

DHEA Modulates Immune Function: A Review of Evidence

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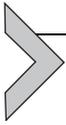
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Abstract

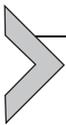
DHEA and DHEA-S have numerous associations with multiple aspects of immune function and are often characterized as beneficial and supportive of immunocompetence. However, closer inspection of these studies reveals confusion regarding the immunological components modified, the mechanisms of action, and degree of impact, and even whether these hormones even have direct action or are mediated by metabolites and interactions with other hormones and hormone receptors. Additionally, much of the research is conducted on rodent models using very high concentrations of hormone supplements, which may not be representative of the effects of these hormones in natural circulating concentrations, or may not translate to human physiology in a meaningful way. Here, we review the effects of DHEA and DHEA-S on immune function and examine the potential roles these hormones play on specific components of immune function. Drawing from the literature on hormone supplementation, as well as studies examining the natural circulating levels of DHEA and DHEA-S on specific immunological components and disease processes, we argue that DHEA has differential

actions on human immune function, and that its effects are further shaped by concentrations of other hormones. Of particular interest is the role of DHEA as an anti-glucocorticoid, and for its actions on both androgen and estrogen receptors. With additional research, DHEA may be useful as a therapeutic, particularly in diseases with high levels of inflammation, or where adrenal production is altered. The convoluted nature of DHEA-immune interactions makes direct effects difficult to interpret, and future research needs to consider direct, intracrine, and downstream effects of these hormones.



1. INTRODUCTION

The adrenal androgen dehydroepiandrosterone (DHEA) has been implicated in a diverse array of physiological processes, despite that it is often considered a precursor hormone with a primary role as a storage pool for downstream androgen and estrogen synthesis (Labrie et al., 1998). Characterizations of the hormone as a “fountain of youth,” as well as the availability of DHEA supplements to be bought over-the-counter as a dietary supplement, make research on DHEA particularly relevant and timely. DHEA has impacts on immune function and disease resistance, but its interactions with other hormones, lack of a clear independent mechanisms of action, discrepancies between human and animal physiologies that make direct conclusions complicated, and confusions about how to characterize the principal actions of this hormone make understanding these effects difficult. In this chapter, we review the current literature on DHEA and immunity, particularly in humans.



2. MECHANISMS OF ACTION IN IMMUNOMODULATION

As DHEA’s numerous associations with immunological outcomes and biomarkers are investigated, the mechanism of action whereby DHEA moderates immunological components remains equivocal. Unlike other steroid hormones, DHEA has no known unique receptor, and its physiological role is described as a precursor for the synthesis of downstream hormones. Multiple avenues whereby DHEA may initiate immunological changes are being explored (Prough, Clark, & Klinge, 2016; see Table 1), although much more research is needed.

Table 1 Potential Mechanisms of Action on Immune Function

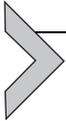
Mechanism	Explanation	Citations
Androgen and estrogen receptors	Concentration-dependent binding to androgen and estrogen receptors	Chen et al. (2005)
NF- κ B	Inhibits transcription factor	Du, Khalil, et al. (2001)
Receptor in T-cells	Evidence of intracellular binding site in T cells	Meikle et al. (1992)
Receptor in monocytes	Evidence of intracellular binding site in monocytes	McLachlan et al. (1996)
IL-2 transcription enhanced	Evidence of enhanced transcription of IL2 mRNA in response to DHEA treatment	Suzuki, Suzuki, Daynes, and Engleman (1991)
Conversion to metabolites	DHEA metabolites show more potent protective responses to viral infections	Loria (2002)

One potential avenue of action is through conversion to downstream hormones in both endocrine and intracrine fashions. As a precursor hormone, DHEA concentrations are physiologically tied to downstream metabolites, and some of the purported actions of DHEA may be a result of modified synthesis of these other hormones. Some of these effects may be the result of conversion to androgens or estrogens, with consequential action on androgen and estrogen receptors via normal processes (Labrie et al., 1998). Other effects may be mediated by downstream metabolites. For example, DHEA enhances immunity in mice infected with lethal viral infections (Loria, Inge, Cook, Szakal, & Regelson, 1988), but further research illustrates that the downstream hormone androstenediol is substantially more effective in modulating immunological responses to infection (Loria & Padgett, 1992). Further, androstenediol is even more successful in limiting viral and bacterial infections and enhancing lymphocyte activity (Loria, 2002). Many other aspects of the immune-endocrine relationship may actually be modulated by downstream DHEA metabolites, instead of through direct actions of DHEA.

