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Review

Diabetes mellitus- and ageing-induced changes in the capacity for long-term depression and long-term potentiation inductions: Toward a unified mechanism

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ABSTRACT

Long-lasting type 1 and type 2 diabetes mellitus (DM) are both associated with impaired cognitive function in humans. Animal models of DM have confirmed the detrimental effect of high blood glucose levels on learning and memory. What are the neural correlates of such impaired cognition? It is widely, although not universally, believed that long-lasting increase and decrease in synaptic strength, known as long-term potentiation (LTP) and depression (LTD), provide an important key to understanding the cellular and molecular mechanisms by which memories are formed and stored. The majority of animal studies that examined the effect of DM on LTD and LTP used the streptozotocin (STZ) rodent model of type 1 DM, with the exception of a few that used genetic models of type 2 DM. Studies in STZ-DM rodents show that cellular processes underlying synapse strengthening or weakening are not altered. Rather, the capacity for LTP induction is reduced whereas that for LTD induction is enhanced. The mechanisms underlying DM-related changes in LTD and LTP inductions are still unknown. However, that the levels of effective postsynaptic depolarization for LTD and LTP inductions are concomitantly shifted in opposite directions put constraints on them. Moreover, that DM-, metaplasticity-, stress- and ageing-related changes in LTD and LTP inductions exhibit the very same phenomenology suggests that they might involve common mechanisms. Dissecting out the mechanisms responsible for DM-related changes in the capacity for LTD and LTP inductions is helping to improve treatment of impaired cognitive function in DM patients.

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1. Introduction

Diabetes mellitus (DM) is clinically defined by high blood glucose levels and by a general inability of the body to control these levels. DM actually represents a heterogenous group of disorders, the most common being type 1 and type 2 DM. Type 1 DM (formally defined as insulin-dependent DM) results from an absolute lack of insulin caused by an immune-mediated destruction of pancreatic β-cells whereas type 2 DM is a relative, rather than absolute, insulin deficiency; hence, the term of maturity-onset non-insulin-dependent DM. Clearly, life style plays a role in type 2 DM and obesity is an extremely important environmental influence. About 90% of DM patients present with type 2 DM. Because the average age of the population is increasing and the incidence of type 2 diabetes is particularly high among elderly people, the overall prevalence of diabetes will increase significantly in the next few years. (World Health Organization).

The morbidity associated with long-lasting DM of either type results from complications that affect eyes, kidneys, heart, blood vessels and nerves. DM also leads to clinically end-organ damage in the central nervous system as a result of both acute and chronic metabolic and vascular disturbances (for review see McCall, 1992; Biessels et al., 1994). The consequences of acute metabolic and vascular insults to the brain such as hypoglycemia and stroke are well recognized (for review see Bell, 1994; Cryer et al., 1994). However, there are also alterations in the brain that develop more insidiously. The chronic deficits associated with DM are much less known (for review see Gispen and Biessels, 2000). Particularly, the role of DM as a risk factor for cognitive decline in the elderly is now receiving growing attention because of the high prevalence of DM (especially type 2) in older populations and several potential mechanisms, vascular and otherwise, by which it may cause cognitive deterioration.

There is now substantial epidemiological evidence to suggest that both type 1 and type 2 DM are associated with cognitive impairment. What is less clear is whether there is a specific pattern of cognitive functions that are affected. Thus, type 1 DM patients might have impairments in learning and memory, problem solving and mental and motor speed (Ryan, 1988; Biessels et al., 1994). The deficit is generally modest (Ryan, 1988), but can be severe (Gold et al., 1994). Similarly, from the same case-control studies that examined the cognitive function in type 2 DM patients, Strachan et al. (1997) concluded to a moderate impairment of verbal memory and Stewart and Liolitsa (1999) saw evidence for deficits in the domain of attention/concentration and in verbal fluency (for review see Allen et al., 2004; Messier, 2005; Greenwood and Winocur, 2005). Nevertheless, these studies clearly indicate that DM is associated with impaired cognitive function. Moreover, epidemiological studies provide evidence for an elevated risk of both vascular and Alzheimer's dementia in type 2 DM albeit with strong interaction of other factors such as hypertension, dyslipidemia and apolipoprotein E phenotype (Ott et al., 1999; Stewart and Liolitsa, 1999; for review see Biessels and Kappelle, 2005).

