European Journal of Clinical Nutrition (2003) 57, Suppl 2, S24–S29
 0954-3007/03 $25.00
www.nature.com/ejcn

ORIGINAL COMMUNICATION

Impaired cognitive function and mental performance in mild dehydration

M-MG Wilson[1,2]* and JE Morley[1,2]

[1]*Division of Geriatric Medicine, St Louis University Health Sciences Center, St Louis, MO, USA; and The GRECC, Veteran's Administration Medical Center, St Louis, MO, USA*

Dehydration is a reliable predictor of impaired cognitive status. Objective data, using tests of cortical function, support the deterioration of mental performance in mildly dehydrated younger adults. Dehydration frequently results in delirium as a manifestation of cognitive dysfunction. Although, the occurrence of delirium suggests transient acute global cerebral dysfunction, cognitive impairment may not be completely reversible. Animal studies have identified neuronal mitochondrial damage and glutamate hypertransmission in dehydrated rats. Additional studies have identified an increase in cerebral nicotinamide adenine dinucleotide phosphate-diaphorase activity (nitric oxide synthase, NOS) with dehydration. Available evidence also implicates NOS as a neurotransmitter in long-term potentiation, rendering this a critical enzyme in facilitating learning and memory. With ageing, a reduction of NOS activity has been identified in the cortex and striatum of rats. The reduction of NOs synthase activity that occurs with ageing may blunt the rise that occurs with dehydration, and possibly interfere with memory processing and cognitive function. Dehydration has been shown to be a reliable predictor of increasing frailty, deteriorating mental performance and poor quality of life. Intervention models directed toward improving outcomes in dehydration must incorporate strategies to enhance prompt recognition of cognitive dysfunction.
European Journal of Clinical Nutrition (2003) **57,** Suppl 2, S24–S29. doi:10.1038/sj.ejcn.1601898

Keywords: dehydration; cognition; memory; frailty; aging

'T is a little thing
To give a cup of water; yet its draught
Of cool refreshment, drained by fevered lips,
May give a shock of pleasure to the frame
More exquisite than when nectarean juice
Renews the life of joy in happiest hours.
Sir Thomas Noon Talfourd (1795–1854)
Ion. Act i. Sc 2.

Introduction

Thirst is a potentially unpleasant sensation that also serves as a strong driving force capable of influencing complex human behavior. In addition, the hedonic qualities associated with assuaging thirst are perceived as a reflection of the mitigation of the undesirable effects of fluid deprivation. Thus, although the precise pathophysiologic mechanisms have yet to be unraveled, the complexity of man's response to thirst and fluid deprivation indicates sophisticated cognitive processing.

The clinical effects of severe dehydration on cognitive function highlight the importance of maintaining optimal hydration status. Such effects are generally the result of profound hypovolemia and subsequent cerebral hypoperfusion (Figure 1). In contrast, the cognitive manifestations of mild dehydration have not been fully explored. The paucity of available data precludes detailed and focused exploration of the pathophysiological mechanisms that underlie disruption of cognitive function in less severe dehydrated states.

Available evidence indicates the increased susceptibility of older adults to dehydration and the resulting complications

***Correspondence: M-MG Wilson, Division of Geriatric Medicine, St Louis University Health Sciences Center, 1402, S. Grand Blvd, Rm M238, St. Louis, MO 63104, USA.**
E-mail: wilsonmg@slu.edu
***Guarantor*: Margaret-Mary G Wilson.**
***Contributors*: M-MGW reviewed the articles, analyzed the data, drafted and edited the manuscript. Both authors were involved in critical revision of the manuscript and approved the final version submitted.**