DHEA can also act directly on steroid hormone receptors. DHEA exhibits agnostic effects on ER- β and may in fact have greater effects on the receptor than estradiol itself (Chen et al., 2005). DHEA has some affinity for ER- α and exhibits antagonistic effects on the AR in high concentrations.

Since both ER- α and ER- β are present on many types of immune cells, including B cells, T cells, monocytes, and natural killer cells (Kovats, 2015), some action of DHEA on immunological parameters may be via ER binding and resultant transcription activities.

Beyond the role of steroid receptors, there is some evidence that DHEA exerts direct effects. DHEA's modulation of inflammatory responses appears to be mediated, at least in part, by its action on NF- κ B. This transcription factor is responsible for activating cytokine expression and plays an important role in inflammatory responses. For example, NF- κ B activation and translocation is decreased in the presence of DHEA in vitro, resulting in reduced inflammatory activity (Du, Khalil, & Sriram, 2001). Finally, DHEA may bind to receptors on T cells and monocytes (McLachlan, Serkin, & Bakouche, 1996; Meikle et al., 1992), although such binding is not yet fully described.



3. DHEA IN INFLAMMATION AND CYTOKINE MODULATION

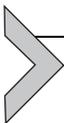
DHEA potently modulates inflammation and cytokine responses to stimulation in a variety of cellular contexts (Table 2). For example, DHEA is very effective at blunting both Th-1 and Th-2 immunological responses, and further suppresses expression of various proinflammatory cytokines (Choi et al., 2008; Du, Guan, Khalil, & Sriram, 2001; Du, Khalil, et al., 2001). These effects appear to be mediated, in part, by regulation of NF- κ B (Du, Khalil, et al., 2001). Other proinflammatory cytokines (e.g., IL-1 β , TNF- α , IFN- γ , etc.) are suppressed by DHEA in a variety of experimental contexts. These cytokine modulations are not trivial, as suppression of TNF- α decreases mortality during severe sepsis (Oberbeck et al., 2001), and immunomodulation of DHEA as a response to supplementation may have beneficial outcomes in various disease states: in women with systemic lupus erythematosus (SLE), DHEA administration results in decreased disease activity and severity (Barry, McGuire, & van Vollenhoven, 1998; Petri et al., 2002; van Vollenhoven, Morabito, Engleman, & McGuire, 1998).

DHEA also plays an important role in regulation of IL-2 secretion, where immunological modulation has beneficial results in adaptive immune responses. DHEA stimulates IL-2 secretion from T cells, resulting in enhanced T-cell cytotoxicity (Suzuki et al., 1991). This effect may result

Table 2 Role of DHEA on Cytokine Release and Action

Cytokine	Effect	Citations
IL-1 β	Inhibits production	Ben-Nathan, Padgett, and Loria (1999)
IL-2	Increases secretion	Suzuki et al. (1991)
IL-4	Increases secretion	Du, Guan, et al. (2001)
IL-5	Inhibits production	Choi et al. (2008)
IL-6	Inhibits production	Straub et al. (1998)
IL-10	Inhibits production	Choi et al. (2008) and Chang, Chu, Chen, Kuo, and Lai (2004)
IL-12	Inhibits production	Du, Khalil, et al. (2001)
TNF- α	Inhibits production	Ben-Nathan et al. (1999), Di Santo et al. (1996), Du, Khalil, et al. (2001), and Oberbeck et al. (2001)
IFN- γ	Inhibits production	Choi et al. (2008), Du, Khalil, et al. (2001), and Moynihan, Callahan, Kelley, and Campbell (1998)

