The HPA axis and GABA-Glutamate Systems as Potential Antidepressant Targets in Prostate Cancer

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Abstract: A common treatment for Prostate Cancer includes androgen-deprivation for a period of months prior to radiation or surgery. Some data suggest that this may exacerbate the already elevated depression levels of these patients, arguing for concomitant application of antidepressant therapy. However, the various waves of antidepressants developed in the last 40 years have shown only arguable specific efficacy over placebo, plus significant side-effects which may hinder treatment decision-making and compliance. This paper outlines two emerging and potential pathways for development of new pharmacological agents for depression that hold promise of helping patients to reduce their depressive symptomatology.

Keywords: Antidepressants, efficacy, GABA, glutamate, HPA.

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The adverse effects of depression (including bipolar depression) on physical health, relationships and cognitive performance are well reported [1-4]. The damaging effects of depression are further indicated by the finding that it poses as great a risk for mortality as does smoking, even when related health factors such as blood pressure, alcohol intake, cholesterol and social status are taken into account [5]. Depression is the principal contributor to the Total Disease Burden [6], and predicted to become the second leading cause of mental illness by 2020 [7, 8].

Receiving a diagnosis of prostate cancer (PCa) is often accompanied by elevated depression [9-11], with the incidence of this psychological disorder at about 26% [12], four or five times the national average for non-PCa men of similar age [13]. When combined with the fact that the risk for developing prostate cancer by age 85 years is 1 in 5 in Australia [14], the possibility of getting PCa and being depressed is significant. There is also evidence that elevated depression in the PCa patient group can have powerful and extended effects by hindering treatment compliance and decision-making [15], perhaps reducing the longer-term success of treatment and further limiting patients' chances of recovery [16]. For example, depression has been shown to cause up to 48% of some cancer patients to withdraw from treatment [17], thus constituting a major medical issue as well as reducing patient well-being.

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Bearing these facts in mind, it is of particular relevance to consider the usage rates and effects of anti-androgen therapy hormone treatment (HT), which is commonly given to PCa patients for 18 months and may even be applied for several years to reduce the size of tumors and symptomatic progress [18, 19]. For example, in a study of 4,892 PCa patients who underwent either radical prostatectomy or external beam radiation therapy, 1,105 (21%) also received HT [20]. However, in their examination of 36,496 PCa patients' records in 1999, Zelefsky and colleagues [21] noted that the incidence of HT was between 31% and 79%, depending upon the risk status of the patients, and that the use of HT had increased from an average of 8% in 1994 to 51% of PCa patients in 1999. It may be that usage rates of HT vary across samples but, at least from these data, it might be concluded that the prescription of HT for PCa patients is not uncommon and therefore justifies consideration of its efficacy and side effects.

Described as a "cornerstone treatment of advanced prostate cancer" in Sharifi, Gully and Darhut's 2005 review of the effectiveness of HT from data published during the preceding 40 years [22], HT can reduce bone pain, fractures, spinal cord compression and ureteral obstruction as well as PCa tumor size, but may not improve long-term survival when used in cases of advanced PCa. By comparison, when used with radiation therapy in less severe PCa, HT does show a survival benefit [22], and may be a treatment of choice. However, some side effects are also apparent, including hot flushes, reduction in bone mineral deposit density, osteoporosis and anemia [22]. HT may also cause or exacerbate fatigue [22] and deficits in memory and cognitive processing, contributing to the development of depression [23-26]. PCa patients undergoing HT also report reduced energy and poorer sexual and urinary function [27] than PCa patients undergoing other treatments [28]. These and other

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side effects may be more closely related to lowered testosterone rather than HT alone [29], a finding that reflects other data regarding the link between hypotestosteronaemia and depression in older men [30], although there are also data suggesting that the link between lowered testosterone and depression may be reciprocal [31], perhaps confounding the issue of mood disorders in older PCa patients who receive HT.

Whichever direction the relationship between HT-induced lowered testosterone and depression moves, PCa patients are significantly more likely to experience mood disorders, particularly depression, than other men of the same age [32], and this may be a result (at least in part) of the application of HT. Therefore, physicians who prescribe HT (for very defensible reasons) may also need to be aware of the increased likelihood of their PCa patients developing depression. As well as being unpleasant, depression can also have deleterious effects on patients' ability to make decisions about their treatment and develop effective lifestyle strategies to deal with the other side effects of HT that they experience and which were mentioned earlier in this paper. As well as the mood-effecting outcomes of HT, there are also data suggesting that PCa patients experience significant fear, anxiety and consequent feelings of helplessness which may also lower their mood independently of HT [33-35].

