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REVIEW

Challenges for translational psychopharmacology research—some basic principles

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Abstract We introduce below several principles that recur in the discussion of translating preclinical findings to clinical applications, and conversely, developing animal models of human disorders:

1. The translation of preclinical data to clinical concerns is more successful when the scope of experimental models is restricted to a core symptom of a psychiatric disorder.

2. Preclinical experimental models gain in clinical relevance if they incorporate conditions that induce maladaptive behavioral or physiological changes that have some correspondence with species-normative behavioral adaptations.

3. Preclinical data are more readily translated to the clinical situation when they are based on converging evidence from several experimental procedures, each capturing cardinal features of the disorder.

4. The more closely a model approximates significant clinical symptoms, the more likely it is to generate data that will yield clinical benefits.

5. The choice of environmental, genetic, and/or physiological manipulations that induce a cardinal symptom or cluster of behavioral symptoms reveals the theoretical approach used to construct the model.

6. Preclinical experimental preparations that are validated by predicting treatment success with a prototypic agent are only able to detect alternative treatments that are based on the same mechanism as the existing treatment that was used to validate the screen.

7. The degree to which an experimental model fulfills the criteria of high construct validity relative to face or predictive validity depends on the purpose of the model.

8. Psychological processes pertinent to affect and cognition can only be studied in preclinical models if they are defined in behavioral and neural terms.

Keywords Preclinical findings · Experimental models · Psychiatric disorder

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After the first decade of modern psychopharmacology, Kelleher and Morse (1968) organized the conceptual and methodological approaches by identifying two types of experiments in this emerging field: type 1 experiments, which use behavioral and physiological procedures as tools to characterize the effects of drugs, and Type 2 experiments, which use a drug as a tool to analyze behavior and its underlying neural mechanisms. Already in this nascent phase of psychopharmacology, one of the research goals was to construct behavioral profiles of prototypic drugs in laboratory animals and to identify core features in these profiles that can be translated to clinical applications. The applications of these models range from identifying drug responses that characterize individuals as being vulnerable or resistant to psychiatric disorders to identifying compounds that are promising as pharmacotherapies. For example, in the very first issues of the journal *Psychopharmacology*, several articles that translated preclinical findings to clinical applications became citation classics. These included attempts to (1) characterize potentially useful anxiolytic pharmacotherapies (Geller and Seifter 1960), or (2) identify the abuse liability of drugs (Deneau et al.

1969), or (3) induce behavioral features such as stereotyped motor routines that could serve as models of psychotic disorders (Ernst 1967).

The 2006 NIH roadmap for medical research demands more rapid and efficient translation of research findings from the bench to the bedside, and conversely, better clinical diagnoses that enable the development of more appropriate experimental model systems. To apply this principle to psychiatric disorders is particularly challenging because of the complex and heterogeneous symptom clusters that determine the diagnoses, the lack of consensus about syndromes, and the multifactorial nature of the underlying disorders (American Psychiatric Association 2000). Developing model systems for psychiatric disorders is also especially difficult because many of the symptoms are subjective experiences that have no clear counterpart in non-verbal animals (e.g., craving for drugs or feelings of sadness or unworthiness). As knowledge of genetic predispositions for psychiatric conditions increase, model systems will be expected to address whether pathophysiological vulnerabilities provide better models than studies in otherwise unperturbed organisms. Here, we introduce several questions and principles that recur in the discussion of translating preclinical findings to clinical applications, and conversely, developing animal models of human disorders.

What exactly is modeled in preclinical procedures? Are experimental procedures screens, assays, models, or paradigms?

To answer these questions, one can resort to the maxim by Rosenblueth and Wiener some 60 years ago (Rosenblueth and Wiener 1945), "the best material model for a cat is another, or preferably the same cat?" Lexical definitions of a scientific "model" refer to a simplified and systematic description of a phenomenon with which it shares essential characteristics. However, it is difficult to develop a productive and theoretically satisfactory model in psychopharmacology because the factors that engender the modeled symptoms or signs of the disorder are often imprecise and incomplete. Definitions of the disorders are revised and updated continuously, with the fifth edition scheduled to appear in 2011 (see American Psychiatric Association 2000). Currently, it is unlikely that any model of psychiatric disorders will be *homologous* with the disorder, but rather the laboratory procedures will model *isomorphic* signs and symptoms (Geyer and Markou 2002). The ultimate goal of model development is the point when the etiology, phenotypic expression, and therapeutic response are homologous between the clinical case and the preclinical experimental preparation. Preclinical models capture some but not necessarily all features of the disorder. For example, in preclinical models of schizophrenia, it is easier to model secondary symptoms of schizophrenia, such as stereotyped motor routines, than it is to model the primary symptoms such as disturbances in thought. Thus, the hyperactive and stereotyped movement patterns in rodents or primates generated by high amphetamine doses are effectively blocked by drugs with antipsychotic potential (Janssen et al. 1965), whereas less progress has been made in modeling the primary or cardinal symptoms of attentional filtering and higher level cognitive processes in non-humans (Geyer et al. 2001; Robbins 2002).