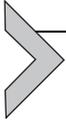
from increased transcription of IL-2 in T-cells through an unknown mechanism (Meikle et al., 1992; Suzuki et al., 1991). Low IL-2 may be related to low levels of DHEA in patients with SLE (Suzuki, Suzuki, Engleman, Mizushima, & Sakane, 1995), and DHEA treatment results in increased IL-2 production (Suzuki, Suzuki, & Sakane, 1996).



4. COMPLEMENT PROTEIN ACTIVITY

DHEA may play a role in innate immunity via regulation of parts of the complement cascade. In vitro experimentation suggests that DHEA increases the expression of C1 inhibitor, a protein that inhibits activation of the complement cascade (Falus et al., 1990; Hidvégi, Fehér, Feher, Koó, & Füst, 1984; McLachlan et al., 1996). However, as concentrations used in in vitro studies may not reflect natural physiology in vivo, and studies such as live subject supplementation have not been conducted, it can be difficult to interpret these findings. Findings from a cross-sectional sample of young orangutans found that DHEA-S, but not DHEA, was higher in animals with reduced complement protein activity (Prall et al., 2015). Similar results were found in a cross-sectional study examining relationships between androgens and immunity in humans (Prall & Muehlenbein, 2015).

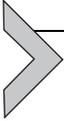
However, larger studies using natural variation in hormone concentrations, or using hormone supplementation, are needed to further support these findings.



5. LYMPHOCYTE PROLIFERATION AND CELLULAR CYTOTOXICITY

A number of studies have investigated DHEA's effects on human lymphocyte and murine splenocyte proliferation in response to mitogens, with highly variable results. Some evidence indicates that DHEA inhibits cellular proliferation in response to multiple mitogens (PHA, ConA, LPS) (Ben-Nathan et al., 1999; Padgett & Loria, 1994; Sakakura, Nakagawa, & Ohzeki, 2006), while other studies suggest that DHEA can result in proliferation only under very certain conditions (Catania et al., 1999; Sakakura et al., 2006; Zhang et al., 1999). These studies vary considerably by methodology, with different cell types, mitogens, DHEA concentration, and timing of DHEA administration. DHEA inhibits proliferation when using T-cell mitogens, but increases proliferation when using B-cell mitogens, suggesting differential actions on adaptive immunity (Sakakura et al., 2006). In studies where physiological concentrations are used, DHEA tends to increase proliferation, but the opposite is true when supraphysiological concentrations are used (Hazeldine, Arlt, & Lord, 2010). These findings highlight the need for *in vitro* experimentation to use androgen concentrations that approximate natural variation found *in vivo*. More naturalistic studies may be of use here. In a small cross-sectional study examining the relationships among salivary androgens and mitogen-stimulated lymphocyte proliferation, there is a negative relationship between DHEA concentrations and lymphocyte responses, particularly in males (Prall & Muehlenbein, 2015), suggesting that the underlying endocrine profile may further modulate how immune responses are shaped by DHEA.

Evidence suggests that DHEA and DHEA-S further shape cytotoxic abilities of immunological components. Natural killer cell cytotoxicity is enhanced by DHEA-S through modulation of the production of IGF-1 in *in vitro* experimentation (Solerte, Fioravanti, & Vignati, 1999). Similar results are found in T-cell responses, where DHEA stimulation results in increased cytotoxicity in human cells *in vitro* (Suzuki et al., 1991). Additionally, monocytes stimulated with both DHEA and lipopolysaccharide, but not DHEA alone, result in increase monocyte toxicity and other immunological responses (McLachlan et al., 1996).



