Neuroscience and Biobehavioral Reviews 155 (2023) 105435

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

A systematic review of preclinical studies exploring the role of insulin signalling in executive function and memory

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ARTICLE INFO

Keywords:
Insulin signalling
Mental health
Comorbidity
Animal models
Systematic review

ABSTRACT

Beside its involvement in somatic dysfunctions, altered insulin signalling constitutes a risk factor for the development of mental disorders like Alzheimer's disease and obsessive-compulsive disorder. While insulin-related somatic and mental disorders are often comorbid, the fundamental mechanisms underlying this association are still elusive. Studies conducted in rodent models appear well suited to help decipher these mechanisms. Specifically, these models are apt to prospective studies in which causative mechanisms can be manipulated via multiple tools (e.g., genetically engineered models and environmental interventions), and experimentally dissociated to control for potential confounding factors. Here, we provide a narrative synthesis of preclinical studies investigating the association between hyperglycaemia – as a proxy of insulin-related metabolic dysfunctions – and impairments in working and spatial memory, and attention. Ultimately, this review will advance our knowledge on the role of glucose metabolism in the comorbidity between somatic and mental illnesses.

1. Introduction

Whilst impaired insulin signalling has been traditionally associated with metabolic dysfunctions like type 1 (T1DM) and type 2 diabetes mellitus (T2DM), metabolic syndrome (MS), and obesity (Klimova et al., 2018; Landau and Pinhas-Hamiel, 2019; van de Vondervoort et al., 2016), recent evidence indicates that it is also associated with impairments in cognitive capabilities (Moheet et al., 2015). Both T1DM and T2DM are associated with mental and motor slowing and decrements in attention and executive functioning (McCrimmon et al., 2012). Memory deficits are frequently reported in patients with T2DM (Zhang et al., 2015); moreover, anhedonia and impulse control disorders (eating disorders and addiction) are often associated with diabetes (De Jonge et al., 2014). These symptoms constitute hallmarks of specific mental disorders in which, accordingly, alterations in insulin signalling have been observed: attention deficit hyperactivity disorder (ADHD) (Landau and Pinhas-Hamiel, 2019), Alzheimer's disease (AD) (Burillo et al., 2021), obsessive-compulsive disorder (OCD) (Grassi et al., 2022), depression (Lyra e Silva et al., 2019), and drug addiction (Brambilla et al., 1976). The socioeconomic costs of these diseases are huge and continue to rise. For example, the International Diabetes Federation estimated that while 537 million adults (20–79 years) are currently diabetic, these numbers are projected to increase steadily by 2045, when 783 million adults will live with this condition. The yearly associated healthcare economic burden of diabetes per se accounts for approximately 1.2 trillion US dollars (da Saúde, 2017). Should altered insulin signalling also represent a risk factor for mental disorders, these costs would further increase. For example, although the contribution of insulin signalling to e.g. AD still needs to be elucidated, approximately 35 million people worldwide currently have this form of dementia (World Health Organization, 2022). Predictably, these numbers are projected to increase at an unsettling rate (approximately 85 million AD patients by 2050) (World Health Organization, 2022). The aforementioned estimations are only the tip of the iceberg whereby they do not account for other

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https://doi.org/10.1016/j.neubiorev.2023.105435
Received 27 April 2023; Received in revised form 4 October 2023; Accepted 23 October 2023
Available online 31 October 2023

insulin-related mental comorbidities like ADHD and OCD. Thus, exploring the role of insulin signalling in executive functions and memory may beget remarkable advantages in terms of public health and its associated costs.

How insulin regulates somatic functions has been the key question of countless scientific studies. Most early investigations focussed on its role in mediating general metabolism (Samson and Garber, 2014). These studies contributed to understanding how insulin regulates glucose homeostasis and energy balance (Boden, 2001; Brown and Walker, 2016; Huang, 2009) and how derailments in these processes result in metabolic disorders like T1DM and T2DM (DeFronzo, 2004), and MS (Banday et al., 2020). The primary deficit in T2DM is insulin resistance (Brunton, 2016), characterised by a reduced insulin sensitivity of cells in peripheral tissues (e.g., muscles, liver, and adipose tissue). This generates hyperfunction of the β-cells of the pancreas which ultimately elicit hyperinsulinemia: an increased production of insulin aimed at maintaining normal blood glucose concentrations. This process gradually impairs β-cells functionality and causes insulin deficiency and hyperglycaemia, with fasting plasma glucose concentrations $>$ 110 mg/dL (Banday et al., 2020) representing the symptomatic threshold for T2DM.

Recently, the interest for the role of insulin has started to extend beyond energy metabolism to encompass the central nervous system (CNS) (Banks et al., 2012; Clarke et al., 1986). Evidence for a role for insulin signalling in the CNS is related to its widely-expressed (Chiu et al., 2008) receptors (e.g. Insulin Receptor, IR, and Insulin Growth Factor-1 receptor IGF-1R) in the brain. The presence of insulin in the brain derives from two main paths: from the periphery as it can cross the blood brain barrier or via direct synthesis by neurons (Creo et al., 2021; Fanelli et al., 2022). Accordingly, beside its role in glucose metabolism, recent evidence indicates that insulin contributes to several cognitive functions, such as learning, memory, integration of sensory information, and modulation of synaptic plasticity (Nisticò et al., 2012).

Genetic, clinical and preclinical (Biessels and Despa, 2018; Blázquez et al., 2014; Koekkoek et al., 2015) studies support the evidence that altered insulin signalling is involved in mental function and disease. For example, several studies reported a correlation between T2DM and AD and observed that insulin signalling may represent a common pathophysiological risk factor (Burillo et al., 2021; Pardeshi et al., 2017). Beyond AD, T2DM patients are at increased risk of milder forms of cognitive decline other than memory, such as processing speed and executive functions (Monette et al., 2014; Palta et al., 2014). These may occur during pre-diabetic stages and slowly worsen over time (Biessels et al., 2014). Importantly, impairments in impulse control, as a characteristic of ADHD, have also been observed in a large cohort of obese patients (Sinclair et al., 2000) further strengthening the potential association between metabolic syndrome and cognitive impairments. Furthermore, genetic and genomic studies reported that dysregulated insulin-dependent signalling cascades are associated with OCD (Bralten et al., 2020; van de Vondervoort et al., 2016). Accordingly, clinical investigations consistently reported that anti-diabetic drugs have beneficial effects on cognitive impairments in both AD, OCD, and other forms of cognitive decline (Fink et al., 2018; Munõz-Jiménez et al., 2020).

Although the historical analysis of this literature suggests that the interest in the somatic function of glucose preceded the interest in its role in the brain, a very early account looked at this relationship from the opposing side. Thus, even before the discovery of insulin, Kooy (Kooy, 1919) hypothesised that mental disorders triggered the emergence of hyperglycaemia. Ultimately, the view that insulin signalling may be involved in both somatic and mental disturbances is now consolidated. Yet, it is unclear whether mental disturbances are secondary to somatic alterations, whether the latter are consequence of the former, or whether they are due to diverse insulin-related mechanisms acting independently in the periphery and the CNS.

The fundamental mechanisms underlying the comorbidity between T2DM and cognitive decline have been investigated in preclinical studies by means of animal models. For example, several authors reported that a consolidated experimental model of AD (transgenic mice expressing human amyloid precursor protein and presenilin 1, APP/PS1) exhibited impaired cognitive capabilities associated with poor glycaemic control (Denver et al., 2018). Similarly, insulin receptor β-subunit deficient mice exhibit impaired memory capabilities associated with altered long-term potentiation, the latter representing a form of synaptic plasticity (Nisticò et al., 2012). Finally, van de Vondervoort and collaborators (van de Vondervoort et al., 2019) reported increased compulsivity and anxiety in an experimental model (TALLYHO/JngJ mice) recapitulating most of the metabolic abnormalities observed in T2DM patients: insulin resistance, hyperglycaemia, hyperinsulinemia, and obesity.

Based on these considerations, we aimed to further detail the role of insulin signalling in the comorbidity between mental and somatic disturbances by systematically analysing the available rodent literature in rodents. To this aim, we propose a qualitative description of available preclinical studies – conducted in adult mice and rats exhibiting hyperglycaemia – investigating the role of impaired glucose metabolism in the comorbidity between somatic and mental impairments (limited to working memory, spatial memory and/or attention).

2. Methods

2.1. Review protocol

The systematic search was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Moher et al., 2015). The protocol (SYRCLE's protocol; Supplementary item 1) for animal intervention studies (de Vries et al., 2015) was submitted to the PROSPERO registry on May 16th, 2022 and registered on June 12th, 2022 (registration number: CRD42022331458).

2.2. Literature search and study identification

A comprehensive systematic literature search was conducted – on April 7th, 2022 – in three online databases (PubMed, Scopus, Web of Science). The search strategy involved, as issues of interest, altered insulin signalling (with hyperglycaemia representing its proxy) and the investigation of the behavioural phenotypes isomorphic to specific symptoms of mental disturbances (i.e., executive function and memory); the search was limited to studies conducted in rats and mice. The complete search strategies used in each database were:

- TITLE-ABS-KEY (hyperglycaemia OR hyperglycemia) AND TITLE-ABS-KEY ((spatial AND memory) OR attention) AND TITLE-ABS-KEY (mouse OR mice OR rat OR rats)) for Scopus database;
- "hyperglycaemia"[Title/Abstract] OR "hyperglycemia" [Title/Abstract] AND "spatial"[Title/Abstract] AND "memory"[Title/Abstract] OR "attention"[Title/Abstract] AND "mouse"[Title/Abstract] OR "mice"[Title/Abstract] OR "rat"[Title/Abstract] OR "rats"[Title/Abstract] for Pubmed;
- TS= ((hyperglycaemia OR hyperglycemia) AND ((spatial AND memory) OR attention) AND (mouse OR mice OR rat OR rats) for Web of Science.

During the first phase of examination (i.e., screening of titles and abstracts), the following prioritization of exclusion criteria was used: (1) language other than English; (2) non-original researches (e.g., reviews, commentaries, editorials, book chapters); (3) no full-text articles (e.g., meeting abstracts); (4) studies in vitro, studies in humans, studies in non-human animals other than rats and mice; (5) outcome measures other than working memory, spatial memory and/or attention. Two observers (MP and AMO) independently screened the articles of the first phase. The additional exclusion criteria in the second phase of full-text screening of the eligible articles were: (5) outcome measures other than

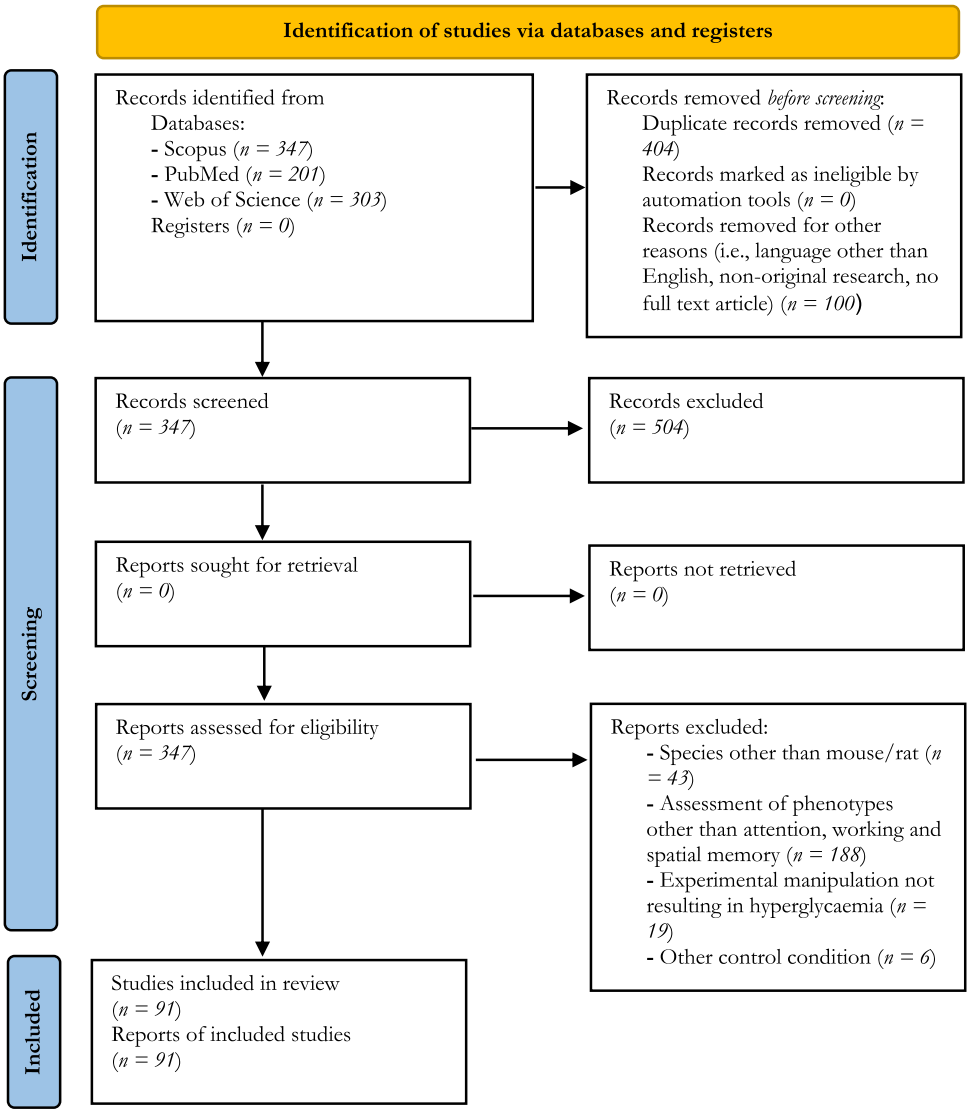

Fig. 1. PRISMA flow diagram for preclinical studies (Moher et al., 2009). Diagram of the identification, screening, eligibility, and inclusion of the literature search.

working memory, spatial memory and/or attention; (6) experimental manipulations not resulting in hyperglycaemia; (7) other control conditions (e.g., low-fat diet used as control instead of standard diet, etc.). The data were independently extracted by two reviewers per site (MP and AMO; AOL and DAS; MS and JCG, respectively) and discrepancies were resolved by principal investigators of each site (SM, JCG, and DAS).