Principle 1: The translation of preclinical data to clinical concerns is more successful when the scope of experimental models is restricted to a cardinal or core symptom of a psychiatric disorder. The earlier approach seeking to mimic the entire disorder with a preclinical model has been less productive.

The problem of identifying features of human disorders in the behavioral studies with animals can be illustrated by using one of the most frequently used experimental procedures or models for developing anxiolytic treatments. For several decades, the standard procedure used to evaluate compounds with anxiolytic potential consisted of a preclinical conflict procedure in which punishment (e.g., shock) suppresses a positively reinforced licking or lever pressing or key pecking response (e.g., Barrett and Vanover 1993; Geller and Seifter 1960; Vogel et al. 1971). Anxiolytic drugs attenuate this suppression. These standardized procedures continue to generate systematic data that are consistent with corresponding measurements in human subjects, as well as with what is known about the neurobiological basis of anxiety. However, the following question may still be posed: is this reversal of behavioral suppression a critical characteristic of clinically effective anxiolytic compounds? The benzodiazepine anxiolytics provided good validation for the procedure, but the procedure was less sensitive with purported anxiolytic compounds targeting serotonergic or glutamatergic receptor subtypes and transporter molecules. To use the procedure with these agents require careful adjustments to the experimental protocols (Barrett et al. 1986; Griebel 1995; Millan 2003; Nordquist et al. 2008; Sanger 1992; Spooren et al. 2001). The procedures for assessing anxiolytic compounds typically assess two objectively defined behavioral changes, the punishment-attenuating effects which are predictive of potentially anxiolytic effects, and the sedative-like and other behaviorally disruptive effects. Both are critical in the development of an effective therapy. A similar strategy guides the fear-potentiated startle procedure where treatments with anxiolytic potential attenuate the classically conditioned potentiation effect but leave the non-potentiated startle reflex intact (Davis et al. 1993;

Grillon 2008; Nordquist et al. 2008). The same logic is also the basis for comparing potentially anxiolytic treatments in rodents that promote exploration of open and brightly lit spaces relative to dark and safe spaces (e.g., elevated plus or zero maze, light/dark transitions, open-field tests). These latter procedures are rapidly implemented since they require no conditioning but limit each research subject to a single trial (Miczek et al. 1995). Behavioral suppression may be the best indicator of compounds that are sufficiently efficacious for clinical potential since the use of modified paradigms and ethological tests have not yielded any improved anxiolytic agents. But, most behavioral models of anxiolytic activity failed to effectively detect the utility of SSRIs for the treatment of anxiety, currently the most commonly used pharmacological treatment.

