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The relationship between oxytocin, dietary intake and feeding: A systematic review and meta-analysis of studies in mice and rats

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ABSTRACT

The neuropeptide oxytocin has been associated with food intake and feeding behaviour. This systematic review aimed to investigate the impact of oxytocin on dietary intake and feeding behaviour in rodent studies. Six electronic databases were searched to identify published studies to April 2018. Preclinical studies in mice and rats were included if they reported: (1) a dietary measure (i.e. food or nutrient and/or behaviour (2) an oxytocin measure, and (3) relationship between the two measures. A total of 75 articles (n = 246 experiments) were included, and study quality appraised. The majority of studies were carried out in males (87%). The top three oxytocin outcomes assessed were: exogenous oxytocin administration (n = 126), oxytocin-receptor antagonist administration (n = 46) and oxytocin gene deletion (n = 29). Meta-analysis of exogenous studies in mice (3 studies, n = 43 comparisons) and rats (n = 8 studies, n = 82 comparisons) showed an overall decrease in food intake with maximum effect shown at 2 h post-administration.

1. Introduction

Oxytocin is best characterised for its role in parturition, the milk-let down reflex and social bonding (Lee et al., 2009). However, there is now significant literature supporting a role for oxytocin in other central nervous system and peripheral functions outside of these classically recognised roles. For example, oxytocin has been implicated in the regulation of a number of behaviours that are known to alter eating behaviours including anxiety, stress and social interaction (Neumann and Slattery, 2016; Heinrichs et al., 2009; Windle et al., 2004). These actions have been highlighted by investigations into the possible therapeutic role of oxytocin in several neuropsychiatric disorders including substance use disorders, and mental health disorders (Buisman-Pijlman et al., 2014; Sarnyai, 2011). Interestingly, a role for oxytocin in food intake and feeding behaviour has also been suggested.

Oxytocin is a nine amino neuropeptide and hormone that is produced primarily in the paraventricular and supraoptic nuclei of the hypothalamus (Lee et al., 2009). For its peripheral functions, oxytocin is released into the systemic bloodstream via the posterior pituitary gland whereby it travels to peripheral targets (e.g. uterus, gastrointestinal tract), or released from axon or dendritic terminals in specific brain regions (Lee et al., 2009; Lawson, 2017). Interestingly, oxytocin receptor expression is high in brain regions involved in the regulation of food intake and energy metabolism, including the hypothalamus (e.g. ventromedial hypothalamus), nucleus accumbens, amygdala, ventral tegmental area, frontal cortex, insula, and the hindbrain (nucleus tractus solitarius) (Lawson, 2017; Blevins and Ho, 2013).

The past decade has seen a significant number of preclinical investigations examining the effects of oxytocin on feeding behaviour in laboratory animals. Rodent studies, particularly in mice and rats, have shown that oxytocin can function as an anorexigenic hormone with both central (i.e. intracranial) and peripheral oxytocin administration reducing food consumption, as well as sucrose (Sinclair et al., 2015; Zhou et al., 2015) and artificial sugar (i.e. saccharin) (Herisson et al., 2016) intake. Oxytocin also reduces alcohol intake (King et al., 2017) which has high caloric value. Further, oxytocin has been shown to influence the motivation to consume food, even under a state of satiety (Arletti et al., 1989, 1990; Benelli et al., 1991; Blevins et al., 2016), and

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oxytocin knockout mice show an increased preference for sucrose (Amico et al., 2005; Sclafani et al., 2007), saccharin (Billings et al., 2006), and sodium compared to wild-type controls (Amico et al., 2001; Puryear et al., 2001). In fact deletion of the genes encoding oxytocin or oxytocin receptor in mice promotes weight gain, late onset obesity and/or dysregulated glucose regulation (Camerino, 2009; Takayanagi et al., 2008; Kasahara et al., 2007).

These findings in animals are only just beginning to be translated into clinical research in humans. With respect to human studies, in a recent systematic review by our group (n = 26 studies) we reported that exogenous oxytocin generally has an anorexigenic effect in healthy individuals (Skinner et al., 2018). For example, intranasal oxytocin administration significantly reduced food intake and improved eating attitudes after a single dose (Skinner et al., 2018). Furthermore, exogenous oxytocin was associated with improved cognitive control of food craving, decreased approach bias towards highly palatable foods, and a reduction in hunger-driven and reward-driven food consumption (Skinner et al., 2018). Interestingly however, there was no significant change in endogenous oxytocin levels following the consumption of a test meal (e.g. high fat meal, alcoholic beverage) or after following a prescribed dietary regime for several days (e.g. high or low sodium diet) (Skinner et al., 2018). Importantly the specific central and peripheral site(s) of actions through which oxytocin mediates these modulatory effects on food intake remains unclear.

The data in humans suggest that exogenous oxytocin administration may have relevance for the therapeutic control of food intake in vulnerable individuals to reduce overeating. Therefore, we considered it important to review and assess the collective outcomes of preclinical studies in mice and rats to help inform avenues for future research in human interventions studies. Accordingly, the primary aim of this review was to investigate the impact of oxytocin function on dietary intake and feeding behaviour in rodent studies. A secondary aim was to conduct a meta-analysis of studies investigating the effects of exogenously administered oxytocin on food or nutrient intakes.

2. Methods

2.1. Search strategy

A systematic search of six electronic databases; Cochrane, CINAHL (The Cumulative Index to Nursing and Allied Health Literature), MEDLINE (Medical Literature Analysis and Retrieval System Online), EMBASE (Excerpta Medica Database), Scopus and Web of Science; was performed. Collectively these databases report that they reliably index records, from 1970 onwards. Therefore, the search was limited to articles published in English from 1970 to April 2018. The key search words and terms are available through Supplementary Material. Additionally, to ensure no relevant studies were missed a manual search of the reference lists of included studies and relevant publications was conducted.

2.2. Study criteria

Preclinical studies in mice and rats ($\geq$6 weeks of age) were included if they met the following inclusion criteria: (1) an outcome measure related to dietary intake (i.e. food or nutrient; including alcohol, an energy producing macronutrient which contributes to dietary energy intake) and/or behaviour (e.g. meal consumption patterns), (2) an outcome measure of oxytocin, and (3) the relationship between the two measures. Reasons for study exclusion were: studies with a non-experimental design; studies conducted in humans or animals other than mice or rats; studies focusing on pregnant or lactating female rodents; animal models with naturally occurring or artificially induced health conditions/diseases known to alter oxytocin function (e.g. pituitary gland disorders); experiments where dietary behaviours were artificially induced (e.g. treatment with angiotensin or furosemide to induce salt appetite; treatment with phenylpropanolamine to induce anorexia, use of gavages in anaesthetised rodents); and experiments using combined treatment interventions (e.g. oxytocin + leptin; oxytocin + cholecystokinin). To maintain homogeneity of the outcomes, studies examining metabolic parameters (e.g. energy expenditure) were not included in the present review. The review methodology was prospectively registered in International prospective register of systematic reviews (PROSPERO, Registration number: CRD42016053015) and follows Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2015).