2.3. Data extraction and synthesis

The study characteristics extracted from the full-text articles eligible for qualitative data included the following categories: (i) bibliographic details (DOI, title, authors, publication year, journal); (ii) study design characteristics (number of experimental groups, number of subjects per group, type of study design); (iii) animal model characteristics (species, strain, sex, age and/or weight at the beginning of the study, type of test used to evaluate spatial memory, working memory and/or attention); (iv) intervention characteristics (type of experimental manipulation adopted to induce hyperglycaemia, details regarding the experimental manipulation, type of non-hyperglycaemic control, details on the assessment of hyperglycaemia, e.g. higher blood glucose concentrations compared to controls, and or to a predefined threshold); (v) outcome measure (direction of the variation of the behavioural phenotypes isomorphic to working memory, spatial memory and/or attention in experimental subjects exhibiting hyperglycaemia and in non-hyperglycaemic controls). If available, data on the variation of glucose metabolism-/insulin signalling related parameters (obtained after the original induction of hyperglycaemia, for example through glucose tolerance, insulin resistance, etc.) were collected.

2.4. Assessment of the risk of bias

To evaluate the methodological quality and validity of the included studies, we used the SYRCLE's Risk of Bias (RoB) tool for animal studies, developed by Hooijmans and co-authors (Hooijmans et al., 2014) by adjusting the Cochrane's RoB tool (Higgins et al., 2011). The RoB tool for animal studies is divided into 10 items (for Selection bias: sequence generation, baseline characteristics, allocation concealment; for Performance bias: random housing, blinding; for Detection bias: random outcome assessment, blinding; for Attrition bias: incomplete outcome data; for Reporting bias: selective outcome reporting; for Other: other sources of bias). With specific reference to the Reporting bias, we note that adequate tools to pre-register the experiments (and thus allow a systematic evaluation of the consistency between the planned and the reported studies) are available only since 2021 (Olevska et al., 2021).

Fig. 2. The radial graph summarizes the studies assessed in the present review as a function of experimental subjects, experimental manipulations, methodologies adopted to confirm the presence of hyperglycaemia, and behavioural outcomes. Accordingly, each 90-degree quadrant describes all of the 91 studies contemplated in the review as a function of a different aspect. Moving from the centre to the periphery of the radial graph, each category is further subdivided into granular details. STZ: streptozotocin, HFD: high fat diet, MSG: monosodium glutamate, NIC: nicotinamide.

Thus, for studies preceding this date, we deemed the Reporting bias as not applicable. Two reviewers per affiliation site (MP and EP; AOL and DAS; MS and JCG) performed the quality assessment of each article by independently assessing the aforementioned criteria.

3. Results

3.1. Study selection

The search strategy described above resulted in 851 bibliographic records. The process of selection is summarized in Fig. 1 by using the PRISMA flow diagram. References were exported to Microsoft Excel and, after duplicates were removed, 447 studies remained. The first selection phase (for language other than English, non-original research, no full text article) resulted in 347 studies; the second selection phase (i.e., full-text articles screening) resulted in 91 studies eligible for inclusion in the systematic review, while a total of 256 articles were excluded for: assessment of phenotypes other than attention, spatial memory, and working memory (n = 188), species other than mouse/rat (n = 44), experimental manipulations not resulting in hyperglycaemia (n = 19), and lack of an appropriate control group (n = 6).

3.2. Study characteristics

The characteristics of the 91 studies included in the present review are summarized in Fig. 2.

Whilst the behavioural phenotypes in association with hyperglycaemia included working and/or spatial memory, and/or attention, only one article (Moreira et al., 2007) simultaneously evaluated all of them using the same lever-press test to discriminate the three different domains (the position of the levers served as a spatial and operant stimulus at the same time and the ability to change a discrimination, once learned, was considered an attentional task). The most evaluated phenotype was spatial memory: of all the studies considered, only in 11 of them was memory not investigated. The most widely adopted procedure to investigate this domain was the Morris water maze, which has

Table 1
Details regarding the experimental manipulation to induce hyperglycaemia and the experimental subjects (f: female; m: male).

N	Ref.	Type of experimental manipulation adopted to induce hyperglycaemia		Details regarding the experimental manipulation	Details on the assessment of hyperglycaemia	Variation of glucose metabolism-/insulin signalling related parameters	Species	Strain	Sex [f; m]	Age and/or weight at the beginning of the study	N of subjects per group {n for behavioural parameters; n for glucose metabolism/ insulin parameters}
1	(Georgy et al., 2013)	pharmacological modulation	STZ	single i.p. injection of 40 mg/kg streptozotocin; 4 weeks of diabetes induction by STZ before testing	higher glucose concentrations compared to predefined threshold (> 210 mg/ dL); with fasting	increase in serum glucose (315.6 vs 104.1 mg/dL) in STZ compared to CTRL at the end of the experiment (i.e., 8 weeks after the initial STZ administration)	rat	Sprague Dawley	m	200–240 g	20–22; n/a
2	(Arnold et al., 2014)	environmental manipulation	HFD	extreme high fat diet (60% kcal from fat) for 17 days and moderate HFD 45% kcal fat diet for 8 weeks	higher morning glucose concentrations both in extreme HFD at 17 days (HFD 210.4 mg/dL, CTRL 167.2) and moderate HFD (biweekly between 08:00 and 10:00) compared to control	glucose tolerance tests (performed at 8 weeks and 4 days) were markedly abnormal indicating diabetes in HFD, compared to CTRL	mouse	C57BL/6 J	m	8 weeks old	5, 5, 10, 10; 5, 5, 10, 10
3	(Joshi et al., 2021)	pharmacological modulation	STZ	single intra-femoral injection of 50 mg/kg of streptozotocin	n/a	n/a	rat	Wistar	m	8–10 weeks old, 250–300 g	12; n/a
4	(Remor et al., 2019)	pharmacological modulation	STZ	single i.p. injection of 55 mg/kg of streptozotocin after a fasting period of 14 h; 10 and/or 60 days of diabetes induction before testing	higher glucose concentrations compared to predefined threshold (> 200 mg/ dL) assessed 4 days after STZ injection	increase in serum glucose in STZ compared to CTRL at 15, 45 and 60 days after STZ injection: nondetectable plasma insulin levels in fasted STZ	rat	Wistar	m	60 days of life, 250–300 g	10; 7–9
5	(Wu et al., 2014)	pharmacological modulation	IS-SS	1.7% isoflurane (IS) or 2.4% sevoflurane (SS) for 4 h; 2 weeks of hyperglycaemia induction by anaesthesia before testing	higher glucose concentrations compared to controls (109.9 mg/dL) in IS (189.2 mg/dL) and in SS (174.1 mg/dL) respectively after 2 h and 1 h of anaesthesia	higher glucose concentrations compared to controls (109.9 mg/ dL) in IS (169.9 mg/dL) after 4 h of anaesthesia and in SS (172.9 mg/dL) after 3 h and (185.0 mg/ dL) after 4 h of anaesthesia	rat	Sprague Dawley	m	PND 14	17, 35, 37; n/a
6	(Moreira et al., 2007)	strain difference	Goto-Kakizaki	no manipulation, spontaneously diabetic	n/a	n/a	rat	Wistar, Goto-Kakizaki	m	16 weeks old, 280–350 g	8,6; n/a
7	(Rodríguez et al., 2016)	environmental manipulation	altered drinking water with arsenic	50 mg of inorganic arsenic (iAs)/L of drinking water for three months	higher glucose concentrations compared to controls; with fasting (12 h), assessed at second month of iAs treatment	increased in blood glucose levels at 30 min after an i.p. injection of 2 g of glucose/kg, in the intraperitoneal glucose tolerance test	mouse	C57BL/6	m	35 g	11; 12
8	(Biessels et al., 1996)	pharmacological modulation	STZ	experiment 1: single intravenous injection of 40 mg/kg of streptozotocin;	blood glucose levels > 15.0 mmol/1 in all STZ-injected animals, 4 days after the injection	experiment 1: increase in blood glucose levels (25.6 vs 5.5 mmol/1) in STZ compared to CTRL at the	rat	Wistar	m	300 g	Experiment 1: 10; 10 Experiment 2: 10; 10

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Table 1 (*continued*)

N	Ref.	Type of experimental manipulation adopted to induce hyperglycaemia		Details regarding the experimental manipulation	Details on the assessment of hyperglycaemia	Variation of glucose metabolism-/insulin signalling related parameters	Species	Strain	Sex [f; m]	Age and/or weight at the beginning of the study	N of subjects per group {n for behavioural parameters; n for glucose metabolism/ insulin parameters}
				experiment 2: single intravenous injection of 40 mg/kg of streptozotocin + subcutaneous release insulin implants at a dose of 1 IU per day		end of the experiment; experiment 2: increase in blood glucose levels (18.9 vs 5.6 mmol/1) in STZ compared to CTRL at the end of the experiment					
9	(Madhavadas et al., 2016)	pharmacological modulation	MSG	neonatal rat pups were injected with MSG (4 mg/g body weight) once daily for 14 consecutive days after birth then tested at 17 months of age	higher blood glucose concentrations compared to controls	after three months of neonatal MSG administration, it was an increase in glucose levels compared to CTRL	rat	Sprague-Dawley	m	neonatal	8; 8
10	(Madhavadas and Subramanian, 2015)	pharmacological modulation	MSG	neonatal rat pups were injected with MSG (4 mg/g body weight) once daily for 14 consecutive days after birth then tested at 18 months of age	higher blood glucose concentrations compared to controls; fasting not specified; at 18 months of age	at 18 months old serum glucose levels of MSG mice were higher than CTRL (313 vs 122.5 mg/ dL)	rat	Sprague-Dawley	m	neonatal	6; 6
11	(Tanokashira et al., 2018)	environmental manipulation	HFD	HFD (60% kcal from fat) from 4 to 29 weeks of age	higher blood glucose concentrations compared to controls; with fasting (6 hrs)	elevated levels of fasting glucose and plasma insulin compared to CTRL at 25 weeks of age	mouse	C57BL/6 J	m	4 weeks old	8; 12
12	(W.H. Wang et al., 2019; W. Wang et al., 2019)	pharmacological modulation, environmental manipulation	STZ, HFD	DIO mice: HFD (60% kcal from fat) for 32 weeks. C57BL/6 J mice: single i.p. injection of 150 mg/kg of streptozotocin, after an overnight fasting. Test performed at 34–36 week (HFD) and 10 weeks (STZ)	HFD mice: higher blood glucose concentrations compared to controls, at 35 weeks of age; STZ mice: higher blood glucose concentrations compared to controls, after 2 weeks of STZ injection	at 35 weeks of age blood glucose concentration of HFD mice were higher compared to CTRL; after 2 weeks of STZ injection, STZ mice exhibited elevated blood glucose levels (>400 mg/ dL).	mouse	C57BL/6 J	m	HFD: 4 weeks old; STZ: 10 weeks old	HFD: 14; 5 STZ: 18–19; 5
13	(Tanokashira et al., 2021)	transgenic approach	Irs2-deficient mice	generation and routine genotyping of the Irs2-deficient mice maintained on a C57BL/ 6 J genetic background after more than six backcrosses	higher blood glucose concentrations compared to controls	$Irs2^{-/-}$/6 J males developed hyperglycaemia after 9 weeks, the $Irs2^{-/-}$/6 J males displayed higher fasting insulin levels and insulin resistance during the insulin tolerance test compared to controls	mouse	$Irs2^{-/-}$/6 J, C57BL/ 6 J	m	4 weeks old	10–15; 8–11
14	(Du et al., 2014)	pharmacological modulation	STZ	single i.v. injection of 150 mg/kg of streptozotocin	higher blood glucose concentrations compared to controls	increase in blood glucose levels (18.21 vs 6.71 mM) and decreased serum insulin levels (5.36	mouse	ICR	m	8–10 weeks old; 20–25 g	7–8; 8–10

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Table 1 (*continued*)

N	Ref.	Type of experimental manipulation adopted to induce hyperglycaemia		Details regarding the experimental manipulation	Details on the assessment of hyperglycaemia	Variation of glucose metabolism-/insulin signalling related parameters	Species	Strain	Sex [f; m]	Age and/or weight at the beginning of the study	N of subjects per group {n for behavioural parameters; n for glucose metabolism/ insulin parameters}
						vs 14.21 mIU/L) in STZ compared to CTRL					
15	(Fang et al., 2017)	pharmacological modulation	STZ	i.v. injection of 150 mg/ kg of streptozotocin	higher blood glucose concentrations compared to predefined threshold (>11.0 mmol/ L)	decrease in serum insulin in STZ mice compared to CTRL (17.41 vs 36.20 mIU/L)	mouse	ICR	m	22–25 g	8; 7
16	(Tabatabaei et al., 2016)	pharmacological modulation	STZ	i.p. injection of 60 mg/ kg of streptozotocin. All females were ovariectomized	higher blood sugar concentrations compared to predefined threshold (>300 mg/dL)	significant increase in Fasting blood sugar in STZ mice compared to CTRL	rat	Wistar	f	190–200 g	10; 10
17	(Rababa'h et al., 2019)	pharmacological modulation	STZ	single i.p injection of 50 mg/kg of streptozotocin	higher blood glucose concentrations compared to predefined threshold (≥ 300 mg/ dL); with fasting	increase in serum glucose level in STZ mice compared to their corresponding control	rat	Wistar	m	200–300 g	9–10; 9–10
18	(Babri et al., 2013)	pharmacological modulation	STZ	single i.p. injection of 60 mg/kg of streptozotocin	higher blood glucose concentrations compared to predefined threshold (> 300 mg/ dL); with fasting	n/a	rat	Wistar	m	250–300 g	7; n/a
19	(Mirshekar et al., 2011)	pharmacological modulation	STZ	single i.p. injection of 60 mg kg of streptozotocin	higher serum glucose concentrations compared to predefined threshold (> 250 mg/ dL)	diabetic rats had an elevated serum glucose level compared to control rats after 4 and 8 weeks of treatment	rat	Wistar	m	10–12 weeks old; 215–285 g	8; 8
20	(Baranowska et al., 2020)	pharmacological modulation	STZ	single i.p. injection of 65 mg/kg of streptozotocin	higher urine glucose concentrations compared to controls	increase in plasma glucose concentration in STZ rats compared to CTRL (440 ± 65 vs. 132 ± 16 mg/dL)	rat	Wistar	m	200 g	10, 11; 10, 11
21	(Utkan et al., 2015)	pharmacological modulation	STZ	single i.p. injection of 50 mg/kg of streptozotocin, STZ-treated rats received 5% glucose solution instead of water for the next 24 h to reduce the death risk due to hypoglycaemic shock	higher blood glucose concentrations compared to predefined threshold (> 200 mg/ dL); with fasting	plasma levels of glucose in diabetic groups were significantly higher than those in control (424.4 ± 15.6 vs 115.7 ± 6.1 mg/dL)	rat	Wistar	m	250–300 g	7; 7
22	(Taylor et al., 2015)	pharmacological modulation	STZ	single i.p. injection of 100 mg/kg, of streptozotocin, on 2 consecutive days, in food deprived mice	higher blood glucose concentrations compared to predefined threshold (>15 mM/L)	at the end of the 8-week experiment, diabetic mice had significantly elevated fasting blood glucose levels relative to vehicle treated non-diabetic mice	mouse	C57BL/6 J wild-type or YFP-H line mice	m	8 weeks old	n/a