The question is, therefore, not as to whether but as to how DM affects the cognitive function. This question can be addressed in animal models of DM. The majority of animal studies that examined the effect of DM on learning and memory used the streptozotocin (STZ) rodent model of type 1 DM, with the exception of a few that used genetic models of type 2 DM. STZ-DM rodents, though they can acquire relatively simple tasks, are clearly impaired in more complex tasks, such as spontaneous alternation behavior (Iwai et al., 2009), Morris water maze spatial test (Biessels et al., 1996; Kamal et al., 2000; Stranahan et al., 2008; Heng et al., 2011), active avoidance task (Flood et al., 1990), an object-discrimination task (Popoviç et al., 2001). Prevention of hyperglycemia by subcutaneous implantation of insulin pellets completely suppresses the learning deficit in the Morris maze (Biessels et al., 1998). Thus, behavioral studies in DM rodents confirm that DM is associated with a learning deficit.

Animal models of DM provide in addition the possibility to search for a neural correlate of the impaired cognition. A generally accepted hypothesis in neurobiology is that, at the cellular level, memories are stored, at least in part, as long lasting, activity-dependent changes in the strength of synaptic transmission. Therefore, long-term potentiation (LTP) and long-term depression (LTD) have been the object of intense investigation because it is widely, although not universally, believed that they provide an important key to understanding the cellular and molecular mechanisms by which memories are formed and stored (for review see Bliss and Collingridge, 1993; Malenka and Nicoll, 1999). Here we review experimental evidence, mainly from neurophysiological studies in STZ-DM rodents, that have characterized DM-related changes in the induction of LTD and LTP and discuss about the possible mechanisms underlying these changes.

2. The streptozotocin rodent model of type 1 diabetes mellitus

2.1. Intrinsic properties of CA1 neurons

Given the very large impact of insulin deficiency and high blood glucose levels on cellular metabolisms, one would predict a general deterioration of intrinsic neuronal properties. However, the intrinsic properties of CA1 neurons appear to be well preserved in STZ-DM rats. There is no difference in the resting membrane potential (V_{mr}), membrane input resistance (Candy and Szatkowski, 2000b; Artola et al., 2005; Kamal et al., 2006; Sasaki-Hamada et al., 2012; but see Heng et al., 2011) and membrane time constant (Kamal et al., 2003, 2006) between STZ-DM and age-matched control rats. However, whereas the amplitude and duration of single action potentials (AP; Kamal et al., 2003; Heng et al., 2011) do not change, their threshold appears to be higher in STZ-DM than control neurons (Heng et al., 2011). STZ-DM also shortens the AP discharge of hippocampal CA1 neurons in response to depolarizing step-current injections, because of the concomitant reduction in transient and persistent Na^+ currents and increase in transient and persistent K^+ currents (Heng et al., 2011). Higher AP threshold and enhanced AP adaptation should both contribute to reduced neuronal excitability. Moreover, the progressive increase in AP duration, that normally takes place during the train of APs as their frequency decreases, and the slow after-hyperpolarization (sAHP) at the end of the depolarizing current step are larger in STZ-DM compared with age-matched control rats (Kamal et al., 2003). The sAHP is due to a Ca^{2+}-dependent-K^+ current (for review see Storm, 1993). During membrane depolarization, Ca^{2+} enters the cell via L-type voltage-sensitive Ca^{2+} channels (Tanabe et al., 1998; Shah and Haylett, 2000; Lancaster et al., 2001). Elevation of the intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) activates Ca^{2+}-dependent-K^+ currents that remain active for as long as $[Ca^{2+}]_i$ is elevated. In STZ-DM rats, the enhancement of sAHP after depolarizing current steps has been shown to result from increased Ca^{2+} influx during the train of APs (Kamal et al., 2003).

2.2. Baseline synaptic transmission in hippocampus

Baseline excitatory synaptic transmission in STZ-DM rats has been found either to be larger (Schaeffer collateral-commissural pathway-CA1 (CC-CA1) synapses: Biessels et al., 1996; Kamal et al., 1999a), smaller (CC-CA1 synapses: Chabot et al., 1997) or not changed (perforant path-dentate gyrus synapses: Stranahan et al., 2008; CC-CA1 synapses: Sasaki-Hamada et al., 2012), compared