While careful noting of patient behavior during consultations, and/or formal psychological or psychiatric assessment, can inform physicians about the affective state of their patients, treatment of the depression that (a) occurs with greater frequency among PCa patients than their healthy peers, (b) may be related to the shock of receiving a diagnosis of PCa, and (c) can be exacerbated by HT, requires care. Such treatment may be undertaken by application of pharmacological agents in the form of antidepressants, as well as *via* psychotherapy techniques. However, although some data indicate that selective serotonin reuptake inhibitors may reduce hot flushes produced by anti-androgen therapy, as well as combat general depressive symptoms [36], the efficacy of traditional pharmacological antidepressant therapies is not absolute [37].

ANTIDEPRESSANTS: MECHANISMS, SIDE EFFECTS, EFFICACY

Traditional antidepressants are based upon the "monoamine hypothesis", that explains depression as arising from a depletion of the neurotransmitters serotonin, noradrenalin and dopamine in the brain due to the re-uptake of these neurotransmitters in the post-synapse by monoamine oxidase. This is plausible because serotonin constitutes the largest cohesive neurotransmitter system in the brain and innervates all brain areas [38], and changes to serotonin influence the core behavioral and somatic functions that underlie depression in laboratory animal studies, including appetite, sleep, sex, pain responses, body temperature and circadian rhythm [39]. In addition, human postmortem studies have shown lowered levels of serotonin in depressed patients [40-42], although serotonin depletion studies indicate that reduced serotonin may be a necessary, but not a sufficient, condition for depression [38, 43]. Noradrenalin is also a major neurotransmitter, and modulates functioning of the prefrontal cortex (which uses working memory to regulate behavior and attention), as well as having an important role in the acquisition of emotionally-arousing memories. Dopamine also modulates activity in brain areas involved with reward and motivation, working memory and attention [44], and has been inculcated in the development of depression [45] although postmortem and depletion studies have been equivocal [38]. Thus, depletions in serotonin, noradrenalin and dopamine have been the principal targets for antidepressants.

However, antidepressants that act *via* blocking the effects of monoamine oxidase have been shown to have only limited efficacy in large trials. For example, Stahl [46] commented that only about two-thirds of actual (non-clinical trial) patients receiving antidepressants actually showed reduced depressive symptoms. Further, a major meta-analytic review of the effectiveness of antidepressants revealed that antidepressants did show a statistically significant superiority over placebo, but that the difference in test scores (1.7 points on the 52-point Hamilton Depression Scale) was "clinically negligible" [47; p. 1, 48]. More recently, Pigott, Leventhal, Alter and Boren [49] reviewed four major meta-analysis of the efficacy of antidepressants and supported Kirsch *et al.*'s comment that the difference between medication and placebo was marginal. While some authors have criticized the use of meta-analysis and the randomized placebo-controlled studies on which they are based, suggesting that these are not valid replicates of actual clinical practice [50] and that those outcome measures of change in depression are "arbitrary" (p. 451 [50]), there are few data which show strong support for the efficacy of traditional antidepressants. When added to the finding that studies which reported positive outcomes from drug treatment for depression were between five and 16 times more likely to be published than reports of negative or unequivocal outcomes [49, 51, 52] the likelihood of research which supports Kirsch and colleagues' conclusions regarding the lack of efficacy of antidepressants, is dramatically increased. Finally, antidepressants elevate the levels of monoamine neurotransmitters within a few days but do not alter mood for several weeks [53], suggesting that they may regulate longer-term trophic effects that are actually responsible for depleted synaptic monoamines [46].

In addition to the uncertain efficacy of traditional anti-depressants, most of these treatments also have significant side-effects for patients, including hypotension, tremors, insomnia, increased appetite (and weight gain), dry mouth, blurred vision, urinary retention, headaches, acute hyper-tension, sedation, confusion and problems with motor coordination, many of which pass after a few weeks at about the same time as the antidepressant effect begins to take place. Other lasting side-effects are constipation and urinary retention, drowsiness and difficulty concentrating. Some patients experience ventricular dysrhythmias, nausea, anorexia, insomnia, loss of libido and failure to reach orgasm [54]. Some antidepressants have also been implicated in elevated risk of patient suicide [55].

Clearly, there are some problems in the prescription of traditional antidepressants to PCa patients who, like most cancer sufferers, experience a major shock and challenge to their equanimity, fear, and confusion, all of which may contribute to the development of depression. However, the

application of HT, with its significant side effects upon patient mood, makes PCa patients (and other patients that receive HT) a particular focus for the development of more effective pharmacological treatments for depression. Two potential pathways to such antidepressant treatments are the HPA axis and the GABA/glutamate neurotransmitter systems, and each of these will be briefly described below.