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Table 1 (*continued*)

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23	(Yang et al., 2014)	pharmacological modulation	STZ	single i.p. injection 65 mg/kg of streptozotocin	higher blood glucose concentrations compared to predefined threshold (>16.7 mmol/L); no details on fasting	n/a	rat	Sprague-Dawley	m	220–250 g	10; 10
24	(Momeni et al., 2021)	pharmacological modulation	STZ	i.p. injections of 50 mg/kg of streptozotocin, for three days	higher blood glucose concentrations compared to predefined threshold (>15 mM); no details on fasting	n/a	mouse	C57BL/6 J	m	4–6 weeks old; 20–22 g	13–14; n/a
25	(de Cossío et al., 2017)	transgenic approach	C57BLKS/J-lepr^{db}/lepr^{db}	db/db mice are deficient for functional leptin receptor and consequently show severe obesity associated with hyperphagia, altered lipid/carbohydrate metabolism, and several indicators of T2D	impaired glucose tolerance (13 h fasted) and insulin sensitivity (non-fasted) in db/db mice after 9 weeks of treatment	n/a	mouse	C57BLKS/J-lepr$^{db/+}$, C57BLKS/J-lepr^{db}/lepr^{db}	m	5 weeks old	13–14; 13–14
26	(Dharavath et al., 2019b)	environmental manipulation	HFD + fructose drink solution	high fat-low protein diet (HFLPD) and 15% oral fructose solution via drinking water for 24 weeks	higher blood glucose concentrations compared to controls; with fasting (8 h)	fasting serum glucose levels and the percent glycosylated Hb were found to be significantly elevated after feeding the animals with HFLPD for 4 weeks, and a similar trend observed till the 24th week of the study	rat	Wistar	f	8–10 weeks old	6; 6
27	(Skapare et al., 2012)	strain difference	Goto-Kakizaki (diabetes), Zucker fa/fa (obesity)	Goto-Kakizaki (diabetes), Zucker fa/fa (obesity)	at 24 weeks, plasma glucose levels were 1.5 x higher than respective controls in the Goto-Kakizaki rats, impaired glucose tolerance in Goto-Kakizaki and Zucker fa/fa rats vs respective controls	n/a	rat	Goto-Kakizaki, Wistar Kyoto (diabetes), Zucker$^{fa/fa}$, Zucker lean (obesity)	m	8 weeks old	12; 12
28	(Malone et al., 2008)	pharmacological modulation	STZ	single i.p. injection of 50 mg/kg of streptozotocin	higher blood glucose concentration compared to predefined threshold (blood glucose levels >200 mg/dL 3 d after STZ administration); no details on fasting	n/a	rat	Wistar	m	4 weeks old; 100 g	20; n/a
29	(Treviño et al., 2015)	environmental manipulation	HFD	the hypercaloric diet (71.4% carbohydrates,	higher blood glucose concentration compared	impaired oral glucose tolerance test with increased levels of 73.4%	rat	Wistar	m	70–100 g	14; 14

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Table 1 (*continued*)

N	Ref.	Type of experimental manipulation adopted to induce hyperglycaemia		Details regarding the experimental manipulation	Details on the assessment of hyperglycaemia	Variation of glucose metabolism-/insulin signalling related parameters	Species	Strain	Sex [f; m]	Age and/or weight at the beginning of the study	N of subjects per group {n for behavioural parameters; n for glucose metabolism/ insulin parameters}
				5.8% fat, 7.3% protein) for 90 days.	to controls; with fasting (5 h)	(30 min), 50.9% (60 min), and 58.9% (90 min) as compared to the controls, with a significant increase in the area under the curve of 60.4%					
30	(Nurdiana et al., 2017)	pharmacological modulation	STZ	injection of 60 mg/kg of streptozotocin	higher blood glucose concentration compared to predefined threshold (blood glucose levels >11 mmol/L a week after STZ administration); with fasting	n/a	rat	Sprague-Dawley	m	4 weeks old; 80 g	6; 6
31	(Hardigan et al., 2017)	pharmacological modulation	STZ	i.p. injection of 50 mg/kg of streptozotocin, for 5 days consecutively	higher blood glucose concentration compared to predefined threshold (HbA1c% >8.0%); with overnight fasting	n/a	mouse	C57BL/6 J	m	10 weeks old	12–13; 7–17
32	(de Senna et al., 2017)	pharmacological modulation	STZ	single i.v. injection into the tail vein of 50 mg/kg of body weight of streptozotocin, after a 6 h fasting period. 20 days of diabetes induction by STZ before testing	higher blood glucose concentration compared to predefined threshold (> 300 mg/dL), 48 h post injection; with fasting 5 h	blood glucose concentrations were significantly higher in STZ groups compared to CTRL groups, 48 h after diabetes induction (96 vs 375 mg/dL) and after 9 weeks of STZ induction (106 mg/dL vs 534 mg/dL)	rat	Wistar	m	3 months old; 270–400 g	15, 13; 15, 13
33	(Wu et al., 2012)	pharmacological modulation	STZ	single i.p. injection of 150 mg/kg of streptozotocin	higher blood glucose concentration compared to predefined threshold (> 300 mg/dL), 3 days after injection of STZ; with fasting (an overnight)	plasma glucose levels were significantly elevated in STZ-treated animals after day 21 days of STZ injection (120.75 vs 502.38 mg/dL)	mouse	ICR	m	20–22 g	8; 8
34	(Lin et al., 2018)	pharmacological modulation	STZ	single i.v. injection of 65 mg/kg body weight of streptozotocin, after overnight fasting, three weeks of diabetes induction by STZ before testing	higher blood glucose concentration compared to predefined threshold (>200 mg/dL), one week after injection of STZ	n/a	rat	Sprague-Dawley	m	180–230 g	6; 6
35	(Collison et al., 2012)	environmental manipulation	altered drinking water with aspartame	ad libitum drinking water containing 0.25 g/L aspartame	higher blood glucose concentration compared to controls	n/a	mouse	C57BL/6 J	m, f	6 weeks old	12; 12

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36	(Zhou et al., 2015a)	pharmacological modulation	STZ	single i.p. injection of 150 mg/kg of streptozotocin, after 12 h fasting	higher blood glucose concentration compared to predefined threshold (≥16.7 mmol/L); fasting not specified, assessed 72 h after STZ injection	at the end of the study blood glucose levels were higher in the STZ group than in the CTRL group	mouse	ICR	m	18–20 g	12; 12
37	(Zhou et al., 2017)	pharmacological modulation	STZ	single i.p. injection of 150 mg/kg of streptozotocin, after 12 h fasting	higher blood glucose concentration compared to predefined threshold (≥16.7 mmol/L); fasting not specified, assessed 3 days after STZ injection	the blood glucose levels in the STZ group were higher than those in the CTRL group	mouse	ICR	m	18–20 g	18; 12
38	(Huang et al., 2012)	pharmacological modulation	STZ	single i.p. injection of 200 mg/kg of streptozotocin (STZ), non-fasting	higher blood glucose concentration compared to predefined threshold (>200 mg/dL); fasting not specified, assessed 10 days after STZ injection	blood glucose were measured on days 1, 10, 32 and 39, the results show that an acute high dose of STZ induced a chronic hyperglycaemic condition	mouse	C57BL/6 J	m	6–8 weeks old	15–20; 15–20
39	(Huang et al., 2007)	pharmacological modulation	STZ	single i.p. injection of 200 mg/kg of streptozotocin, non-fasting. 16–22 days of diabetes induction by STZ before testing	higher blood glucose concentration compared to predefined threshold (>200 mg/dL); fasting not specified, assessed 10 days after STZ injection	blood glucose concentrations were measured on days 1, 10, 15, and 23, blood glucose levels were significantly increased at day 10, 15, and 23 compared to the level of day 1, in STZ mice	mouse	C57BL/6 J	m	6–8 weeks old	9–12; 9–12
40	(Huang et al., 2019)	pharmacological modulation	STZ	i.p injection of 100 mg/kg of streptozotocin on days 1, 2, 8, and 9, after 6 h fasting. 34–42 days of diabetes induction by STZ before testing	higher blood glucose concentration compared to predefined threshold (≥200 mg/dL); fasting not specified, assessed on day 14	STZ increased the blood glucose levels 14 days after the STZ injection	mouse	3 ×Tg-AD	m	6 months old	15, 8; 15, 8
41	(Lin et al., 2017)	environmental manipulation	HFD	high-fructose-high-coconut oil diet for 20 weeks. 20 weeks of diets before testing	at week 20 the rats fed the HFD had significantly higher glucose and insulin compared to the control group ($p < 0.05$)	fasting blood glucose levels of the HFD group was generally higher and significantly increased starting at week 16 compared to animals on the control diets	rat	Wistar	m	6 weeks old; 200 g	8, 12; 8, 12
42	(He et al., 2020)	pharmacological modulation, environmental manipulation	STZ+HFD	i.p injection of 85 mg/kg of streptozotocin twice within 72 h, after a 3-week high-fat diet feeding	higher blood glucose concentration compared to predefined threshold (>11.6 mmol/L); fasting not specified, assessed 6 h after the STZ injection	a marked increase in fasting blood glucose level was observed in HFD/STZ mice, oral glucose tolerance test: a significant increase in glucose concentration in	mouse	C57BL/6 J	m	4 weeks old	10, 10; 7, 7

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N	Ref.	Type of experimental manipulation adopted to induce hyperglycaemia		Details regarding the experimental manipulation	Details on the assessment of hyperglycaemia	Variation of glucose metabolism-/insulin signalling related parameters	Species	Strain	Sex [f; m]	Age and/or weight at the beginning of the study	N of subjects per group {n for behavioural parameters; n for glucose metabolism/ insulin parameters}
						HFD/STZ mice at all time points					
43	(Zhou et al., 2018)	pharmacological modulation	STZ	single i.p. injection of 150 mg/kg of streptozotocin; long-acting insulin glargine was administered subcutaneously to mice from the seventh day of STZ injection, until the end of experiment (starting dose of 2 IU/kg and then the dose was adjusted according to the glucose levels)	higher blood glucose levels compared to predefined threshold (>16.7 mmol/L), assessed after 3 and 7 days of STZ injection	after STZ injection, STZ mice presented significantly higher values of glycemia compared to CTRL	mouse	C57BL/6 J	m	20–25 g	12; 12
44	(Sibiya and Mabandla, 2017)	pharmacological modulation	STZ	single i.p. injection of 60 mg/kg of streptozotocin	higher blood glucose concentration compared to controls; without fasting	blood glucose concentrations were significantly higher in STZ groups compared to control groups at week 5	rat	Sprague-Dawley	m	250–300 g	6; 6
45	(Kumar and Maqbool, 2020)	pharmacological modulation	STZ + nicotinamide	injection of 65 mg/kg of streptozotocin after nicotinamide (110 mg/kg in normal saline, i.p.) injection (dose volumes 3 mL/kg). Glucose solution (10%) was provided for the next 24 h to avoid acute hypoglycaemia in rats	higher blood glucose concentration compared to a predefined threshold (200 mg/dL); with fasting (overnight), assessed on day 5	blood glucose concentrations were significantly higher in STZ groups compared to control groups, at day 5 and day 26	rat	Wistar	m	180–200 g	6; 6
46	(Choeiri et al., 2005)	transgenic approach	Ins2C96Y Akita mice	no manipulation, spontaneously diabetic	higher blood glucose concentration compared to controls; with fasting (18 h)	already at age of 7 weeks, Akita mice had higher fasting blood glucose levels than their corresponding CTRL mice	mouse	C57BL/6 wild type (CTRL) and Ins2C96Y Akita	m	6–7 weeks old	6; 6
47	(Marissal-Arvy et al., 2018)	pharmacological modulation	STZ	i.p. injection of 65 mg/kg of streptozotocin/day for 2 days. 3 weeks of diabetes induction before testing	higher blood glucose concentration compared to a predefined threshold (>200 mg/dL); fasting not specified, assessed 3 days after STZ injection	n/a	rat	Sprague-Dawley	m	3 weeks old; 50–55 g	8; 8
48	(Braga et al., 2021)	environmental manipulation	HFD	the animals from the HFD group received, for twelve weeks, ad libitum, a high-fat diet (12 kJ% protein, 27 kJ% carbohydrates and 61 kJ % lipids)	higher blood glucose concentration compared to controls, with fasting (6 h)	after 4 weeks: the HFD not altered basal glucose levels, significant increase in glucose levels of HFD group a T60. After 8 weeks: the HFD group displayed a significant	mouse	C57BL/6	f	12 months old; 22–27 g	10, 11; 10, 11