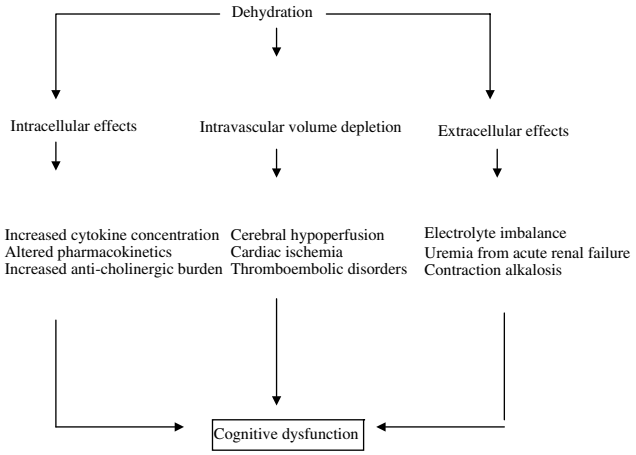

Figure 1 Pathophysiology of cognitive dysfunction in moderate and severe dehydration.

(Silver, 1987; Rolls & Phillips, 1990). Dehydration in older adults has been shown to be a reliable predictor of increasing frailty, progressive deterioration in cognitive function and an overall reduction in quality of life (Warren *et al*, 1994; Miller *et al*, 1998). These adverse long-term outcomes of dehydration in the elderly mandate further research into the pathophysiology and manifestations of mild dehydration in order to facilitate early recognition and prompt intervention. In addition, the increased susceptibility of older adults to the complications of dehydration provides a sensitive cohort in which the manifestations of subtle degrees of dehydration may be readily observed.

Pathophysiology

Available studies have identified several domains of cognitive function that are affected by dehydration (Sharma *et al*, 1986; Gopinathan *et al*, 1988). Gopinathan *et al* (1988) examined changes in cognitive function in 11 healthy adult subjects under varying degrees of dehydration induced by a combination of water restriction and heat stress. Resulting data indicated a significant correlation between cognitive dysfunction and severity of dehydration. Subjects exhibited progressive impairment in mathematical ability, short-term memory and visuomotor function once 2% body fluid deficit was achieved (Gopinathan *et al*, 1988). Cian *et al* (2000) demonstrated impaired long-term memory following dehydration resulting from heat stress. In a later study, Cian *et al* (2000) also demonstrated impairment in short- and long-term memory, visuospatial function, perceptive discrimination and reaction time in dehydrated subjects. The subjects studied also demonstrated increased subjective perception of fatigue following prolonged dehydration, validating the clinical association of hydration status with quality of life (Cian *et al*, 2001).

In the absence of an operational definition of cognition, several working models of cognitive awareness have been developed, based on unification of physiological, psychological and philosophical concepts. Of these, the most convincing is Barr's global workspace theory (Barr, 1993). This is based on the concept that cognition is of limited capacity. Thus, cognitive processes perceived as working in parallel are actually functioning in competition with each other. Selected activities are presumed to dominate cognitive awareness by harnessing executive function more effectively than other competing processes. Utilizing Barr's theory, Cohen attempts to explain the effect of dehydration on cognitive function in a simplistic, albeit, rather plausible manner (Cohen, 1983). Based on the assumption that complex tasks require increased attention, Cohen proffers that acute stressors such as dehydration compete for executive attention and awareness with parallel processes occurring in other cognitive domains, thereby compromising overall cognitive performance.

In the light of the obvious complexity of the neurobiological mechanisms involved in cognition, it is unlikely that a unitary explanation will emerge to account for cognitive dysfunction in dehydrated states. Current research trends driven by hypotheses based on the integration of cellular and hormonal theories, as explanations for cognitive dysfunction in dehydrated states, are perhaps more appropriate (Table 1).

