Nutrition Research Reviews (2008), **21**, 42–55
doi:10.1017/S0954422408945182

The role of dietary niacin intake and the adenosine-5′-diphosphate-ribosyl cyclase enzyme CD38 in spatial learning ability: is cyclic adenosine diphosphate ribose the link between diet and behaviour?

Genevieve S. Young* and James B. Kirkland

Department of Human Health and Nutritional Sciences, University of Guelph, Guelph, Ontario, Canada

The pyridine nucleotide NAD^+ is derived from dietary niacin and serves as the substrate for the synthesis of cyclic ADP-ribose (cADPR), an intracellular Ca signalling molecule that plays an important role in synaptic plasticity in the hippocampus, a region of the brain involved in spatial learning. cADPR is formed in part via the activity of the ADP-ribosyl cyclase enzyme CD38, which is widespread throughout the brain. In the present review, current evidence of the relationship between dietary niacin and behaviour is presented following investigations of the effect of niacin deficiency, pharmacological nicotinamide supplementation and CD38 gene deletion on brain nucleotides and spatial learning ability in mice and rats. In young male rats, both niacin deficiency and nicotinamide supplementation significantly altered brain NAD^+ and cADPR, both of which were inversely correlated with spatial learning ability. These results were consistent across three different models of niacin deficiency (pair feeding, partially restricted feeding and niacin recovery). Similar changes in spatial learning ability were observed in *Cd38*$^{-/-}$ mice, which also showed decreases in brain cADPR. These findings suggest an inverse relationship between spatial learning ability, dietary niacin intake and cADPR, although a direct link between cADPR and spatial learning ability is still missing. Dietary niacin may therefore play a role in the molecular events regulating learning performance, and further investigations of niacin intake, CD38 and cADPR may help identify potential molecular targets for clinical intervention to enhance learning and prevent or reverse cognitive decline.

Niacin: Behaviour: Spatial learning: Cyclic adenosine diphosphate ribose: NAD^+

Introduction

Niacin is the term used to describe vitamers including nicotinamide (pyridine-3-carboxyamide; Fig. 1(a)), nicotinic acid (pyridine-3-carboxylic acid; Fig. 1(b)), and a variety of pyridine nucleotide structures, such as NAD (Fig. 1(c)) and NADP (Fig. 1(d))[1]. NAD is synthesised from nicotinic acid via the Preiss–Handler pathway[2] or from nicotinamide via the Dietrich pathway[3]. Niacin, through NAD, can also be formed from the essential amino acid tryptophan. When niacin is derived from tryptophan, approximately 1 mg of the vitamin is formed from 60 mg of the amino acid, although the efficiency of conversion is affected by factors such as tryptophan and niacin intake and the amino acid, carbohydrate, vitamin B_6 and fat content of the diet[4,5]. As NAD^+, niacin is involved in a number of biochemical processes, including energy metabolism (redox reactions), protein modification by mono- and poly-(ADP-ribose) polymerases, and synthesis of intracellular Ca signalling molecules[1].

There is a long history of research concerning niacin status and brain function. Niacin deficiency in humans causes pellagra, which is characterised by sun-sensitivity and dementia. Neurological changes in pellagra patients begin peripherally, with signs such as muscle weakness, twitching and burning feelings in the extremities and altered gait[6]. Early psychological changes include depression and apprehension, but these progress to more severe changes, such as vertigo, loss of memory, deep depression, paranoia and delirium, hallucinations and violent behaviour[7], similar to schizophrenia[8]. While there are pathological changes in the spinal cord in advanced pellagra, there is a

Abbreviations: cADPR, cyclic adenosine diphosphate ribose; IP_3, inositol 1,4,5-triphosphate; LTD, long-term depression; LTP, long-term potentiation; NAADP, nicotinic acid adenine dinucleotide phosphate; NMDAR, *N*-methyl-D-aspartate receptor; MWM, Morris water maze; RyR, ryanodine receptor.

*** Corresponding author:** Dr Genevieve Young, fax +1 519 763 5902, email gyoung01@uoguelph.ca

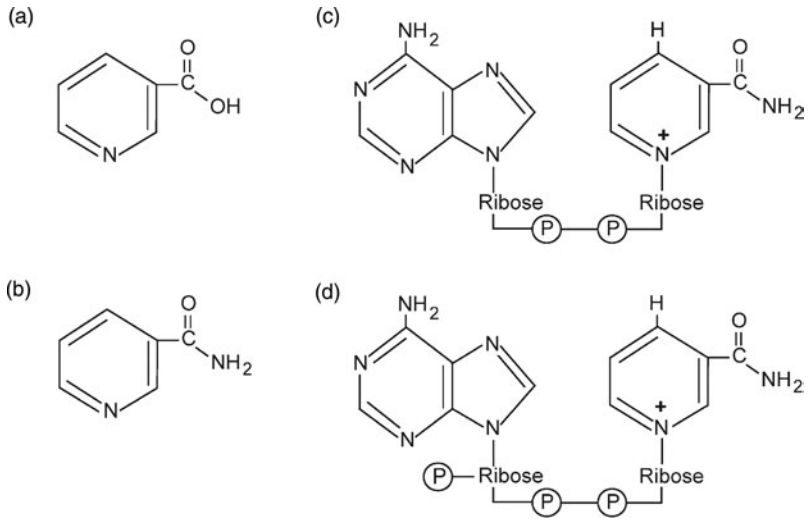

Fig. 1. Chemical structures of niacin compounds: (a) nicotinamide; (b) nicotinic acid; (c) nicotinamide adenine dinucleotide (NAD^+); (d) nicotinamide adenine dinucleotide phosphate ($NADP^+$).

striking recovery of psychological function when insane pellagra patients are treated with nicotinic acid, with a disappearance of many symptoms in 1–2 d[7]. These observations suggest that a compound derived from niacin is involved in neural signalling pathways. The recent discovery that the intracellular Ca signalling molecule cyclic ADP-ribose (cADPR) is derived from NAD^+ (Fig. 2)[9] suggests that cADPR might be the link between niacin status and behaviour. cADPR is involved in synaptic plasticity in the hippocampus[10,11], a region of the brain that regulates spatial learning[12]. As NAD^+ is derived from dietary niacin, cADPR levels might be expected to change with dietary niacin intake. The relationship between niacin, cADPR and hippocampal synaptic plasticity is the basis for the investigations described in the present review.

Discussion

Intracellular calcium

Modulation of intracellular Ca ion concentration is a universal mechanism by which extracellular signals are transduced into an intracellular response[13]. Ca levels inside the cell are controlled by both ion influx through channels in the plasma membrane and by release from intracellular stores, and Ca channels in plasma and organelle membranes open in response to extracellular signals in a spatial and temporally specific pattern to cause both local and global increases in intracellular ion concentration[14]. Intracellular Ca stores in the cell include (1) the endoplasmic reticulum[15], (2) the mitochondria[16–18], (3) the nuclear envelope[19–21], (4) the Golgi apparatus[22], (5) secretory granules[23] and (6) endosomes[24]. There are two other intracellular Ca mobilising molecules in addition to cADPR: nicotinic acid adenine dinucleotide phosphate (NAADP), which is formed from phosphorylated NAD[25], and D-myo-inositol 1,4,5-triphosphate (IP_3)[26]. A summary of the characteristics of IP_3, cADPR and NAADP is presented in Table 1[9,25,27–44]. Multiplicity of Ca signalling pathways may serve several functions, including redundancy to ensure that Ca signalling occurs and variation in the spatial and temporal Ca response[45]. Other compounds such as lysophosphatidic acid[46], sphingosine 1-phosphate[47] and ADP-ribose[48] are also involved in intracellular Ca mobilisation, although these do not necessarily function as second messengers.

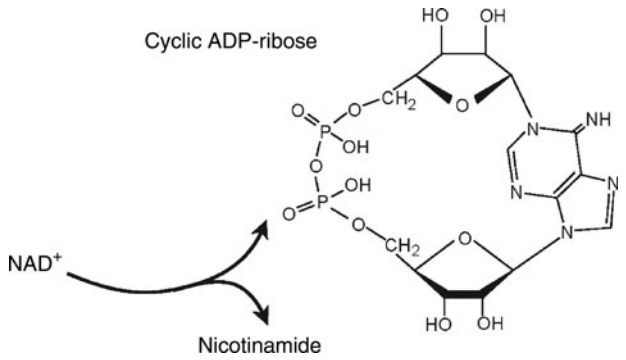

Fig. 2. Structure and origin of cyclic adenosine diphosphate ribose.

Ca signalling plays a crucial role in regulating many neuronal processes. As reviewed by Berridge[49], N- and P/Q-type voltage-activated channels are localised in synaptic terminals, where they regulate neurotransmitter release by generating a local Ca transient which activates synaptotagmin and triggers exocytosis. L-type voltage-activated channels are found on the cell body and proximal dendrites and regulate gene transcription. Synaptic plasticity is thought to be mediated by Ca entry through both voltage- and receptor-operated channels, and by release from IP_3 receptors and ryanodine receptors (RyR). As will be discussed later, modulation of intracellular Ca is required for both long-term potentiation (LTP) and long-term depression (LTD), cellular mechanisms which are thought to contribute to learning and memory[50]. Similar to neurons, astrocytes also regulate intracellular function through generation of Ca signals; as well, they control the function of neighbouring neurons through global Ca transients[51].

https://doi.org/10.1017/S0954422408945182 Published online by Cambridge University Press

Table 1. Characteristics of inositol 1,4,5-triphosphate (IP_3), cyclic adenosine diphosphate ribose (cADPR) and nicotinic acid adenine dinucleotide phosphate (NAADP)

	IP_3	cADPR	NAADP
Substrate	Phosphatidyl inositol 4,5-bisphosphate[27]	NAD^+[9]	$NADP^+$[25]
Ca stores	ER/SR[27]	ER/SR[30]	Lysosomes/reserve granules[32]
	Nuclear envelope[28]	Nuclear envelope[31]	Nuclear envelope[33]
	Golgi apparatus[29]		ER[30]
Receptors	IP_3R type I[34]	RyR type II[35]	NAADPR[36]
	IP_3R type II[34]	RyR type III[35]	RyR type I[37]
	IP_3R type III[34]		RyR type II[38]
CICR	Yes[27]	Yes[39]	No[40]
Brain localisation	Hippocampus[41]	Hippocampus[41]	Medulla[42]
	Striatum[41]	Striatum[41]	Midbrain[42]
	Cerebellum[41]	Cerebellum[41]	Thalamus[42]
Synthetic enzymes	Phospholipase C[27]	CD38[39]	CD38
		BST-1[39]	
		CD157[39]	
		Aplysia[39]	
		Soluble cyclase[43]	

ER, endoplasmic reticulum; SR, sarcoplasmic reticulum; IP_3R, IP_3 receptor; RyR, ryanodine receptor; NAADPR, NAADP receptor; CICR, Ca-induced Ca release.