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						increase in the basal glucose levels; significant increase in glucose levels of HFD group a T60, significant increase in the AUC of HFD compared to CTRL. After 12 weeks: significant increase in the basal glucose levels in mice from HFD group; significant increase in glucose levels of HFD a T30 and T60; significant increase in the AUC of HFD compared to CTRL.					
49	(Van Der Kooij et al., 2018a)	environmental manipulation	chronic social defeat stress	social defeat in the home cage of the aggressor mouse lasting 10 s of aggressive encounter; these episodes were repeated three times with different. Following the triple social defeat, C57 mice were housed overnight with their opponent separated by the metal grid. The social defeat was repeated for 10 consecutive days	higher blood glucose concentration compared to controls, with fasting (1 h)	glucose levels were significantly increased on the morning, 2 days post-CSD in comparison with controls, in a glucose tolerance test performed 9 days post-CSD in fasted animals, glucose levels were increased at T30 compared with control mice	mouse	C57BL/6	m	8 weeks old	10, 23; 10, 24
50	(Bhutada et al., 2010)	pharmacological modulation	STZ	i.p. injection of 60 mg/ kg of streptozotocin; streptozotocin-treated rats received 5% of glucose solution instead of water for 24 h after injection of streptozotocin to reduce death due to hypoglycaemic shock	higher blood glucose concentration compared to predefined threshold (250 mg/dL); with fasting (3 h), assessed 48 h after STZ injection	treatment 1: 38 days after STZ injection, plasma glucose levels were highly elevated in STZ rats as compared to CTRL rats (111.6 vs 401 mg/ dL); treatment 2: at the end of the experiment, plasma glucose levels were highly elevated in STZ rats as compared to CTRL rats (101.8 vs 400.33 mg/dL)	rat	Wistar	m	200–225 g	Treatment 1: 12; 12 Treatment 2: 6; 6
51	(Pathan et al., 2008)	environmental manipulation	HFD	the high fat diet (58% fat, 25% protein and 17% carbohydrate, as a percentage of total kcal)	after 4 weeks of experimental diet feeding, an increase in plasma glucose was	n/a	rat	Sprague-Dawley	m	150–190 g	8; 6

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				was administered ad libitum, for a period of 5 weeks. Each rat in high fat diet group consumed 105 kcal/day	observed in high fat diet fed rats (glucose level mg/dL 128.47 ± 2.45) compared to control (glucose level mg/dL 99.86 ± 2.76)						
52	(Esmaeili et al., 2017)	pharmacological modulation	STZ	single i.p. injection of 65 mg/kg of streptozotocin, for three successive days	higher blood glucose concentration compared to predefined threshold (blood glucose levels exceeded 7.8 mmol/L), seven days after STZ injection; with fasting	n/a	rat	Wistar	m	200–300 g	8; 10
53	(Ren et al., 2013)	pharmacological modulation	STZ	single i.p. injection of 55 mg/kg of streptozotocin, for 15 days, after 12 h fasting	higher blood glucose concentration compared to predefined threshold (blood glucose levels of 16.7 mM) at 72 h after streptozotocin injection; with fasting	fasting blood glucose levels were significantly decreased in control group compared with the diabetes mellitus group, at 4, 9 weeks and 80 days after streptozotocin injection	rat	Sprague-Dawley	m	10 weeks old	15; 15
54	(Yeh et al., 2015)	pharmacological modulation, environmental manipulation	STZ+HFD	HFD (60% energy from fat) for 2 weeks + i.p. injections of 50 mg/kg of streptozotocin. The HFD continued until mice were killed after 11 or 22 weeks of dietary	increased in fasting blood glucose level in HFD group vs CTRL at 4, 11 and 22 weeks	increased in fasting blood glucose level in HFD group vs CTRL at 4, 11 and 22 weeks	mouse	APP/PS1 transgenic mice and their WT littermates	m, f	10 weeks old	13, 4, 7, 9 for NCD WT, NCD AD, HFSTZ WT, and HFSTZ AD respectively; 21, 15, 25, and 18 for NCD WT, NCD AD, HFSTZ WT
55	(Pei and Sun, 2018)	pharmacological modulation	STZ	single i.p. injection of 50 mg/kg of streptozotocin, after overnight fasting	higher blood glucose concentration compared to predefined threshold: blood glucose levels more than or equal to 16.7 mmol/L, 72 h after STZ injection; fasting not specified	n/a	mouse	ICR	m	Adult, 18–20 g	15; 15
56	(Ye et al., 2018)	transgenic approach	C57BLKS/J-lepr^{db}/lepr^{db}	diabetic mice	higher blood glucose concentrations compared to controls during 12 weeks of treatment; with fasting (hours not specified)	oral glucose tolerance test blood glucose was conducted after an overnight fasting. mice were orally gavage with glucose solution (1 g/ Kg), followed by blood glucose measurement at 0, 30-, 60-, 90-, and 120-min. Glucose total area under the curve in db/db	mouse	C57BLKS/J-lepr^{db}/lepr^{db}, non-diabetic mice (db/ m)	m	7 weeks old	10; 10

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						mice was significantly higher than db/m mice					
57	(Mao et al., 2008)	pharmacological modulation	STZ	single i.v. tail vein injection of 45 mg/kg of streptozotocin	higher blood glucose concentration compared to predefined threshold: plasma glucose level of 15 mmol/L or higher on day 7 following STZ administration, blood glucose was monitored daily and the STZ rats showed initial high blood glucose levels (> 22 mM) that continually increased during the 8-week period; fasting not specified	in the Oral Glucose Tolerance Test, during the 2 h following glucose ingestion, the CTRL rats exhibited smaller area under curve than STZ rats, the diabetic rats exhibited much lower insulin levels (16.7 ± 1.0 lIU/mL) compared to the control rats (39.5 ± 19.3 lIU/mL)	rat	Wistar	m	Adult (155–190 g)	7; 7
58	(T. H.J. Liu et al., 2020; T.H. Liu et al., 2020)	pharmacological modulation, environmental manipulation	STZ+HFD	HFD for 3 weeks followed by injection of STZ. The animals were kept on the HFD for the rest of the experimental period. Diabetes was induced through a single i.p. injection of 35 mg/kg streptozotocin, for 7 weeks.	higher blood glucose concentration compared to predefined threshold: serum glucose level was above 200 mg/dL at week 11; with fasting (12 h).	glucose levels were assessed for 3 weeks after STZ injection to ensure that diabetes was not reversed. Fasting blood glucose increased to more than 200 mg/dL over the weeks; in the HFD/STZ groups it was significantly higher than control	rat	Wistar	m	6 weeks old (200–210 g)	6; 6
59	(Patel and Udayabanu, 2014)	pharmacological modulation	Dexamethasone	Dexamethasone (1 mg/kg/day, i.m.) for 12 weeks	higher blood glucose concentrations compared to controls (116.75%); fasting not specified	n/a	mouse	Swiss albino	m, f	Adult, 24–30 g	8–10; 8–10
60	(J.T.H. Liu et al., 2020; J. Liu et al., 2020)	pharmacological modulation, environmental manipulation	STZ+HFD	HFD diet for 8 weeks + i.p. injection of 30 mg/kg of streptozotocin, under fasting conditions	higher blood glucose concentration compared to predefined threshold: blood glucose levels > 11.1 mmol/L on the fifth day after STZ injections; with fasting (hours not specified)	fasting blood glucose and insulin were measured at the end of all experiments and showed that the HFD and the STZ injection induced hyperglycaemia and insulin resistance	rat	Sprague-Dawley	m	120–150 g; 5 weeks old	8; 6
61	(Jin et al., 2018)	pharmacological modulation	MSG	monosodium glutamate treated rodents are used as an animal model of T2DM, experimental pups were administered 50% water-soluble MSG by subcutaneous	higher blood glucose concentrations compared to controls at 3 months old; with fasting (12 h)	MSG exposure during the neonatal period significantly increased levels of fasting blood glucose and fasting insulin, in 3-month-old rats compared with age-	rat	Sprague-Dawley	m	neonatal	10; 10

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				injection at a dosage of 4 mg/g body weight at postnatal days 1, 3, 5, 7, and 9		matched rats from the control group, the insulin sensitivity index was also reduced in 3-month-old MSG-treated rats compared with age-matched rats from the control group					
62	(H.W. Wang et al., 2019; H. Wang et al., 2019)	pharmacological modulation	injection of glucose	glucose fluctuation group: i.p. injection of 0.375 mL/kg of glucose (250 g/L) following with an injection of 1 U of insulin to make a fluctuating blood glucose level. Chronic HYP group: i.p. injection of 0.375 mL/kg of glucose (250 g/L) to make a continuously high blood glucose level	blood glucose was determined at 8:00, 8:30, 10:00, 11:00, 14:00, 14:30, 16:00, 17:00, and 20:00 to monitor the fluctuation of blood glucose in all groups, blood glucose levels at each time points demonstrated the model was built successfully	n/a	rat	Goto-Kakizaki and Winstar control	f	adult (180–200 g)	10; 10
63	(Babic et al., 2018)	environmental manipulation	cookie pellet with clozapine	12 mg/kg of clozapine for 6 weeks, three times daily at 8-hourly intervals	higher blood glucose concentrations compared to controls at baseline; with fasting (overnight)	blood glucose levels in the clozapine group did not return to a homeostatic level by the end of the Oral Glucose Tolerance Test, indicative of poor insulin response to rising blood glucose levels and suggests the presence of a diabetic phenotype in these rats	rat	Sprague–Dawley	f	200–220 g	11–12; 10–12
64	(Lee et al., 2014)	pharmacological modulation	STZ	i.p. injection of 65 mg/kg of streptozotocin, with 12 h of fasting at week 1	higher blood glucose concentrations compared to controls at 12 weeks in the Glucose tolerance test; with fasting (overnight)	n/a	rat	Wistar	m	6 weeks old	6; 6
65	(Wu et al., 2020)	transgenic approach	C57BLKS/J-lepr^{db}/lepr^{db}	db/db mouse models of Type 2 diabetes	higher blood glucose concentrations compared to controls at 16 weeks; with fasting (overnight)	for Glucose Tolerance Test, the mice were fasted overnight, and then intraperitoneally injected with glucose at a dose of 2 g/kg body weight, for Insulin Tolerance Test, the mice were fasted for 5 h, and then intraperitoneally injected	mouse	C57BLKS/J-lepr^{db}/lepr^{db}, and non-diabetic db/m	m	12 week old	10; 10

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						with insulin at a dose of 0.75 U/kg body weight					
66	(Wang et al., 2015)	pharmacological modulation	STZ	i.p. injection of 60 mg/kg of streptozotocin, on 5 consecutive days in 3-month-old mice, after 5 h fasting	higher blood glucose concentration compared to predefined threshold: blood glucose level > 250 mg/dL, 2 weeks after initiation of STZ injection (339.07 ± 50.9 mg/dL in non Tg/STZ mice and 342.88 ± 36.2 mg/dL in Tg/STZ mice); fasting not specified	two months later, blood glucose levels for diabetic mice remained significantly high in both Tg (498.09 ± 33.5 mg/dl) and non Tg (517.09 ± 27.6 mg/dl) mice	mouse	C57BL/6 J	m	3 month old	6–8; 5–10
67	(Lee and Yang, 2019)	pharmacological modulation, environmental manipulation	STZ+HFD	high-fat chow diet (HFD; 60% kcal fat) + STZ (100 mg/kg)	higher blood glucose concentrations compared to control: 102 ± 11 mg/dL for control group and 425 ± 29 mg/dL for all HFD groups at week 8; with fasting (3 h)	after an overnight fasting for 16, the animals were fed with glucose solution (2 g/kg body weight) via stomach gavage, at 15, 30, 60, 90, and 120 min after the fasting blood glucose concentrations were significantly increased by HFD diet and STZ injection	mouse	ICR	m	6 weeks old	8; 8
68	(Ren et al., 2019)	pharmacological modulation, environmental manipulation	STZ+HFD	HFD (30% fat, 20% sugar, 15% protein, 2.5% cholesterol, 1% sodium cholic acid and 31.5% custom carbohydrate) for 6 weeks + i.p. injection of 40 mg/kg of streptozotocin	higher glucose concentration compared to control at all weeks; with fasting (8 h)	oral glucose tolerance test was performed on C57/BL6 mice following overnight-fasting period at the 6th week post-treatment, HFD-STZ group had higher glucose concentration compared to control	mouse	C57BL/6 J	m	6–8 weeks old, weighing 20–22 g	6; 6
69	(Noor and Zahid, 2017)	pharmacological modulation, environmental manipulation	STZ+HFD	diabetes was induced by switching the mice to high-fat diet (HFD) and two i.p. injection of 100 mg/kg of streptozotocin, at 6 and 9 weeks of age, after overnight fasting	higher blood glucose concentration compared to predefined threshold: blood glucose level > 12 mmol/L, assessed after eight days of STZ injection; with fasting (hours not specified)	n/a	mouse	BALB/c	m	n/a	10; 10
70	(Zhang et al., 2016)	pharmacological modulation	STZ + nicotinamide	i.p. injection of 210 mg/kg of nicotinamide (NTM) and of 60 mg/kg of streptozotocin	higher blood glucose concentration compared to predefined threshold (>250 mg/dL) assessed 2 days after NTM-STZ injection: without fasting	rats confirmed hyperglycaemia status 30 days after NTM-STZ injection	rat	Wistar	m	13 months old	8; 20