It is noteworthy that these models related to anxiety disorders focus on adaptive responses to aversive events such as distress calls due to maternal separation, behavioral inhibition due to punishment contingencies, suppressed exploratory behavior, or fear-potentiated startle reflexes. These behaviors represent normal adaptations that are important in the survival of the individual and the species and may serve as indicators of measureable behavioral targets to monitor underlying states. Such methods can be used to characterize the effects of therapeutic drugs. For example, the experimental models for the discovery of antidepressant treatments rely on behavioral adaptations to inescapable, highly aversive situations. In one such model, animals are placed in a water tank, and after an initial period of attempting to escape, they typically assume a floating posture. This immobility response was initially labeled "behavioral despair" and it continues to be used to assess the effectiveness of potential antidepressant treatments (Porsolt et al. 1978). In fact, a more parsimonious interpretation of the energy-conserving passive immobile floating response portrays the immobility as an adaptive, passive coping response (Koolhaas et al. 1999; Weiss and Kilts 1995). In another example, species-typical aggressive and defensive behavior in confrontations between resident and intruder animals are commonly used as model systems for investigating potentially therapeutic interventions of violent patients. However, it has been argued that simple suppression of territorial aggression may not be the appropriate procedure to detect pathological aggression in humans, and instead, escalated forms of aggressive behavior in animals may more appropriately model violent outbursts in human patients (Miczek et al. 2004; Miczek et al. 2007a). Thus, treatments that interfere with or suppress adaptive responses are not necessarily appropriate for direct translation to solving a clinical problem. These models may be more understandable if the clinical condition is thought of as an exaggeration of the normal behavioral response. Depressed individuals demonstrate augmented passive behaviors and coping styles, and aggressive individuals demonstrate a normal level of aggression equivalent to that produced only by escalated aggression models. Then, replacement of the abnormal coping response with a more adaptive pattern of behavior makes sense. There is a related controversy in models of drug abuse, which focus mostly on stable patterns of drug intake and only rarely model the transition to escalated, compulsive-like drug use and relapse (Ahmed 2005; Ahmed and Koob 1998). One may question whether the stable patterns of intake provide an appropriate model for the development of potential medications (Haney and Spealman 2008).

Principle 2: Preclinical experimental models gain in clinical relevance if they incorporate conditions that induce maladaptive behavioral or physiological changes that have some correspondence with species-normative behavioral adaptations.

The development of experimental models to detect anxiolytic, antidepressant, antipsychotic, and antiaggressive treatments is complicated by the heterogeneity of the psychiatric disorders. For example, most current models of anxiety-like behaviors in experimental animals focus on responses relevant to pharmacological treatments for generalized anxiety disorder. In contrast, there is little information on experimental models for treatment of post-traumatic stress or obsessive-compulsive or phobic disorders. A potentially valuable test for studying other forms of anxiety may be procedures using startle responses that are exaggerated either by discrete, sudden fear-provoking stimuli or uncertain, distal anxiety-inducing contexts (Grillon 2008; Nordquist et al. 2008). These procedures may reveal a core symptom of phobias, post-traumatic stress, or panic disorders related to the phasic startle potentiation that are distinct from the sustained form of aversive conditioning typically used to model generalized anxiety disorder.

There are also limitations in current models of affective disorders and aggressive behaviors. For example, deficits in reward processes in depression or during withdrawal from chronic administration of psychomotor stimulant drugs have been modeled using intracranial electrical self- stimulation (ICSS) in non-humans (Markou and Koob 1991). However, ICSS cannot be readily translated directly to human subjects, and it is not clear whether the ICSS model is appropriate for the heterogeneous psychiatric conditions that involve depressive symptoms and anhedonia. In aggression research, it is apparent that there are distinct types of aggression, including the important distinction between hostile–impulsive–antisocial–intensely violent outbursts and the calculating, instrumental aggressive acts (Miczek et al.

1994; Miczek et al. 2004; Miczek et al. 2007b; Vitiello and Stoff 1997). Again, it is a challenge to both preclinical and clinical researchers to identify appropriate, discrete behavioral procedures that differentiate these processes.

In part to address the limitations of single behavioral screening tests, it is common for researchers searching for pharmacotherapies to employ a battery of tests. The idea here is that these tests may converge to approximate the targeted psychiatric dimension. However, one may question the value of combining several tests, each with limitations. For example, what is the added value of measuring a laboratory rat's locomotion from a dark, safe place to a brightly lit, open area in the elevated plus or zero maze, light/dark box and open-field test in an effort to characterize a potentially anxiolytic treatment? The use of multiple test procedures helps to increase confidence that a drug candidate is active under varied behavioral circumstances. It has been argued that different kinds of tests can be combined to establish the activity of a drug at different components of anxiety. So, contrasting the effects of a drug on tests where anxiogenic-like manipulation suppresses ongoing behavior (conditioned suppression, elevated plus maze) with tests where anxiety augments a particular response (potentiated startle, conditioned burying) can be used to demonstrate its activity under a broader variety of circumstances and increase confidence in its eventual clinical relevance. In the elevated plus-maze procedure, the animal's exploratory behavior of an unprotected open arm provides one operational definition of anxiety (Montgomery 1955). However, quick approach and exploration of an open area in an elevated plus maze may also reflect impulsive sensation-seeking behavior not related to the symptom of anxiety. Thus, an animal's assessment and avoidance of an open space or its approach to novel environs may be influenced by several factors, including factors unrelated to the construct of interest. The multiple determinants of specific behaviors such as activity and exploratory behavior may also be revealed from genetic analysis. For example, quantitative trait analysis has identified a locus (QTL) on the first chromosome that appears to influence exploration, whereas a QTL on the fourth chromosome appears to influence the level of activity and a QTL on chromosome 15 appears to be related to avoidance (Turri et al. 2001). Which of these behavioral features are specific to the hypothetical construct "anxiety" remains unresolved. The inclusion of several converging behavioral measurements addressing a single construct is one way to address this problem. So far, the major support for these frequently used procedures relates to pharmacological validation by medications that are clinically effective in the treatment of generalized anxiety disorders. As discussed below, this type of validation is built on circular reasoning and curtails innovative research efforts.