Cyclic adenosine diphosphate ribose

cADPR has been found to mobilise intracellular Ca in numerous cell types, including protozoa, and those of plants, animals and man[52]. cADPR mobilises Ca ions via Ca-induced Ca release, whereby the Ca^{2+}-releasing mechanism is sensitised by the addition of Ca^{2+}[53]. cADPR synthesis is stimulated by cGMP[54]. cADPR also activates extracellular Ca influx[55,56]. The function of cADPR has been investigated in a wide range of cell types, and a summary of the intracellular effects of cADPR is presented in Table 2 (summarised in part from Guse[52]). Table 2[21,56–92] shows that cADPR administration brings about a variety of changes in neurons, including neurotransmitter release.

The principal target of cADPR is the RyR[53]. cADPR might bind directly to the RyR, or an additional binding protein might be required. The binding protein FKPB 12·6 has been found to act as a cADPR-binding protein in several cell types, including pancreatic islets[84] and smooth muscle cells[66,64]. Binding of cADPR to a target protein might cause release of the protein from the RyR, allowing opening of the RyR Ca channel[93]. The Ca-binding protein calmodulin is involved in cADPR-mediated Ca release from the RyR[94], and tyrosine phosphorylation of the RyR increases cADPR-mediated Ca release[95]. RyR, which are primarily found on the endoplasmic reticulum/sarcoplasmic reticulum (ER/SR) membrane, are not evenly distributed throughout the cell and distribution patterns vary across cell types[93]. In addition to the ER/SR, RyR are also found in mitochondria[96] and in the nuclear envelope[97,98]. Of the three RyR isoforms, cADPR has been shown to bind to type II and III[54,99]. An alternative mechanism has been proposed for cADPR whereby cADPR promotes refilling of depleted Ca stores rather than acting on RyR to induce Ca release[100]. The precise target of cADPR and any associated binding proteins is still not well understood.

CD38

The synthesis of cADPR is catalysed by the ADP-ribosyl cyclase family of enzymes. These include: CD38, a type II ectoenzyme that is also expressed intracellularly[39]; BST-1, also known as CD157, a bone marrow stromal cell-surface antigen[101]; a soluble cyclase characterised from the ovotestes of the *Aplysia* mollusk and of dogs[39]; a membrane-bound cyclase from canine spleen[102]; a membrane-bound cyclase from mouse brain[103]. The ADP-ribosyl cyclase enzymes are multifunctional, catalysing three reactions: (1) cyclisation of NAD^+ (ADP-ribosyl cyclase activity), (2) hydrolysis of cADPR to ADP-ribose (cADPR hydrolase activity) and (3) hydrolysis of NAD^+ to ADP-ribose (NAD^+ hydrolase activity)[39]. ADP-ribosyl cyclase enzymes also catalyse the exchange of nicotinamide and nicotinic acid to form NAADP[39].

CD38 is the most highly investigated ADP-ribosyl cyclase enzyme, and for years it has generated discussion related to its 'topological paradox'. This paradox questions how CD38, which has an active site facing the exterior of the cell, can regulate the synthesis of an intracellular signalling molecule[104]. BST-1 (CD157) shows a similar extracellular location[101]. As explanation, it has been demonstrated that cells possess connexin 43 hemichannels that allow passage of NAD^+ from the inside to the outside of the cell[105]. There is also bidirectional transport of cADPR through CD38 itself[106]. Intracellular NAD^+, which is found at micromolar concentrations (as compared with nanomolar concentrations extracellularly), can move down its concentration gradient through the connexon 43 channels to the ectocellular active site of CD38. CD38 can then catalyse the formation of cADPR, which passes through the central channel formed by the homodimeric structure of the protein[107]. Alternatively, cADPR can pass into the cell through nucleoside transporters[108]. The process of nucleotide transport can occur via an autocrine mechanism, with the NAD^+ and cADPR affecting the emitting cell, or a paracrine mechanism, with the nucleotides affecting cells in the vicinity of the emitting cell[107]. For example, increasing extracellular cADPR increases proliferation in human haematopoietic cells[109] and in 3T3 fibroblasts[110]. In the brain, astrocytes respond to extracellular cADPR by increasing intracellular Ca levels which in turn increase neurotransmitter release[111], while in

https://doi.org/10.1017/S0954422408945182 Published online by Cambridge University Press

Table 2. Intracellular effects of cyclic adenosine diphosphate ribose

Tissue or cell	Summary of effects	Organism
Cardiac (myocytes)	Induces Ca release, increases SR Ca content	Rat[57–59]
Smooth muscle (coronary, pulmonary, longitudinal)	Induces Ca release, modulates ion flux, vasodilation	Rabbit[60,61] Porcine[62,63] Bovine[64–66] Rat[67]
Skeletal muscle	Induces Ca release, increases muscle tension	Sheep[68] Porcine[69] Mouse[70]
Pituitary	Induces Ca release	Rat[71]
Dorsal root ganglion	Activates inward Ca current	Rat[72]
Brain (thalamocortical, myenteric, midbrain dopamine, and presynaptic neurons; dentate gyrus granule cell)	Induces Ca release, facilitates CICR, modulates ion flux, neurotransmitter release	Rat[73–75] Mouse[76] Bovine[77] *Aplysia*[78]
T-lymphocyte	Induces Ca release, stimulates Ca influx	Mouse[79] Human[80]
Natural killer cell	Induces Ca release	Human[81]
Neutrophil	Induces Ca release, stimulates Ca influx	Mouse[56]
Pancreas (pancreatic acinar, pancreatic islet)	Induces Ca release	Mouse[82] Rat[83–85]
Lacriminal acinar cell	Induces Ca release	Rat[86]
Parotid acinar cell	Induces Ca release	Rat[87]
Oocyte	Induces Ca release	Sea urchin[88] Ascidian[89] Star fish[90]
Hepatocyte	Induces Ca release	Mouse[21] Rat[91]
Mesangial cell	Induces Ca release	Rat[92]

SR, sarcoplasmic reticulum; CICR, Ca-induced Ca release.

bovine tracheal smooth muscle cells, extracellular cADPR increases intracellular Ca and potentiates acetylcholine-induced contraction[112]. However, CD38 is also localised to intracellular membranes, including the nucleus and the endoplasmic reticulum[97,98,113–115], which suggests that this enzyme also has an intracellular site of action. And, as previously mentioned, other soluble and membrane-bound ADP-ribosyl cyclase enzymes have been identified, so there is evidence for both intracellular and extracellular cyclases, although much remains to be understood about their precise roles in cADPR synthesis. Both CD38-[115] and non-CD38[43,103]-dependent ADP-ribosyl cyclase activity has been found in the brain. Distribution of CD38 in both rat[116] and human[117] brain is widespread.

Cyclic adenosine diphosphate ribose and hippocampal synaptic plasticity

LTP and LTD, which are long-lasting increases and decreases (respectively) in synaptic strength, are used experimentally to model learning and memory[118]. While there are various forms of LTD and LTP that differ in many respects, in all cases there is an increase in intracellular Ca levels. Induction of LTP requires a substantial rise in intracellular Ca, while a more moderate rise in intracellular Ca results in induction of LTD[50]. At least in *N*-methyl-D-aspartate acid receptor (NMDAR)-dependent forms, the signal cascade generated following LTP induction involves activation of Ca-dependent protein kinases such as Ca calmodulin kinase II[119,120], while that generated following LTD induction involves activation of Ca-dependent phosphatases such as calcineurin[121,122]. With respect to Ca-release channels, RyR are particularly concentrated in the dendritic spines of the hippocampus, in contrast to IP_3 receptors, which are concentrated in the dendritic shafts[41]. The Ca in dendritic spines has been proposed as being especially important in synaptic plasticity[123], so Ca released from RyR might be particularly essential for modulating hippocampal synaptic function.

There is considerable evidence that cADPR is required for a form of LTD in hippocampal neurons, although the exact mechanism by which cADPR exerts this effect is unclear. Both NMDAR-dependent and metabotropic-glutamate-receptor-dependent forms of LTD are found in the hippocampus of juvenile rats[124], and there is evidence for Ca release from ryanodine-sensitive stores in both. Early studies found that administration of dantrolene, a ryanodine channel blocker, blocked LTD and enhanced LTP in NMDAR-dependent hippocampal LTD[125], while Ca influx through low-voltage-activated Ca channels and release of Ca from ryanodine-sensitive Ca stores was linked to a form of NMDAR-independent hippocampal LTD[126]. Later studies suggested that hippocampal LTD induction required release of Ca from both pre- and postsynaptic stores, with a ryanodine-sensitive channel as the presynaptic store and probably IP_3 as the postsynaptic store[127]. Further investigation of the presynaptic role of RyR in hippocampal LTD determined that NMDAR-dependent LTD is followed by postsynaptic synthesis of NO and presynaptic activation of guanylyl cyclase, which probably enhances cADPR formation and the release of Ca from ryanodine-sensitive stores[10,11]. cADPR was finally shown experimentally to be associated with this presynaptic form of LTD in Reyes-Harde *et al.*[11]. Presynaptic modulation of

https://doi.org/10.1017/S0954422408945182 Published online by Cambridge University Press

LTD involves changes in neurotransmitter release, either through reductions in quantal size or frequency of transmission[124]. It was recently shown that the NO/LTD cascade at the frog neuromuscular junction involves activation of calmodulin and the Ca-sensitive enzyme calcineurin[128]. The authors proposed that in this pathway, there is a long-lasting depression of transmitter release due to sustained activity of the NO signalling pathway following calcineurin-mediated dephosphorylation of NOS, which results in sustained NO production[128]. As previously discussed, both NMDAR-dependent and metabotropic-glutamate-receptor-dependent forms of LTD could involve modulation of the presynaptic neuron by a retrograde messenger, so these results are consistent with known LTD characteristics.