NEWER DEVELOPMENTS

HPA Axis

One of the more recently-investigated pathways to treat depression is *via* re-establishment of normal function in the hypothalamic-pituitary-adrenal (HPA) axis, generally regarded as the biological focus of an individual's vulnerability to depression [56]. The HPA axis responds to stress by secreting corticotropin-releasing hormone (CRH) from the hypothalamus which then instigates the secretion of adrenocorticotropic hormone (ACTH) from the pituitary into the bloodstream, which in turn causes the synthesis and release of cortisol from the adrenal cortex [57]. Chronic stress can therefore lead to elevated levels of cortisol, which also contributes to an elevated risk of depression [58]. Higher levels of its trophic precedents CRH and ACTH, plus cortisol itself, are consistently seen within depressed patients [59, 60], with some data [61] indicating that up to 80% of depressed patients have elevated cortisol levels. Gold, Drevets and Charney [62] described several pathways between elevated cortisol and depression, including alteration of prefrontal cortex function, amygdala and hypothalamus hyperactivity and reductions in volume and function of the hippocampus.

Antidepressant treatments based upon HPA axis function have included antiglucocorticoids to inhibit cortisol synthesis (aminoglutethimide, ketoconazole, metyrapone) [63], with some supportive data from animal studies [64] and with depressed patients [65]. CRH has been targeted by Gold, Licinio, Wong and Croussos [66] and Holsboer [60] in studies using the CRH-antagonist R121919, which has been shown to reduce major depressive disorder in clinical Phase I studies [67, 68], although these initial data require evaluation in full clinical trials.

GABA and Glutamate

One other possible avenue for future development of antidepressant medications may lie with the neurotransmitters glutamate and gamma-aminobutyric acid (GABA). Malfunction of these neurotransmitters upsets the balance between their excitatory (glutamate) and inhibitory (GABA) effects of upon brain synaptic activity, supporting potential links to depression *via* loss of cognitive ability [69], neuron and glial apoptosis [70], dysregulation of growth factors in the brain [71], interference in dopamine firing [72] and decreased serotonin and noradrenalin expression [73]. Several research studies have demonstrated that depressed patients experience malfunction of GABA and glutamate systems [72, 74-79] and that glutamatergic drugs which target the receptors AMPA, NMDA and KA may enhance synaptic signalling within the glutamate system, but no trials of the effects of medications based upon these data have yet been reported [80]. Other potential research foci for development of new antidepressants lie in examination of brain-derived neurotrophic factor [81], selective serotonin receptors [82], cytokines [83], the anti-epileptic Pregabalin [84], and a concentration upon neuronal plasticity rather than neurogenesis [85].

IMPLICATIONS FOR CLINICAL PRACTICE

HT remains a treatment of choice for at least one in five PCa patients and most probably more. While there are sound data supporting its application in many cases of PCa, HT also has significant side effects that may instigate or exacerbate patient feelings of depression. Because lowered mood states can detract from patients' decision-making and lifestyle management of their disease and its treatment, consideration of possible use of antidepressant therapy is important for clinicians. However, these therapies also have significant side effects and their efficacy may be questioned.

Therefore, although still in their infancy as regards clinical use, the development of newer antidepressant medications based upon HPA-axis and GABA models holds promise for the clinical oncologist in several ways. First, as PCa increases in incidence with an aging population, it may be expected that greater numbers of patients will present with this disease, and that at least a proportion of them will experience depression as a result of the shock of receiving a diagnosis of cancer, as well as *via* the side effects of HT. Second, the application of a wider range of hormone-based therapies (including anti-androgens) can also be expected to increase, not only because they are well-established in the treatment of metastatic disease, but also because recent randomized trial data [86] have shown their efficacy in neo-adjuvant (prior to radiotherapy) and adjuvant (following radiotherapy) treatments, particularly improvements in the length of time patients are free from biochemical and other evidence of recurrent disease. The use of ultrasensitive PSA testing following initial treatment by surgery or radiotherapy has led to earlier detection of recurrent disease and the early use of hormone-based therapies in that setting is under investigation [87]. With these newer hormonal-based treatments, new challenges to psychological patient well-being may also arise, as well as those currently presented by HT. Third, if the initial findings from HPA-axis and GABA development trials continue, antidepressants based on these models may be relatively free of the deleterious side effects noted above for traditional antidepressants and, as such, may constitute an alternative pharmacotherapy for the treatment of depression among PCa patient groups.

Therefore, development and clinical trialing of some of these new approaches to antidepressants briefly mentioned here may lead to significant improvements in patients' psychological well-being as well as avoidance of some of the complications from existing antidepressants that may adversely affect cancer treatment outcomes (such as poor treatment compliance and premature withdrawal from treatment). If their effectiveness is demonstrated *via* traditional clinical evaluation protocols, these screening tools and interventions could become a routine part of prostate cancer treatment, as well as suggesting new lines of research in other cancers, particularly breast cancer, in which the use of HT is also common.

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