2.3. Study selection

After the removal of duplicates, studies conducted in humans and those focusing on pregnant or lactating female rodents were excluded (JS). The identified studies were initially screened based on their title and abstracts by two independent reviewers (JS and EJC). Full text articles were then assessed for eligibility (JS, EJC and TB) with discrepancies decided by discussion using a third reviewer (CD or TB). Consensus was reached for all included studies.

2.4. Data extraction

Studies were initially categorised by the oxytocin outcome measure. Data extraction was performed by one author (JS), using a standardised table developed for this review (Supplentary material: Tables 1–7), and cross checked independently by one other author (EJC). The extraction tool was pilot tested on six randomly selected included studies and refined by author consensus to ensure all relevant data was being captured. For studies where outcome data was not reported numerically, and instead displayed graphically, graphs were exported to an online web digitiser program (WebPlotDigitizer, (Rohatgi, 2017) available from http://arohatgi.info/WebPlotDigitizer/) to obtain mean and standard deviation (SD) or standard error of the mean (SEM). This was completed for seven exogenous studies (full details in Supplementary Material). Previously published literature has shown the WebPlotDigitizer is an effective method to collect data with high levels of intercoder reliability and validity (Drevon et al., 2016).

2.5. Data synthesis and meta-analysis

Results of the systematic review are presented in as a narrative analysis to describe the included studies. For a more rigorous analysis of experiments administering exogenous oxytocin a meta-analysis was conducted. Specific principals which have been previously published for meta-analysis (Vesterinen et al., 2014) in pre-clinical studies were followed, including using the lowest value where a range of animals was reported for a group. For studies reporting food intake (grams) as an outcome at time points following oxytocin administration, oxytocin dose and the administration site, meta-analyses was performed with R statistical software (R: A language and environment for statistical computing, 2018) using the meta for package (Viechtbauer, 2010) (Version r x 64 3.5.1) and completed separately for mice and rats. For each study, an effect size (Hedge's g, which includes a correction factor for small sample size bias) and corresponding 95% confidence intervals were calculated as the standardized mean difference between the two treatment conditions (oxytocin and vehicle). To account for multiple measures per study a series of multilevel models were investigated with nested random effects for study, administration site (central or peripheral), dose (because this could not be reliably converted into standardised concentrations) and time, using REML estimation. Two fixed effect moderator variables, administration site (central or peripheral), and time (as a categorical variable, and also treated as continuous, in separate models), were included with the random effects above to form a mixed effects meta-regression models. Model comparisons using Likelihood Ratio Tests were used to determine if random effects were

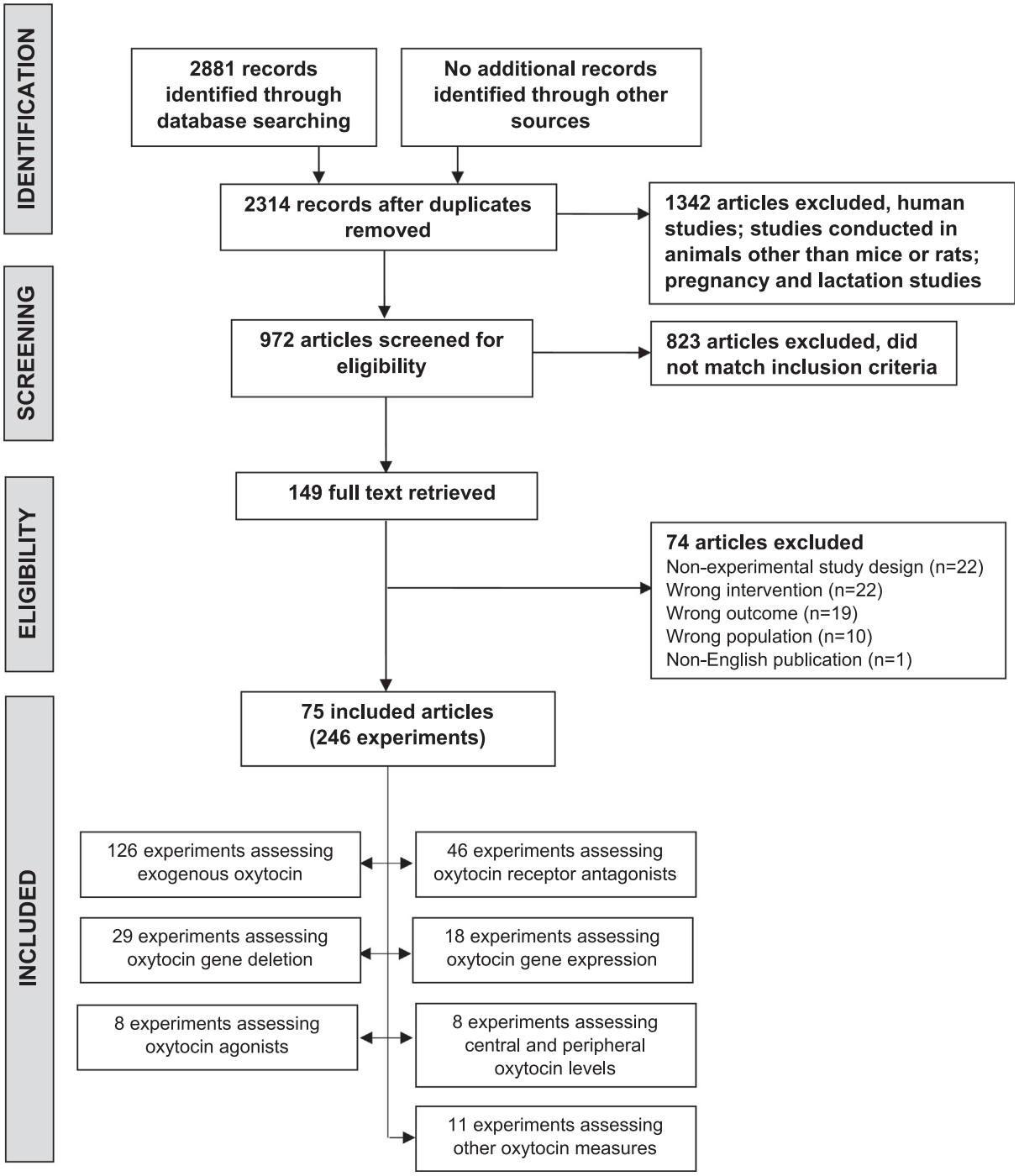

Fig. 1. Flow diagram of article identification retrieval and inclusion for this systematic review.

significant and if not important the models were simplified by removing them. Residual plots were used to examine homogeneity of variance and normality. To assess for publication bias, funnel plots were produced and visually inspected. [Dataset and R script are available in Supplementary Material].