Several experimental procedures used to develop potential pharmacotherapies for anxiety rely on behavioral inhibition. Indeed, a behavioral inhibition system has been postulated as the common neural target for the action of anxiolytic drugs (Gray et al. 1984). However, there are complexities in the analysis of inhibitory behavior. First, the suppression of behavior due to non-reinforcement (i.e., extinction) is readily dissociated from suppression due to punishment contingencies by pharmacological interventions (Miczek 1973; Sanger 1985). Further, the neurobiological mechanisms that control inhibition of ongoing behavior are distinct from those that inhibit the initiation of a behavioral response (Eagle et al. 2008). One alternative procedure that may be appropriate for developing anxiolytic treatments is the fear-potentiated startle. In fact, promising anxiolytic compounds including positive modulators of the $GABA_A$ receptors or agonists at $5\text{-}HT_{1A}$ or $mGlu_{2/3}$ receptors modulate the startle response by prior presentation of a stimulus that was associated with electric shock (Grillon et al. 2003; Helton et al. 1998).

Principle 3: Preclinical data are more readily translated to the clinical situation when they are based on converging evidence from at least two, and preferably more, experimental procedures, each capturing cardinal features of the modeled disorder.

The demand for preclinical models for clinical treatment has spawned more pragmatic research strategies and tactics, including relatively non-targeted experimental screens. An early example is the popular and highly cited Irwin screen (Irwin 1968) that identified basic and simple drug-induced changes in a broad range of behavioral categories in mice. This type of observational screen has led to the current high through-put computerized systems for behavioral phenotyping (Crawley et al. 1997), although the rationale and expected outcome of some of these measures remain relatively poorly defined functions of CNS activity. Sometimes, screens for specific pharmacotherapeutic potential appear relatively far removed from the pathogenesis or symptomatology of the targeted disorder. For example, olfactory bulbectomy in the rat or the tail-suspension test have been proposed as rapid and efficient screens for compounds with antidepressant potential despite the relatively modest conceptual rationale for these techniques (Kelly et al. 1997; Steru et al. 1985). The use of screens as test systems gain relevance when consistent changes can be shown under the same conditions that predispose individuals to the development of psychiatric disorders. For example, increased immobility in the forced-swim test is produced by chronic stress, genetic breeding, diabetes, cardiovascular disease, endocrine dysfunction, and compromise of the immune system, all conditions which

predispose for the development of depression (Cryan et al. 2005). Other experimental preparations such as the anti-muricidal test for antidepressant-like drugs have not withstood critical and ethical analysis and disappeared from the preclinical laboratory (Fuller 1996; Horovitz et al. 1965).

What are the criteria that allow a screen to be considered as model, given the often interchangeable and indiscriminate usage of both terms for experimental preparations that are used in the study of compounds with pharmacotherapeutic potential? Among the most important considerations is the theoretical principle on which the preparation is based. So far, no model has captured the essence of the multi-factorially determined, polygenic, developmentally organized disorders in a truly homologous manner. Indeed, homology maybe an unrealistic criterion for a preclinical model. A screen is usually characterized by practical considerations of being a rapid, high through-put, preferably automated procedure. Most often, the term model is applied to an experimental preparation that has more theoretical aspirations; ideally, a model consists of an experimental preparation that engenders a cardinal symptom of a psychiatric disorder. Consider the escalation in cocaine taking over time when the individual has prolonged access to the drug (Ahmed and Koob 1998) or persistent cocaine taking that is resistant to aversive consequences (Deroche-Gamonet et al. 2004; Vanderschuren and Everitt 2004). These procedures begin to capture essential features of the compulsive nature of cocaine addiction. In recent years, the most pretentious term "paradigm" is used interchangeably with the terms "model" or "screen" in emulation of Isaac Newton's introduction of the experimental paradigm in physics.