As just mentioned, release of Ca from ryanodine-sensitive stores was associated with depotentiation of previously established LTP in the rat dentate gyrus[125]. RyR have also been associated with the induction of the late form of LTP in the hippocampus in a process requiring NO, cGMP and cGMP protein-dependent kinase[129]. As cADPR synthesis is stimulated by cGMP[54], it may also be involved in this cascade. RyR have been further implicated in weak LTP, as induced by a small conditioning stimulus, but not in the LTP that follows a moderate or strong conditioning protocol[130]. However, the evidence linking cADPR with LTP is not as clear as for LTD. In the only direct investigation of cADPR and LTP, administration of the cADPR antagonist 8-Br-cADPR had no effect on LTP induction[11] using an NMDAR-induction protocol. However, there are different types of LTP and several induction protocols that can be used, so this result is not conclusive. Investigations of type III RyR knockout mice, which might provide indirect evidence of the role of cADPR in LTP, have yielded conflicting results. In one study, RyR III knockout mice were found to exhibit decreased LTP in the CA1 region of the hippocampus and a decrease in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor response, although this did not appear to be due to changes in receptor density[131]. In a second study, RyR III knockout mice were found to exhibit facilitated LTP in the CA1 region of the hippocampus, with a corresponding impairment of LTD[132]. And in a third study, RyR III knockout mice showed no change in CA1 LTP[133]. Each of these studies used different LTP induction protocols and experimental conditions, which shows that it is difficult to compare LTP results across studies when the same procedures are not used. Also, different strains of mice were used in these experiments, so there may have been differences between knockout models as well.

Due to the importance of the hippocampus in spatial learning[12,134], altered hippocampal synaptic plasticity might be expected to affect this ability. Although there are no studies which directly link cADPR with spatial learning ability, two studies of the RyR III knockout mouse also looked at performance of these animals in the Morris water maze (MWM), which was introduced in 1981 as a tool to investigate spatial learning and memory in neurobehavioural research[135]. As with LTP, these studies report different effects of RyR III gene deletion on behaviour. In Futatsugi *et al.*[132], knockout mice showed improved spatial learning ability as evidenced by greater spatial accuracy in a probe trial, while in Balschun *et al.*[133], loss of RyR III had a negative effect on spatial learning ability, with animals showing reduced flexibility in relearning a new platform location. Although these results are not consistent, the studies also found that hippocampal neurons had different electrophysiological properties. The effect of RyR and cADPR on spatial learning ability is not clear at this time, although it has been shown that spatial learning increases the expression of RyR type II in the rat hippocampus[136].

Dietary niacin, brain cyclic adenosine diphosphate ribose and spatial learning

We investigated the effect of dietary niacin on brain cADPR and MWM performance using three different models of niacin deficiency and one model of niacin supplementation[137]. In each, male weanling Long–Evans rats were used since performance of female rats in the water maze has also been show to vary across the oestrous cycle[138] and tryptophan metabolism in females has been observed to change with hormonal variations[139]. Long–Evans rats are the most commonly used rats in water maze experiments, and their ability to perform successfully has been well validated[140]. Although the use of weanling rats introduces some concerns about potential dietary effects on synaptogenesis and myelination, which are not complete until 60 d after birth[141], we have previously shown that young rats show a much greater sensitivity to niacin deficiency than older rats, possibly due to a reduced tryptophan → NAD^+ conversion ability (JB Kirkland, unpublished results). The diets used in these experiments are modelled after AIN-93G (designed by the American Institute of Nutrition, formulated to meet gestation, lactation and growth requirements)[142], with 20 % casein replaced by 7 % casein and 6 % gelatin (Table 3). This represents a low level of protein, and tryptophan content is limiting in order to minimise tryptophan → NAD^+ conversion. The micronutrient levels are as described for AIN-93G, with the exception of niacin content in deficient and high-dose diets. Nicotinamide was chosen as the supplemented form of niacin because the brain shows a preference for using nicotinamide in the synthesis of NAD^+ over any other precursors, and there is an active mechanism for nicotinamide uptake into the brain, where it is distributed evenly[143]. Pharmacological nicotinamide supplementation has been investigated as a treatment for type 1 diabetes in children, so the level of nicotinamide used was comparable with the human consumption of 1–3 g nicotinamide per d in the diabetes prevention trials[144].

For all of our experiments, statistical analyses were performed using SPSS (version 12.0 for Windows; SPSS Inc., Chicago, IL, USA). The P value was set at $\leq 0{\cdot}05$. A trend was defined as a P value between 0·05 and 0·1. The Kolmogorov–Smirnov and Shapiro–Wilk tests were used to evaluate normality. As the water maze data in each experiment showed an abnormal distribution on at least one experimental day, non-parametric tests were used to assess water maze performance. The Friedman test was performed to determine the within-subjects effect, and the Kruskal–Wallis test was performed to determine the between-subjects effect. The within-subjects factor was time

https://doi.org/10.1017/S0954422408945182 Published online by Cambridge University Press

Table 3. Composition of experimental diets (g/kg diet)

	Niacin-deficient diet	Control diet	Niacin-supplemented diet
Cerelose	720	719·997	716
Casein	60	60	60
Gelatin	70	70	70
Cellulose	50	50	50
AIN-93 mineral mix[142]	35	35	35
Vitamin mix*	10	10	10
Methionine	3	3	3
Choline bitartrate	2	2	2
Nicotinic acid	0	0·003	0
Nicotinamide	0	0	4
Soya oil	50	50	50

* Vitamin mix composition: sucrose, 97 543 mg/kg; vitamin B_{12}, 1 mg/kg; vitamin E (DL-α-tocopheryl acetate), 20 000 mg/kg; biotin, 20 mg/kg; calcium pantothenate, 1600 mg/kg; folic acid, 200 mg/kg; vitamin K (phylloquinone), 50 mg/kg; pyridoxine HCl, 700 mg/kg; riboflavin, 600 mg/kg; thiamin HCl, 600 mg/kg; retinyl palmitate, 800 mg/kg; cholecalciferol, 2·5 mg/kg.

(test day) and the between-subjects factor was diet. For probe trial analysis, one-way ANOVA were run comparing the number of platform crossings at each of the four possible platform locations. Two-tailed independent *t* tests were used to compare mean swim speeds and brain nucleotides. Data were not transformed before analysis.

In the first niacin-deficiency model, niacin-deficient rats were compared with pair-fed controls (*n* 8). Control rats were pair fed a diet containing 30 mg added nicotinic acid per kg diet throughout the duration of the experiment. This level is considered adequate to fully meet the needs of rats, and is found in AIN-93 formulations and most commercial rat chows. In the water maze, niacin-deficient rats showed superior spatial learning ability during acquisition on day 2 ($P = 0{\cdot}01$), day 3 ($P = 0{\cdot}05$), day 5 ($P = 0{\cdot}007$) and day 6 ($P = 0{\cdot}001$) out of 7 d of testing, and tended to do so on day 4 ($P = 0{\cdot}1$) (Fig. 3(a)). There was also a trend ($P = 0{\cdot}09$) for higher spatial accuracy in a probe test. Brain NAD^+ was decreased by 42 % and brain cADPR by 36 % (Table 4). The pair-feeding model was used to control for differences in feed intake between niacin-deficient and control rats, since a deficiency of niacin, like most micronutrients, causes anorexia[145]. In our experiments, niacin-deficient weanling rats usually consume between 5 and 8 g food per d over periods of up to 5 weeks[137]. In contrast, food intake of healthy rats should increase during the growth period, and normal levels can be more than twice that consumed during niacin deficiency[146]. Both niacin-deficient and pair-fed rats are consequently significantly deprived of food, particularly in the later experimental weeks, and show a significantly reduced body weight when compared with normative rat growth charts.

In the second niacin-deficiency model, niacin-deficient rats were compared with partially feed-restricted controls (nine niacin-deficient rats and eight partially feed-restricted rats). Control rats were pair fed for the first 16 d of the experiment, and then fed *ad libitum* for 4 d before and during the entire period of water maze testing. In the water maze, we observed that niacin-deficient rats again showed superior performance on day 3 and day 4 ($P < 0{\cdot}05$) of 6 d of testing, and tended to do so on day 6 ($P = 0{\cdot}08$) (Fig. 3(b)), although the spatial accuracy of the two groups was comparable in a probe test. Brain NAD^+ and cADPR were not measured. The food intake and body weight of the two groups diverged greatly once the control group was placed on *ad libitum* feeding. The goal of this feeding strategy was to reduce hunger during the period of behavioural testing, while minimising the developmental differences that would result between niacin-deficient rats and rats fed *ad libitum* throughout the entire experiment.

In the third niacin-deficiency model, currently niacin-deficient rats were compared with niacin-recovered rats (*n* 9). All rats were maintained on a niacin-deficient diet during the first phase of water maze testing, and then half were recovered from the deficiency through niacin refeeding during the second phase of water maze testing. Nicotinamide was used since it is the preferred substrate for NAD^+ in most tissues, including the brain[147] and should therefore allow for a more rapid replenishment of niacin metabolites. The 4 d period of niacin refeeding before the second phase of water maze testing was designed to mimic the period of nutritional rehabilitation typically required for resolution of the symptoms of pellagrous dementia[145]. During the first phase of water maze testing, when all rats were niacin deficient, a retrospective analysis of performance revealed no significant differences between the two groups. However, during the second phase of water maze testing, when the recovered rats were being refed niacin, there was a significant effect of diet on day 4 ($P = 0{\cdot}01$) and a trend on day 2 ($P = 0{\cdot}09$) (Fig. 3(c)), with comparable spatial accuracy in the probe test. It is important to note that during the second phase of testing, rats were no longer naive and had already undergone extensive water maze training, so the sensitivity of the test to detect subtle differences in spatial learning ability would be reduced. Brain NAD^+ was decreased by 43 % and brain cADPR by 25 % (Table 4). This approach sought to determine the flexibility of learning and brain cADPR to niacin refeeding.

In the niacin-supplementation model, niacin-supplemented rats were compared with control rats (eighteen supplemented rats and fifteen control rats). Niacin-supplemented rats were fed a diet containing 4 g added nicotinamide/kg diet. The amount of food eaten daily during this period by each rat was determined and was correlated to body weight, allowing for an estimation of the average amount of food eaten daily per g body weight. The amount was initially determined at 0·15 g food/g body weight, and this value was used to calculate the amount of food provided on each day of the experimental period. This level of food provision was used throughout the experiment, as the daily residual food suggested that it allowed *ad libitum*, or nearly *ad libitum*, feeding to all animals. In the water maze, supplemented rats showed inferior spatial learning ability on day 3 ($P = 0{\cdot}04$) of 6 d of testing (Fig. 3(d)). Brain NAD^+ was increased by 38 % and brain cADPR by 14 % (Table 4).