2.6. Quality of evidence

The quality of the included studies was reviewed independently by two authors (JS and EJC) using the SYRCLE risk of bias tool, scoring internal and external validity for each study (Hooijmans et al., 2014). The tool has ten domains, and for each domain studies were rated as either "yes" indicating a low risk of bias; "no" indicating a high risk of bias; or "unclear" if insufficient details had been reported. No studies were excluded based on quality ratings.

3. Results

3.1. Description of studies

The search strategy, summarised in Fig. 1, identified 2314 potentially eligible articles after exclusion of duplicates. After the removal of studies not meeting the inclusion criteria, the search strategy yielded 972 articles for screening. No additional articles were identified in the reference search. Initial screening of title and abstracts identified 149 articles that received a detailed assessment of the full text articles. A

total of 74 studies were excluded, the major reasons for exclusion were: non-experimental study design (n = 22) and wrong intervention (n = 22). A total of 75 articles (n = 246 experiments) are presented in the current review.

3.2. Study characteristics

A total of 246 experiments were performed in mice (n = 93) and rats (n = 153), between 1989 and 2018 (Supplementary material: Tables 1–7). Experimental sample sizes ranged from 4 to 108. The exact number of rodents was not specified in 38 experiments (Zhou et al., 2015; Herisson et al., 2016; Takayanagi et al., 2008; Arletti et al., 1990; Benelli et al., 1991; Blevins et al., 2016; Altirriba et al., 2014; Baskin et al., 2010; Herisson et al., 2014; Ho et al., 2014; Maejima et al., 2015; Morton et al., 2012; Olszewski et al., 2014; Peters et al., 2012; Suyama et al., 2016; Uchoa et al., 2009; Burlet et al., 1992; Rinaman and Rothe, 2002; Zhang and Cai, 2011; Noble et al., 2014), but rather given as a range. Sample sizes were not reported in four experiments (Ho et al., 2014; MacFadyen et al., 2016; Olszewski et al., 2010). Two hundred and fourteen (87%) of the included experiments were performed in males exclusively, 19 in females exclusively and 13 in both males and female rodents. Experiments were conducted in 16 different countries, with the majority performed in USA (45%), followed by New Zealand (24%) and Sweden (8%). Most experiments (n = 174) were conducted under a 12:12 light/dark cycle and 72 experiments (Blevins et al., 2016; Peters et al., 2012; Rinaman and Rothe, 2002; Noble et al., 2014; MacFadyen et al., 2016; Zhou et al., 2015; Herisson et al., 2016; King et al., 2017; Baskin et al., 2010; Herisson et al., 2014; Ho et al., 2014; Maejima et al., 2015; Morton et al., 2012; Bjorkstrand and Uvnas-Moberg, 1996; Iwasaki et al., 2014; Maejima et al., 2014; Cox et al., 2013; Bjorkstrand and Eriksson, 1992; Ryan et al., 2017; Maejima et al., 2011; Ong et al., 2017; Roberts et al., 2017; Maejima et al., 2017) performed dietary intake measurements solely during the dark phase (i.e. the time of day a rodent would typically consume food). Short-term (≤ 24 h) test durations (n = 144) ranged from 10 min to 24 h (median 120 min) and longer term (> 24 h) durations (n = 102) ranged from 42 h to 10 months (median 7 days). Test durations in 20% of experiments lasted longer than five days. During experimentation, the majority of animals were individually housed (n = 218) except for 15 experiments, where animals were housed in pairs (n = 3 experiments, employed a social context design) (Herisson et al., 2016; Olszewski et al., 2010; Balazova et al., 2016; Hartley et al., 2003; Olszewski et al., 2015) or 4–6 per cage. (Bjorkstrand and Eriksson, 1992; Uvnas-Moberg et al., 1996; Verty et al., 2004) Details of housing numbers were not reported for 20 experiments (Sinclair et al., 2015; Camerino, 2009; Altirriba et al., 2014; Maejima et al., 2011; Ong et al., 2017; Maejima et al., 2017; Lokrantz et al., 1997).

3.3. Oxytocin measures

Various oxytocin measures were used and experiments were subsequently grouped into one of the following seven categories for analysis: (1) exogenous oxytocin administration (n = 125 Altirriba et al., 2014; Peters et al., 2012; Maejima et al., 2011; 2017; Balazova et al., 2016; Sinclair et al., 2015; Zhou et al., 2015; Herisson et al., 2016; Arletti et al., 1989, 1990; Benelli et al., 1991; Blevins et al., 2016; Ho et al., 2014; Maejima et al., 2015; Morton et al., 2012; Zhang and Cai, 2011; Noble et al., 2014; MacFadyen et al., 2016; Bjorkstrand and Uvnas-Moberg, 1996; Iwasaki et al., 2014; Maejima et al., 2014; Cox et al., 2013; Uvnas-Moberg et al., 1996; Verty et al., 2004; Lokrantz et al., 1997; Bernal et al., 2007, 2010a, 2010b; Diaz-Cabiale et al., 2000; Ibragimov et al., 1988; Olson et al., 1991a; Mullis et al., 2013; Peters et al., 2017; Klockars et al., 2017a, 2018, 2017b); (2) oxytocin receptor antagonist administration (n = 46 Herisson et al., 2016; Arletti et al., 1989, 1990; Olszewski et al., 2014; Uchoa et al., 2009; Rinaman and Rothe, 2002; Zhang and Cai, 2011; Olszewski et al., 2010, 2015; Uvnas-Moberg et al., 1996; Lokrantz et al., 1997; Olson et al., 1991a; Mullis et al., 2013; Olson et al., 1991b; Baskin et al., 2010; Herisson et al., 2014; Ho et al., 2014); (3) oxytocin gene deletion (n = 29 Amico et al., 2005; Sclafani et al., 2007; Billings et al., 2006; Amico et al., 2001; Puryear et al., 2001; Camerino, 2009; Takayanagi et al., 2008; Rinaman et al., 2005; Miedlar et al., 2007; Amico et al., 2003; Vollmer et al., 2006; Vollmer et al., 2013); (4) oxytocin gene expression (n = 19 Herisson et al., 2016, 2014; Suyama et al., 2016; Uchoa et al., 2009; Olszewski et al., 2010, 2015; Klockars et al., 2018, 2017; Duncko et al., 2003; Mitra et al., 2010; Olszewski et al., 2009; Pirnik et al., 2012; Greenwood et al., 2015; Silva et al., 2002; Hume et al., 2017); (5) oxytocin agonist administration (n = 8 Olszewski et al., 2014; Olson et al., 1991a); (6) central (n = 1) (Burlet et al., 1992) and peripheral oxytocin concentrations (n = 7 Blevins et al., 2016; Morton et al., 2012; Zhang and Cai, 2011; Hartley et al., 2003; Greenwood et al., 2015; Morris et al., 1995); and (7) other oxytocin measures (oxytocin receptor overexpression, n = 2 Bahi et al., 2016); oxytocin receptor knockdown, n = 3 (Ong et al., 2017); oxytocin receptor neuron activation, n = 4 (Ryan et al., 2017); oxytocin neuron lesions, n = 1 (Wu et al., 2012); and oxytocin antisense, n = 1 (Morris et al., 1995).