6. DHEA SUPPLEMENTATION RESULTS IN BENEFICIAL IMMUNOMODULATION AND DISEASE OUTCOMES

In vitro studies implicate specific cellular processes impacted by variation in DHEA concentrations. Further examination of DHEA supplementation in humans and other animals yields particular insight into how DHEA, along with naturally circulating concentrations of other hormones, can influence immunological components, and ultimately disease processes. Additionally, DHEA is available as an over-the-counter nutritional supplement, making studies of oral DHEA supplementation logistically easier than many other hormones in humans.

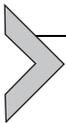
Numerous lab-based rodent studies illustrate the beneficial role of exogenous DHEA on disease outcomes and survival in experimental infections. DHEA treatment results in decreased mortality as a result of sepsis (Oberbeck et al., 2001) and *Escherichia coli* infection in mice (Gennari and Alexander, 1997). DHEA treatment in mice also increases survival to viral infection, increases time to disease onset, and decreases viral levels (Ben-Nathan, Lachmi, Lustig, and Feuerstein, 1991; Ben-Nathan et al., 1992; Loria et al., 1988). DHEA supplementation in mice infected with retroviruses also shows significant modulation of immunological components, including elevations of IL-2 and IFN- γ , and increased proliferation of T and B cells (Araghi-Niknam et al., 1997; Zhang et al., 1999). In rats experimentally infected with *Trypanosoma cruzi* and treated with DHEA, parasitemia decreases compared to those not receiving DHEA (Brazão et al., 2010; Del Vecchio Filipin et al., 2010; Santos et al., 2007).

Supplementation research reveals further evidence that DHEA can serve as a vaccine adjuvant capable of bolstering immunological responses, particularly in elderly individuals. DHEA treatment in mice prior to vaccination increases splenic response to the pneumococcal vaccine and increases antibody responses from the tetanus toxoid vaccine (Araneo et al., 1995; Garg and Bondada, 1993). However, human trials have yielded contradictory results. DHEA and DHEA-S supplementation increase antibody titers to influenza vaccination in several studies of elderly subjects (Araneo et al., 1995; Degelau et al., 1997). Several other studies find no change, or even reduced responsiveness, to influenza and tetanus vaccines (Ben-Yehuda, Danenberg, Zakay-Rones, Gross, and Friedman, 1998; Danenberg et al., 1997; Evans et al., 1996). Again, variation in dosage concentration, length, timing, and immunological measurements may play some role in these

discrepancies. Sorting out these discrepancies is necessary before DHEA can be considered as an effective vaccine adjuvant for the elderly.

Despite this ambiguity, many human DHEA supplementation studies report multiple immunological impacts. For example, DHEA supplementation elevates natural killer cell cytotoxicity and natural killer cell number (Casson et al., 1993; Khorram et al., 1997), and increases B- and T-cell mitogenic responses, although there are some inconsistencies in these results (Casson et al., 1993; Coles et al., 2005; Khorram et al., 1997; Kohut et al., 2003). There is little evidence of modification or altered production of cytokines or immunoglobulins, with only one study finding that DHEA supplementation in subjects with low basal DHEA-S resulted in elevated mitogen-stimulated IL-2 and IL-6 (Casson et al., 1993; Khorram et al., 1997; Kohut et al., 2003).

Supplementation studies are useful to show that variation in DHEA itself can impact immune function and health. However, some caution must be noted in interpretation of these results, as concentrations of hormones used can vary widely among studies. Supplementation often results in hormone concentrations much higher than what would be physiologically normal. Additionally, rodent studies must be interpreted cautiously, as rodents have different enzymatic pathways for hormone synthesis, making results from rodents difficult to generalize to human physiology (Maninger, Wolkowitz, Reus, Epel, & Mellon, 2009). More generally, while study outcomes may be muddled by systematic differences in supplementation concentration and duration, and disease and immune outcomes measured, results generally point to immunological benefits of elevated DHEA concentrations (Table 3).



