] reported that amygdala volumes are significantly larger in bipolar patients. Such increased volumes were positively correlated with number of manic episodes compared with both normal subjects and schizophrenic patients. This may suggest that the amygdala may also be involved in affective states other than anxiety and depressive disorders.

CONCLUSIONS

The above data suggest the involvement of the amygdala in both mood and anxiety disorders. Paradoxically, while there is ample animal data to suggest the involvement of the amygdala in anxiety disorders, there is a relative lack of human studies. Data from depressed subjects suggest that the amygdala may also be involved in major depression. Evidence from animal and human studies indicate that response to treatment is associated with the normalizing of activated amygdala in these disorders. These data suggest that this altered amygdala activity may be associated with primary pathophysiological processes, although its involvement in secondary adaptational processes cannot be ruled out.

Shared mechanisms for anxiety disorders and major depression are suggested by various authors [see Gorman and Coplan, 1996; Stein et al., 1994; Kendler et al., 1992]. Such mechanisms may be either of primary pathophysiologic or of secondary adaptational nature. The study of shared mechanism along these lines may open new avenues to understand these mechanisms. We hope that the presentation of the above rules will facilitate a debate regarding the importance of differentiating illness-related primary pathophysiologic from secondary adaptive processes. Presumably, such a debate will enable the refining of these rules or their replacement by more appropriate ones.

Finally, the above rules should be applied with caution. Corroborative data from animal and normal human studies should direct the proper choice of biological parameters to be analyzed by these rules. Also, although not exemplified here (data can be provided upon request), we suggest that the magnitude of change, effect size, and the percentage of patients that demonstrate a certain perturbation will also direct the selection of relevant parameters.

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