3.4. Dietary characteristics

Dietary characteristics examined in relation to oxytocin measures, in descending order, included the intake (measured as grams, g/kg, mL or kcal) of and/or exposure to: overall food intake (n = 92 Herisson et al., 2016; Camerino, 2009; Takayanagi et al., 2008; Altirriba et al., 2014; Baskin et al., 2010; Uchoa et al., 2009; Maejima et al., 2017; Balazova et al., 2016; Uvnas-Moberg et al., 1996; Verty et al., 2004; Wu et al., 2012; Huang et al., 1996; Arletti et al., 1989, 1990; Benelli et al., 1991; Blevins et al., 2016; Ho et al., 2014; Maejima et al., 2015; Morton et al., 2012; Rinaman and Rothe, 2002; Zhang and Cai, 2011; Noble et al., 2014; Olszewski et al., 2010; Bjorkstrand and Uvnas-Moberg, 1996; Iwasaki et al., 2014; Maejima et al., 2014; Ryan et al., 2017; Maejima et al., 2011; Ong et al., 2017; Bernal et al., 2007, 2010a, 2010b; Diaz-Cabiale et al., 2000; Ibragimov et al., 1988; Olson et al., 1991a; Klockars et al., 2017a, 2018, 2017b; Olson et al., 1991b; Rinaman et al., 2005), carbohydrates (n = 45; sucrose, Amico et al., 2005; Sclafani et al., 2007; Herisson et al., 2014; Olszewski et al., 2010, 2015; Mullis et al., 2013; Miedlar et al., 2007; Hume et al., 2017; Sinclair et al., 2015; Zhou et al., 2015; Herisson et al., 2016; King et al., 2017; Klockars et al., 2017a, 2018, 2017b; Duncko et al., 2003; Mitra et al., 2010; Olszewski et al., 2009) glucose, (Herisson et al., 2014; Lokrantz et al., 1997) fructose, (Herisson et al., 2014) polycose, (Sclafani et al., 2007; Herisson et al., 2014) and cornstarch (Sclafani et al., 2007; Herisson et al., 2014), high fat diet (n = 32 Blevins et al., 2016; Morton et al., 2012; Zhang and Cai, 2011; Maejima et al., 2011; Roberts et al., 2017; Maejima et al., 2017; Klockars et al., 2017; Pirnik et al., 2012), sodium (n = 16 Amico et al., 2001; Puryear et al., 2001; Ryan et al., 2017; Bernal et al., 2007; Greenwood et al., 2015; Morris et al., 1995; Amico et al., 2003; Vollmer et al., 2006, 2013), non-carbohydrate sweetener (saccharin, n = 20 Herisson et al., 2016; Blevins et al., 2016; Billings et al., 2006; Herisson et al., 2014; MacFadyen et al., 2016; Klockars et al., 2017a, 2018, 2017b), alcohol (n = 14 (King et al., 2017; Peters et al., 2012; MacFadyen et al., 2016; Peters et al., 2017; Silva et al., 2002; Bahi et al., 2016), Intralipid emulsion, n = 2 (Olszewski et al., 2010; Miedlar et al., 2007), palatable solution [i.e. high in sodium and fat (n = 1 Vollmer et al., 2013)], liquid only diet (Ensure nutrition drink, n = 1 Ryan et al., 2017), and soya isoflavones (n = 1 Hartley et al., 2003). Dietary behaviours examined in relation to oxytocin measures included: meal durations or time spent feeding (n = 9 Ong et al., 2017; Olson et al., 1991a; Arletti et al., 1989, 1990; Benelli et al., 1991; Blevins et al., 2016), latency to first meal (n = 7 Arletti et al., 1989, 1990; Benelli et al., 1991; Blevins et al., 2016), nutrient/taste preferences (n = 3 Sinclair et al., 2015; Sclafani et al., 2007; Bahi et al., 2016), food/sucrose reinforced classical and operant

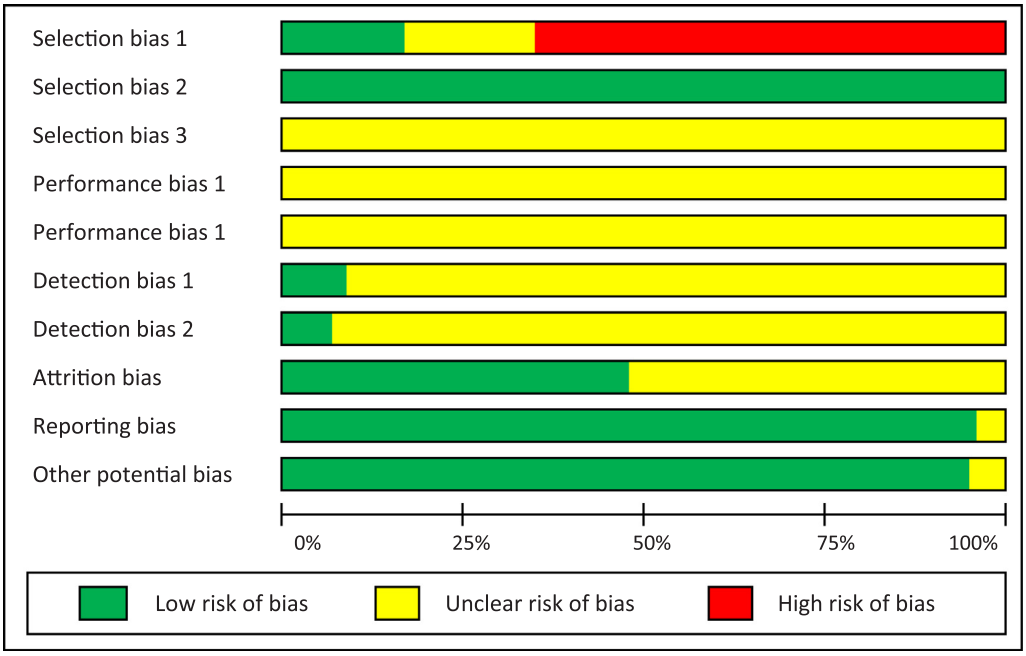

Fig. 2. Risk of bias assessment of the 75 studies included in this systematic review. For each domain, studies were rated as either "yes" indicating a low risk of bias; "no" indicating a high risk of bias; or "unclear" if insufficient details had been reported.