7. DHEA AND INFECTION IN HUMAN POPULATIONS

To understand better the relationships among naturally circulating concentrations of DHEA and immunological measures, a number of studies have examined DHEA concentrations in relation to infection status using a cross-sectional sampling method (Table 4). While these studies cannot elucidate mechanistic relationships between DHEA and immunological responses, they nonetheless provide further evidence that DHEA variation can have important implications in health and disease. Some caution must be taken when interpreting these results, as various infections are known to impact androgen concentrations (Muehlenbein, Hirschtick, Bonner, & Swartz, 2010), including DHEA (Galindo-Sevilla et al., 2007; Libonati, de Mendonça, Maués, Quaresma, & de Souza, 2006; Prall & Muehlenbein, 2014).

Table 3 Studies of DHEA Supplementation and Immune Outcomes in Humans

Sex	Mean Age	Treatment	Length of Supplementation	Results	Citations
Females		DHEA supplementation	3 weeks	↑ Natural killer cell cytotoxicity, CD8+/CD5+ cells ↓ CD4+ T cells, lymphocyte proliferation No change in IL-6 production	Casson et al. (1993)
Males		DHEA and androstenedione supplementation	28 days	↑ PBMC proliferation to PHA No change in lymphocyte proliferation to LPS or ConA, production of IL-1 β , IL-2, IL-4, IL-10, IFN- γ	Kohut et al. (2003)
Both	41	DHEA supplementation in patients with Addison's disease	12 weeks	↑ Treg cells, lymphocyte proliferation ↓ NK cells, NKT cells No change in IL-7	Coles et al. (2005)
Females	36.2/53.3	DHEA supplementation in patients with SLE	12 months	↓ SLE disease activity No change in erythrocyte sedimentation rate, CBC	van Vollenhoven et al. (1998)
Males		DHEA supplementation in symptomatic HIV-infected males	16 weeks	↑ Lymphocyte response to CMV ↓ CD4 count, neopterin No change in CD8 cells, % CD4 lymphocytes, β -2 microglobulin, delayed type hypersensitivity response, lymphocyte proliferation	Dyner et al. (1993)
Both	73	DHEA supplementation and influenza vaccination	4 days	↓ Antibody titer to select influenza strains	Ben-Yehuda et al. (1998)
Males	63	DHEA supplementation in subjects with low DHEA-S	20 weeks	↑ Monocyte number, B-cell number, B mitogenic response, T-cell mitogenic response, mitogen-stimulated IL-2 and IL-6, NK cell number, and cytotoxicity No change in IgG, IgA, IgM, total T lymphocyte number, T cell subset numbers	Khorram, Vu, and Yen (1997)

Continued

Table 3 Studies of DHEA Supplementation and Immune Outcomes in Humans—cont'd

Sex	Mean Age	Treatment	Length of Supplementation	Results	Citations
Both	73.4	DHEA supplementation and influenza vaccination	4 days	↓ Antibody titer to select influenza strains	Danenberg, Ben-Yehuda, Zakay-Rones, Gross, and Friedman (1997)
Both	73	DHEA-S supplementation and influenza or tetanus toxoid vaccination	4 days	↑ Antibody titer to vaccination (HAI assay) to influenza No changes in antibody response to tetanus toxoid	Araneo et al. (1995)
Both	78.61	Influenza vaccination with DHEA-S adjuvant	Single dose	↑ Antibody titer to vaccination (HAI assay) in select groups	Degelau, Guay, and Hallgren (1997)
Females		Systemic lupis erythematous patients supplemented with DHEA	6 months	↓ Disease activity	Barry et al. (1998)
Both	70.5	DHEA-S supplementation with influenza or tetanus vaccination	2 or 4 days	No change in antibody responses to tetanus or influenza	Evans et al. (1996)