Hormonal theories

The activation of the renin–angiotensin system in response to hypohydration, resulting in an increase in arginine vasopressin (AVP), is well documented. Early studies suggest that prostaglandin E (PGE) plays a pivotal role in the modulation of AVP release in hypohydrated states (Leskell, 1976; Weitzman & Kleeman, 1979). In animal studies, PGE has been shown to augment the release of AVP in response to injection of hypertonic saline (Yamamoto *et al*, 1976). Studies seeking to identify other biological indicators of hydration status have shown an increase in serum cortisol levels with dehydration. Achieving euhydration, in such cases, is associated with normalizing of the serum cortisol levels (Francesconi *et al*, 1989). The results of the aforemen-

Table 1 Theories of hormonal and cellular responses to dehydration and their effects on cognitive function

Hypercortisolemia	Impairs active learning, short-term memory and verbal memory
Elevated cerebral arginine vasopressin	Enhances memory
Enhanced NOS release	Involved in homeostatic preservation of cognitive function in dehydration
Mitochnodrial dysfunction	Activates voltage-dependent calcium channels resulting in neuronal death
Glutamate hypertransmission	Altered cellular energetics, reduced adenylate cyclase activity and intracellular calcium mobilization
Cytokines elaboration	Possible mediators of acute phase response in heat-induced dehydration

tioned studies favor the hypothesis that cognitive dysfunction resulting from mild dehydration may result from the central effect of alterations in the hormonal profile. However, review of more recent studies reveals conflicting results. Animal studies indicate that although corticosteroid hormones may not influence passive learning, hypercortisolemia tends to worsen active learning and compromise short-term memory (Vedhara *et al*, 2000).

The deleterious effects of pharmacological steroids on cognitive function are well recognized. However, Newcomer *et al* (1999) also demonstrated a reduction in verbal memory following the administration of exogenous cortisol at physiological doses. In contrast, Buchanan and Lovallo (2001), examining the effect of exogenous cortisol administration on human memory, demonstrated enhancement of memory specifically associated with emotionally arousing information. Studies have also demonstrated an association between hypocortisolemia and enhanced short-term memory, although there was no correlation with verbal memory (Vedhara *et al*, 2000). The theory of a hormonal basis for cognitive dysfunction resulting from dehydration is further challenged by the results of several studies identifying a positive effect of cerebral DDAVP on memory (Beckwith *et al*, 1990). Elaborate cell culture studies have also identified increased neurite length and bifurcation points following exposure to vasopressin receptor agonists. These findings challenge the role of peripheral AVP in the genesis of cognitive dysfunction resulting from dehydration. It remains unclear however as to whether there is a linear correlation between peripheral and central levels of AVP. Nevertheless, the identification of vasopressin-induced neurotrophism warrants further research into the effect of hormones on cognitive function in dehydrated persons (Chen *et al*, 2000).

Additional evidence also implicates central neurotransmitters in the genesis of cognitive dysfunction in dehydrated persons. Animal studies reveal an increased density of nicotinamide adenine dinucleotide phosphate-diaphorase (NADPH-diaphorase) in forebrain circumventricular structures of rats following a 72-h period of dehydration (Ciriello *et al*, 1996). Notably, cellular and histochemical studies indicate that NADPH-diaphorase and nitric oxide synthase (NOS) share identical ultrastructural locations (Calka *et al*, 1994). These data indicate a likely role for NOS as a mediator in central homeostatic mechanisms regulating fluid balance. Nitric oxide (NO) has gained increasing recognition as a critical neurotransmitter molecule. Available data on ultrastructural enzyme location reveal that NOS is present in most parts of the brain and plays a crucial role as either a retrograde messenger or a paracrine factor in facilitating long-term potentiation of memory (Salemme *et al*, 1996). Animal studies support the role of NO as a central diffusible messenger in facilitating learning and memory. Additional studies identifying reduced NO production in older rats suggest that NO plays a role in the genesis of age-related memory impairment (Noda *et al*, 1997). Based on these data, aging may result in a relative reduction in the compensatory increase of NO with dehydration, thereby explaining the increased susceptibility of older adults to delirium following relatively mild degrees of dehydration.