Principle 4: A simple screen becomes a theoretically adequate model to the extent that it incorporates the cardinal symptoms characterizing the disorder. The more closely a model approximates significant clinical symptoms, the more likely it is to generate data that will yield clinical benefits.

The theoretical assumptions for selecting environmental, neurochemical, and genetic manipulations in order to model core symptoms

Historically, the independent variables that have been used to generate psychiatric symptoms in experimental models include environmental, neurochemical, and genetic insults, usually derived from the theoretical framework of the model's origin. For example, the environmental manipulations of separation from the maternal attachment or deprivation of social contact during a critical developmental period are potent determinants of behavioral disturbances that persist throughout the lifetime (Harlow and Suomi 1974; Suomi et al. 1975). These disturbances appear relevant to several human disorders, including affective disorders and alcohol dependence (Fahlke et al. 2000; Huot et al. 2001). A striking example of an interaction between environmental and genetic factors is the finding that men who underwent salient experiences during a critical developmental period and possessed an allelic variant of the MAO-A gene exhibited high rates of antisocial violent behavior as adults (Caspi et al. 2002). This illustration of a gene–environment interaction demonstrates a powerful approach that has yet to be fully exploited in preclinical models to study affective disorders, violence, drug and alcohol abuse.

Some experimental models developed for studying drug treatments involve highly complex environmental manipulations. For example, Willner and colleagues modified a chronic stress model to study depressive-like symptoms (Katz et al. 1981; Willner et al. 1987; Willner 1997). This procedure involved several weeks of continuous exposure to unpredictable and varied stressors that produced deficits in the preference for sweets, and these deficits appear to be reversed by chronic treatment with antidepressants. However, with complex procedures of this kind, it becomes difficult to identify the necessary and sufficient environmental manipulations that are responsible for the emergence of deficient reward processes. This problem is exacerbated by the fact that it is difficult to replicate the anhedonia-like outcome after chronic mild stress (Phillips and Barr 1997; Reid et al. 1997) and the variations of this complex procedure that have been developed to address the problem.

A more successful example of an environmental manipulation to produce a psychiatric symptom is the activity-based model of anorexia in rodents (Routtenberg and Kuznesof 1967). Rodents that are given access to a running wheel and limited access to food eventually fail to compensate with increased food intake, resulting in a decline in body weight but an increase in activity. These animals develop immunodeficiency, atrophy of the spleen and thymus, stress ulcers, and ultimately die if not rescued (Casper et al. 2008). This behavioral and physiological profile incorporates several essential features of anorexia nervosa, such as lower food intake while hungry, weight loss, escalated activity, and associated endocrine changes (Casper et al. 2008) and therefore represents a useful model for investigating treatment medications. This activity-based model is likely to be superior to other manipulations with stressors such as food restriction, restraint, or social isolation, which do not capture as many of the essential features of anorexia nervosa. Although specific stressors engender a distinctive behavioral and neurobiological response pattern (Pacak and Palkovits 2001), the phenotype

of anorexia is likely to be heterogeneous, as well as multiply determined, so that more than one model may be needed to fully understand the problem.

One of the most venerable environmental stressful manipulations for engendering behavioral abnormalities with relevance to psychiatric symptoms is isolated housing, as studied in both captive feral and laboratory-bred animals. When rats are isolated early in life, profound behavioral deficits emerge that are relevant to sensorimotor gating in the prepulse inhibition procedure. However, social isolation in a territorial species like mice differs considerably in behavioral outcome from a similar manipulation in colonial species such as rats or most primates. The "isolation syndrome," as originally termed (Valzelli 1973), was the gradual induction of aggressive behavior, which was viewed as a psychopathology in otherwise placid laboratory mice. In fact, adult male members of the genus *Mus* are quite intolerant of rival males and expel them from their territories, and the isolated male mouse resembles in many respects a territorial male (Brain 1975). Thus, isolation housing may produce symptoms of psychopathology in rats, but in mice, it reveals normal species-typical behavior.