Table 4 DHEA-S and Infection and Immune Function in Human Populations

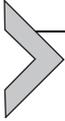
Origin	Age/Sex	N	Immune Measures	Results	Citations
Kenya	12–25 Males	248	<i>Plasmodium falciparum</i> parasitemia	DHEA-S negatively associated with parasitemia	Kurtis et al. (2001)
Kenya	12–18 Females	648	<i>P. falciparum</i> parasitemia	DHEA-S negatively associated with parasitemia	Leenstra et al. (2003)
Brazil	15–47 Both	24	<i>P. falciparum</i> parasitemia	DHEA declined with parasitemia during treatment	Libonati et al. (2006)
Ethiopia	<9–40+ Both	135	<i>Schistosoma</i> infection intensity, IgG isotypes	Higher DHEA-S associated with decreased infection intensity, decreased IgG isotypes	Abebe et al. (2003)
Philippines	7–30 Both	727	<i>Schistosoma</i> infection intensity, reinfection following treatment	Higher DHEA-S associated with lower infection intensity, resistance to reinfection, and reinfection intensity	Kurtis et al. (2006)
Philippines	7–30 Both	731	C-reactive protein, IL-6 in heavily parasitized population	DHEA-S negatively related to C-reactive protein, IL-6	Coutinho et al. (2007)
Mexico	11–79 Both	40	IL-6 in individuals infected with leishmaniasis	DHEA negatively related to IL-6 and lower in infected individuals	Galindo-Sevilla et al. (2007)
Bolivia	8–23 Both	171	Secretory IgA	DHEA-S positively related to sIgA	Hodges-Simeon, Prall, Blackwell, Gurven, and Gaulin (2017)

As a potent modulator of inflammatory responses, DHEA-S has been associated with *Schistosoma* infection in several studies. For example, Abebe, Birkeland, Gaarder, Petros, and Gundersen (2003) evaluated the relationships among DHEA-S, immunity, and infection in Ethiopian adolescents and adults. While DHEA-S was negatively related to several immunoglobulins relevant to immunological responses against *Schistosoma*, DHEA-S concentration was significantly negatively related to infection intensity (Abebe et al., 2003). Similarly, adolescents and adults in the Philippines with high concentrations of DHEA-S showed lower *Schistosoma* infection intensity, and lower reinfection intensity following treatment (Kurtis et al., 2006). These findings mimic studies of DHEA and DHEA-S treatment in mice (Fallon, Richardson, Jones, & Dunne, 1998; Morales-Montor et al., 2001).

DHEA-S has been implicated as moderating malaria parasitemia in association with growth and development. For example, Kurtis, Mtalib, Onyango, and Duffy (2001) found that DHEA-S had effects on *Plasmodium falciparum* parasitemia in Kenyan males, again independent of age. Similar results were found in Kenyan females, where elevated DHEA-S predicted lower parasitemia and higher hemoglobin levels (Leenstra et al., 2003). These authors argue that age-independent associations between DHEA-S and immunity are mediated by the immunomodulatory properties of DHEA-S. However, more recent evidence suggests that DHEA can directly impact *P. falciparum* via inhibition of G6PD activity (Zhang et al., 2017). Whether DHEA and DHEA-S impact malarial infection via immunomodulation or through a direct effect, these results strongly implicate elevations in DHEA or DHEA-S as mediators of malaria resistance.

The modulation of inflammatory activity in response to chronic parasite infection can have important impacts beyond regulation of parasitemia. Prolonged exposure to proinflammatory responses can have detrimental effects on body condition, and elevations in DHEA-S during development may counteract these responses. To determine how DHEA-S mediates proinflammatory responses in populations with chronic parasite burden, Coutinho et al. (2007) examined the relationships among DHEA-S, nutritional status, CRP, and IL-6 in a sample from the Philippines. Inflammatory markers predicted undernutrition, although DHEA-S was negatively related to inflammation and positively associated with nutritional status, implicating DHEA-S as a potential molecule exerting protective effects on nutritional status. These findings explain further the age-related changes in morbidity associated with parasite infection. The ability of

DHEA and DHEA-S to exert some protective effect against parasite-induced wasting could have important implications for reproduction and survival in humans.