Cellular theories

Current literature permits only hypothetical formulation of the role of neurotransmitters in the cognitive manifestations of dehydration. Similarly, the cellular mechanisms involved in the cognitive manifestations of dehydration are yet to be objectively elucidated. Experimental models examining neuronal vulnerability to different acute insults suggest alternative theories of dehydration-related neurotoxicity.

Regardless of the initiating insult, neuronal death tends to be initiated by pathological membrane depolarization that results in a critical accumulation of intracellular calcium (Lee *et al*, 1999). The precise chain of events as it relates to the particular insult is still unclear. In addition, the observation that neuronal subtypes differ in their degree of vulnerability to acute insults complicates this area of study even further (Haddad & Jiang, 1993). However, neuronal subtypes that are more vulnerable are more likely to be affected by milder insults. The striatum is one example of an extremely vulnerable region that serves as a convenient experimental model for the study of cellular response to injury (Calabresi *et al*, 2000). This has led to the development of several interesting theories. The energy deprivation theory is based on the effect of acute cellular injury in disrupting mitochondrial function. The resultant loss of ATP-dependent ionic segregation and subsequent failure to maintain the normal ionic gradient triggers inappropriate membrane depolarization. Consequently, voltage-dependent calcium channels are activated resulting in intracellular calcium accumulation and eventually neuronal death (Martin *et al*, 1994; Dimagl *et al*, 1999; Lee *et al*, 1999).

Excitotoxicity resulting from glutamate hypertransmission is another favored theory that may account for the neuronal response to acute insults (Choi & Rothmann, 1990; Obrenovitch & Urenjjak, 1994). Two categories of glutamate receptors have been identified, namely, ionotropic glutamate (iGlu) receptors linked to cation channels and metabotropic glutamate (mGlu) receptors that are coupled to second messenger systems. The latter group of receptors is further divided into three subgroups. Subgroup 1 promotes intracellular calcium mobilization, while subgroups 2 and 3 are negatively coupled to adenylate cyclase activity. Acute insults result in sustained glutamate-mediated excitatory activation of both iGlu and mGlu receptors, resulting in the activation of an intracellular metabolic pathway that leads to increased enzymatic activity of phospholipase C and increased accumulation of intracellular calcium (Chen *et al*, 1996; Tallaksen-Greene & Albin, 1996; Bernard *et al*, 1997) (Figure 2).

Glutamate hypertransmission may also provide the link between cellular dehydration and altered cellular energetics. Häusinger *et al* (1993) working with isolated cells showed

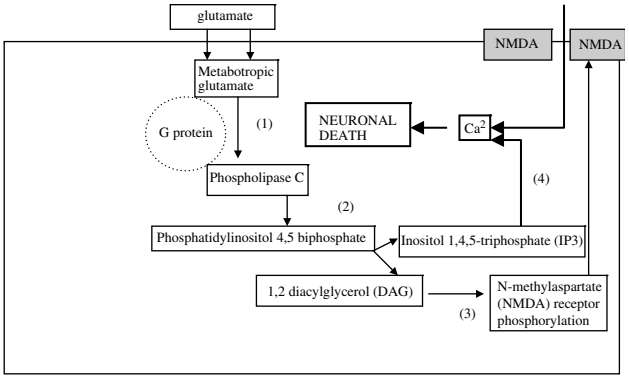

Figure 2 Excitotoxicity resulting from excessive glutamate receptor activation: (1) Activation of glutamate receptors activates phospholipase C (PLC) via a G protein; (2) PLC induces the production of IP3 and DAG; (3) DAG results in NMDA receptor phosphorylation, increasing intracellular calcium influx; and (4) IP3 synergistically increases intracellular calcium ions.

that cellular dehydration triggers increased protein catabolism. Increased tissue liberation of glutamine, which is the most abundant free amino acid, may result from this process. Data indicating a reduction in the intracellular concentration of glutamine following tissue injury supports this theory (Rennie *et al*, 1989).