conditioning (n = 7 Zhou et al., 2015; Cox et al., 2013; Ibragimov et al., 1988), food/sucrose intake in familiar vs. social settings and novel environments (n = 9 Herisson et al., 2016; Olszewski et al., 2014, 2015), food deprivation (n = 8 Bjorkstrand and Eriksson, 1992; Klockars et al., 2017) and fasted vs refed states (n = 4 Suyama et al., 2016; Uchoa et al., 2009; Burlet et al., 1992). In nine experiments, conditioned taste aversion and kaolin consumption were used to evaluate any potential aversive drug effects (e.g. nausea, malaise and concomitant anorexia) associated with oxytocin administration (Herisson et al., 2016; Blevins et al., 2016; Noble et al., 2014; Iwasaki et al., 2014; Roberts et al., 2017; Klockars et al., 2017a, 2018) Across all the included studies the most common secondary outcome measures examined were, in descending order, body weight (n = 40), appetite hormones and blood parameters (n = 13), water intake (n = 8), natriuresis and osmolality and (n = 7), locomotor activity (n = 7) and grooming behaviour (n = 3).

3.5. Quality of the included studies

Risk of bias evaluation of the 75 included articles in this review is reported in Fig. 2 (full details in Supplementary Material). For three of the 10 domains (i.e. selection bias 2, reporting bias and other biases) the quality of the included articles were assessed as having a low risk of bias for the majority of articles (97%). For five domains, the overall quality of the included articles (97%) were assessed as having an unclear risk of bias due to the lack of detailed information regarding allocation concealment, random housing, blinding of assessors to interventions and outcomes. There was an unclear risk of attrition bias in 52% of studies with the number of animals not accounted for both before and after experimentation. In 65% of studies, animals were not randomly allocated to the experimental and control groups (i.e. absence of sequence generation) indicating a high risk of selection bias. Baseline characteristics of animals were comparable between experimental and control groups in all studies.

3.6. Studies assessing the effect of exogenous oxytocin administration on dietary intake and behaviour

The majority of experiments included in this review reported the effects of exogenous oxytocin administration on dietary intake (n = 114) and behaviour (n = 19). Ninety-one were performed in rats and 34 in mice. The most frequent strain of rodent used was Sprague-Dawley rats (n = 71 experiments) and C57BL/6 mice or C57BL/6 substrains (n = 32 experiments). In 30 experiments, rodent models with the following pre-existing traits were included: diet-induced obese (DIO) mice/rats (n = 25), (Blevins et al., 2016; Morton et al., 2012; Zhang and Cai, 2011; Maejima et al., 2011; Roberts et al., 2017; Maejima et al., 2017) diabetic and leptin resistant mice with (n = 1, B6.V-Lepob/JRj mice Altirriba et al., 2014) and without obesity (n = 2, BKS db/db mice Iwasaki et al., 2014), obese rats with defective leptin signalling (n = 1, Zucker rats Balazova et al., 2016); n = 1, Koletsky rats (Morton et al., 2012) and rapidly growing rats (n = 1) (Uvnas-Moberg et al., 1996). Sample sizes ranged from 6 to 108, and 20% of experiments utilised a cross-over design. Experimental durations ranged from 1 h to 28 days. Administration route, site, and dose of oxytocin are reported in Table 1. Injections and intranasal oxytocin administration occurred up to 120 min prior to feeding, and post-treatment dietary measurements ranged from 0.5 to 24 h. Measurements of dietary intake/behaviour while rodents were receiving central or peripheral infusions of oxytocin ranged from 2 h to 28 days. The majority of experiments (n = 115) administered saline as the control or vehicle dose, six used artificial cerebrospinal fluid (aCSF) (Zhang and Cai, 2011; Noble et al., 2014; Olson et al., 1991a), three used distilled water (Bernal et al., 2007, 2010a, 2010b) and in one experiment (Zhou et al., 2015) the type of vehicle used was not reported.

Centrally and peripherally administered oxytocin (n = 52 experiments) was found to have no significant effect on food intake (standard chow) in 11 experiments (Bjorkstrand and Uvnas-Moberg, 1996; Maejima et al., 2017; Bernal et al., 2007, 2010a, 2010b; Diaz-Cabiale et al., 2000), but significantly reduced overall intake of standard chow in the majority of studies (n = 37 experiments Herisson et al., 2016; Altirriba et al., 2014; Zhang and Cai, 2011; Noble et al., 2014; Iwasaki et al., 2014; Maejima et al., 2014; Balazova et al., 2016; Uvnas-Moberg et al., 1996; Verty et al., 2004; Olson et al., 1991a; Arletti et al., 1989, 1990; Benelli et al., 1991; Blevins et al., 2016; Ho et al., 2014; Maejima et al., 2015; Morton et al., 2012; Klockars et al., 2017a, 2018, 2017b). Six experiments reported decreases in food intake (standard chow) ranging from 19 to 66% in the 1–18 h post-administration period,

Table 1
Experimental route, site, and dose of exogenous oxytocin administration.