The consistency of the finding of improved spatial learning ability in each niacin-deficiency model is striking. This, combined with the opposite observation following nicotinamide supplementation, is supportive of an inverse relationship between spatial learning ability and dietary niacin intake in very young rats. Although the link between dietary niacin, spatial learning ability and cADPR is

https://doi.org/10.1017/S0954422408945182 Published online by Cambridge University Press

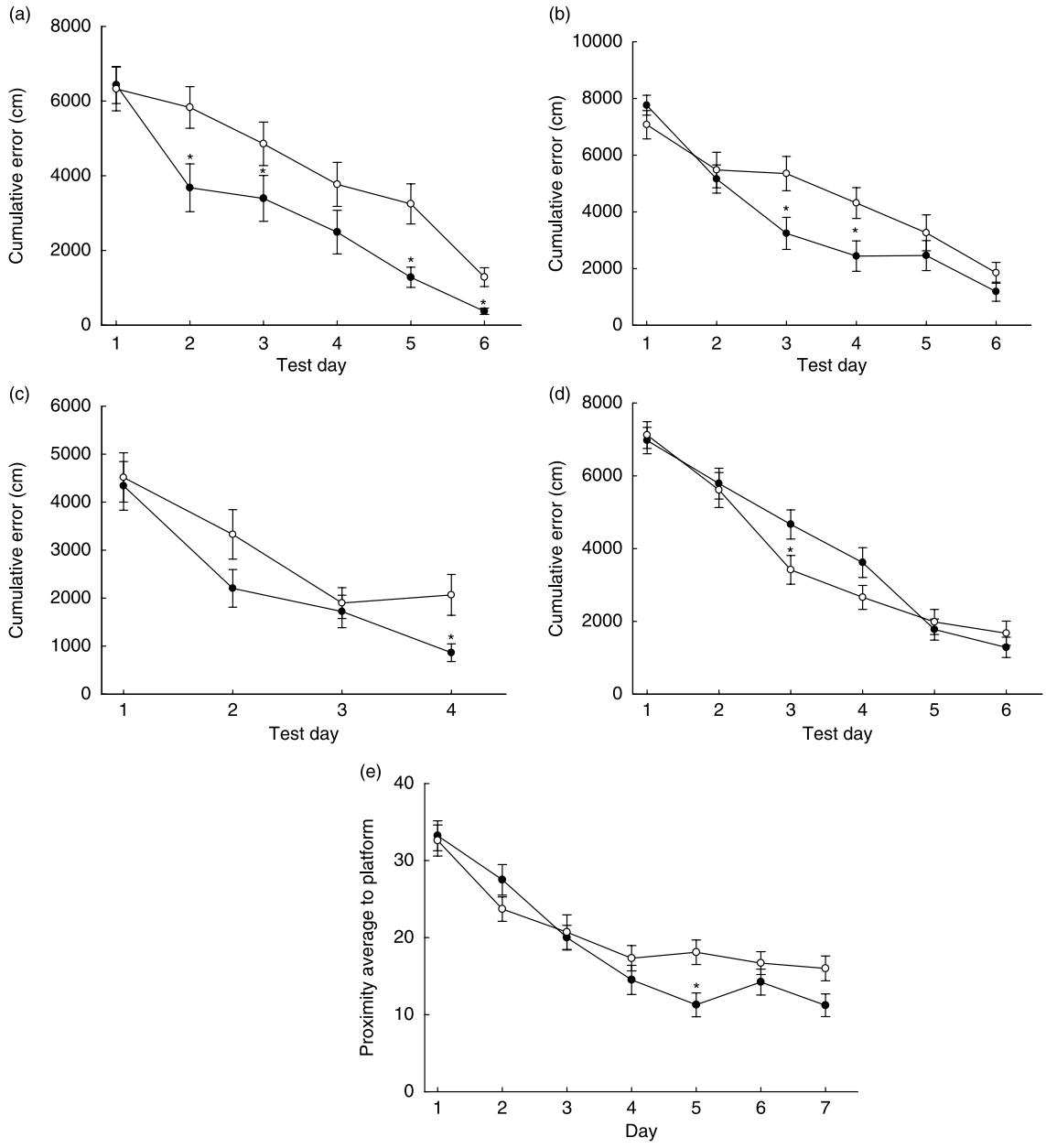

Fig. 3. (a) Cumulative error of niacin-deficient (−●−) and pair-fed (−○−) rats in the water maze. Rats were tested in three daily trials across 6 d with an inter-trial interval of 2 h. The results of the three daily trials were averaged to give a mean value for each day of testing. Values are means (*n* 8), with their standard errors represented by vertical bars. * Mean value was significantly different from that of the pair-fed rats ($P \leq 0{\cdot}05$). (b) Cumulative error of niacin-deficient (−●−; *n* 9) and partially feed-restricted (−○−; *n* 8) rats in the water maze. Rats were tested in three daily trials across 6 d with an inter-trial interval of 2 h. The results of the three daily trials were averaged to give a mean value for each day of testing. Values are means, with their standard errors represented by vertical bars. * Mean value was significantly different from that of the partially feed-restricted rats ($P \leq 0{\cdot}05$). (c) Cumulative error of niacin-deficient (−●−) and niacin-recovered (−○−) rats during reversal training in the water maze. Rats were tested in three daily trials across 4 d with an inter-trial interval of 2 h. The reversal training followed an initial acquisition phase in the water maze and 4 d of niacin refeeding. The results of the three daily trials were averaged to give a mean value for each day of testing. Values are means (*n* 9), with their standard errors represented by vertical bars. * Mean value was significantly different from that of the niacin-recovered rats ($P \leq 0{\cdot}05$). (d) Cumulative error of niacin-supplemented (−●−; *n* 18) and control (−○−; *n* 15) rats in the water maze. Rats were tested in three daily trials across 6 d with an inter-trial interval of 2 h. The results of the three daily trials were averaged to give a mean value for each day of testing. Values are means, with their standard errors represented by vertical bars. * Mean value was significantly different from that of the control rats ($P \leq 0{\cdot}05$). (e) Proximity averages to the platform during hidden platform testing by *Cd38*$^{-/-}$ (−●−) and wild-type (−○−) mice across 7 d of testing. Mice were tested in three daily trials across 6 d with an inter-trial interval of 2 h. The results of the three daily trials were averaged to give a mean value for each day of testing. Values are means (*n* 10), with their standard errors represented by vertical bars. * Mean value was significantly different from that of the wild-type rats ($P \leq 0{\cdot}05$). Fig. 3(a–d) were originally published in Young *et al.* (2007)[137]. Fig. 3(e) was originally published in Young *et al.* (2008)[149].

https://doi.org/10.1017/S0954422408945182 Published online by Cambridge University Press

Table 4. Brain NAD^+ and cyclic adenosine diphosphate ribose (cADPR) in rats with differing niacin intakes and in *Cd38*$^{-/-}$ mice (nmol/g tissue)
(Mean values with their standard errors)

	NAD^+		cADPR	
	Mean	SEM	Mean	SEM
Niacin-deficient *v.* pair-fed rats (*n* 8)				
Niacin deficient	70	5	0·11	0·005
Pair fed	120*	20	0·17*	0·01
Niacin-deficient *v.* recovered rats				
Niacin deficient (*n* 9)	120	20	0·12	0·005
Niacin recovered (*n* 8)	210*	30	0·16*	0·009
Niacin-supplemented *v.* control rats				
Niacin supplemented (*n* 18)	220*	20	0·25*	0·01
Control (*n* 15)	160	10	0·22	0·01
Cd38$^{-/-}$ *v.* wild-type mice (*n* 15)				
Cd38$^{-/-}$	350	10	0·18*	0·006
Wild type	220	10	0·21	0·005

* Mean value was significantly different from that of rats in the comparative group ($P \leq 0·05$).

correlational, dietary niacin might affect brain function through cADPR modulation. Like niacin, brain cADPR shows an inverse relationship with spatial learning ability, and while cADPR levels are quickly restored to normal following niacin refeeding, the cognitive benefits associated with the deficiency rapidly disappear.

CD38, brain cyclic adenosine diphosphate ribose and spatial learning

We also investigated the effect of CD38 gene deletion on brain cADPR[148] and MWM performance[149]. The *Cd38*$^{-/-}$ mouse was originally generated to study the role of CD38 in humoral immunity, and has subsequently been used in investigations of airway smooth muscle function[150], glucose tolerance[151], osteogenesis[152] and innate immunity[56,153]. While the original study of the *Cd38*$^{-/-}$ mouse reported comparable behaviour between knockout and wild-type animals[154], there have been no comprehensive investigations of specific behavioural functions in this transgenic model. *Cd38*$^{-/-}$ mice were generated by gene targeting[154] and were backcrossed for twelve generations to C57BL/6J[56]. This practice complies with the recommendation of the Banbury Conference that targeted mutations be maintained in congenic lines[155], although it is nonetheless likely that the knockouts carry alleles for genes that flank the mutation locus[156]. Backcrossing for twelve generations would reduce the length of the chromosome segment from the background genotype to about 16 cM, which when considered in relation to the mouse genome, would contain approximately 300 genes[157]. So, the *Cd38*$^{-/-}$ mouse would contain more than 99 % C57BL/6J genes. When inbred mouse strains are evaluated in the MWM, C57BL/6 mice are often characterised as being the strain of choice, and their ability to learn the task has been validated experimentally[158].

We observed that brain cADPR was increased ($P < 0·001$) in the *Cd38*$^{-/-}$ mouse as compared with wild-type controls (*n* 15)[148] (Table 4). This is in contrast to Partida-Sánchez *et al.*[56] and Ceni *et al.*[103], who previously measured levels of cADPR in these tissues and found them to be non-significantly decreased. While our levels of brain cADPR are comparable with other published reports, the degree of variability in each group is reduced, which we believe is due to modifications that we have made to the fluorimetric cycling assay for cADPR. These modifications are shown to increase the recovery of cADPR, improve the functionality of the assay, and reduce between-subject variability[159]. In fact, we observed a significant reduction of brain cADPR despite a difference of only 16 % between wild-type and knockout mice, in contrast to the 20 % non-significant reduction observed by Partida-Sanchez *et al.*[56] and the 18 % non-significant reduction observed in Ceni *et al.*[103]. We also observed that levels of NAD^+ in the brain were increased by 160 %[148] ($P < 0·001$) (Table 4). CD38 is a multifunctional enzyme that functions as both a cyclase and a hydrolase enzyme, forming ADP-ribose from hydrolysis of NAD^+ or cADPR. Since the ratio of cyclase:hydrolase activity is low[160], the loss of NAD^+ hydrolase activity might explain an increase in NAD^+ of this magnitude, and the differential activity of this enzyme would result in a much greater effect on NAD^+ increase than on cADPR reduction, which is what we observed.