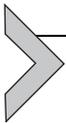
8. IMMUNOMODULATION VIA INTERACTIONS WITH GLUCOCORTICOIDS

Any review of the physiological effects of DHEA would be incomplete without some discussion of its interactions with glucocorticoids. As an adrenal androgen, DHEA responds to hypothalamic–pituitary–adrenal (HPA) stimulation and is in fact more sensitive to stimulation than is cortisol (Arvat et al., 2000). However, DHEA inhibits catecholamine release from the adrenal medulla (Liu & Wang, 2004), and its effects as an antiglucocorticoid have been characterized in numerous tissues and physiological systems (Browne, Wright, Porter, & Svec, 1992; Hu, Cardounel, Gursoy, Anderson, & Kalimi, 2000; Kimonides, Spillantini, Sofroniew, Fawcett, & Herbert, 1999; Shafagoj, Opoku, Qureshi, Regelson, & Kalimi, 1992). The mechanism behind these effects is unclear but appears to be unrelated to interference on binding on the glucocorticoid receptor (Mohan & Cleary, 1992). Within tissues, action may occur via modulation of 11 β -HSD1, the enzyme responsible for synthesizing cortisol from cortisone, which is reduced in the presence of DHEA (Apostolova, Schweizer, Balazs, Kostadinova, & Odermatt, 2005). These actions, whether through DHEA directly or via downstream metabolites, are hypothesized to exert similar action on immune cells (Hazeldine et al., 2010).

Several studies involving rodents have explored the roles of DHEA supplementation on immunity or disease parameters in the presence of acute stress. For example, DHEA supplementation reverses suppression of IL-2 synthesis by glucocorticoids both in vitro and in vivo (Daynes, Dudley, & Araneo, 1990). Likewise, DHEA exposure protects against glucocorticoid-induced thymic involution and suppression of lymphocyte proliferation (Blauer, Poth, Rogers, & Bernton, 1991; May, Holmes, Rogers, & Poth, 1990). In comparing immune and disease outcomes in mice infected with lethal viruses and subjected to cold stress, Ben-Nathan et al. (1992) demonstrated that DHEA administration reduced mortality and viral levels compared with untreated mice.

Such work has not yet been extended to humans, but initial results from a small-cross-sectional study suggest that DHEA responses to acute stress

do play a role in modulation of immunological responses during stress (Prall, Larson, & Muehlenbein, 2017). Whether DHEA has similar actions in reducing disease severity during infection remains to be seen. However, exploration of the relative concentrations of cortisol to DHEA, and corresponding health outcomes, can give some indication of this physiological relationship (Hechter, Grossman, & Chatterton, 1997). For example, cortisol/DHEA-S was related to mortality and metabolic syndrome in Vietnam era army veterans (Phillips et al., 2010a, 2010b). The ratio of DHEA to cortisol has also been linked with disease severity and mortality during septic shock (Arlt et al., 2006).



9. CONCLUSIONS

The studies outlined here suggest that DHEA, whether through direct action or through intracrine conversion to a metabolite, evokes potent responses from multiple immune components. DHEA appears to downregulate the complement cascade via increased expression of the C1 inhibitor, although few studies have examined this system specifically. DHEA has potent effects in cytokine production, downregulating inflammatory cytokines while directly upregulating IL-2 synthesis. DHEA generally acts to enhance lymphocyte proliferation, and increases T cell and NK cell cytotoxicity. Many of these results are derived from *in vitro* experimentation, but are supported by numerous studies showing the beneficial effects of DHEA supplementation on disease parameters and organism survival. Additional studies of supplementation as a vaccine adjuvant in humans are promising, but are compromised by differences in study design, and conflicting results suggest further study is required. Studies examining correlations between DHEA and some immune or disease parameter provide further evidence of the beneficial effect of DHEA and DHEA-S.

The mechanisms by which these actions occur remain equivocal. DHEA is a purported antiglucocorticoid, and it is clear that elevated DHEA is beneficial to immunocompetence in times of infection and acute HPA activation in mice. However, in a naturalistic context outside of supraphysiological dosing, the relationships among chronic and acute HPA activation, immunity, and hormone concentrations require further exploration.

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