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71	(Li et al., 2012)	transgenic approach	C57BLKS/J-lepr^{db}/lepr^{db}	db/db mice had more tau phosphorylated at S396 and total tau in their hippocampi than their non-diabetic control db+ mice	higher blood glucose concentrations compared to controls at 6 weeks old; with fasting (hours not specified)	the db/db mice had a higher fasting blood glucose level than the control mice when they were 6 weeks old, and that difference continued when the mice were 24 weeks old	mouse	C57BLKS/J-lepr^{db}/lepr^{db}, and non-diabetic db/m	m	6 week old	11; 11
72	(Gu et al., 2017)	environmental manipulation	psychological-stress model (PSD) in Zucker diabetic fatty rat	the PSD group was subjected to three stress stimulations: restriction, rotation, and congest	higher blood glucose concentrations compared to controls; with fasting (14 h)	n/a	rat	Zuker diabetes fatty (ZDF)	m	5 weeks old	3; 3
73	(Ahmed et al., 2020)	pharmacological manipulation	STZ	single i.p. injection of 45 mg/mL of streptozotocin, after 16 hr fasting	higher blood glucose concentrations compared to predefined threshold (10 mM), with fasting (16 h)	blood glucose in STZ-administered rats ranged from ~15–20 mM, vs ~4–7 mM in vehicle-administered controls	rat	Sprague–Dawley	m	200–220 g	10; 10
74	(Ahmed et al., 2019)	pharmacological manipulation	STZ	single i.p. injection of 45 mg/kg of streptozotocin, following 16 hr fasting	higher blood glucose concentrations compared to predefined threshold (7.0 mM); with fasting (hours not specified)	in STZ-treated hyperglycaemic group there was a gradual increase in fasting blood glucose (>7 mM after 1–3 weeks of STZ induction which drastically elevated to 11.51 and 13.69 mM after 6 and 9 weeks respectively)	rat	Sprague–Dawley	m	180–220 g	10; 10
75	(Liu et al., 2022)	transgenic approach	C57BLKS/J-lepr^{db}/lepr^{db}	db/db mouse models of Type 2 diabetes	hyperglycaemia not measured and was instead assumed based on the db/db model	n/a	mouse	db/db	m	12 weeks old, 25–49 g	9; 9
76	(Diegues et al., 2014)	pharmacological modulation	Alloxan	single i.v. injection of 32 mg/kg of ALX	higher blood glucose compared to threshold (14–35 mmol/L)	glucose levels in control groups ranged between 7.4 and 7.7 mmol/L, vs glucose levels in diabetic groups which ranged from 21 to 25 mmol/L after 6 weeks	rat	Wistar	m	38 days old, 175–200 g	10; 10
77	(Kamsrijai et al., 2020)	pharmacological manipulation	STZ	single i.p. injection of 60 mg/kg of streptozotocin, on the 15th day of the experiment	higher glucose concentration compared to threshold (>300 mg/dL); with fasting (12 h)	STZ-administered groups had higher fasting blood glucose (~430 mg/L) compared to control groups (180–190 mg/L)	rat	Wistar	m	6 weeks old, 160–180 g	9; 9
78	(Rejdak et al., 2001)	environmental manipulation	oral administration of glucose	oral administration of 40% glucose solution (4 g/kg), 30 min before the experiment	higher blood glucose concentrations compared to controls	hyperglycaemic group had higher blood glucose (272.3 ± 46.1 mg/dL) compared to controls	mouse	Swiss	m	20–30 g	20–35; 20–35

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					(272.3 ± 46.1 mg/dL); without fasting						
79	(Lazcano et al., 2014)	pharmacological manipulation	STZ	single i.p. injection of 80 mg/kg on the 15th day of the experiment	higher blood glucose concentrations compared to predefined threshold (200 mg/dL); without fasting	control group blood glucose levels were 86.01 ± 1.3, 82.81 ± 1.6, 77.81 ± 2.5, 81.9 ± 1.43, and 77.81 ± 2.5 mg/dL, whereas diabetic group were 82.25 ± 2.4, 264.10 ± 7.11, 299.80 ± 7.19, 348.8 ± 12.1, and 363.2 ± 11.4 mg/dL	rat	Wistar	m	180–220 g	7; 7
80	(Cai et al., 2020)	pharmacological modulation, environmental manipulation	STZ+HFD	single i.p. injection of 35 mg/kg of streptozotocin, followed by administration of high fat diet for 8 weeks	higher blood glucose concentrations compared to controls (~300 mg/dL vs ~120 mg/dl); with fasting (6 h)	animals in experimental group exhibited an increasing fasting blood glucose level over 8 weeks ranging from ~150 mg/dL in week 1 to ~300 mg/dL in week 8, animals in the control group showed fasting blood glucose ranging from ~120 mg/dL in week 1–140 mg/dL in week 8	rat	Sprague–Dawley	m	18 weeks old, 250 g	10; 10
81	(Wen et al., 2020)	transgenic approach	C57BLKS/J-lepr^{db}/lepr^{db}	db/db mice utilised as a model of Type 2 diabetes and obesity	higher blood glucose concentrations compared to controls, with fasting (4 h)	n/a	mouse	C57BLKS/J-lepr^{db}/lepr^{db}	m	8 months old	10; 10
82	(Li et al., 2018)	strain difference	KKAy mice	KKAy mice, a genetic model of type 2 diabetes with obesity and insulin resistant hyperglycaemia	higher blood glucose concentrations compared to predefined threshold (random blood glucose ≥ 11.1 mmol/L or fasting blood glucose ≥ 7.0 mmol/L), with fasting	KKAy group had higher random blood glucose levels in week 4, 8 and 12 of the experiment of ~30 mmol/L, 25 mmol/L and 25 mmol/L respectively vs ~8 mmol/L in controls at all timepoints, the KKAy group also had higher fasting blood glucose in week 4, 8 and 12 of ~22 mmol/L, 20 mmol/L and 22 mol/L respectively vs ~8 mmol/L in controls at all timepoints	mouse	KKAY	m	30 ± 5 g	6; 6

(*continued on next page*)

Table 1 (*continued*)

N	Ref.	Type of experimental manipulation adopted to induce hyperglycaemia		Details regarding the experimental manipulation	Details on the assessment of hyperglycaemia	Variation of glucose metabolism-/insulin signalling related parameters	Species	Strain	Sex [f; m]	Age and/or weight at the beginning of the study	N of subjects per group {n for behavioural parameters; n for glucose metabolism/ insulin parameters}
83	(Ahmadi et al., 2017)	pharmacological modulation	STZ	single i.p. injection of 55 mg/kg of streptozotocin	higher blood glucose concentrations compared to predefined threshold (250 mg/dL), with fasting (overnight)	serum glucose levels in control non-diabetic mice were approximately ~120 mg/dL vs ~450 mg/dL in diabetic mice (exceeding the 250 mg/dL threshold set based on clinical criteria for chronic hyperglycaemia)	Rat	Wistar	m	270–300 g	7; 7
84	(Wirt et al., 2021)	pharmacological manipulation	STZ	i.p. injection of staggered and low doses of streptozotocin at 20 mg/kg/mL following 6 h fasting on day 1, 2, 3, 14, 15, 35 and 36	higher blood glucose concentrations compared to predefined threshold (≥250 mg/dL); with fasting	animals in the experimental group exhibited a sustained fasting blood glucose reading > 250 mg/dl compared to vehicle-administered controls which did not reach this threshold	rat	Long-Evans	m	8–12 months old, 400–550 g	3, 5; 3, 5
85	(Nakaoku et al., 2019)	environmental manipulation	HFD	mice fed high-fat diet for 5.5 months (60% fat, 20% carbohydrate, and 20% protein)	higher blood glucose concentrations compared to controls; with fasting (6 h)	n/a	Mice	PS19	m	6 weeks old	15–17; 15–17
86	(Delkhosh-Kasmaie et al., 2018)	pharmacological manipulation	STZ	single i.p. injection of 55 mg/kg of streptozotocin, after 12 hr fasting	higher blood glucose concentrations compared to predefined threshold (250 mg/dL); with fasting (12 h)	blood glucose levels in control group were 79.2 ± 3.61, 76.8 ± 4.03 and 86 ± 3.34 mg/dL on days 15, 25 and 35 of the experiment, respectively, blood glucose concentrations reached to 394.5 ± 22.32 and 406.8 ± 19.38 and 420 ± 21.71 mg/dL on days 15, 25 and 35 after induction of diabetes, respectively	rat	Wistar	m	180–210 g	6; 6
87	(Lupien et al., 2003)	pharmacological modulation	STZ	anesthetized under 5% isoflurane, 95% oxygen for 1 min, and injected s. c. with 50 mg/kg of streptozotocin, overnight fasting	higher blood glucose concentrations compared to predefined threshold (360 mg/dL), without fasting	blood glucose levels were significantly higher in diabetic mice with vehicle and IGF-1 (515 ± 73, 495 ± 99 mg/dL) vs non-diabetic control (125.0 ± 11 mg/dL)	rat	Wistar	m	10 weeks old	7–12; 7–12
88	(Heng et al., 2011)	pharmacological modulation	STZ	single i.p. injection of 60 mg/kg of streptozotocin	higher blood glucose concentrations compared to predefined	blood glucose level in the diabetic group was significantly higher than the control group	rat	Sprague–Dawley	m	250–280 g	20; 20

(*continued on next page*)

Table 1 (*continued*)

N	Ref.	Type of experimental manipulation adopted to induce hyperglycaemia		Details regarding the experimental manipulation	Details on the assessment of hyperglycaemia	Variation of glucose metabolism-/insulin signalling related parameters	Species	Strain	Sex [f; m]	Age and/or weight at the beginning of the study	N of subjects per group {n for behavioural parameters; n for glucose metabolism/ insulin parameters}
					threshold (16.7 mmol/ L); without fasting	(~20 mmol/L vs ~5 mmol/L), by the end of week 5, blood glucose levels in the diabetic group remained significantly elevated					
89	(Jash et al., 2020)	pharmacological modulation	STZ	i.p. injection of 120 mg/ kg of streptozotocin	higher blood glucose concentrations compared to predefined threshold (300 mg/dL); with fasting (4 h)	glucose levels persistently higher and above threshold in diabetic group	mouse	C57BL/6 J	m	4 weeks old	6; 6
90	(Rajab et al., 2017)	pharmacological modulation	STZ	i.p. injection of 55 mg/ kg of streptozotocin, daily for five days	higher blood glucose concentrations compared to predefined threshold (280 mg/dL); without fasting	non-fasting blood glucose measurements (22.1 mM) which were significantly higher than the control mice (8.1 mM)	mouse	BALB/C	m	20–25 g	12–14; 12–14
91	(Sharifzadeh et al., 2017)	pharmacological modulation	STZ	single i.p. injection of 60 mg/kg streptozotocin	higher blood glucose concentrations compared to predefined threshold (250 mg/dL); with fasting	streptozotocin-induced diabetic rats showed consistent fasting hyperglycaemia throughout the study	rat	Wistar	m	250–300 g	8–10; 8–10

been applied in 68 of the 91 studies (n: 1,4,5,7,8,14–16,18,20–24,26,29, 30,33–46,50–62,64–66,68–70,72–77,79,80,82,83,85–91). Some of these studies also used the elevated plus-maze learning task (Bhutada et al., 2010), the novel-object recognition test (Taylor et al., 2015) and/or the Barnes maze test (Jin et al., 2018; Momeni et al., 2021) to retest the same spatial memory phenotype. The Barnes maze test was used exclusively (and not as a restest) by three other authors (Li et al., 2012; Madhavadas et al., 2016; Madhavadas and Subramanian, 2015) while three articles used a variation of the novel-object recognition test: object location (Braga et al., 2021; Van Der Kooij et al., 2018) and place-recognition test (de Senna et al., 2017). Moreover, the radial arm water maze test (Malone et al., 2008; Rababa'h et al., 2019), the T-maze (Joshi et al., 2021; Tanokashira et al., 2021; W. H. Wang et al., 2019; W. Wang et al., 2019), and the Y-maze (n: 15,25,47,49) were employed as spatial memory tasks.

Although the Morris water maze test is currently used for spatial memory, it has been originally devised to dissociate "spatial mapping" and "working-memory" theories of hippocampal function; accordingly, five articles of the present review (n: 15,34,64,73,74) used this test to assess working memory. The latter was also examined in 17 studies, which assessed spontaneous alternation as a proxy for working memory: of these, five articles used a T-maze test (n: 2,11,12,63,84), either in its original dry version or in a water incarnation (Tanokashira et al., 2018; W. H. Wang et al., 2019; W. Wang et al., 2019), nine used the Y-maze test (n: 13,19,27,31,49,67,78,81,89), while only one (Choeiri et al., 2005) employed the four-arm maze test. The remaining two articles used the passive avoidance test (Georgy et al., 2013) and the step-down inhibitory avoidance task (Remor et al., 2019) to assess aversive associative memory. With respect to these tasks, we note that, as also described by the authors themselves (Georgy et al., 2013; Remor et al., 2019), they are predominantly used to investigate emotional memory rather than working memory. Yet, the same authors also specified that they considered these cortical-dependent tasks related to working memory, whereby the latter affects the impact of aversive stimuli.

Regarding attention, only two articles analysed it through a rewarded lever press task (Moreira et al., 2007) (the ability to change the discrimination of the rewarded lever, once it had been learned, was considered an attentional task) and the nest construction (Yeh et al., 2015), that according to the authors, is a task involving a broad network of brain regions and has previously been used to evaluate attention in mice (Filali and Lalonde, 2009).

Herein, we evaluated the different experimental manipulations adopted to induce hyperglycaemia, the details on the assessment of hyperglycaemia, and the type of non-hyperglycaemic control (Table 1). All articles with no appropriate control condition (e.g., low-fat diet used as control instead of standard diet, control group not exposed to vehicle, etc.) were excluded. Therefore, all control conditions belong to the following categories: (1) control strains, be them inbred or outbred, specific for those models that spontaneously exhibited variations in glucose metabolism/insulin signalling; (2) a corresponding control condition for the environmental manipulation (e.g. subjects exposed to standard diet for models based on dietary interventions); (3) wild-type or hemizygous mice as controls for genetically-engineered mice; (4) vehicle-treated animals for the pharmacological modulation. In nine manuscripts (n: 18,21,44,58,60,64,67,68,70), the information on the type of non-hyperglycaemic control was unclear; we took this limitation into consideration during the assessment of the risk of bias.

While detailing the methodologies adopted to induce hyperglycaemia, we observed that 48 studies (n: 1,3,4,8,14–24,28,30–34, 36–40,43,44,47,50,52,53,55,57,64,66,73,74,77,79,83,84,86–91) capitalized upon the administration of streptozotocin (STZ), a natural toxic agent capable of affecting the functionality of pancreatic β-cells. In some of them, the injection of STZ was associated with insulin to modulate the level of hyperglycaemia (Biessels et al., 1996) or to induce temporal fluctuations in blood glucose concentrations (H. W. Wang et al., 2019; H. Wang et al., 2019). The remaining studies that induced hyperglycaemia *via* a pharmacological approach used different drugs such as isoflurane/sevoflurane (Wu et al., 2014), monosodium glutamate (Jin et al., 2018; Madhavadas et al., 2016; Madhavadas and Subramanian, 2015), nicotinamide plus STZ (Kumar and Maqbool, 2020; Zhang et al., 2016), dexamethasone (Patel and Udayabanu, 2014) and alloxan (Diegues et al., 2014). With respect to environmental manipulations, the majority of studies fed mice with high fat diet (HFD) (n: 2,11,26,29,41, 48,51,85) and/or moderate HFD (Arnold et al., 2014); a minority of studies exploited other approaches like psychological stress (Gu et al., 2017; Van Der Kooij et al., 2018a), drinking water supplemented with arsenic, aspartame or fructose (Collison et al., 2012; Rodríguez et al., 2016; Dharavath et al., 2019), administration of cookie pellets with clozapine (Babic et al., 2018), and glucose injection (Rejdak et al., 2001; H. W. Wang et al., 2019; H. Wang et al., 2019). Pharmacological and environmental manipulations to obtain hyperglycaemia were combined in nine studies (n: 12,42,54,58,60,67,68,69,80) considered in this review (STZ + HFD). One of them (W. H. Wang et al., 2019; W. Wang et al., 2019) adopted these two approaches in separated experimental groups (a group treated with STZ and a different one subjected to HFD). A genetic approach, as the independent variable responsible for hyperglycaemia, was exploited in eight articles: in particular, one study has been conducted on Irs2-deficient mice (Tanokashira et al., 2021), six on the Lepr $^{db/db}$ mouse (n: 25,56,65,71,75,81) and one on the Ins2C96Y Akita (Choeiri et al., 2005). Finally, three studies were conducted on strains that spontaneously exhibit diabetes-like abnormalities: Goto-Kakizaki and Zucker rats (Moreira et al., 2007; Skapare et al., 2012) and KKAy mice (Li et al., 2018).