Increased elaboration of cytokines and subsequent stimulation of neuroendocrine activity are central features of the metabolic response to acute insult (Hill & Hill, 1998). However, the specific effect of cytokines in the mediation of the cognitive response to dehydration is still unclear. Data implicating tumor necrosis factor (TNF) and interleukin-1 (IL-1) as mediators in the acute phase response complicating thermal injuries may prove relevant to heat induced dehydration (Mester *et al*, 1994). However, available evidence indicates that systemic cytokine release fails to account for all the observed responses to acute insult and tissue injury. With the exception of IL-6, systemic cytokine elaboration cannot be consistently identified in patients with acute injury (Hill & Hill, 1998). Tissue-specific cytokine elaboration may prove to be a more attractive hypothesis. Animal studies have identified TNF receptors in the murine brain and elaborate IL-1 nerve fibers within the hypothalamus of rats. Rat astrocytes have also been shown to produce of TNF *in vivo* (Lieberman *et al*, 1989; Kinouchi *et al*, 1991; Hill *et al*, 1996). Additional studies have implicated several cytokines, namely IL-1, 2,6 and granulocyte–macrophage CSF in hippocampal neurotransmitter modulation (Bianchi *et al*, 1998). Thus, although the roles of cytokines and cytokine receptors are yet to be fully elucidated, existing data justifies further research in this area.

Clinical implications

Homeostasis is a complex, yet well integrated, set of physiological responses designed to oppose deviation from the norm. In the majority of cases, such responses are well coordinated and result in a rapid restoration of normal function following the activation of a chain of appropriate compensatory responses. However, in a few cases, especially in the presence of multiple coexisting insults, an excessive homeostatic response may occur that paradoxically triggers damaging processes. Thus, although physiological derangement resulting from fluid loss is very often treated rather simplistically with replacement therapy, it is likely that high-risk patients may benefit from metabolic manipulation in order to combat the threat of inappropriate activation of homeostatic responses.

Although the cellular and hormonal events associated with the neuronal response to dehydration are yet to be fully elucidated, there is an abundance of clinical evidence implicating dehydration as a common precipitant of acute confusion (Levkoff *et al*, 1988; Hoffman, 1991; Francis & Kapoor, 1992; Murray *et al*, 1993; Bianchi *et al*, 1998; Mentes *et al*, 1998). Delirium is a common manifestation of dehydration that clearly reflects the global impact of dehydration on cerebral function. However, the three areas of the brain most vulnerable to the effects of dehydration are the reticular activating system, which subserves attention and wakefulness; the autonomic structures that regulate psychomotor and regulatory functions; and the cortical and mid-brain structures that are responsible for thought, memory and perception (Neelon & Champagne, 1992).

The syndrome of delirium is characterized by the transient nature of its occurrence and the potential reversibility inherent in this diagnosis. Thus, clinicians often assume that the identification and treatment of dehydration with appropriate replacement therapy should result in complete resolution of any associated cognitive dysfunction. However, the lack of data demonstrating a firm correlation between objective indices of tissue hydration and cognitive function challenges the notion that dehydration presents exclusively as acute confusion and is inherently a relatively benign and reversible condition.

Neelon and Champagne's (1992) models for the patterns of onset of acute confusion may be extended to incorporate parallel changes in the patterns of onset of hydration levels (Figure 3). Particularly within vulnerable subgroups of the population such as the elderly, this model may enhance awareness and detection of the complete spectrum of cognitive abnormalities that may result from fluid depletion.

Within the older population, cognitive impairment has been shown to herald the onset of functional decline in dehydrated patients. This course of events may be attributed to the hierarchical sequence of the domains of impact of dehydration, namely, cognitive function, task processing, functional decline and quality of life. This sequence further underscores the importance of the development and use of an appropriate intervention model, based not only on the simplistic and defensive theory of replacement, but also on more long-term anticipatory strategies.