A classic manipulation to induce symptoms in psychiatric disorders relies on pharmacological or neurotoxic treatments. Here, the conceptual framework is determined by the presumed mechanism of the inducing agent (Lane and Dunnett 2008). Thus, if a potentially therapeutic intervention is thought to be related to glutamate, then an inducing drug treatment is likely to be an agent with a glutamatergic mechanism of action such as phencyclidine or dizocilpine or ketamine. In many instances, the pharmacological manipulation used in a model acts by a mechanism with effects opposite to those of known therapeutic drugs. For example, dopamine agonists may be used to identify potential antipsychotic drugs, which act as antagonists at DA D2 receptors. This approach is used to identify antipsychotics by attempting to reverse the apomorphine-induced disruption of prepulse inhibition or the reversal of apomorphine-induced stereotypies. Such an approach is aptly labeled as "receptor" or "neurotransmitter tautology," clearly not conducive to innovative efforts (Geyer and Markou 2002).

A similar approach to induce symptoms that are related to major psychiatric disorders relies on neural insults, especially brain lesions. For example, lesioning hippocampal tissue in 1-week-old rat pups results in hyperresponsivity to stimulant and stress challenges and deficits in sensory gating deficits and social interactions in adulthood, symptoms that resemble features of schizophrenia (Lipska et al. 1993; Lipska et al. 1995; Sams-Dodd et al. 1997; Sams-Dodd et al. 1997). Although specific lesions have some value in identifying underlying processes, they are limited by the fact that they interrupt only one component of a highly complex and interactive neural circuit.

During the past two decades, the most intensively studied experimental manipulations to induce one or more core symptoms relies on molecular genetic methods (Casper et al. 2008; Geyer and Markou 2002; Zhuang et al. 1999). By now, it is evident that the bottom-up genetic approach that focuses on the overexpression or deletion of single genes becomes only relevant when it is developmentally time-limited, specific to brain regions, and independent from the genetic background. So far, the gene knockout methodology has been of limited value to focus the mechanistic inquiry into the neurobiological mechanisms of aggressive behavior, with gene manipulations on every chromosome having some influence (Miczek et al. 2001). Studies of the melanocortin system in obesity reveal a most productive use of manipulating the expression of a particular gene (Casper et al. 2008). The deletion of the gene for the melanocortin-4 receptor produced a mouse that showed adult-onset obesity, hyperphagia, hyper-insulinemia, and increased linear growth (Huszar et al. 1997). The role of this receptor in obesity was further established by pharmacological agonist and antagonist effects and eventually led to the identification of mutations in the melanocortin system in obese humans (Krude et al. 1998). The promise of such translational research is supported by the fact that 4–6% of morbidly obese individuals commonly show mutations of the gene encoding the melanocortin-4 receptor. In contrast to monogenic obesity, polygenic, developmentally, and multifactorially determined disorders are more common and require alternative strategies for translational research.

Principle 5: The choice of environmental, genetic, and/or physiological manipulations that induce a cardinal symptom or cluster of behavioral and physiological symptoms reveals the theoretical approach used to construct the model.

Which kind of validity is necessary for a preclinical model to render it translatable to clinical concerns?

Issues of validity have been discussed previously in the context of medications with antipsychotic, anxiolytic, antidepressant, or drug abuse treatment potential (Geyer and Markou 2002; Kornetsky 1989; McKinney and Bunney 1969; Schuster 1975; Willner 1984). These analyses typically distinguish between different types of validity, ranging from construct, predictive, to face validity. For example, does amphetamine-induced hyperactivity represent a valid model of amphetamine psychosis or non-drug-induced psychoses? In terms of face validity, this experimental preparation is severely lacking, but in terms of predictive validity for the reversal by so-called typical and atypical compounds with antipsychotic activity, it repre-

sents a simple initial screen for compounds with dopamine D2 receptor antagonism. Similarly, the forced-swim test (Porsolt et al. 1978), particularly in its modified form (Detke et al. 1995), achieves very good predictive validity in identifying effective antidepressant treatments and rejecting ineffective compounds (Cryan et al. 2002). By contrast, the construct and face validity of this and the related tail-suspension test remain questionable because there is no clear relationship to the etiology and symptomatology of the modeled disorder.

Principle 6: Preclinical experimental preparations that are validated by predicting treatment success with a prototypic agent are only able to detect alternative treatments that are based on the same mechanism as the existing treatment that was used to validate the screen.