We also observed that like niacin-deficient rats, *Cd38*$^{-/-}$ mice show improved performance in the MWM as compared with wild-type controls (*n* 10). *Cd38*$^{-/-}$ mice had a significantly shorter latency to the hidden platform on day 5 ($P = 0·05$) of 7 d of testing, and there was a trend for a shorter latency on day 7 ($P = 0·1$). Analysis of the proximity average, which takes into account how close the animal comes to the platform[161], confirmed that on day 5 *Cd38*$^{-/-}$ mice performed significantly better than wild-type mice ($P = 0·001$), while on day 7, there was a trend ($P = 0·07$) for better performance by the *Cd38*$^{-/-}$ mice (Fig. 3(e)). The mean proximity averages were lower for *Cd38*$^{-/-}$ mice from day 4 to day 7, demonstrating a consistent pattern for *Cd38*$^{-/-}$ mice to perform better than wild-type mice in the water maze on these days. In the probe trial, there was a trend ($P = 0·07$) for *Cd38*$^{-/-}$ mice to cross the target location more times than wild-type mice. Although the effect of CD38 gene deletion on water maze performance was less than seen in niacin deficiency, the results are nonetheless consistent with our previous observation of reduced brain cADPR and improved spatial learning ability in niacin-deficient rats. The magnitude of cADPR change was greater in the niacin-deficiency models than in *Cd38*$^{-/-}$ mice (25–35 *v.* 16 %), so when considered relative to this, these results suggest that although CD38 forms only a proportion of brain cADPR, its removal impacts on brain function by a similar mechanism as that of niacin deficiency. Unlike niacin-deficient rats, which have reduced brain NAD^+[137], the spatial learning effect in *Cd38*$^{-/-}$ mice is observed with increased brain NAD^+.

This was a revealing observation, as it identified total cADPr, and/or CD38-catalytic activity (capable of cADPr or NAADP synthesis), as parameters that correlated with MWM performance across all models (niacin-deficient/control/pharmacological nicotinic acid diets in rats, *Cd38*$^{-/-}$ *v.* wild-type mice). Conversely, brain NAD^+, and, by extension, the assumed activity of all other NAD^+-dependent enzymes did not correlate with performance across all models.

https://doi.org/10.1017/S0954422408945182 Published online by Cambridge University Press

Conclusion

The link between niacin and cADPR provides a fresh insight into the pathophysiology of pellagra, particularly with respect to pellagrous dementia, for which explanations based on redox reactions and energy metabolism did not adequately explain the aetiology of the clinical symptoms. Recovery of psychological function within days when insane pellagra patients are treated with niacin[7] suggests that the dementia is caused by alterations in neural signalling pathways, rather than structural pathological changes. Altered Ca signalling due to changes in levels of cADPR could provide the missing link between the vitamin deficiency and the symptoms of the disease. Our findings of enhanced spatial learning in niacin-deficient rats and in *Cd38*$^{-/-}$ mice may be due to changes in the hippocampal synaptic plasticity, and there is some published evidence to support this hypothesis. In a knockout model, deletion of type III RyR improved spatial learning ability, impaired LTD, and facilitated LTP[162]. Although cADPR was not directly implicated in this study, cADPR binds to RyR III[163], so the effects of gene deletion may be due to reduced cADPR-induced Ca signalling, which would also be observed with niacin deficiency. However, in previous work, loss of RyR III had a negative effect on spatial learning ability, with animals showing reduced flexibility in relearning a new platform location[133], so there are conflicting reports. Other studies have shown that animals which show facilitated LTD display impaired spatial learning[164,165], so if LTD is indeed impaired by decreased cADPR, spatial learning might be expected to improve. Further studies are required to investigate precisely the effects of niacin and cADPR on hippocampal electrophysiology. We are currently exploring this avenue as well as investigating the effect of dietary niacin and water maze training on gene expression in the hippocampus.

Although the evidence linking cADPR, CD38 and spatial learning ability presented in the present review is correlational, consistency of the findings across several different models greatly strengthens this relationship. Further validation comes from the observation that changes in spatial learning ability vary proportionately with the degree of changes in brain cADPR concentration. Niacin-deficient rats show the greatest decrease in cADPR, and the greatest improvement in spatial learning ability, while *Cd38*$^{-/-}$ mice show a more modest decrease in cADPR, and a more modest improvement in spatial learning ability. Unlike in niacin-deficient rats, this occurred with an increase in brain NAD^+, providing support for the causative role of cADPR in altered maze performance. In contrast, niacin-supplemented rats show a small increase in cADPR, and a small spatial learning impairment. These findings are supportive of an inverse relationship between spatial learning ability and dietary niacin intake in very young rats, although a direct link between cADPR and spatial learning ability is still missing. Clearly, brain cADPR and spatial learning ability are significantly affected by dietary niacin. Intake of this nutrient may therefore play a role in the molecular events regulating learning performance, and further investigations of niacin intake, CD38 and cADPR may help identify potential molecular targets for clinical intervention to enhance learning and prevent or reverse cognitive decline.

Acknowledgements

The present review was supported by funding from the Natural Sciences and Engineering Research Council (NSERC) of Canada and National Institutes of Health (NIH) grant CA-43894. There are no conflicts of interest.

G. S. Y. was the primary author of the paper which was adapted from her PhD thesis. J B K. was G. S. Y.'s advisor.

References

1. Kirkland JB (2006) Niacin. In *Handbook of Vitamins*, 4th ed., pp. 191–232 [RB Rucker, J Zempleni, JW Suttie and DB McCormick, editors]. Boca Raton, FL: Taylor & Francis.
2. Preiss J & Handler P (1958) Biosynthesis of diphosphopyridine nucleotide. I. Identification of intermediates. *J Biol Chem* **233**, 488–492.
3. Dietrich LS, Fuller L, Yero IL & Martinez L (1966) Nicotinamide mononucleotide pyrophosphorylase activity in animal tissues. *J Biol Chem* **241**, 188–191.
4. Shibata K, Mushiage M, Kondo T, Hayakawa T & Tsuge H (1995) Effects of vitamin B_6 deficiency on the conversion ratio of tryptophan to niacin. *Biosci Biotechnol Biochem* **59**, 2060–2063.
5. Shibata K (1999) Nutritional factors that regulate on the conversion of L-tryptophan to niacin. *Adv Exp Med Biol* **467**, 711–716.
6. Buniva (1981) Observations in pellagra: it would not appear to be contagious. In *Pellagra*, pp. 11–12 [KJ Carpenter, editor]. Stroudsburg, PA: Hutchinson Ross.
7. Spies TD, Bean WB & Ashe WF (1981) Recent advances in the treatment of pellagra and associated deficiencies. In *Pellagra*, pp. 213–225 [KJ Carpenter, editor]. Stroudsburg, PA: Hutchinson Ross.
8. Hoffer A (1970) Pellagra and schizophrenia. *Psychosomatics* **11**, 522–525.
9. Lee HC, Walseth TF, Bratt GT, Hayes RN & Clapper DL (1989) Structural determination of a cyclic metabolite of NAD^+ with intracellular Ca^{2+}-mobilizing activity. *J Biol Chem* **264**, 1608–1615.
10. Reyes-Harde M, Potter BV, Galione A & Stanton PK (1999) Induction of hippocampal LTD requires nitric-oxide-stimulated PKG activity and Ca^{2+} release from cyclic ADP-ribose-sensitive stores. *J Neurophysiol* **82**, 1569–1576.
11. Reyes-Harde M, Empson R, Potter BV, Galione A & Stanton PK (1999) Evidence of a role for cyclic ADP-ribose in long-term synaptic depression in hippocampus. *Proc Natl Acad Sci U S A* **96**, 4061–4066.
12. Redish AD & Touretzky DS (1998) The role of the hippocampus in solving the Morris water maze. *Neural Comput* **10**, 73–111.
13. Berridge MJ, Lipp P & Bootman MD (2000) The versatility and universality of calcium signalling. *Nat Rev Mol Cell Biol* **1**, 11–21.
14. Carafoli E, Santella L, Branca D & Brini M (2001) Generation, control, and processing of cellular calcium signals. *Crit Rev Biochem Mol Biol* **36**, 107–260.
15. Meldolesi J & Pozzan T (1998) The endoplasmic reticulum Ca^{2+} store: a view from the lumen. *Trends Biochem Sci* **23**, 10–14.
16. Pozzan T, Magalhaes P & Rizzuto R (2000) The comeback of mitochondria to calcium signalling. *Cell Calcium* **28**, 279–283.