Since the presence of hyperglycaemia was an inclusion criterion, we systematically evaluated how this has been assessed. Hyperglycaemia was ascertained in the vast majority of the studies, in comparison either with the control group (37 studies) or with a predefined threshold (50 articles). While most of the articles assessed glucose concentrations in the blood, one measured it in serum (Mirshekar et al., 2011) and another in urine (Baranowska et al., 2020). In two instances (Liu et al., 2022; Moreira et al., 2007) hyperglycaemia was not directly measured, and its presence was assumed based on the known characteristics of the experimental model (inbred strains). Two articles confirmed hyperglycaemia by assessing blood glucose concentrations but did not report the data (Joshi et al., 2021; H. W. Wang et al., 2019; H. Wang et al., 2019). Those articles that confirmed the presence of hyperglycaemia resting upon a predefined threshold, adopted a similar approach with a threshold ranging between 250 and 280 mg/dL in nine studies (n: 19,50, 66,70,83,84,86,90,91); between 300 or 360 mg/dL in eight studies (n: 16,17,18,32,33,77,87,89); between 200 and 210 mg/dL in 12 studies (n: 1,4,21,28,34,38,39,40,45,47,58,79); and > 7nmol/L (corresponding to 126 mg/dL) in 20 studies (n: 15,22–24,30,36,37,42,43,52,53,55,57,60, 69,73,74,76,82,88); a single study (Hardigan et al., 2017) measured, as threshold, the glycated haemoglobin (HbA1c >8.0%). A variation of glucose/insulin metabolism, after the original validation of the hyperglycaemic state, was also detected during or at the end of the experimental schedule to confirm hyperglycaemia in most of the manuscripts (68 of the 91 reviewed articles).

Since blood glucose concentrations fluctuate as a function of the time elapsed between the last meal and its measurement, we deemed it relevant to evaluate whether and how fasting has been considered in the relevant articles. While in 39 articles glucose concentrations have been measured following a fasting period, in seven studies (n: 44,70,78,79, 87,88,90) it was assessed without fasting. The remaining articles did not provide details regarding this parameter.

All the studies reported were conducted in mice (40 articles) or rats (51 articles). Mouse strains included: ICR mice (n: 14,15,33,36, 37,55,67), Swiss mice (Patel and Udayabanu, 2014; Rejdak et al., 2001), C57BL/6 J strain (n: 2,7,11,12,22,24,31,35,38,39,42,43,48,49,66,68, 89), BALB/c (Noor and Zahid, 2017; Rajab et al., 2017), transgenic mice with mutations linked to Alzheimer's disease such as APP/PS1 (Yeh et al., 2015), 3 ×Tg-AD (Huang et al., 2019) and PS19 (Nakaoku et al.,

2019), spontaneous diabetes-associated dysfunctions animal models such as KKAy mice (Li et al., 2018), Ins2^{C96Y} Akita mice (Choeiri et al., 2005), *Irs2*$^{-/-}$/6 J mice (Tanokashira et al., 2021) and C57BLKS/J-lepr^{db}/lepr^{db} (n: 25,56,65,71,75,81). Studies conducted in rats used a transgenic line of non-obese model of T2DM like Goto-Kakizaki (Moreira et al., 2007; Skapare et al., 2012; H. W. Wang et al., 2019; H. Wang et al., 2019) and a rat model of genetic obesity, the Zucker $^{fa/fa}$ (Gu et al., 2017; Skapare et al., 2012), while the most common strain was Wistar (n: 1,2,14,16,17,18,20,24,27,28,32,42,43, 49,56,57,69,75–77,82,85,87–91) followed by Sprague–Dawley (n: 1,5, 9,10,23,30,34,44,47,51,53,60,61,63,73,74,80,88) and Long-Evans (Wirt et al., 2021).

Only eight articles used female subjects (n: 16,26,35,48,54, 59,62,63), three of which (Collison et al., 2012; Patel and Udayabanu, 2014; Yeh et al., 2015) entailed a pool of males and females. All experimental subjects were adult at the time of behavioural and metabolic phenotyping. Only in three articles did the treatment to induce hyperglycaemia begin at a neonatal stage (Jin et al., 2018; Madhavadas et al., 2016; Madhavadas and Subramanian, 2015). Given that our aim was the comparison between the hyperglycaemic group and the relative controls, all the studies had a between-subjects study design; in one of them (Rodríguez et al., 2016), the behavioural and metabolic tests were performed in two independent groups with the same experimental treatment.

3.3. Hyperglycaemia and behavioural outcomes

The effects of hyperglycaemia on the behavioural parameters of interest (within each test) are illustrated in Table 2. The tables include, under separate headings, the direction of the variation of the behavioural phenotypes isomorphic to working memory, spatial memory, and attention, respectively. Most of the studies observed an impairment in the behavioural phenotype in the comparison between hyperglycaemic subjects and their relative controls; only one study (Dharavath et al., 2019a), conducted in female rats, reported an improvement in the spatial memory domain after 16 and 20 weeks of a HFD treatment lasting 24 weeks (although, at the end of treatment, they reported an impairment), and 11 papers described no significant difference between the two groups of interest for spatial (n: 7,8,12,17,22,39,42,43,46) and working memory (n: 13,46,63).

3.4. Other considerations

Although possible treatment therapies of hyperglycaemia were not the purpose of our review, some of the presented studies have also analysed the effects of several treatments. Therefore, while we are not able to provide a systematic review of this aspect, we believe that these considerations may help analysing the predictive validity of animal models of diabetes (i.e., whether treatments used in our species are also effective in experimental models), in terms of changes in blood glucose concentrations and cognition. Although metformin is a first-line therapy for the treatment of diabetes, only in three articles (Delkhosh-Kasmaie et al., 2018; Li et al., 2012; Tanokashira et al., 2018) has it been used as a treatment for diabetes-associated dysregulation. In all of them, metformin ameliorates diabetes-associated decline in hippocampal neurogenesis, learning and memory. Several authors used alternative approaches such as herbal medicines (Mao et al., 2008; Mirshekar et al., 2011; Tabatabaei et al., 2016; Wu et al., 2012), dark chocolate (Madhavadas et al., 2016), prebiotic and probiotic (de Cossío et al., 2017; T. H. J. Liu et al., 2020; T.H. Liu et al., 2020) and physical exercise or a backward switch from HFD to a regular diet (Braga et al., 2021; de Senna et al., 2017). All these treatments ameliorated metabolic and cognitive dysfunctions related to the hyperglycaemic condition in the animal model. While metformin is a validated anti-diabetic drug, these alternative treatments clearly deserve special consideration on whether results can be translated to humans or not.

Sex differences constitute an additional important aspect that would warrant a systematic approach. While this aspect was not among the primary scope of our study, we can nonetheless provide some preliminary considerations. Of all the 91 studies considered, only eight included female subjects. In two of them, the authors pooled subjects of both sexes thus limiting the possibility to discern between males and females (see Table 1, n: 54,59). One study (see Table 1, n: 35) reported a direct comparison between males and females and observed gender-specific effects, with males more affected by hyperglycaemia than females. The remaining five articles (see Table 1, n: 16,26,48,62,63) presented data on female subjects only. One of them (see Table 2, n: 26) constitutes the only instance in which hyperglycaemia resulted in a temporary cognitive improvement: i.e. hyperglycaemia resulted in improved spatial memory 16 and 20 weeks after the beginning of a high fat diet, and in impaired spatial memory four weeks later. The other four studies either reported a general impairment (see Table 2, n: 16,48,62) or lack of differences (see Table 2, n: 63) as a function of hyperglycaemia. While these articles partly reverberate the results observed in the studies conducted in males, their scant number poses some caveats as to whether the findings reported in the majority of studies (male-biased) may translate to females.

3.5. Risk of bias (RoB)

The risk of bias assessment of all included studies is shown in Fig. 3. The assessment of RoB included all the final 91 articles, for which often the experimental details were only partly reported (Avey et al., 2016). This resulted in an overall unclear risk of bias (52.09%). Yet, when data were correctly reported, there was a generally low risk of bias based on SYRCLE's RoB tool (33.19%), with a limited percentage of high risk of bias (5.27%). The judgement "not applicable" resulted in a 9.45% overall risk of bias but it was only influenced by the "Reporting bias" (Hooijmans et al., 2014).

4. General discussion

The primary purpose of the present systematic review was to identify whether experimental rats and mice characterized by hyperglycaemia also exhibit behavioural abnormalities in the domains of working and spatial memory, and attention. The studies of interest are characterized by hyperglycaemia, which has been induced via different methodologies, be them pharmacological interventions, environmental modulations, transgenic approaches, naturally occurring mutations based on strain differences, or a combination. All of them allow the analysis of mechanisms related to diabetes and are important to understand the pathogenesis and progression of the disease as well as to evaluate potential therapeutic strategies with an elevated translational value. Accordingly, an animal model relevant for the study of diabetes, should mirror the pathophysiology and natural course of diabetes, and/or develop complications of the disease with an aetiology similar to the human condition (Varga et al., 2015). These considerations are particularly relevant to diabetes, which is characterised by multiple facets and different main diagnoses: T1DM is an autoimmune disease in which pancreatic β-cells are targeted to be destroyed by antibodies produced by immune cells (Gillespie, 2006). In contrast, the pancreatic β-cells are active in T2DM and synthesize insulin but at dysregulated level and/or not sufficiently efficiently (Brunton, 2016). Chronically elevated blood glucose concentrations represent a commonality in T1DM or T2DM. Since T1DM is characterized by the deficiency of insulin production, the deficit is achieved in experimental animals through chemical destruction of pancreatic β-cells or through breeding of rodents that spontaneously develop diabetes. Although the endpoint of β-cell destruction is similar to T1DM in humans, the mechanism for the β-cell destruction is not autoimmune, therefore the aetiology differs from the human condition. On the other hand, T2DM animal models should recapitulate insulin resistance, a certain degree of β-cell failure, and obesity. It

Table 2
Behavioural test for each cognitive domain of interest and relative outcomes; bold text refers to an improvement and italic text refers to a no change in that phenotype, otherwise there was an impairment of the domain investigated.

N	Ref.	OUTCOME and TEST to evaluate working memory	OUTCOME and TEST to evaluate spatial memory	OUTCOME and TEST to evaluate attention
1	(Georgy et al., 2013)	Passive avoidance test	Morris water maze test	n/a
2	(Arnold et al., 2014)	T-maze test	n/a	n/a
3	(Joshi et al., 2021)	n/a	T-maze test	n/a
4	(Remor et al., 2019)	Step-down inhibitory avoidance task	Morris water maze test	n/a
5	(Wu et al., 2014)	n/a	Morris water maze test	n/a
6	(Moreira et al., 2007)	lever press task (total presses)	lever press task (left versus right lever discrimination)	lever press task (active presses in FR2, FR3, FR5 and PR)
7	(Rodríguez et al., 2016)	n/a	*Morris water maze test*	n/a
8	(Biessels et al., 1996)	n/a	*Morris water maze test*	n/a
9	(Madhavadas et al., 2016)	n/a	Barnes maze test	n/a
10	(Madhavadas and Subramanian, 2015)	n/a	Barnes maze test	n/a
11	(Tanokashira et al., 2018)	Water T-maze	n/a	n/a
12	(W.H. Wang et al., 2019; W. Wang et al., 2019)	Water T-maze	*Water T-maze test*	n/a
13	(Tanokashira et al., 2021)	*Y-maze test*	Water T-maze test	n/a
14	(Du et al., 2014)	n/a	Morris water maze test	n/a
15	(Fang et al., 2017)	Morris water maze test	Y-maze test	n/a
16	(Tabatabaei et al., 2016)	n/a	Morris water maze test	n/a
17	(Rababa'h et al., 2019)	n/a	*Radial arm water maze test*	n/a
18	(Babri et al., 2013)	n/a	Morris water maze test	n/a
19	(Mirshekar et al., 2011)	Y-maze	n/a	n/a
20	(Baranowska et al., 2020)	n/a	Morris water maze test	n/a
21	(Utkan et al., 2015)	n/a	Morris water maze test	n/a
22	(Taylor et al., 2015)	n/a	Morris water maze test and *novel object recognition test*	n/a
23	(Yang et al., 2014)	n/a	Morris water maze test	n/a
24	(Momeni et al., 2021)	n/a	Barnes maze test and Morris water maze test	n/a
25	(de Cossío et al., 2017)	n/a	Y-maze test	n/a
26	(Dharavath et al., 2019a)	n/a	**Morris water maze test**	n/a
27	(Skapare et al., 2012)	Y-maze test	n/a	n/a
28	(Malone et al., 2008)	n/a	Radial water maze test	n/a
29	(Treviño et al., 2015)	n/a	Morris water maze test	n/a
30	(Nurdiana et al., 2017)	n/a	Morris water maze test	n/a
31	(Hardigan et al., 2017)	Y-maze test	n/a	n/a
32	(de Senna et al., 2017)	n/a	Place recognition test	n/a
33	(Wu et al., 2012)	n/a	Morris water maze test	n/a
34	(Lin et al., 2018)	Morris water maze test	Morris water maze test	n/a
35	(Collison et al., 2012)	n/a	Morris water maze test	n/a
36	(Zhou et al., 2015b)	n/a	Morris water maze test	n/a
37	(Zhou et al., 2017)	n/a	Morris water maze test	n/a
38	(Huang et al., 2012)	n/a	Morris water maze test	n/a
39	(Huang et al., 2007)	n/a	*Morris water maze test*	n/a
40	(Huang et al., 2019)	n/a	Morris water maze test	n/a
41	(Lin et al., 2017)	n/a	Morris water maze test	n/a
42	(He et al., 2020)	n/a	*Morris water maze test*	n/a
43	(Zhou et al., 2018)	n/a	*Morris water maze test*	n/a
44	(Sibiya and Mabandla, 2017)	n/a	Morris water maze test	n/a
45	(Kumar and Maqbool, 2020)	n/a	Morris water maze test	n/a
46	(Choeiri et al., 2005)	*Four-arm maze test*	*Morris water maze test*	n/a
47	(Marissal-Arvy et al., 2018)	n/a	Y-maze test	n/a
48	(Braga et al., 2021)	n/a	Object location test	n/a
49	(Van Der Kooij et al., 2018a)	n/a	Y-maze test and Object location task	n/a
50	(Bhutada et al., 2010)	n/a	Morris water maze test and Elevated plus maze learning task	n/a
51	(Pathan et al., 2008)	n/a	Morris water maze test	n/a
52	(Esmaeili et al., 2017)	n/a	Morris water maze test	n/a
53	(Ren et al., 2013)	n/a	Morris water maze test	n/a
54	(Yeh et al., 2015)	n/a	Morris water maze test	Nest construction
55	(Pei and Sun, 2018)	n/a	Morris water maze test	n/a
56	(Ye et al., 2018)	n/a	Morris water maze test	n/a
57	(Mao et al., 2008)	n/a	Morris water maze test	n/a
58	(T. H.J. Liu et al., 2020; T.H. Liu et al., 2020)	n/a	Morris water maze test	n/a
59	(Patel and Udayabanu, 2014)	n/a	Morris water maze test	
60	(J.T.H. Liu et al., 2020; J. Liu et al., 2020)	n/a	Morris water maze test	n/a
61	(Jin et al., 2018)	n/a	Barnes maze test and Morris water maze test	n/a
62	(H.W. Wang et al., 2019; H. Wang et al., 2019)	n/a	Morris water maze test	n/a
63	(Babic et al., 2018)	*T-Maze alternation test*	n/a	n/a