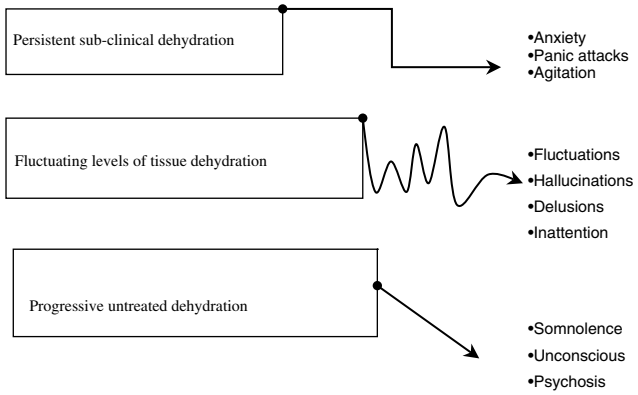

Figure 3 Theoretical model of the clinical trajectories of cognitive dysfunction resulting from variable degrees of dehydration.

Unexplored themes

An objective approach to the clinical detection and management of dehydration is hampered by the paucity of data defining the pathophysiological and cellular mechanisms underlying this disease process. The syndrome of dehydration is relatively unique, in that meaningful research must incorporate parallel exploration of quantitative indices of hydration status and outcome measures. The development and validation of risk assessment and monitoring tools is a critical component of this process. In addition, research into adjunctive measures aimed at limiting adverse effects of dehydration is warranted. Evidence of neurotoxicity resulting from dehydration suggests that traditional fluid replacement may be inadequate as sole therapy for cognitive dysfunction arising from dehydration. Further research into the use of innovative therapies such as prostaglandin inhibitors, NO modulators and antibodies targeting specific cytokines may prove useful.

References

Barr BJ (1993): How does a serial, integrated and very limited stream of consciousness emerge from a nervous system that is mostly unconscious, distributed parallel and of enormous capacity? *Ciba Found. Symp.* **174**, 282–290.

Beckwith BE, Petros TV & Knutson KK (1990): Effects of DDAVP on gender-specific verbal and visuospatial tasks in healthy young adults. *Peptides* **11**, 1313–1315.

Bernard V, Somogyi P & Bolam JP (1997): Cellular, subcellular and subsynaptic distribution of AMPA-type glutamate receptor subunits in the neostriatum of the rat. *J. Neurosci.* **17**, 819–833.

Bianchi M, Sacerdote P & Panerai AE (1998): Cytokines and cognitive function in mice. *Biol. Signals Receptors* **7**, 45–54.

Buchanan TW & Lovallo (WR2001): Enhanced memory for emotional material following stress-level cortisol treatment in humans. *Psychoneuroendocrinology* **26**, 307–317.

Calabresi P, Centonze D & Bernardi G (2000): Cellular factors controlling neuronal vulnerability in the brain. *Neurology* **55**, 1249–1255.

Calka J, Wolf G & Brosz M (1994): Ultrastructural demonstration of NADPH-diaphorase histochemical activity in the supraoptic nucleus of normal and dehydrated rats. *Brain Res. Bull.* **34**, 301–308.

Chen Q, Patel R, Sales A, Qji G, Kim J, Monreal AW & Brinton RD (2000): Vasopressin-induced neurotrophism in cultured neurons of the cerebral cortex: dependency on calcium signaling and protein kinase activity. *Neuroscience* **101**, 19–26.

Chen Q, Veenman CL & Reiner A (1996): Cellular expression of ionotropic glutamate receptor sub-units on specific striatal neuron types and its implication for striatal vulnerability in glutamate-mediated excitotoxicity. *Neuroscience* **73**, 715–731.

Choi DW & Rothmann SM (1990): The role of glutamate neurotoxicity in hypoxic-ischemic neuronal death. *Ann. Rev. Neurosci.* **13**, 171–182.

Cian C, Barraud PA, Melin B & Raphel C (2001): Effects of fluid ingestion on cognitive function after heat stress or exercise-induced dehydration. *Int. J. Psychophysiol.* **42**, 243–251.