From the viewpoint of translational medicine, simple screens, although reliable and efficient, fail to foster innovation in characterizing core features of a psychiatric disorder. There is an essential circularity in identifying treatments that work principally on a target and mechanism of a known treatment. Instead, behavioral and physiological functions, preferably approximations of the cardinal symptoms of a disorder, may offer more productive and theoretically satisfactory targets for model development. This limitation is apparent in drug discrimination procedures, which are designed to identify the stimulus properties of compounds with CNS activity. Although the drug discrimination method is highly informative and shows good concordance between laboratory animals to human subjects, its innovation is limited by its reliance on a well-characterized prototypic drug.

Another model whose validation depends on a single pharmacological agent is the neurotoxin-induced nigrostriatal cell death and motor dysfunctions for capturing essential symptoms of the neurodegenerative Parkinsonian movement disorder (PD; Lane and Dunnett 2008). The neurotoxin 6-hydroxydomanine in rodents or 1-methyl 4-phenyl 1,2,3, 6-tetrahydropyridine in monkeys produce long-lasting dopaminergic depletion and motor dysfunctions typical of PD (Jenner et al. 1984; Ungerstedt 1971a, b). These models have been validated mainly by responses to L-dopa, one of the most common drugs used in PD therapy. Thus, although these toxin-based models provide some translational value, they fail to model other aspects of the disease, such as involvement of non-dopaminergic cells and the lack of neuronal Lewy body aggregations. These latter features may be one of the reasons why novel pharmacotherapies have not translated well into the clinic.

Pharmacological validation is the major criterion used in experimental models for assessing liability for drug abuse and for developing drug abuse pharmacotherapy (Haney and Spealman 2008). One interesting feature of the drug abuse models in humans is the apparent dissociation between the subjective effects of craving for a drug such as cocaine and the actual cocaine intake. Although many compounds decreased self-reported craving for cocaine (for example, gabapentin, desipramine, pergolide, risperidone, ecopipam, selegeline, venlafaxine, and naltrexone), few of these drugs change cocaine use under controlled conditions (e.g., Fischman et al. 1990; Hart et al. 2004). Only one drug, modafinil, an alpha-adrenergic agonist with significant glutamatergic and dopaminergic actions, appears to reduce both the subjective and self-administration effects of cocaine (Hart et al. 2008). The dissociation between subjective ratings and actual cocaine use has been difficult to predict on the basis of the current preclinical models and should prompt more investigation of preclinical procedures, e.g., to characterize modafinil's profile more adequately.

Because the definition of psychiatric disorders are continuously being refined and modified, it is unreasonable to expect complete homology between a disorder and an experimental model in the laboratory, and as such, face validity can be achieved only partially. Moreover, some of the cardinal symptoms of psychiatric disorders are essential subjective feelings and states (e.g., sadness, guilt, or cravings) and are by definition difficult to define operationally in animal models. The value of a model may also depend on whether there are existing treatments available. For example, a model of cognitive dysfunction in Alzheimer's disease is useful if it predicts any behavioral improvement since there are few drugs currently available that produce substantial clinical improvement. In contrast, models of schizophrenia face a more considerable evaluative hurdle since effective antipsychotic drugs are available. In the case of schizophrenia, the need is greater for models for cognitive dysfunction. In the case of depression, what is needed is a model simulating the gradual onset of antidepressant effects.

Principle 7: The degree to which an experimental model fulfills the criteria of high internal or construct validity relative to face validity or predictive validity depends on the purpose of the model. It is more difficult to develop a model that provides insight into the etiology of a disorder than to predict therapeutic potential relative to a prototypic treatment.

How do we study affective processes in preclinical models and translate them to the clinic?

The evolutionary history of emotional expressions has long been traced to non-human organisms (Darwin 1872). Several lines of evidence indicate that affective and cognitive disorders have strong evolutionary roots, and it

appears reasonable to model the precursors of affective and cognitive processes in non-human species (Berridge and Kringelbach 2008; Panksepp 2003). For example, the distress of infants separated from maternal care can be quantified in rodents by recording ultrasonic vocalizations in precisely defined frequency ranges (Fish et al. 2000; Miczek et al. 1995; Vivian et al. 1997). A most intriguing analysis of different kinds of vocalizations proposes differentiating calls that represent distinctive affective expressions in specific behavioral contexts; these vocalizations may communicate affect during sexual intercourse, agonistic confrontations, maternal care, nociceptive reactions, withdrawal from intense drug taking, and during drug seeking (Burgdorf et al. 2001; Miczek et al. 1995; Mutschler and Miczek 1998; Panksepp et al. 1980; Winslow and Insel 1991). These species-typical vocal responses during salient situations may represent the precursors to expressions of affect in humans.