17. Gilabert JA, Bakowski D & Parekh AB (2001) Energized mitochondria increase the dynamic range over which inositol 1,4,5-trisphosphate activates store-operated calcium influx. *EMBO J* **20**, 2672–2679.
18. Collins TJ, Berridge MJ, Lipp P & Bootman MD (2002) Mitochondria are morphologically and functionally heterogeneous within cells. *EMBO J* **21**, 1616–1627.
19. Malviya AN, Rogue P & Vincendon G (1990) Stereospecific inositol 1,4,5-[^{32}P]trisphosphate binding to isolated rat liver nuclei: evidence for inositol trisphosphate receptor-mediated calcium release from the nucleus. *Proc Natl Acad Sci U S A* **87**, 9270–9274.
20. Nicotera P, Orrenius S, Nilsson T & Berggren PO (1990) An inositol 1,4,5-trisphosphate-sensitive Ca^{2+} pool in liver nuclei. *Proc Natl Acad Sci U S A* **87**, 6858–6862.
21. Gerasimenko OV, Gerasimenko JV, Tepikin AV & Petersen OH (1995) ATP-dependent accumulation and inositol trisphosphate- or cyclic ADP-ribose-mediated release of Ca^{2+} from the nuclear envelope. *Cell* **80**, 439–444.
22. Pinton P, Pozzan T & Rizzuto R (1998) The Golgi apparatus is an inositol 1,4,5-trisphosphate-sensitive Ca^{2+} store, with functional properties distinct from those of the endoplasmic reticulum. *EMBO J* **17**, 5298–5308.
23. Yoo SH (2000) Coupling of the IP3 receptor/Ca^{2+} channel with Ca^{2+} storage proteins chromogranins A and B in secretory granules. *Trends Neurosci* **23**, 424–428.
24. Gerasimenko JV, Tepikin AV, Petersen OH & Gerasimenko OV (1998) Calcium uptake via endocytosis with rapid release from acidifying endosomes. *Curr Biol* **8**, 1335–1338.
25. Lee HC & Aarhus R (1995) A derivative of NADP mobilizes calcium stores insensitive to inositol trisphosphate and cyclic ADP-ribose. *J Biol Chem* **270**, 2152–2157.
26. Streb H, Irvine RF, Berridge MJ & Schulz I (1983) Release of Ca^{2+} from a nonmitochondrial intracellular store in pancreatic acinar cells by inositol-1,4,5-trisphosphate. *Nature* **306**, 67–69.
27. Mikoshiba K, Furuichi T, Miyawaki A, *et al*. (1993) Inositol trisphosphate receptor and Ca^{2+} signalling. *Philos Trans R Soc Lond B Biol Sci* **340**, 345–349.
28. Moore-Nichols D, Arnott A & Dunn RC (2002) Regulation of nuclear pore complex conformation by IP(3) receptor activation. *Biophys J* **83**, 1421–1428.
29. Surroca A & Wolff D (2000) Inositol 1,4,5-trisphosphate but not ryanodine-receptor agonists induces calcium release from rat liver Golgi apparatus membrane vesicles. *J Membr Biol* **177**, 243–249.
30. Gerasimenko JV, Sherwood M, Tepikin AV, Petersen OH & Gerasimenko OV (2006) NAADP, cADPR and IP3 all release Ca^{2+} from the endoplasmic reticulum and an acidic store in the secretory granule area. *J Cell Sci* **119**, 226–238.
31. Gerasimenko O & Gerasimenko J (2004) New aspects of nuclear calcium signalling. *J Cell Sci* **117**, 3087–3094.
32. Churchill GC, Okada Y, Thomas JM, Genazzani AA, Patel S & Galione A (2002) NAADP mobilizes Ca(2+) from reserve granules, lysosome-related organelles, in sea urchin eggs. *Cell* **111**, 703–708.
33. Gerasimenko JV, Maruyama Y, Yano K, Dolman NJ, Tepikin AV, Petersen OH & Gerasimenko OV (2003) NAADP mobilizes Ca^{2+} from a thapsigargin-sensitive store in the nuclear envelope by activating ryanodine receptors. *J Cell Biol* **163**, 271–282.
34. Mikoshiba K, Furuichi T & Miyawaki A (1994) Structure and function of IP3 receptors. *Semin Cell Biol* **5**, 273–281.
35. Guse AH (2005) Second messenger function and the structure-activity relationship of cyclic adenosine diphosphoribose (cADPR). *FEBS J* **272**, 4590–4597.
36. Galione A & Petersen OH (2005) The NAADP receptor: new receptors or new regulation? *Mol Interv* **5**, 73–79.
37. Hohenegger M, Suko J, Gscheidlinger R, Drobny H & Zidar A (2002) Nicotinic acid-adenine dinucleotide phosphate activates the skeletal muscle ryanodine receptor. *Biochem J* **367**, 423–431.
38. Mojzisova A, Krizanova O, Zacikova L, Kominkova V & Ondrias K (2001) Effect of nicotinic acid adenine dinucleotide phosphate on ryanodine calcium release channel in heart. *Pflugers Arch* **441**, 674–677.
39. Lee HC, Graeff R & Walseth TF (1995) Cyclic ADP-ribose and its metabolic enzymes. *Biochimie* **77**, 345–355.
40. Chini EN & Dousa TP (1996) Nicotinate-adenine dinucleotide phosphate-induced Ca(2+)-release does not behave as a Ca(2+)-induced Ca(2+)-release system. *Biochem J* **316**, 709–711.
41. Sharp AH, McPherson PS, Dawson TM, Aoki C, Campbell KP & Snyder SH (1993) Differential immunohistochemical localization of inositol 1,4,5-trisphosphate- and ryanodine-sensitive Ca^{2+} release channels in rat brain. *J Neurosci* **13**, 3051–3063.
42. Patel S, Churchill GC, Sharp T & Galione A (2000) Widespread distribution of binding sites for the novel Ca^{2+}-mobilizing messenger, nicotinic acid adenine dinucleotide phosphate, in the brain. *J Biol Chem* **275**, 36495–36497.
43. Ceni C, Muller-Steffner H, Lund F, Pochon N, Schweitzer A, De Waard M, Schuber F, Villaz M & Moutin MJ (2003) Evidence for an intracellular ADP-ribosyl cyclase/NAD^+-glycohydrolase in brain from CD38-deficient mice. *J Biol Chem* **278**, 40670–40678.
44. Aarhus R, Graeff RM, Dickey DM, Walseth TF & Lee HC (1995) ADP-ribosyl cyclase and CD38 catalyze the synthesis of a calcium-mobilizing metabolite from NADP. *J Biol Chem* **270**, 30327–30333.
45. da Silva CP & Guse AH (2000) Intracellular Ca(2+) release mechanisms: multiple pathways having multiple functions within the same cell type? *Biochim Biophys Acta* **1498**, 122–133.
46. Melendez AJ & Allen JM (2002) Phospholipase D and immune receptor signalling. *Semin Immunol* **14**, 49–55.
47. Young KW & Nahorski SR (2001) Intracellular sphingosine 1-phosphate production: a novel pathway for Ca^{2+} release. *Semin Cell Dev Biol* **12**, 19–25.
48. Lee HC (2001) Physiological functions of cyclic ADP-ribose and NAADP as Ca messengers. *Annu Rev Pharmacol Toxicol* **41**, 317–345.
49. Berridge MJ (1998) Neuronal calcium signaling. *Neuron* **21**, 13–26.
50. Franks KM & Sejnowski TJ (2002) Complexity of calcium signaling in synaptic spines. *Bioessays* **24**, 1130–1144.
51. Scemes E (2000) Components of astrocytic intercellular calcium signaling. *Mol Neurobiol* **22**, 167–179.
52. Guse AH (2004) Regulation of calcium signaling by the second messenger cyclic adenosine diphosphoribose (cADPR). *Curr Mol Med* **4**, 239–248.
53. Galione A, Lee HC & Busa WB (1991) Ca(2+)-induced Ca^{2+} release in sea urchin egg homogenates: modulation by cyclic ADP-ribose. *Science* **253**, 1143–1146.
54. Galione A, White A, Willmott N, Turner M, Potter BV & Watson SP (1993) cGMP mobilizes intracellular Ca^{2+} in sea urchin eggs by stimulating cyclic ADP-ribose synthesis. *Nature* **365**, 456–459.

55. Guse AH, Berg I, da Silva CP, Potter BV & Mayr GW (1997) Ca^{2+} entry induced by cyclic ADP-ribose in intact T-lymphocytes. *J Biol Chem* **272**, 8546–8550.
56. Partida-Sánchez S, Cockayne DA, Monard S, *et al*. (2001) Cyclic ADP-ribose production by CD38 regulates intracellular calcium release, extracellular calcium influx and chemotaxis in neutrophils and is required for bacterial clearance *in vivo*. *Nat Med* **7**, 1209–1216.
57. Meszaros LG, Bak J & Chu A (1993) Cyclic ADP-ribose as an endogenous regulator of the non-skeletal type ryanodine receptor Ca^{2+} channel. *Nature* **364**, 76–79.
58. Lukyanenko V & Gyorke S (1999) Ca^{2+} sparks and Ca^{2+} waves in saponin-permeabilized rat ventricular myocytes. *J Physiol* **521**, 575–585.
59. Cui Y, Galione A & Terrar DA (1999) Effects of photoreleased cADP-ribose on calcium transients and calcium sparks in myocytes isolated from guinea-pig and rat ventricle. *Biochem J* **342**, 269–273.
60. Kuemmerle JF & Makhlouf GM (1995) Agonist-stimulated cyclic ADP ribose. Endogenous modulator of Ca(2+)-induced Ca^{2+} release in intestinal longitudinal muscle. *J Biol Chem* **270**, 25488–25494.
61. Wilson HL, Dipp M, Thomas JM, Lad C, Galione A & Evans AM (2001) ADP-ribosyl cyclase and cyclic ADP-ribose hydrolase act as a redox sensor. A primary role for cyclic ADP-ribose in hypoxic pulmonary vasoconstriction. *J Biol Chem* **276**, 11180–11188.
62. Kannan MS, Fenton AM, Prakash YS & Sieck GC (1996) Cyclic ADP-ribose stimulates sarcoplasmic reticulum calcium release in porcine coronary artery smooth muscle. *Am J Physiol* **270**, H801–H806.
63. Prakash YS, Kannan MS, Walseth TF & Sieck GC (1998) Role of cyclic ADP-ribose in the regulation of [Ca2+]i in porcine tracheal smooth muscle. *Am J Physiol* **274**, C1653–C1660.
64. Li PL, Tang WX, Valdivia HH, Zou AP & Campbell WB (2001) cADP-ribose activates reconstituted ryanodine receptors from coronary arterial smooth muscle. *Am J Physiol Heart Circ Physiol* **280**, H208–H215.
65. Li PL, Zou AP & Campbell WB (1998) Regulation of KCa-channel activity by cyclic ADP-ribose and ADP-ribose in coronary arterial smooth muscle. *Am J Physiol* **275**, H1002–H1010.
66. Tang WX, Chen YF, Zou AP, Campbell WB & Li PL (2002) Role of FKBP12·6 in cADPR-induced activation of reconstituted ryanodine receptors from arterial smooth muscle. *Am J Physiol Heart Circ Physiol* **282**, H1304–H1310.
67. Boittin FX, Dipp M, Kinnear NP, Galione A & Evans AM (2003) Vasodilation by the calcium-mobilizing messenger cyclic ADP-ribose. *J Biol Chem* **278**, 9602–9608.
68. Sitsapesan R & Williams AJ (1995) Cyclic ADP-ribose and related compounds activate sheep skeletal sarcoplasmic reticulum Ca^{2+} release channel. *Am J Physiol* **268**, C1235–C1240.
69. Lopez JR, Cordovez G, Linares N & Allen PD (2000) Cyclic ADP-ribose induces a larger than normal calcium release in malignant hyperthermia-susceptible skeletal muscle fibers. *Pflugers Arch* **440**, 236–242.
70. Fulceri R, Rossi R, Bottinelli R, Conti A, Intravaia E, Galione A, Benedetti A, Sorrentino V & Reggiani C (2001) Ca^{2+} release induced by cyclic ADP ribose in mice lacking type 3 ryanodine receptor. *Biochem Biophys Res Commun* **288**, 697–702.
71. Koshiyama H, Lee HC & Tashjian AH Jr (1991) Novel mechanism of intracellular calcium release in pituitary cells. *J Biol Chem* **266**, 16985–16988.
72. Currie KP, Swann K, Galione A & Scott RH (1992) Activation of Ca(2+)-dependent currents in cultured rat dorsal root ganglion neurones by a sperm factor and cyclic ADP-ribose. *Mol Biol Cell* **3**, 1415–1425.
73. Morikawa H, Khodakhah K & Williams JT (2003) Two intracellular pathways mediate metabotropic glutamate receptor-induced Ca^{2+} mobilization in dopamine neurons. *J Neurosci* **23**, 149–157.
74. White AM, Watson SP & Galione A (1993) Cyclic ADP-ribose-induced Ca^{2+} release from rat brain microsomes. *FEBS Lett* **318**, 259–263.
75. Budde T, Sieg F, Braunewell KH, Gundelfinger ED & Pape HC (2000) Ca^{2+}-induced Ca^{2+} release supports the relay mode of activity in thalamocortical cells. *Neuron* **26**, 483–492.
76. Shirasaki T, Houtani T, Sugimoto T & Matsuda H (2001) Spontaneous transient outward currents: modulation by nociceptin in murine dentate gyrus granule cells. *Brain Res* **917**, 191–205.
77. Morita K, Kitayama S & Dohi T (1997) Stimulation of cyclic ADP-ribose synthesis by acetylcholine and its role in catecholamine release in bovine adrenal chromaffin cells. *J Biol Chem* **272**, 21002–21009.
78. Mothet JP, Fossier P, Meunier FM, Stinnakre J, Tauc L & Baux G (1998) Cyclic ADP-ribose and calcium-induced calcium release regulate neurotransmitter release at a cholinergic synapse of *Aplysia*. *J Physiol* **507**, 405–414.
79. Bourguignon LY, Chu A, Jin H & Brandt NR (1995) Ryanodine receptor-ankyrin interaction regulates internal Ca^{2+} release in mouse T-lymphoma cells. *J Biol Chem* **270**, 17917–17922.
80. Guse AH, da Silva CP, Emmrich F, Ashamu GA, Potter BV & Mayr GW (1995) Characterization of cyclic adenosine diphosphate-ribose-induced Ca^{2+} release in T lymphocyte cell lines. *J Immunol* **155**, 3353–3359.
81. Inngjerdingen M, Al Aoukaty A, Damaj B & Maghazachi AA (1999) Differential utilization of cyclic ADP-ribose pathway by chemokines to induce the mobilization of intracellular calcium in NK cells. *Biochem Biophys Res Commun* **262**, 467–472.
82. Thorn P, Gerasimenko O & Petersen OH (1994) Cyclic ADP-ribose regulation of ryanodine receptors involved in agonist evoked cytosolic Ca^{2+} oscillations in pancreatic acinar cells. *EMBO J* **13**, 2038–2043.
83. Gobel A, Krause E, Feick P & Schulz I (2001) IP(3) and cyclic ADP-ribose induced Ca(2 +) release from intracellular stores of pancreatic acinar cells from rat in primary culture. *Cell Calcium* **29**, 29–37.
84. Noguchi N, Takasawa S, Nata K, Tohgo A, Kato I, Ikehata F, Yonekura H & Okamoto H (1997) Cyclic ADP-ribose binds to FK506-binding protein 12·6 to release Ca^{2+} from islet microsomes. *J Biol Chem* **272**, 3133–3136.
85. Takasawa S, Nata K, Yonekura H & Okamoto H (1993) Cyclic ADP-ribose in insulin secretion from pancreatic β cells. *Science* **259**, 370–373.
86. Gromada J, Jorgensen TD & Dissing S (1995) Cyclic ADP-ribose and inositol 1,4,5-triphosphate mobilizes Ca^{2+} from distinct intracellular pools in permeabilized lacrimal acinar cells. *FEBS Lett* **360**, 303–306.
87. Ozawa T & Nishiyama A (1997) Characterization of ryanodine-sensitive Ca^{2+} release from microsomal vesicles of rat parotid acinar cells: regulation by cyclic ADP-ribose. *J Membr Biol* **156**, 231–239.
88. Rusinko N & Lee HC (1989) Widespread occurrence in animal tissues of an enzyme catalyzing the conversion of NAD^+ into a cyclic metabolite with intracellular Ca^{2+}-mobilizing activity. *J Biol Chem* **264**, 11725–11731.

