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Review

Mapping patterns of depression-related brain regions with cytochrome oxidase histochemistry: Relevance of animal affective systems to human disorders, with a focus on resilience to adverse events

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ABSTRACT

The search for novel antidepressants may be facilitated by pre-clinical animal models that relay on specific neural circuit and related neurochemical endpoint measures, which are anchored in concrete neuroanatomical and functional neural-network analyzes. One of the most important initial considerations must be which regions of the brain are candidates for the maladaptive response to depressogenic challenges. Consideration of persistent differences or changes in the activity of cerebral networks can be achieved by mapping oxidative metabolism in ethologically or pathogenetically relevant animal models. Cytochrome oxidase histochemistry is a technique suitable to detect regional long-term brain activity changes relative to control conditions and has been used in a variety of animal models. This work is summarized and indicates that major changes occur mainly in subcortical areas, highlighting specific brain regions where some alterations in regional oxidative metabolism may represent adaptive changes to depressogenic adverse life events, while others may reflect failures of adaptation. Many of these changes in oxidative metabolism may depend upon the integrity of serotonergic neurotransmission, and occur in several brain regions shown by other techniques to be involved in endogenous affective circuits that control emotional behaviors as well as related higher brain regions that integrate learning and cognitive information processing. These brain regions appear as primary targets for further identification of endophenotypes specific to affective disorders.

Contents

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1. Introduction: conceptual issues surrounding animal models of affective disorders – what has been achieved and what are optimal directions for inquiry?

Affective disorders constitute a major public health issue (Murray and Lopez, 1997) and represent much of the unmet needs in health care (Wittchen and Jacobi, 2005). Our understanding of depression went through a revolution after the serendipitous discoveries of clinical antidepressant effects of monoamine oxidase and synaptic biogenic amine reuptake inhibitors in the late 1950s (Healy, 2000). Thus restitution of affective homeostasis can be achieved in many patients, but by no means all, through the facilitation of a variety of neurochemical pathways, the initial common denominator of which is still thought to be enhancement of monoamine (noradrenaline, serotonin and dopamine) neurotransmission at postsynaptic receptors (Slattery et al., 2004). When effective, these clinical effects are thought to reflect diverse downstream effects such a facilitation of brain growth factors such as e.g., brain.derived neurotrophic factor (BDNF).

Yet many of the available pharmacotherapeutic measures are increasingly perceived as unsatisfactory, especially after the multicenter STAR*D study that only yielded 28% remissions with a widely used SSRI antidepressant (Warden et al., 2007). Currently much hope is placed on discovery and verification of new leads not only from pre-clinical animal models (Chang and Fava, 2010; Healy, 2000; also see Burgdorf et al., this issue) but the integration of classic theories of depression (Bowlby, 1980; also see Zellner et al., this issue) with our emerging understanding of the underlying primary-process emotional circuits (Panksepp and Watt, 2011; Watt and Panksepp, 2009; see also Coenen et al., this issue).

In the quest for novel and even better antidepressant treatments, major efforts have been made to develop relevant animal models. Attempts to provide reliable measures for predicting clinical antidepressant efficacy have been successful: several reasonably easy to use screening methods with good predictive value are available for use in rodents (Cryan et al., 2002). Nevertheless, as no definite new lead has emerged from the exploitation of these techniques to yield new and better antidepressants, one has to consider the possibility that high sensitivity of currently used preclinical models for existing antidepressants may not be an optimal guide for detecting new neurochemical targets and novel compounds that may have more robust and generally effective therapeutic effects. There is a strong implicit tendency to interpret traditional (and rather gross/general) behavioral changes in drug screening tests as signs of depression, which may be incorrectly deemed adequate models of human depression itself, despite caveats (e.g., Harro and Oreland, 2001; O'Neill and Moore, 2003). An alternative view is that the next generation of models need to focus on manipulating and monitoring relevant brain affective circuits more directly (Panksepp, 2010). Since such a critical analyses have not yet penetrated the field, although perhaps implicit in the recent emergence of alternative models, we will address pre-clinical models of depression from that vantage. Without a common public database we have very little knowledge of how many false positive (Type I errors) or false negatives (Type II errors) such findings have produced.