Cian C, Koulmann N, Barraud PA, Raphel C, Jimenez C & Melin B (2000): Influence of variation of body hydration on cognitive function: effect of hyperhydration, heat stress and exercise-induced dehydration. *J. Psychophysiol.* **14**, 29–36.

Ciriello J, Hochstenbach SL & Pastor Solano-Flores L (1996): Changes in NADPH diaphorase activity in forebrain structures of the laminae terminalis after chronic dehydration. *Brain Res.* **708**, 167–172.

Cohen S (1983): After effects of stress on human performance during a heat acclimatization regimen. *Aviat. Space Environ. Med.* **54**, 709–713.

Dimagl U, Iadecola C & Moskowitz MA (1999): Pathobiology of ischemic stroke: an integrated view. *Trends Neurosci.* **22**, 391–397.

Francesconi RP, Sawka MN, Hubbard RW & Pandolf KB (1989): Hormonal regulation of fluid and electrolytes: effects of heat exposure and exercise in the heat. In: *Hormonal regulation of fluid and electrolytes*. ed. JR Claybaugh & CE Wade, pp 45–85. New York and London: Plenum Press.

Francis J & Kapoor W (1992): Prognosis after hospital discharge of older medical patients with delirium. *J. Am. Geriatr. Soc.* **40**, 601–606.

Gopinathan PM, Pichan G & Sharma MA (1988): Role of dehydration in heat stress-induced variations in mental performance. *Arch. Environ. Health* **43**, 15–17.

Haddad GG & Jiang C (1993): O_2 deprivation in the central nervous system: on the mechanisms of neuronal response, differential sensitivity and injury. *Prog. Neurobiol.* **40**, 277–318.

Häussinger D, Roth E, Lang F & Gerok W (1993): Cellular hydration state: an important determinant of protein catabolism in health and disease. *Lancet* **341**, 1330–1332.

Hill AG & Hill GL (1998): Metabolic response to severe injury. *Br. J. Surg.* **85**, 884–890.

Hill AG, Jacobson L, Gonzalez J, Rounds J, Majzoub JA & Wilmore DW (1996): Chronic central nervous system exposure to interleukin-1 beta, but not interleukin-6, mediates catabolism in rats. *Am. J. Physiol.* **271**, R1142–R1148.

Hoffman N (1991): Dehydration in the elderly: Insidious and manageable. *Geriatrics* **46**, 35–38.

Kinouchi K, Brown G, Pasternak G & Donner DB (1991): Identification and characterization of receptors for tumor necrosis factor-alpha in the brain. *Biochem. Biophys. Res. Commun.* **181**, 1532–1538.

Lee J-M, Zipfel GJ & Choi DW (1999): The changing landscape of ischemic brain injury mechanisms. *Nature* **399**(Suppl), A7–A14.

Leskell LG (1976): Influence of PGE on cerebral mechanisms involved in control of fluid balance. *Acta Physiol. Scand.* **93**, 286.

Levkoff S, Safrana C, Cleary P, Gallop J & Phillips R (1988): Identification of factors associated with the diagnosis of delirium in elderly hospitalized patients. *J. Am. Geriatr. Soc.* **36**, 1099–1104.

Lieberman AP, Pitha PM, Shin HS & Shin ML (1989): Production of tumor necrosis factor and other cytokines by astrocytes stimulated with lipopolysaccharide or a neurotropic virus. *Proc. Natl. Acad. Sci. USA* **86**, 6348–6352.

Martin RL, Lloyd HE & Cowan AI (1994): The early events of oxygen and glucose deprivation: setting the scene for neuronal death? *Trends Neurosci.* **17**, 251–257.

