Synaptic Transmission and Chronic Drug Use

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Summary of Barden (2004)

Barden (2004) presents an assessment of the hypothalamic-pituitary-adrenocortical (HPA) changes that can result from successful antidepressant therapy. Barden asserts that evidence indicates incorrect action by the glucocorticoid receptor (GR) system may have an important involvement in these HPA changes.

The key mechanism for HPA activation is in hypothalamic corticotropin-releasing hormone (CRH) which acts in conjunction with vasopressin. Cortisol secretion, a key element in this process in humans (corticosterone in rodents), which is stimulated by the ACTH. Control of sensitivity to ACTH is mediated in part by sympathetic innervation in the adrenal gland. That action in turn is mediated by such effects as the circadian rhythm, and stress levels. In addition, feedback action from adrenal steroids contribute to HPA activation levels. The GR appears to be a key in mediating the impact of the HPA through its mediation of the high-stress levels of glucocorticoids and the negative impact those have on the HPA system.

Barden (2004) Experiments

Barden (2004) reports also that his group prepared a modified germ line of mice in which defective glucocorticoid feedback was artificially induced. The goal of this experiment was to determine if lack of responsiveness to corticosteroids found in many depressed patients was causally lined to both the pathogenesis and the patients' responsiveness to antidepressant drugs. When tested, these mice demonstrate similar HPA system changes consistent with those seen in patients with affective disorders and depression (Barden 2004). These characteristics include increased HPA activity, resistance to dexamethasone, feeding issues, and cognitive problems. A second strain of mouse developed with brain-specific loss of GR function found HPA systems activated at times opposed to the mouse's normal circadian rhythms, such as in early morning. This time-shift is characteristic of depressed patients also. These experiments demonstrated that dysfunction in the GR system may be causally linked to the neuroendocrine elements of affective disorders (Barden 2004). Barden's team also demonstrated that the symptoms are reversed when the mice are treated with antidepressants. They have also demonstrated that mice with brain-generated malfunctioning GR systems also demonstrate circadian phase shifts of the HLA systems consistent with those seen in patients with affective disorders.

When antidepressants are successful, patients with affective disorders see a normalization of the operation of the HLA system, possibly by increasing the ability of the brain to bind the corticosteroid immunoreactivity. Furthermore, these changes were not dependent on any preferential inhibitory action that the antidepressants had on the reuptake of monoamine neurotransmitters. In further experiments with mice, Barden (2004) demonstrated that antidepressants may change corticosteroid receptor capacity and thus simultaneously decrease ACTH, corticosterone levels and adrenal sizes. This action implies that depressed patients may have less effective corticol feedback systems.

These results have led Barden (2004) to conclude that antidepressants may have, as a primary action, the stimulation of corticosteroid receptor gene expression. This would result in decreased HPA activity and reduced expression of CRH, both implicated in depression. It is unclear whether HPA system normalization is a requirement for mood improvement. This

provides clues for future development of antidepressants that focus on HPA regulation.

Synaptic Effects and Chronic Drug Use (Barden, 2004)

Excessive levels of ACTH and glucocorticoids are found in patients with severe depression and imply some serious dysfunction of the HPA system in those patients (Barden, 2004). Cushing's syndrome, a result of excessive levels of cortisol, either from disease states or from taking glucocorticoids, may cause symptoms that are clinically undifferentiable from primary psychiatric illnesses. Because HPA is sensitive to stress and also is tied to the correct functioning of the GR system, understanding the HPA and its relationship to antidepressants is a crucial element in improving that therapy.

It is thought that in at least some depressed patients, an abnormal circadian secretion pattern may not respond to exogenous steroid administration (Barden, 2004). Experiments have provided evidence that the corticotrophic cells have lost their sensitivity to CRH or possibly a restricted responding secretion of ACTH to CRH activation signals (Barden, 2004). It is believed that this latter is more common, with a reduced ACTH response to CRH secretions. There may also be other factors reducing ACTH responsiveness. There also are clear genetic susceptibilities to affective disorders that may make individuals more or less sensitive to disruptions in these neurochemical pathways (Barden, 2004).

Even with genetic susceptibility, depressive disorders are generally triggered by stress. Some evidence indicates that elevated levels of glucocorticoid can result in reduced number of GR-containing cells in the hippocampus which mediates the suppression of CRH neurons in the paraventricular nuclear (Barden, 2004). Diminished corticosteroid receptor concentration due to various dysfunctions or gene expression may also be a factor in explaining the altered HPA systems of severely depressed patients (Barden, 2004). Evidence for this is not conclusive, nor is it clear whether the initial issue is in the hippocampus or hypothalamus or whether there are other factors that cause such dysregulation.

In chronic drug use, similar synaptic effects are also present. Chronic drug use can result in alterations of gene transcription, alterations in gene expression, and thus to changes in protein synthesis on the cellular level. Opiod dependence has been strongly linked to altered HPA axis functions (Wand et al., 2002). As a result, the changes in HPA documented in Barden (2004) have a direct link to issues of chronic opiod use.

Barden (2004) Compared to Foster & Neufeld (2013)

Barden's experimental results with the malfunctioning GR systems and antidepressants lend support to Foster and Neufeld (2013) who noted that the HPA reactivity was directly linked to depression. Foster and Neufeld, however, also linked HPA reactivity to the microbiota of the individual. The results Barden (2004) and others initially reported on the relationship of HPA dysfunction with affective disorders such as depression are reported in Foster and Neufeld as accepted understanding of the function of the HPA axis. In particular, however, Foster and Neufeld reported that other evidence showed a direct link between microbiota in the gut and HPA activity. These microbiota play an important part in programming the HPA axis during infancy, as well as help determine the mechanisms for stress reactivity later in life. Other studies have found that food-borne pathogens (*Citrobacter rodentium and Compylobacter jejuni*, for example) can directly influence CNS functioning via stress circuitry. These studies implied that both neural and immune systems pathways are used to control HPA activity (Foster & Neufeld 2013). The evidence also implies that there is a critical window during development in which the

microbiota can influence CNS wiring with respect to stress-behaviors (Foster & Neufeld 2013). While Barden's experiments showed that malfunctioning GR systems affect the HPA action, Foster and Neufeld point out that microbiota, particularly in certain growth stages of young mice, can partially control the development of the HPA functions as well. Thus, Bardon (2004) supports Foster and Neufeld (2013), but the latter extends the causal factors to include other sources of GR and HPA dysfunction.

At the synaptic level the sensory neurons in the ENS are the primary direct connection between the microbiota and the CNS. The sensory neurons connect to enteric neurons that control the motility of the gut. In addition, the microbiota appear to have synaptic-like connections to the vagal nerves in the gut. In mice that are "germ free" (GF) these sensory neurons tend to be less responsive than in normal mice. Yet, if fed probiotics, the sensory response of the neurons improves toward normal levels. This implies that changes in electrophysiological responses occur in ENS neurons as a direct result of changes in the microbiota (Foster & Neufeld 2013).

These results imply that long-term antidepressant effectiveness may be mediated by the use of probiotics to assist in microbiota-level adjustment of the HPA system toward more normal levels.

References

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