https://doi.org/10.1017/S0954422408945182 Published online by Cambridge University Press

89. Albrieux M, Lee HC & Villaz M (1998) Calcium signaling by cyclic ADP-ribose, NAADP, and inositol trisphosphate are involved in distinct functions in ascidian oocytes. *J Biol Chem* **273**, 14566–14574.
90. Moccia F, Nusco GA, Lim D, Ercolano E, Gragnaniello G, Brown ER & Santella L (2003) Ca^{2+} signalling and membrane current activated by cADPr in starfish oocytes. *Pflugers Arch* **446**, 541–552.
91. Khoo KM, Han MK, Park JB, Chae SW, Kim UH, Lee HC, Bay BH & Chang CF (2000) Localization of the cyclic ADP-ribose-dependent calcium signaling pathway in hepatocyte nucleus. *J Biol Chem* **275**, 24807–24817.
92. Yusufi AN, Cheng J, Thompson MA, Dousa TP, Warner GM, Walker HJ & Grande JP (2001) cADP-ribose/ryanodine channel/Ca^{2+}-release signal transduction pathway in mesangial cells. *Am J Physiol Renal Physiol* **281**, F91–F102.
93. Guse AH (2004) Biochemistry, biology, and pharmacology of cyclic adenosine diphosphoribose (cADPR). *Curr Med Chem* **11**, 847–855.
94. Lee HC, Aarhus R, Graeff R, Gurnack ME & Walseth TF (1994) Cyclic ADP ribose activation of the ryanodine receptor is mediated by calmodulin. *Nature* **370**, 307–309.
95. Guse AH, Tsygankov AY, Weber K & Mayr GW (2001) Transient tyrosine phosphorylation of human ryanodine receptor upon T cell stimulation. *J Biol Chem* **276**, 34722–34727.
96. Beutner G, Sharma VK, Giovannucci DR, Yule DI & Sheu SS (2001) Identification of a ryanodine receptor in rat heart mitochondria. *J Biol Chem* **276**, 21482–21488.
97. Khoo KM & Chang CF (2002) Identification and characterization of nuclear CD38 in the rat spleen. *Int J Biochem Cell Biol* **34**, 43–54.
98. Adebanjo OA, Anandatheerthavarada HK, Koval AP, *et al*. (1999) A new function for CD38/ADP-ribosyl cyclase in nuclear Ca^{2+} homeostasis. *Nat Cell Biol* **1**, 409–414.
99. Schwarzmann N, Kunerth S, Weber K, Mayr GW & Guse AH (2002) Knock-down of the type 3 ryanodine receptor impairs sustained Ca^{2+} signaling via the T cell receptor/CD3 complex. *J Biol Chem* **277**, 50636–50642.
100. Lukyanenko V, Gyorke I, Wiesner TF & Gyorke S (2001) Potentiation of Ca(2 +) release by cADP-ribose in the heart is mediated by enhanced SR Ca(2 +) uptake into the sarcoplasmic reticulum. *Circ Res* **89**, 614–622.
101. Itoh M, Ishihara K, Tomizawa H, Tanaka H, Kobune Y, Ishikawa J, Kaisho T & Hirano T (1994) Molecular cloning of murine BST-1 having homology with CD38 and *Aplysia* ADP-ribosyl cyclase. *Biochem Biophys Res Commun* **203**, 1309–1317.
102. Kim H, Jacobson EL & Jacobson MK (1993) Synthesis and degradation of cyclic ADP-ribose by NAD glycohydrolases. *Science* **261**, 1330–1333.
103. Ceni C, Pochon N, Villaz M, Muller-Steffner H, Schuber F, Baratier J, De Waard M, Ronjat M & Moutin MJ (2006) The CD38-independent ADP-ribosyl cyclase from mouse brain synaptosomes: a comparative study of neonate and adult brain. *Biochem J* **395**, 417–426.
104. De Flora A, Guida L, Franco L & Zocchi E (1997) The CD38/cyclic ADP-ribose system: a topological paradox. *Int J Biochem Cell Biol* **29**, 1149–1166.
105. Bruzzone S, Guida L, Zocchi E, Franco L & De Flora A (2001) Connexin 43 hemi channels mediate Ca^{2+}-regulated transmembrane NAD^+ fluxes in intact cells. *FASEB J* **15**, 10–12.
106. Franco L, Guida L, Bruzzone S, Zocchi E, Usai C & De Flora A (1998) The transmembrane glycoprotein CD38 is a catalytically active transporter responsible for generation and influx of the second messenger cyclic ADP-ribose across membranes. *FASEB J* **12**, 1507–1520.
107. De Flora A, Zocchi E, Guida L, Franco L & Bruzzone S (2004) Autocrine and paracrine calcium signaling by the CD38/NAD^+/cyclic ADP-ribose system. *Ann N Y Acad Sci* **1028**, 176–191.
108. Guida L, Bruzzone S, Sturla L, Franco L, Zocchi E & De Flora A (2002) Equilibrative and concentrative nucleoside transporters mediate influx of extracellular cyclic ADP-ribose into 3T3 murine fibroblasts. *J Biol Chem* **277**, 47097–47105.
109. Podestà M, Zocchi E, Pitto A, *et al*. (2000) Extracellular cyclic ADP-ribose increases intracellular free calcium concentration and stimulates proliferation of human hemopoietic progenitors. *FASEB J* **14**, 680–690.
110. Franco L, Zocchi E, Usai C, Guida L, Bruzzone S, Costa A & De Flora A (2001) Paracrine roles of NAD^+ and cyclic ADP-ribose in increasing intracellular calcium and enhancing cell proliferation of 3T3 fibroblasts. *J Biol Chem* **276**, 21642–21648.
111. Verderio C, Bruzzone S, Zocchi E, Fedele E, Schenk U, De Flora A & Matteoli M (2001) Evidence of a role for cyclic ADP-ribose in calcium signalling and neurotransmitter release in cultured astrocytes. *J Neurochem* **78**, 646–657.
112. Franco L, Bruzzone S, Song P, Guida L, Zocchi E, Walseth TF, Crimi E, Usai C, De Flora A & Brusasco V (2001) Extracellular cyclic ADP-ribose potentiates ACh-induced contraction in bovine tracheal smooth muscle. *Am J Physiol Lung Cell Mol Physiol* **280**, L98–L106.
113. Sun L, Adebanjo OA, Koval A, *et al*. (2002) A novel mechanism for coupling cellular intermediary metabolism to cytosolic Ca^{2+} signaling via CD38/ADP-ribosyl cyclase, a putative intracellular NAD^+ sensor. *FASEB J* **16**, 302–314.
114. Munshi CB, Graeff R & Lee HC (2002) Evidence for a causal role of CD38 expression in granulocytic differentiation of human HL-60 cells. *J Biol Chem* **277**, 49453–49458.
115. Ceni C, Pochon N, Brun V, *et al*. (2003) CD38-dependent ADP-ribosyl cyclase activity in developing and adult mouse brain. *Biochem J* **370**, 175–183.
116. Yamada M, Mizuguchi M, Otsuka N, Ikeda K & Takahashi H (1997) Ultrastructural localization of CD38 immunoreactivity in rat brain. *Brain Res* **756**, 52–60.
117. Mizuguchi M, Otsuka N, Sato M, Ishii Y, Kon S, Yamada M, Nishina H, Katada T & Ikeda K (1995) Neuronal localization of CD38 antigen in the human brain. *Brain Res* **697**, 235–240.
118. Malenka RC & Bear MF (2004) LTP and LTD: an embarrassment of riches. *Neuron* **44**, 5–21.
119. Malinow R, Schulman H & Tsien RW (1989) Inhibition of postsynaptic PKC or CaMKII blocks induction but not expression of LTP. *Science* **245**, 862–866.
120. Silva AJ, Wang Y, Paylor R, Wehner JM, Stevens CF & Tonegawa S (1992) α Calcium/calmodulin kinase II mutant mice: deficient long-term potentiation and impaired spatial learning. *Cold Spring Harb Symp Quant Biol* **57**, 527–539.
121. Mulkey RM, Endo S, Shenolikar S & Malenka RC (1994) Involvement of a calcineurin/inhibitor-1 phosphatase cascade in hippocampal long-term depression. *Nature* **369**, 486–488.
122. Mulkey RM, Herron CE & Malenka RC (1993) An essential role for protein phosphatases in hippocampal long-term depression. *Science* **261**, 1051–1055.
123. Sabatini BL, Oertner TG & Svoboda K (2002) The life cycle of Ca(2+) ions in dendritic spines. *Neuron* **33**, 439–452.