(*continued on next page*)

Table 2 (*continued*)

N	Ref.	OUTCOME and TEST to evaluate working memory	OUTCOME and TEST to evaluate spatial memory	OUTCOME and TEST to evaluate attention
64	(Lee et al., 2014)	Morris water maze test	n/a	n/a
65	(Wu et al., 2020)	n/a	Morris water maze test	n/a
66	(Wang et al., 2015)	n/a	Morris water maze test	n/a
67	(Lee and Yang, 2019)	Y-maze test	n/a	n/a
68	(Ren et al., 2019)	n/a	Morris water maze test	n/a
69	(Noor and Zahid, 2017)	n/a	Morris water maze test	n/a
70	(Zhang et al., 2016)	n/a	Morris water maze test	n/a
71	(Li et al., 2012)	n/a	Barnes maze test	n/a
72	(Gu et al., 2017)	n/a	Morris water maze test	n/a
73	(Ahmed et al., 2020)	Morris water maze test	Morris water maze test	n/a
74	(Ahmed et al., 2019)	Morris water maze test	Morris water maze test	n/a
75	(Liu et al., 2022)	n/a	Morris water maze test	n/a
76	(Diegues et al., 2014)	n/a	Morris water maze test	n/a
77	(Kamsrijai et al., 2020)	n/a	Morris water maze test	n/a
78	(Rejdak et al., 2001)	Y-maze test	n/a	n/s
79	(Lazcano et al., 2014)	n/a	Morris water maze test	n/a
80	(Cai et al., 2020)	n/a	Morris water maze test	n/a
81	(Wen et al., 2020)	Y-maze test	n/a	n/a
82	(Li et al., 2018)	n/a	Morris water maze test	n/a
83	(Ahmadi et al., 2017)	n/a	Morris water maze test	n/a
84	(Wirt et al., 2021)	T-maze test	n/a	n/a
85	(Nakaoku et al., 2019)	n/a	Morris water maze test	n/a
86	(Delkhosh-Kasmaie et al., 2018)	n/a	Morris water maze test	n/a
87	(Lupien et al., 2003)	n/a	Morris water maze test	n/a
88	(Heng et al., 2011)	n/a	Morris water maze test	n/a
89	(Jash et al., 2020)	Y-maze test	Morris water maze test	n/a
90	(Rajab et al., 2017)	n/a	Morris water maze test	n/a
91	(Sharifzadeh et al., 2017)	n/a	Morris water maze test	n/a

appears that no single animal model involves all of these characteristics, but some of them could provide very similar traits in one or more aspects of diabetes (T1DM and/or T2DM) in humans.

Although we selected the relevant studies based on hyperglycaemia, our primary interest was the role of insulin signalling. Therefore, an important prerequisite is that hyperglycaemia constitutes a valid proxy of altered insulin signalling. To assess this prerequisite, we first discuss the extent to which the experimental models considered in this review adequately mimic diabetes. Following this examination, we proceed with the evaluation of the association between diabetes and cognitive alterations. Finally, we interpret the observed results as a function of their risk of bias.

4.1. Pharmacological induction of hyperglycaemia

Some experimental models utilise a chemical approach to induce diabetes, particularly in the form of diabetogenic agents such as streptozotocin and alloxan. Alloxan is a toxic glucose analogue whose accumulation in pancreatic β-cells inhibits insulin secretion and induces reactive oxygen species formation that are ultimately responsible for the death of the cells (Cefalu, 2006). Streptozotocin is a highly selective pancreatic islet β-cell-cytotoxic agent and inhibits insulin secretion causing a state of insulin-dependent diabetes mellitus (Lenzen, 2008). It is often administered at a single high dose to produce an immediate blood glucose concentration > 500 mg/dL and to cause β-cell total necrosis (Cefalu, 2006). However, lower doses of STZ administered multiple times, are capable to delay the onset of hyperglycaemia with a partial damage of pancreatic islets. This slower process triggers an inflammatory process that causes an additional loss of β-cells, which, in turn, results in insulin deficiency, hyperglycaemia, polydipsia, and polyuria (Radenković et al., 2016). This response more closely resembles T1DM in pathogenesis and morphologic changes than the single, high-dose of STZ (Furman, 2015). Another protocol of diabetes induction entails the concurrent administration of STZ and nicotinamide, wherein the latter partially protects the β-cells damage induced by the former (Fukaya et al., 2013; Szkudelski, 2012). This combination

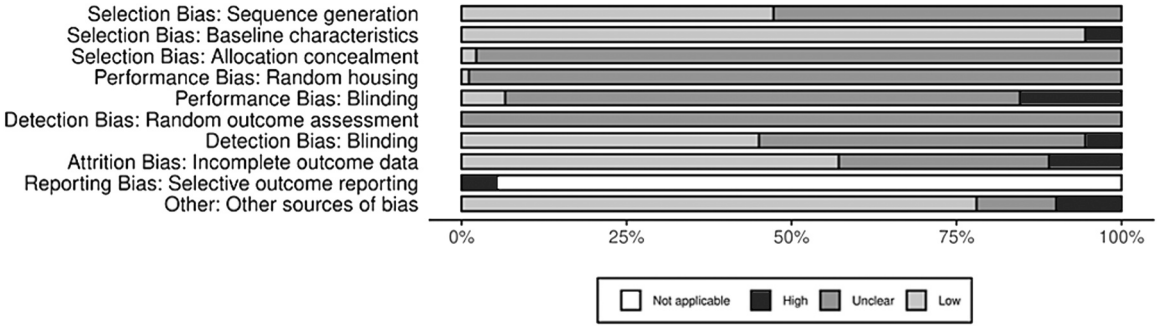

Fig. 3. Risk of bias assessment, score (%) per risk of bias item. The RoB tool for animal studies is divided into 10 items. "Random outcome assessment" bias was considered "Unclear" because the details on the sequence of animal testing were never reported. "Reporting bias" was judged as "not applicable" for all the studies published before 2021. In this respect it should be noted that the "Reporting bias" item was prospectively included in the SYRCLE's tool (in agreement with the Cochrane's tool) although at present it is difficult to assess, as protocols for animal studies are not yet mandatorily registered in central, publicly accessible databases (Hooijmans et al., 2014; Olevska et al., 2021).

produces a model of insulin-deficient, but not insulin-resistant T2DM that is a major feature of most human cases. It is characterized by stable, moderate hyperglycaemia associated with an approximately 60% loss of β-cell function.

Although most of the reviewed articles used models of diabetes (see Table 1), our interest was directed towards any type of manipulation capable of inducing hyperglycaemia. Some scholars used different drugs to achieve this goal or to study the behavioural effects of glucose dysregulation. One of these studies reported that isoflurane and sevoflurane (Wu et al., 2014) may impair glucose tolerance by decreasing insulin secretion and glucose utilization. An additional pharmacological approach was constituted by the use of monosodium glutamate (MSG), that is frequently used as a flavour enhancer in the food industry. Some evidence indicate that MSG treatment in animals, during the first day of life, leads to the development of obesity and hyperglycaemia in adulthood (Bahadoran et al., 2019; Dolnikoff et al., 2001). Although these observations suggest that MSG may constitute a useful agent for the induction of T2DM-like abnormalities in animals, the underlying mechanisms are not completely understood and thus may be secondary. As one of the reviewed articles showed, chronic dexamethasone administration may induce diabetes-related metabolic dysfunctions in animal models (Patel and Udayabanu, 2014). Dexamethasone represents a first-line anti-inflammatory drug. Unfortunately, long-term therapy is associated with metabolic side effects, including hyperglycaemia, hypertension, and hepatic steatosis that contribute to insulin resistance and diabetes (Cefalu, 2006). Additionally, one manuscript used an antipsychotic drug, clozapine. While it generally improves the cognitive symptoms of schizophrenia, it can cause serious metabolic side-effects (Siskind et al., 2016), likely mediated by its impact on glucagon-like peptide (Siskind et al., 2019). Usually, all these pharmacological models are invaluable when studying the mechanisms by which hyperglycaemia may contribute to microvascular complications such as neuropathy, nephropathy, and retinopathy. However, because they may be toxic to organs and tissues other than the pancreatic islet β-cells, these models do not precisely mimic the human condition (Zhang et al., 2008). Chemically-induced models present a phenotype that closely resembles that observed in T1DM patients; yet, the mechanisms underlying β-cell damage are different from the human disease. Thus, while the construct validity of these models may be limited, their predictive validity is highly relevant.

4.2. Environmental induction of hyperglycaemia

To mimic the nutritional determinants of T2DM, several authors adopted a differential strategy entailing the administration of HFD. In these instances, experimental subjects are exposed to an HFD nutritional regime to induce insulin resistance. This regime has been sometimes associated with the concurrent administration of a moderate dose of STZ to reduce β-cell capacity (Reed et al., 2000), a combination resulting in hyperglycaemia, hyperinsulinemia and insulin resistance (Yorek, 2016). The use of HFD to induce insulin resistance and to produce mild or moderate insulin deficiency may represent a valid experimental model of T2DM, whereby it can provide relevant information regarding many of the complications associated with human diabetes. HFD has also been utilized to model chronic inflammation, which is an important pathogenic mechanism of T2DM. Chronic overfeeding triggers inflammation, which leads to alterations in peripheral insulin receptor-associated signalling and thus reduces the sensitivity to insulin-mediated glucose clearance. These events ultimately result in elevated fasting glucose and insulin concentrations as well as in a reduction in glucose tolerance, all of which constitute relevant indicators of insulin resistance (Heydemann, 2016; Nagy and Einwallner, 2018). Moreover, a long-term HFD induces metabolic disorders, oxidation, inflammation, changes in islet size, and irregular secretory functions in the pancreas (Wu et al., 2022; Zhao et al., 2022). Strong evidence supporting HFD as a valid methodology to reproduce the complications associated with T2DM is the fact that it induces telencephalic insulin resistance associated with systemic hyperglycaemia (Cefalu, 2006). This is often associated with a chronic hyperactivation of cortical and hippocampal neurons which may ultimately predispose toward cognitive impairments.

An alternative manipulation adopted to modulate metabolic functions capitalised upon psychosocial stress as a strategy to induce hyperglycaemia. Specifically, chronic psychosocial stress in mice has been reported to increase peripheral and central glucose concentrations and, subsequently, to relate to the emergence of stress-induced cognitive impairments (Van Der Kooij et al., 2018b). It has been suggested that psychosocial and metabolic stress share common underlying mechanisms with glucose dysregulation having a central role. These findings have been associated with the metabolic consequences of environmental stressors in our species, wherein chronic stressors, low socioeconomic status, severe mental health problems, or aggressive behaviour have been shown to increase the risk of T2DM (Hackett and Steptoe, 2016; Winchester et al., 2016). Accordingly, animal models have shown that exposure to experimental stressors may anticipate the onset of chronic subclinical inflammation (Black, 2003). Additionally, animal models that mimic T2DM and T2DM-related metabolic conditions suggest that insulin resistance may lead to chronic inflammation, which may in turn induce cognitive decline (Kelly and Ismail, 2015). It remains to be determined, however, whether central glucose dysregulation is linked to stress-induced cognitive impairments or whether abnormal glucose metabolism may contribute to individual susceptibility to the adverse consequences of chronic stress.