Mentes J, Culp K, Wakefield B, Gaspar P, Papp CG, Mobily P & Tripp-Reimer T (1998): Dehydration as a precipitating factor in the development of acute confusion in the frail elderly. In: *Hydration and Aging. Facts, Research, and Intervention in Geriatric Series*. ed. B Vellas, JL Albarede, PJ Garry, pp 83–98. Paris, New York: Serdi & Springer.

Mester M, Carter EA, Tompkins RG, Gelfand JA, Dinarello CA, Burke JF & Clark BD (1994): Thermal injury induces very early production of interleukin-1 alpha in the rat by mechanisms other than endotoxemia. *Surgery* **115**, 588–596.

Miller DK, Perry HM & Morley JE (1998): Relationship of dehydration and chronic renal insufficiency with function and cognitive status in older US blacks. In: *Hydration and Aging. Facts, Research, and Intervention in Geriatric Series*. ed. B Vellas, JL Albarede, PJ Garry, pp 149–159. New York: Serdi and Springer.

Murray A, Levkoff S, Wetle T, Beckett L, Cleary P, Schor J, Lipsitz B, Rowe J & Evans D (1993): Acute delirium and functional decline in the hospitalized elderly patient. *J. Gerontol. Sci.* **48**, M181–M186.

Neelon V & Champagne M (1992): Managing cognitive impairment: The current bases for practice. In: *Key Aspects of Eldercare: Managing falls, incontinence and cognitive impairment*. eds. S Funk, E Tournquist, M Champagne, pp 122–131. New York: Springer.

Newcomer JW, Selke G, Melson AK, Hershey T, Craft S, Richards K & Alderson AL (1999): Decreased memory performance in healthy humans induced by stress-level cortisol treatment. *Arch. Gen. Psychiatry* **56**, 527–533.

Noda Y, Yamada K & Nabeshima T (1997): Role of nitric oxide in the effect of aging on spatial memory in rats. *Behav. Brain Res.* **83**, 153–158.

Obrenovitch TP & Urenjjak J (1994): Altered glutamatergic transmission in neurological disorders: from high extracellular glutamate to excessive synaptic efficacy. *Prog. Neurobiol.* **51**, 39–87.

Rennie MJ, MacLennan PA, Hundal HS, Weryk B, Smith K, Taylor PM, Egan C & Watt PW (1989): Skeletal muscle glutamine transport, intramuscular glutamine concentration, and muscle-protein turnover. *Metabolism* **38**, 47–51.

Rolls BJ & Phillips PA (1990): Aging and disturbances of thirst and fluid balance. *Nutr. Rev.* **48**, 137–144.

Salemme E, Diano S, Maharajan P & Maharajan V (1996): Nitric oxide, a neuronal messenger. *Its role in hippocampal plasticity. Riv. Biol.* **89**, 87–107.

Sharma VM, Sridharan K, Pichan G & Panwar MR (1986): Influence of heat stress-induced dehydration on mental functions. *Ergonomics* **29**, 791–799.

Silver AJ (1987): Aging and risks for dehydration. *Cleveland Clin. J. Med.* **57**, 341–344.

Tallaksen-Greene SJ & Albin RL (1996): Splice variants of glutamate receptor sub-units 2 and 3 in striatal projection neurons. *Neuroscience* **75**, 1057–1064.

Vedhara K, Hyde J, Gilchrist ID, Tytherleigh M & Plummer S (2000): Acute stress, memory, attention and cortisol. *Psychoneuroendocrinology* **25**, 535–549.

Warren JL, Bacon WE, Harris T, McBean AM, Foley DJ & Phillips C (1994): The burden and outcomes associated with dehydration among US elderly. *Am. J. Pub. Health* **84**, 1265–1269.

Weitzman RE & Kleeman CR (1979): The clinical physiology of arginine vasopressin secretion and thirst. *West. J. Med.* **131**, 373–400.

Yamamoto M, Share L & Shade RE (1976): Vasopressin release during ventriculocisternal perfusion with Prostaglandin E_2. *J. Endocrinol.* **71**, 325.