Classically, one of the earliest preclinical models of emotional behavior in rodents and non-human primates is the conditioned emotional response consisting of the suppression of ongoing instrumental behavior during the presentation of a stimulus that predicted the delivery of an aversive electric shock (Brady 1956). Initially, it was shown that antipsychotic drugs attenuated the behavioral suppression by the conditioned stimulus, but then, it was found that benzodiazepine drugs, which were known to be anxiolytic in humans, showed less consistent effects, and the model was subsequently replaced by punishment procedures (Millan 2003; Wuttke and Kelleher 1970). These models are based on the idea that conditioned emotional responses suppress ongoing behavior. The fear-potentiated startle response is another procedure based on a similar idea. In that procedure, an innocuous light stimulus that has been paired with an electric shock leads to a potentiated startle response when it is presented prior to a startling loud tone. By inference, this potentiation effect is attributed to a discrete fear state that is induced by the classically conditioning procedure (Davis et al. 1993; Grillon 2008).

Principle 8: Behaviorally defined symptoms are more useful than subjective or internal states in models used to translate clinical to preclinical measures and vice versa. Psychological processes pertinent to affect and cognition can only be studied in preclinical models if they are defined in behavioral and neural terms.

The study of pleasure and its neural basis is important for several psychiatric disorders such as anhedonia in depressives or in schizophrenics or in drug abusers (Ahmed and Koob 1998; Berridge and Kringelbach 2008; Markou and Koob 1991; Willner et al. 1987). One model for studying pleasure consists of observable responses to tastes. Newborn human infants exhibit distinctive tongue protrusions when encountering sweet tastes, which contrast with the gaping response to bitter tastes. These behavioral expressions of affect have their homologues in great apes, monkeys, and rodents (e.g., Grill and Norgren 1978; Steiner et al. 2001). Early studies of drug reward proposed an important role for mesolimbic DA in the hedonic features of reward for social, sexual, and food-motivated behavior and for drug taking (Wise 2006). However, more recent studies suggest a range of alternative interpretations (Baldo and Kelley 2007; Berridge 2007; Salamone et al. 2007), including a role of mesolimbic DA in reward prediction, motivation, attention, learning about reward, and incentive salience (Barbano and Cador 2007; Berridge and Kringelbach 2008; Robbins and Everitt 2007). In fact, phasic and tonic DA activity in mesocorticolimbic projections may characterize the anticipation, as well as the consequence of highly salient events, both intensely rewarding and ostensibly aversive (e.g., Ferrari et al. 2003; Horvitz 2000; Scott et al. 2006). The efforts to deconstruct the processes underlying reinforcement and reward in terms of behavior and neural coding offer rich opportunities for translation to studies in humans. Moreover, imaging studies in humans have begun to focus on generator mechanisms for basic and higher-order pleasures in subcortical structures and orbitofrontal cortex (Kringelbach 2008; Panksepp 2003).

Two other measures used to assess hedonia or reward are taste for sweet fluids and threshold for brain stimulation reward (Grill and Norgren 1978; Markou and Koob 1991). However, each of these models also have limitations. While the taste for sweet appears to be a direct index of pleasure, it may also be confounded by other factors such as caloric value and fluid balance, especially in experimental models that incorporate environmental stressors. The brain stimulation measure is limited to preclinical studies, and it is not clear whether it models the full clinical profile of anhedonia. Nevertheless, it has been proven informative in studies characterizing drugs of abuse, antidepressants, and antipsychotic treatments (Moreau et al. 1995; Wise et al. 1992). Clearly, there is a continuing need for insightful and predictive experimental models of disturbances in affect to test new antidepressant pharmacotherapies.

Conclusions

The close links between preclinical and clinical studies in psychopharmacology have been fueled by methodological innovations and refinements that enhance the translational value of experimental models. In the course of the first six decades of psychopharmacological research, a wide range of experimental models have successfully contributed to the study of neurobiological mechanisms and medication

development. In this discussion of the principles that govern translational research in psychopharmacology, we have attempted to emphasize the importance of a sound conceptual basis for selecting core symptoms of psychiatric disorders when constructing experimental models.

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