Route and site of administration	Number of experiments	Dosage ranges
Infusions		
Peripheral	13 (Blevins et al., 2016; Altirriba et al., 2014; Iwasaki et al., 2014; Maejima et al., 2011, 2017; Balazova et al., 2016)	36–1600 μg/kg/day, or 5–50 nmol/day
Intracranial (third or fourth ventricle)	12 (Blevins et al., 2016; Roberts et al., 2017)	16–200 nmol/day
Peripheral injections		
Intraperitoneal	37 (Sinclair et al., 2015; Zhou et al., 2015; King et al., 2017; Arletti et al., 1989, 1990; Benelli et al., 1991; Ho et al., 2014; Maejima et al., 2015; Morton et al., 2012; Peters et al., 2012; Zhang and Cai, 2011; MacFadyen et al., 2016; Bjorkstrand and Uvnas-Moberg, 1996; Iwasaki et al., 2014; Cox et al., 2013; Maejima et al., 2011; Ibragimov et al., 1988)	~17–10,000 μg/kg, or ~22.5–1200 mU/kg
Subcutaneous	8 (Maejima et al., 2011; Uvnas-Moberg et al., 1996; Bernal et al., 2007; Bernal et al., 2010a, 2010b)	1.0 mg/kg, or 0.5 mL × 11 to 22 μg, or 0.5 mL × 5–10 IU/mL, or 1600 μg/kg
Intravenous	10 (Klockars et al., 2017a)	0.03–0.3 μg/kg
Intracranial injections		
Lateral ventricle	15 (Arletti et al., 1989, 1990; Benelli et al., 1991; Peters et al., 2012; Bjorkstrand and Uvnas-Moberg, 1996; Maejima et al., 2014; Verty et al., 2004; Lokrantz et al., 1997; Diaz-Cabiale et al., 2000; Morton et al., 2012; Olson et al., 1991a; Peters et al., 2017)	1.0–10.0 μg, or 0.5 μg/2 L, or 1.0 μg/5 L, or 0.1–10.0 IU, or 0.5–20 nmol, or 0.4 nmol/0.5 μl
Third ventricle	2 (Morton et al., 2012; Zhang and Cai, 2011)	1.0 μl
Nucleus accumbens (core or shell)	5 (Herisson et al., 2016)	0.03–3.0 μg
Ventromedial hypothalamic nucleus	9 (Noble et al., 2014; Klockars et al., 2017b)	0.1–1.0 nmol, or 0.3–1.0 μg
Ventral tegmental area	1 (Mullis et al., 2013)	0.3–1.0μg
Arcuate nucleus	1 (Maejima et al., 2014)	0.4 nmol/0.5 μl
Basolateral or central nuclei of amygdala	7 (Klockars et al., 2018)	0.1–1.0 μg
Topical		
Intranasal	1 (Maejima et al., 2015)	0.1–10 μg/10 μl

(Herisson et al., 2016; Benelli et al., 1991; Morton et al., 2012; Noble et al., 2014) with greater reductions reported within the first hour (50–66% Benelli et al., 1991; Noble et al., 2014). In contrast, Bjorkstrand and Uvnas-Moberg (1996) found in four experiments that oxytocin treated rats ate significantly more standard chow than saline treated rats. Altirriba et al. (2014) found during their 14 day trial in obese (diabetic and leptin resistant) and lean mice that the effects of chronic subcutaneous (SC) infusion of oxytocin on reducing intake of (standard chow) was only significant on day 1 in lean mice. Whereas, in obese mice maintained on the same standard chow diet as their lean counterparts, effects were sustained for 14 days with more marked effects during the first week (Altirriba et al., 2014). Similarly, Roberts et al. (2017) found chronic 3 V oxytocin administration in mice and rats, and 4 V administration in rats, produced no sustained effect on energy intake in chow fed lean rodents, but produced a sustained effect on the of reduction of food intake (~2–3 weeks) in high fat diet-fed DIO mice and rats. Blevins et al. (2016) and Maejima et al. (2011) reported reductions in food intake in DIO rats during the chronic treatment period were largely transient. Zhang and Cai (2011) found in DIO mice, twice daily (AM vs. PM) central injections of oxytocin significantly decreased both daytime and night-time food intake (high fat diet) similarly, whereas twice daily peripheral administration had a more marked effect on daytime intake. Oxytocin was found to increase the latency to begin feeding and reduce meal durations in both hungry and sated animals (6 of 6 experiments in rats) (Arletti et al., 1989, 1990; Benelli et al., 1991; Blevins et al., 2016). Oxytocin had no effect on hunger or reward-driven food intake (standard chow, sucrose or saccharin) when rats were placed in a social setting (n = 2) (Herisson et al., 2016). During choice, no-choice and operant self-administration feeding paradigms, the administration of oxytocin had no effect on low sodium diet (n = 1) (Bernal et al., 2007) or glucose intake (n = 1) (Lokrantz et al., 1997); IP and intracranial injections of oxytocin decreased sucrose (8 of 17 experiments) (Cox et al., 2013; Mullis et al., 2013; Klockars et al., 2018; Sinclair et al., 2015; Zhou et al., 2015; Herisson et al., 2016; King et al., 2017) and saccharin (2 of 9 experiments) (Herisson et al., 2016) intake in fasted and non-fasted rodents. In obese and lean rodents exposed to a chow diet higher in fat (~60% kcal from fat) than standard chow (~13% kcal from fat), intracranial infusion and SC infusion or injection of oxytocin reduced energy intakes in 11 of 15 experiments (Blevins et al., 2016; Maejima et al., 2011; Roberts et al., 2017; Maejima et al., 2017). Oxytocin had no effect on the intake of a palatable high fat emulsion (n = 1) (Maejima et al., 2011). Klockars et al. (2017a) found oxytocin did not shift rats' preference from sucrose to high fat emulsion when given a two-bottle choice test. Oxytocin decreased alcohol intake in 10 of 11 experiments (King et al., 2017; Peters et al., 2012; MacFadyen et al., 2016; Peters et al., 2017), with two experiments reporting that decreases in intake ranged from 30 to 40% in the 1–2.5 h post-administration period (MacFadyen et al., 2016). Peters et al. (2012) found oxytocin had no effect on stress-induced alcohol consumption (n = 2). Sinclair et al. (2015) found tastes response to both aversive (bitter, sour and salty) and appetitive (sweet and umami) stimuli were depressed following oxytocin injection. No aversive drug effects were found across nine experiments evaluating kaolin intake and conditioned taste aversion associated with oxytocin administration (Herisson et al., 2016; Blevins et al., 2016; Noble et al., 2014; Iwasaki et al., 2014; Roberts et al., 2017; Klockars et al., 2017a, 2018) In summary, the findings from the majority of experiments indicate acute doses of oxytocin are effective in reducing food (both standard chow and chow higher in fat), carbohydrate and alcohol intakes. Chronic treatments were more effective in producing sustained reductions in food intakes in obese rodents.

3.6.1. Meta-analysis results

The meta-analysis (forest plot available in Supplementary Material) for rats (8 studies, n = 82 comparisons) was based on a multilevel mixed effects model to account for correlation resulting from replicate experiments. Three nested factors (i.e. study, administration site and dose) were found to be important and formed the random effects part of