4.3. Genetic determinants of hyperglycaemia

Animal models with naturally occurring mutations have traditionally constituted a unique resource potentially mimicking the construct validity of the disease whereby: (i) they become spontaneously diabetic; and (ii) the course of the disease is markedly influenced by genetic background. The Lepr $^{db/db}$ mice represent one of the most widely studied genetically-induced experimental models of diabetes. They are homozygous for the spontaneous mutation of the leptin receptor (Lepr) that is involved in food intake, energy expenditure, and body weight (Berger et al., 2021). Mice carrying this spontaneous mutation exhibit obesity, chronic hyperglycaemia, pancreatic β-cell atrophy, and hypoinsulinemia. Mutations in leptin receptor have been shown to cause early-onset severe obesity and insulin resistance in mice and humans (Wang et al., 2014). While, in humans, it is difficult to disentangle whether insulin resistance precedes or is secondary to the development of obesity, in mice, the temporal association of these symptoms can be prospectively investigated. Studies conducted in Lepr $^{db/db}$ mice seem to suggest that the onset of insulin resistance anticipates the onset of obesity. Thus, Lepr $^{db/db}$ mice have a natural history of the disease similar to that observed in humans whereby they become hyperinsulinemic early in life (within 2 weeks of age, i.e. before consuming chow) and develop obesity by 3–4 weeks. Hyperglycaemia, associated with a β-cell failure, becomes manifest at age 4–8 weeks (Bates et al., 2005); this is followed by a compensatory hyperplasia of the islet of Langerhans which keeps being associated with hyperinsulinemia until the latest stages of life (18–20 months)("97 - B6 db Strain Details, 0006"). Another genetically engineered diabetic and obese model is the KKay mouse. This mouse was generated by transferring the Ay gene (conferring these mice an unusual yellow coat colour) onto a glucose-intolerant mouse strain (KK). While mice of the KK strain develop diabetes of polygenic origin, the Ay mutation leads to obesity as a function of the *agouti* protein being expressed in incorrect locations ("68 - Strain Details, 0024"). By approximately two months of age, due to insulin resistance, KKay mice develop the following diabetes-like abnormalities: hyperglycaemia, hyperinsulinemia, glucose intolerance, and obesity. The KKAy mice have excessively large pancreatic islets and degranulated pancreatic β-cells. Their obesity is partially due to fat cell hypertrophy, caused by a drop in dopamine and noradrenaline in the

hypothalamus ("The Characteristics of KKAy Mice - Maze Engineers"). Due to these features, these mice resemble both the early (β-cells impairment in the pancreas and hyperglycaemia) and the late stages of diabetes (β-cells can no longer release insulin and insulin replacement therapy is required).

The Akita strain ("48 - Akita Strain Details, 0035") constitutes an additional experimental model of spontaneous diabetes. These mice are characterised by a mutation at the level of the Ins2 gene, one of the two genes encoding for insulin in mice (the second one being Ins1). A mutation in the Ins2 gene leads to incorrect folding of the insulin protein, which in turn results in toxicity in pancreatic β-cells, reducing β-cell mass and insulin secretion. Heterozygous Ins2Akita mice develop insulin dependent diabetes, including hyperglycaemia, hypoinsulinemia, polydipsia, and polyuria within four weeks of age, thus representing a valid experimental model of T1DM. Just as in humans men are more often affected than women, so also in rodents diabetes-like abnormalities appear more frequent in males than in females (Tramunt et al., 2020). Accordingly, in Akita mice, the phenotype is more severe in males than females ("48 - Akita Strain Details, 0035").

Other authors engineered mouse models based on different components of the insulin signalling pathways. Specifically, Tanokashira and collaborators (Tanokashira et al., 2021) capitalised upon the role of the insulin receptor substrate-2 (Irs-2), which plays a fundamental role in metabolism and growth of every tissue. Irs2 knockout mice exhibit a progressive development of a T2DM-like phenotype: while they show hyperglycaemia as early as three days of age, they become diabetic by 10 weeks when they exhibit reduced β-cell mass and insulin resistance in skeletal muscle and liver ("21 - IRS-2 KO Strain Detail, 0044").

Diabetic rats also represent an important research tool. For example, the Zucker diabetic fatty rat (ZDF) is usually used as a model for the study of T2DM associated with obesity ("Zucker Rat/Charles River"). Like db/db mice, ZDF rats present a mutation on the leptin receptor, which induces obesity and hyperglycaemia within the first few months of age. The diabetic like features exhibited by ZDF rats appear to be associated with an inability to increase β-cell mass; this results in an insufficient insulin secretion, which ultimately fails to compensate for the obesity-dependent insulin resistance (Clark et al., 1983). Thus, although there are similarities between the human condition and the abnormalities exhibited by ZDF rats, the latter may be characterised by limited degree of construct validity whereby humans with T2DM do not have inadequate β-cell proliferation in early life (Garnett et al., 2005). The Goto-Katazaki (GK) (Guest, 2019) rat is another model used for the study of diabetes. The GK rat is non-obese, has a decreased β-cell mass, and is characterised by liver and skeletal muscle-insulin resistance. Due to impaired insulin secretion, fasting blood glucose concentrations are also slightly increased. Disease progression of this rat has been associated with chronic inflammation and hence utilized in the study of pathophysiology and therapeutic studies of diabetes (Xue et al., 2011). An excess adipose tissue is linked to chronic inflammation as a consequence of the attraction of macrophages in the adipose tissue. It is this increased macrophage infiltration that in part suggests a link between obesity, inflammation and the development of diabetes (Surmi and Hasty, 2008).

4.4. Hyperglycaemia as a comorbidity in experimental models of cognitive disturbances

While most of the reviewed studies exploited experimental models of metabolic disturbances induced via alterations at some level of the insulin signalling pathways, some others capitalised upon the known association between T2DM and cognitive impairments and late-onset AD (Hamzé et al., 2022; Kandimalla et al., 2017; Pardeshi et al., 2017; Watanabe et al., 2015). These pathologies have been reported to share several pathophysiological features and common risk factors (Devi et al., 2012; Niedowicz et al., 2014). In mice without pre-existing AD-like symptoms, the induction of diabetes (genetically, pharmacologically or by diet) is associated with an hyperphosphorylation of tau protein (Li et al., 2007; Son et al., 2012). Complementarily, some of the reviewed articles used transgenic mice with mutations linked to Alzheimer's disease such as APP/PS1 (Yeh et al., 2015), 3 ×Tg-AD (Huang et al., 2019) and PS19 (Nakaoku et al., 2019) and observed that they became hyperglycaemic.

Ultimately, although there is not a single animal model recapitulating all the causative factors and associated phenotypic abnormalities observed in our species, the comprehensive consideration of available literature strongly supports the notion that preclinical studies may beget relevant information in the understanding and therapy of insulin-related somatic and mental abnormalities.

4.5. Test paradigms to confirm the presence of hyperglycaemia in experimental models

In all of the screened studies, the presence of hyperglycaemia has been assessed via multiple methodologies that differed in terms of reference values, control groups, timing of evaluation, sample collection, and presence of fasting. Therefore, while these differential approaches captured a welcome heterogeneity in the study of complex phenomena, they nonetheless reduced the capability to cross compare different studies. Within this realm, some considerations may be sensible: for example, the use of the same approach to test blood glucose concentrations for both control and treated groups (e.g., either a non-fasting state or a fasting state) shall benefit this field of investigation; likewise, a clear definition of hyperglycaemia shall be useful. Indeed, while the threshold of hyperglycaemia in our review has not always been constant and unique, the spectrum of thresholds used is close to what happens in our species. Generally, the blood glucose concentration threshold was > 250 mg/dL in non-fasting conditions and > 150 mg/dL in fasting conditions. One important benefit of a standardized reference value is the fact that it may align and adjust the experimental techniques across laboratories thus favouring the reproducibility and external validity of these studies.

4.6. Test paradigms to confirm the presence of cognitive impairments in experimental models

A different consideration pertains to the test paradigms required to assess individual cognitive capabilities, for which different methodologies exist and that for which a univocal standard is neither feasible nor necessarily advisable. As mentioned above, the main aim of this review was to assess whether hyperglycaemic rodents exhibited alterations in working and spatial memory, and attention. Of these parameters, spatial memory has received the highest level of interest by this scientific community. This is substantiated by the fact that of the 91 studies, nearly all investigated this phenotype and all of them reported consistent impairments. It is important to emphasize that spatial memory has been addressed via different experimental paradigms (i.e. Morris water maze, Barnes maze, novel-object recognition, T- Y- and radial-arm-maze). The convergence of results adopting different methodologies, both in terms of inducing hyperglycaemia and the behavioural readout employed, strengthens the association between hyperglycaemia and spatial memory, whereby it has been observed under heterogeneous conditions (Richter et al., 2010). As discussed elsewhere, heterogenized experiments have been reported to yield more stable results and to be characterized by a reduced number of false positives compared to homogenized experiments (Macrì and Richter, 2015). These findings support the view that alternative experimental strategies may indeed enhance the reproducibility and translational value of preclinical animal research.

4.7. Insulin signalling and cognition: candidate biological determinants

As we reviewed, hyperglycaemia – as a proxy of insulin-related metabolic dysfunctions – led to consistent impairments in the cognitive domains of interest. There are strong preclinical, epidemiological and clinical evidence (Biessels et al., 2008; Rom et al., 2019; Van Den Berg et al., 2010; Zhang et al., 2021) in support of the association between diabetes and cognitive dysfunctions, which may concern one or different domains, including processing speed, executive function, learning and memory (Arnoriaga-Rodríguez et al., 2020; Backeström et al., 2021; Omladič et al., 2020; Sadanand et al., 2016; Sattar et al., 2017). Diabetes can be viewed as a metabolic disorder resulting in accelerated cognitive ageing in terms of dementia and cognitive decline. Ultimately, diabetes-related cognitive impairments may be viewed as another long-term complication of diabetes. There is also evidence suggesting that hyperglycaemia per se has detrimental effects on cognitive function, whereby acute hyperglycaemia has been associated with poor cognitive outcomes, potentially as a function of accumulation of reactive oxygen species in the brain.

People with long-standing diabetes and no other diagnosed diabetes-related complications have poorer working memory (Awad et al., 2017; Gallardo-Moreno et al., 2022). This finding has been related to the fact that hyperglycaemia per se may induce structural abnormalities in the prefrontal cortex (Lyoo et al., 2013), a brain region involved in working memory. Additionally, hyperglycaemia has been associated with changes in different regions of the brain, including the hippocampus (Nevo-Shenker and Shalitin, 2021). Accordingly, hyperglycaemia, in young patients with T1DM, has been shown to influence long-delay spatial memory months after that first diagnosis (Semenkovich et al., 2016). Likewise, changes in hippocampal synaptic plasticity and subsequent impairments in spatial memory, are well documented in animal models of T1DM and T2DM (Soares et al., 2013). Whereas numerous clinical studies (Broadley et al., 2017; Pappas et al., 2019; Redondo et al., 2016; Sattar et al., 2017; Zhao et al., 2020) have demonstrated a correlation between executive functions and diabetes, only in two articles of the present review has this domain been investigated. Thus, further preclinical studies are needed to elucidate the mechanism underlying the association between diabetes and executive function.

A number of possible mechanisms to explain the association between dysglycaemia, hyperglycaemia and cognitive dysfunction have been suggested. As reported above, one hypothesis is that chronic exposure to elevated glucose concentrations may accelerate cognitive decline (Awad et al., 2004; Messier et al., 2011). Moreover, impaired insulin signalling in the brain may represent a highly promising research avenue. Specifically, while having an important function in glucose transport, the highly abundant insulin receptors in the brain have been implicated in cognitive processes. Several observations suggest that cognitive decline is a consequence of insufficient insulin action in the brain, either due to insulin resistance, insulin deficiency or both. Insulin signalling in the brain has important roles in brain physiology and cognition (Biessels and Reagan, 2015).

4.8. Caveats associated with risk of bias

In order to evaluate the degree of confidence with which the conclusions of our work can be extrapolated on a large scale, we carefully assessed the RoB associated with several methodological aspects. Had we identified a widespread elevated RoB, our considerations would be substantially devalued. Yet, the elevated RoB was observed only in a fraction of the domains relevant to the scopes of our review (detailed in the following lines). Specifically, according to SYRCLE's protocol, the overall high RoB identified in the studies considered in the present review was 5.27%. This value was computed as the average of the instances (percent) in which we identified an elevated RoB for a given category. In particular, we observed instances of elevated RoB in the following items: (1) "Baseline characteristics": while we considered hyperglycaemia as a baseline value of interest, two articles of the review did not explicitly report whether this prerequisite had been met but rather referred to the already available evidence that the animal model of interest was characterised by hyperglycaemia; (2) "Performance bias: blinding" and "Detection bias: blinding": in few instances we observed that blinding could not be guaranteed whereby the individual who planned the study also performed the experiments and analysed the data; (3) "Attrition bias: incomplete outcome data": with respect to this item, we observed that few studies failed to report in the analysis all the experimental subjects used in the experiment without providing an explicit explanation for these attrition rates; (4) "Other source of bias": we took into account studies in which the solution administered to the control group (vehicle) was not specified; (5) "Reporting bias": with respect to this parameter, we attempted to identify whether the experiments reported in the published experiments matched those that were officially planned/registered. In this specific case, the analysis was limited to the articles published after 2021, when the Animal Study Registry (Olevska et al., 2021) a platform wherein animal studies can be registered) has been launched. We note, however, that this parameter is difficult to assess whereby protocols for animal studies are not yet mandatorily registered in central, publicly accessible database (Olevska et al., 2021). As a consequence, be it due to the absence of enforcement and/or limited availability of repositories, none of the studies considered in the present review had been previously registered. We believe that this aspect warrants particular consideration by the preclinical scientific community. As a matter of fact, while on the one hand we deem this aspect sufficiently relevant to be included in the SYRCLE's protocol, on the other hand, we apparently have limited interest and tools to implement it on a large scale.

An additional warning to our community can also be derived from the unclear overall risk of bias, which in the present review attained a value of 52.09%. While an unclear risk of bias does not directly denote inappropriate study planning/execution/reporting, it nonetheless hinders the possibility to thoroughly grasp its fundamental details, especially in light of the current reproducibility crisis. We posit that the reporting of methodological details in animal studies shall considerably improve, and that the promotion of high-quality standards for registration and reporting of animal studies shall represent a desired goal in preclinical research.

5. Conclusions

Our systematic review strongly supports the view that hyperglycaemia in experimental models of metabolic dysfunctions is associated with cognitive impairments. It is thus plausible that hyperglycaemia, as a core feature of diabetes, disturbing insulin signalling and favouring insulin resistance, not only affects systemic metabolism, but also directly impacts the brain, by disturbing cerebral insulin pathways and the associated cognitive functions. Complementarily, although this was not the core aim of our study, hyperglycaemia has been observed in experimental subjects that were originally selected based on their known cognitive impairments and not on their metabolism. Therefore, just as hyperglycaemia may constitute a risk factor for cognitive impairments, so also the latter can influence the former, ultimately binding diabetes and cognition in a recurrent cycle.

Acknowledgements

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 847879 (to SM, DS, AOL and JG) and from Regione Lazio (grant agreement POR FESR Lazio 2014–2020, ID code G08487 to SM).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2023.105435.

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