https://doi.org/10.1017/S0954422408945182 Published online by Cambridge University Press

124. Nicoll RA, Oliet SH & Malenka RC (1998) NMDA receptor-dependent and metabotropic glutamate receptor-dependent forms of long-term depression coexist in CA1 hippocampal pyramidal cells. *Neurobiol Learn Mem* **70**, 62–72.
125. O'Mara SM, Rowan MJ & Anwyl R (1995) Dantrolene inhibits long-term depression and depotentiation of synaptic transmission in the rat dentate gyrus. *Neuroscience* **68**, 621–624.
126. Wang Y, Rowan MJ & Anwyl R (1997) Induction of LTD in the dentate gyrus *in vitro* is NMDA receptor independent, but dependent on Ca^{2+} influx via low-voltage-activated Ca^{2+} channels and release of Ca^{2+} from intracellular stores. *J Neurophysiol* **77**, 812–825.
127. Reyes M & Stanton PK (1996) Induction of hippocampal long-term depression requires release of Ca^{2+} from separate presynaptic and postsynaptic intracellular stores. *J Neurosci* **16**, 5951–5960.
128. Etherington SJ & Everett AW (2004) Postsynaptic production of nitric oxide implicated in long-term depression at the mature amphibian (*Bufo marinus*) neuromuscular junction. *J Physiol* **559**, 507–517.
129. Lu YF, Kandel ER & Hawkins RD (1999) Nitric oxide signaling contributes to late-phase LTP and CREB phosphorylation in the hippocampus. *J Neurosci* **19**, 10250–10261.
130. Raymond CR & Redman SJ (2002) Different calcium sources are narrowly tuned to the induction of different forms of LTP. *J Neurophysiol* **88**, 249–255.
131. Shimuta M, Yoshikawa M, Fukaya M, Watanabe M, Takeshima H & Manabe T (2001) Postsynaptic modulation of AMPA receptor-mediated synaptic responses and LTP by the type 3 ryanodine receptor. *Mol Cell Neurosci* **17**, 921–930.
132. Futatsugi A, Kato K, Ogura H, Li ST, Nagata E, Kuwajima G, Tanaka K, Itohara S & Mikoshiba K (1999) Facilitation of NMDAR-independent LTP and spatial learning in mutant mice lacking ryanodine receptor type 3. *Neuron* **24**, 701–713.
133. Balschun D, Wolfer DP, Bertocchini F, Barone V, Conti A, Zuschratter W, Missiaen L, Lipp HP, Frey JU & Sorrentino V (1999) Deletion of the ryanodine receptor type 3 (RyR3) impairs forms of synaptic plasticity and spatial learning. *EMBO J* **18**, 5264–5273.
134. Morris RG, Garrud P, Rawlins JN & O'Keefe J (1982) Place navigation impaired in rats with hippocampal lesions. *Nature* **297**, 681–683.
135. Morris RGM (1981) Spatial localization does not require the presence of local cues. *Learn Mem* **12**, 239–260.
136. Zhao W, Meiri N, Xu H, Cavallaro S, Quattrone A, Zhang L & Alkon DL (2000) Spatial learning induced changes in expression of the ryanodine type II receptor in the rat hippocampus. *FASEB J* **14**, 290–300.
137. Young GS, Jacobson EL & Kirkland JB (2007) Water maze performance in young male Long–Evans rats is inversely affected by dietary intakes of niacin and may be linked to levels of the NAD^+ metabolite cADPR. *J Nutr* **137**, 1050–1057.
138. Warren SG & Juraska JM (1997) Spatial and nonspatial learning across the rat estrous cycle. *Behav Neurosci* **111**, 259–266.
139. Shibata K & Kondo T (1993) Effects of progesterone and estrone on the conversion of tryptophan to nicotinamide in rats. *Biosci Biotechnol Biochem* **57**, 1890–1893.
140. D'Hooge R & De Deyn PP (2001) Applications of the Morris water maze in the study of learning and memory. *Brain Res Brain Res Rev* **36**, 60–90.
141. Akiyama K, Ichinose S, Omori A, Sakurai Y & Asou H (2002) Study of expression of myelin basic proteins (MBPs) in developing rat brain using a novel antibody reacting with four major isoforms of MBP. *J Neurosci Res* **68**, 19–28.
142. Reeves PG, Nielsen FH & Fahey GC Jr (1993) AIN-93 purified diets for laboratory rodents: final report of the American Institute of Nutrition *ad hoc* writing committee on the reformulation of the AIN-76A rodent diet. *J Nutr* **123**, 1939–1951.
143. Spector R (1979) Niacin and niacinamide transport in the central nervous system. *in vivo* studies. *J Neurochem* **33**, 895–904.
144. Pozzilli P, Browne PD & Kolb H (1996) Meta-analysis of nicotinamide treatment in patients with recent-onset IDDM. The Nicotinamide Trialists. *Diabetes Care* **19**, 1357–1363.
145. Kirkland JB & Rawling JM (2001) Niacin. In *Handbook of Vitamins*, 3rd ed., pp. 213–254 [RB Rucker, J Zempleni, JW Suttie and DB McCormick, editors]. New York: Marcel Dekker, Inc.
146. Ahmed MG, Bedi KS, Warren MA & Kamel MM (1987) Effects of a lengthy period of undernutrition from birth and subsequent nutritional rehabilitation on the synapse: granule cell neuron ratio in the rat dentate gyrus. *J Comp Neurol* **263**, 146–158.
147. Jacobson EL, Dame AJ, Pyrek JS & Jacobson MK (1995) Evaluating the role of niacin in human carcinogenesis. *Biochimie* **77**, 394–398.
148. Young GS, Choleris E, Lund FE & Kirkland JB (2006) Decreased cADPR and increased NAD(+) in the Cd38(−/−) mouse. *Biochem Biophys Res Commun* **346**, 188–192.
149. Young GS, Choleris E, Lund F & Kirkland JB (2008) Like niacin deficient rats, $Cd38^{-/-}$ mice show improved performance in the water maze. *Curr Topics in Nutr Res* (In the Press).
150. Deshpande DA, White TA, Guedes AG, Milla C, Walseth TF, Lund FE & Kannan MS (2005) Altered airway responsiveness in CD38-deficient mice. *Am J Respir Cell Mol Biol* **32**, 149–156.
151. Kato I, Yamamoto Y, Fujimura M, Noguchi N, Takasawa S & Okamoto H (1999) CD38 disruption impairs glucose-induced increases in cyclic ADP-ribose, [Ca2+]i, and insulin secretion. *J Biol Chem* **274**, 1869–1872.
152. Sun L, Iqbal J, Dolgilevich S, *et al*. (2003) Disordered osteoclast formation and function in a CD38 (ADP-ribosyl cyclase)-deficient mouse establishes an essential role for CD38 in bone resorption. *FASEB J* **17**, 369–375.
153. Partida-Sanchez S, Randall TD & Lund FE (2003) Innate immunity is regulated by CD38, an ecto-enzyme with ADP-ribosyl cyclase activity. *Microbes Infect* **5**, 49–58.
154. Cockayne DA, Muchamuel T, Grimaldi JC, Muller-Steffner H, Randall TD, Lund FE, Murray R, Schuber F & Howard MC (1998) Mice deficient for the ecto-nicotinamide adenine dinucleotide glycohydrolase CD38 exhibit altered humoral immune responses. *Blood* **92**, 1324–1333.
155. Anonymous (1997) Mutant mice and neuroscience: recommendations concerning genetic background. Banbury Conference on genetic background in mice. *Neuron* **19**, 755–759.
156. Crusio WE (2004) Flanking gene and genetic background problems in genetically manipulated mice. *Biol Psychiatry* **56**, 381–385.
157. Gerlai R (1996) Gene-targeting studies of mammalian behavior: is it the mutation or the background genotype? *Trends Neurosci* **19**, 177–181.
158. Crawley JN, Belknap JK, Collins A, *et al*. (1997) Behavioral phenotypes of inbred mouse strains: implications and

recommendations for molecular studies. *Psychopharmacology (Berl)* **132**, 107–124.
159. Young GS & Kirkland JB (2006) Modifications to increase the efficiency of the fluorimetric cycling assay for cyclic ADP-ribose. *Comb Chem High Throughput Screen* **9**, 633–637.
160. Schuber F & Lund FE (2004) Structure and enzymology of ADP-ribosyl cyclases: conserved enzymes that produce multiple calcium mobilizing metabolites. *Curr Mol Med* **4**, 249–261.
161. Gallagher M, Burwell R & Burchinal M (1993) Severity of spatial learning impairment in aging: development of a learning index for performance in the Morris water maze. *Behav Neurosci* **107**, 618–626.
162. Takeshima H, Ikemoto T, Nishi M, *et al*. (1996) Generation and characterization of mutant mice lacking ryanodine receptor type 3. *J Biol Chem* **271**, 19649–19652.
163. Higashida H, Hashii M, Yokoyama S, Hoshi N, Chen XL, Egorova A, Noda M & Zhang JS (2001) Cyclic ADP-ribose as a second messenger revisited from a new aspect of signal transduction from receptors to ADP-ribosyl cyclase. *Pharmacol Ther* **90**, 283–296.
164. Yang J, Han H, Cao J, Li L & Xu L (2006) Prenatal stress modifies hippocampal synaptic plasticity and spatial learning in young rat offspring. *Hippocampus* **16**, 431–436.
165. Xiong W, Yang Y, Cao J, Wei H, Liang C, Yang S & Xu L (2003) The stress experience dependent long-term depression disassociated with stress effect on spatial memory task. *Neurosci Res* **46**, 415–421.

https://doi.org/10.1017/S0954422408945182 Published online by Cambridge University Press