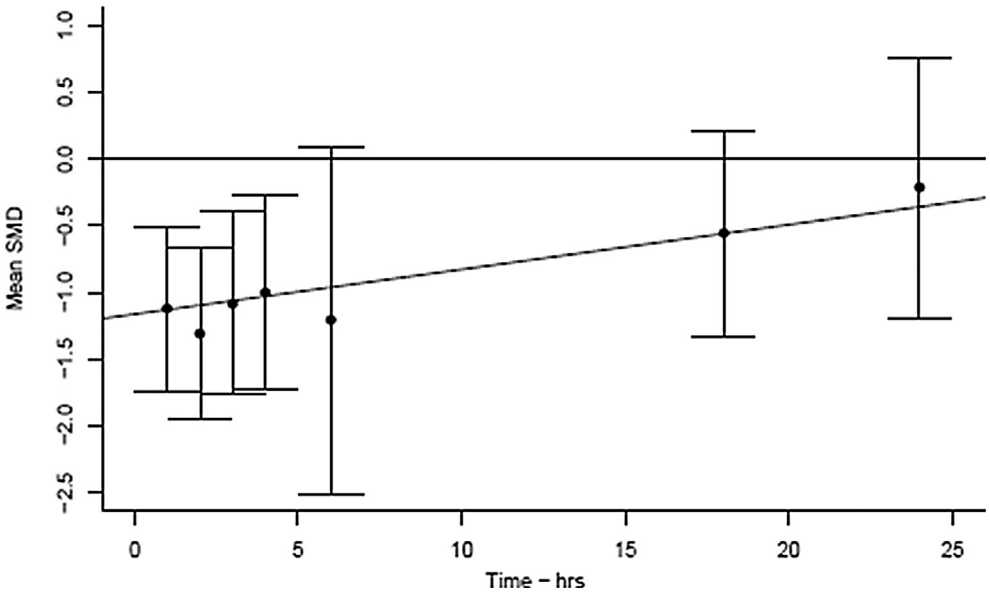

Fig. 3. Multilevel mixed effects meta-analysis. Results of 8 studies (n = 82 comparisons) in rats of the mean effect of acute oxytocin administration compared with control treatment on cumulative food intake (standardised mean difference and 95% confidence interval) over time (hours). The vertical line through zero represents the line of no treatment effect (overlaid with the line of best fit for continuous time effect). Food intake was significantly reduced by oxytocin treatment at 1, 2, 3 and 4 h ($p = 0.0004$, $p < 0.0001$, $p = 0.0021$, and $p = 0.007$, respectively); no significant effect at 6, 18 and 24 h ($p = 0.07$, $p = 0.16$, and $p = 0.67$, respectively).

the model. The fixed effects part of the model was used to examine the effect of two moderators, administration site (central and peripheral), not significant ($p = 0.26$); and time since meal (chow) presentation, significant ($p = 0.02$, treated as a categorical variable and intercept term in the model). Time was also examined as a continuous variable, $p = 0.001$. The final model was simplified to only contain the time effect, either in its continuous form or categorical form. For the categorical version of time, the fitted model means (no intercept term in the model, $p = 0.001$) and 95% confidence intervals are shown in Fig. 3, with the line of best fit for continuous time effect from the alternative model representation overlaid over the mean effects. The first four mean differences for 1, 2, 3 and 4 h respectively are all significantly lower than zero with the 95% confidence intervals not containing zero. The 6 h mean difference is similar, but is not significantly different to zero, and as it is only based on one record and has poor power. At the longer time periods of 18 h and 24 h the mean differences are not significantly different to zero.

The meta-analysis (forest plot available in Supplementary Material) was repeated for mice (3 studies, n = 43 comparisons; all injections given peripherally). The final model, containing only the time effect (other factors not significant), on food intake following oxytocin administration, was not significant when treated as a continuous variable (with intercept term in the model, $p = 0.21$). When time was examined as a categorical variable (no intercept term in the model, $p < 0.001$) the mean differences for 1, 2, 3 and 6 h are all significantly lower than zero with the 95% confidence intervals not containing zero. At 24 h the mean difference is not significantly different to zero (Fig. 4).

Bias. Within each study the original effect sizes were affected by time (as a moderator). Therefore to test for potential bias, residuals were used in funnel plots as these have been adjusted for the mean values for each of the time periods. The funnel plots (Supplementary Material) associated with each meta-analysis (rats or mice) show some degree of asymmetry. Rank correlation test for rats (Kendall's $tau = -0.3111$, $p < 0.0001$) and mice (Kendall's $tau = -0.5216$, $p < 0.0001$) indicate bias may be present. The asymmetry in the funnel plots shows more negative effects associated with larger standard errors which indicates that studies with positive effects are likely not being published. This may be for smaller studies that have lower sample sizes (or more variable studies).

3.7. Studies assessing the effect of oxytocin receptor antagonists on dietary intake and behaviour

Forty-six experiments assessed the effect of oxytocin receptor antagonists on dietary intake and behaviour, 33 were performed in rats and 11 in mice. Sample sizes ranged from 6 to 51, and five experiments utilised a cross-over design. Experimental durations ranged from 10 min to one week. Oxytocin receptor antagonists administered included [$d(CH_2)_5^1$, $Tyr(Me)^2$, Orn8]-OT; L-368,899; [1-(3-mercaptopropionic acid), 2-0-ethyl-D-Tyr, 4-Thr,8_Orn]-OT; 1-deamino-2-D-Tyr-(OEt)-4-Thr-8-Orn-oxytocin; [$d(CH_2)_5$,$Tyr(Me)2$,Orn^8] vasotocin and non-penetrable L-371,257. One study (Rinaman and Rothe, 2002) did not report the antagonist used. Routes of oxytocin receptor antagonist administration included: ICV (n = 1) or SC (n = 1) infusions for 3 to 5 days; intraperitoneal injection (IP; n = 14); intracranial injections [intracerebroventricular, n = 9 (lateral ventricle, n = 8; third ventricle, n = 2; fourth ventricle, n = 2); ventral tegmental area, n = 3; ventromedial, n = 3; nucleus accumbens core, n = 2; basolateral and central nuclei of the amygdala, n = 4]; and SC or intravenous injections (IV; n = 6). Oxytocin receptor antagonist doses administered via osmotic pump infusions were 40 μg/h^{-1}/kg (SC delivery) and 1 μg/rat (lateral ventricle delivery). IP injection ranged from 0.1 to 30 mg/kg; intracranial injections ranged from 0.3 to 10 mg/kg, or 0.1 to 10 μg, or 1 to 3 μl or 0.8 to 20 nmol; SC dose of 1.5 mg/kg; and IV injections of 1.0 μg or 30 μg/kg. Injections occurred up to 45 min prior to feeding, and post-treatment measurement of dietary intake/behaviour ranged from 30 min to 7 days. All experiments included a vehicle dose, either saline (n = 42) or aCSF (n = 4), and 14 experiments compared the effect of oxytocin to oxytocin receptor antagonist (Herisson et al., 2016; Arletti et al., 1989, 1990; Ho et al., 2014; Rinaman and Rothe, 2002; Uvnas-Moberg et al., 1996; Lokrantz et al., 1997; Olson et al., 1991a; Mullis et al., 2013). In 18 experiments, rodents were pre-treated with an oxytocin receptor antagonist before the administration of oxytocin (Ho et al., 2014; Rinaman and Rothe, 2002; Uvnas-Moberg et al., 1996; Lokrantz et al., 1997; Olson et al., 1991a; Mullis et al., 2013; Herisson et al., 2016; King et al., 2017; Arletti et al., 1989, 1990; Klockars et al., 2017a, 2018, 2017b).