A unifying feature of most currently used models of depression is that they use a behavioral readout that is brought about by something that we, humans, consider stressful and aversive, and that can be attenuated or reversed by clinically efficient antidepressants. Testing conditions have been optimized for detection of these behavioral changes (e.g., reduced sucrose intake as a hedonic measure) and those specific kinds of antidepressant effects (e.g., restoration of sucrose intake), often with no attempt at any discussion of the psychological-affective components of depression that are most evident clinically (e.g., namely why depression feels so bad (see Zellner et al., this issue), with increasing concern about the face validity of many commonly used measures (e.g., do depressed humans reduce their intake of sweets).

Possibly because of the need for extensive optimization before popular model systems can be used in reliable ways, laboratories often fail at their first attempts to reproduce original findings (see e.g., Willner, 1997), especially since environmental variables considered unspecific can interact strongly with the very general stressful interventions commonly used in shaping depression-related behavioral outcomes (Chesler et al., 2002; Wahlsten et al., 2003). The universal need for optimization of pre-clinical psychiatric models unfortunately often makes the interpretation of observed effects of established antidepressants less straightforward than is commonly believed.

Putting the above in perspective, what could guide further pre-clinical depression model development into a more fruitful and affectively more rigorous directions? We suggest there are two rather different but potentially convergent approaches. At the behavioral level, instead on relying just on such general stress measures such as general locomotor activity, struggling in deep water, and measures strongly related to homeostasis such as sucrose intake, more use should be made of direct manipulation of and behavioral expressions of relevant affective states that have been related to the primary-process (or *basic*) emotional circuits of the brain (Panksepp, 1982, 1998; for a discussion of primary-process conceptualizations, see Panksepp's lead essay of this issue). Likewise, it is especially important to combine such manipulations with direct measure of how brain-specific emotional stressors modify long-term arousal of specific brain systems, especially affective ones such as those that mediate 'reward' and 'punishment' effects with direct brain stimulation (Panksepp, 2010).

In such alternative approaches, a study of more specific behavioral reflections of basic emotions, such as primal emotional vocalizations, may be especially useful in understanding affective shifts that may lead to psychopathologies. But for optimal progress, such more naturalistic emotional measures need to be supplement by measures of long-lasting brain changes, including those that have the capacity to highlight chronic shifts in higher brain regions that mediated cognitive information processing, that may be involved in therapeutic drug efficacies. What we can currently be confident of is that current depression therapeutics can instigate long-term brain changes that can be promoted significantly with various pharmacological interventions. However, many effective medications take a long time to yield optimal therapeutic effects, suggesting diverse downstream cascades that are set in motion by the initial pharmacologically provoked synaptic changes (Duman, 2009). In any event, if we were able to identify consistent *in vivo* neuroanatomical and neurochemical readouts of depression, these could serve as superior biomarkers for predicting antidepressant effects. The relevant variables in question may be monoamine-related, growth-factor related, etc., but it is important to have objective and hopefully selective neuroanatomical and neurochemical indicators of clinically relevant depressive vectors as well as therapeutic ones.

The promise of pathogenetic models with neurochemical readouts is quite obvious but the proper brain targets may be difficult to identify, requiring investments initially in measures of long-term brain changes that correlate with depressive cascades. One key will be increasing our capacity to monitor changing sensitivities in basic affective circuits of the brain, a challenge that is starting to be met by monitoring brain circuits that generate emotional vocalizations and reward and punishment functions of brain circuits. The role of more cognitive brain circuits is harder to study. In any event, the key issue for both is improving our ability to specify which specific brain locations/networks deserve ever more attention for