Central and peripheral administration of oxytocin receptor antagonist significantly increased overall food intake compared to vehicle in six experiments (Arletti et al., 1989, 1990; Baskin et al., 2010; Ho et al., 2014; Zhang and Cai, 2011; Huang et al., 1996), but was found to have no significant effect in five experiments (Uchoa et al., 2009; Olszewski et al., 2010; Uvnas-Moberg et al., 1996; Klockars et al., 2017b; Olson

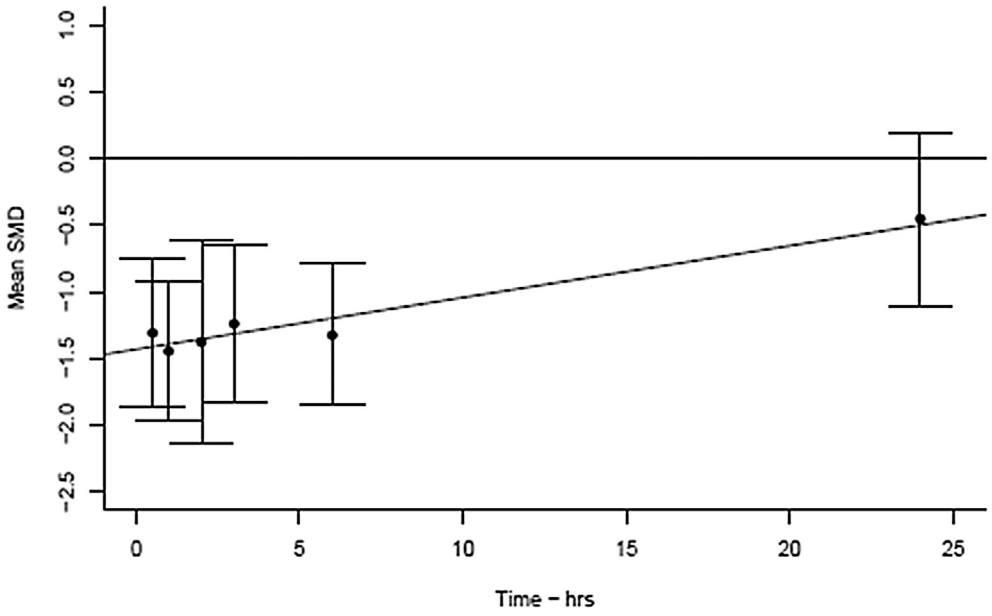

Fig. 4. Multilevel mixed effects meta-analysis. Results of 3 studies (n = 43 comparisons) in mice of the mean effect of acute oxytocin administration compared with control treatment on cumulative food intake (standardised mean difference and 95% confidence interval) over time (hours). The vertical line through zero represents the line of no treatment effect (overlaid with the line of best fit for continuous time effect). Food intake was significantly reduced by oxytocin treatment at 0.5, 1, 2, 3 and 6 h ($p < 0.0001$, $p < 0.0001$, $p = 0.0004$, $p < 0.0001$, and $p < 0.0001$, respectively); no significant effect at 24 h ($p = 0.17$).

et al., 1991b). Baskin et al. (2010) reported food intake of treated rats increased by 77% in the 4 h post administration period compared to vehicle. Olson et al. (1991a) found high doses (20 nmol) of oxytocin receptor antagonist inhibited food intake. Eleven experiments found the anorexigenic action of oxytocin on food intake, including the latency to consume and consumption duration, was counteracted by pre-treatment with an oxytocin receptor antagonist (Herisson et al., 2016; Arletti et al., 1989, 1990; Ho et al., 2014; Rinaman and Rothe, 2002; Olson et al., 1991a; Klockars et al., 2017a, 2018, 2017b). Ho et al. (2014) reported the systemic administration (IP) of a non-penetrant oxytocin receptor antagonist attenuated the inhibitory effects elicited by fourth ventricular administration of oxytocin. Zhang and Cai (2011) found twice daily (AM vs. PM) central oxytocin receptor antagonist injections increased daytime and night-time food intakes significantly, with a more marked effect on daytime intake, whereas twice daily peripheral administration affected daytime intake only. During choice and no-choice feeding paradigms, when compared to controls, oxytocin receptor antagonist treated rodents in 15 of 17 experiments had increased intakes of carbohydrates: sucrose (n = 10 Herisson et al., 2016, 2014; Olszewski et al., 2010; Mullis et al., 2013), glucose (n = 2 Herisson et al., 2014; Lokrantz et al., 1997), polycose (n = 2 Herisson et al., 2014), cornstarch (n = 2 Herisson et al., 2014) and fructose (n = 2 Herisson et al., 2014); and non-carbohydrate saccharin (n = 2 Herisson et al., 2016, 2014). Pre-treatment with an oxytocin receptor antagonist was found to abolish the anorexigenic effect of oxytocin on sucrose, glucose and saccharin (n = 8 Herisson et al., 2016; Lokrantz et al., 1997; Mullis et al., 2013; Klockars et al., 2017a, 2018); alcohol (n = 1 King et al., 2017) and palatable fat intake (Intralipid emulsion, n = 1 Klockars et al., 2017a). Oxytocin receptor antagonist treatment when given alone had no effect on Intralipid emulsion intake (n = 1 Olszewski et al., 2010). When mice were presented concurrently with palatable lipid and sucrose solutions (n = 1 Olszewski et al., 2010), or saccharin and sucrose solutions (n = 1 Herisson et al., 2014) mice consumed more sucrose. Olszewski et al. (2015) found that when dominant and subordinate mice were treated with an oxytocin receptor antagonist, dominant mice consumed increased amounts of sucrose in both non-social and social contexts, whereas subordinate mice only consumed more sucrose in the non-social environment. In summary, the majority of experiments found acute and chronic administration of penetrable oxytocin receptor antagonists increased intakes of food (i.e. standard chow, carbohydrates, saccharin and alcohol), with the exception of Intralipid emulsion. Antagonist administration, prior to oxytocin treatments, counteracted oxytocin's anorexigenic effects, on food intakes including Intralipid emulsion.

3.8. Studies assessing the effect of oxytocin agonists on dietary intake and behaviour

Eight experiments assessed the effect of oxytocin agonists on dietary intake and behaviour. Four experiments, conducted by Olson et al. (1991a) assessed the effect of ICV administered oxytocin agonist (e-L-β-MePhe^2) on food intake (n = 3) and time spent feeding (n = 1) in Sprague-Dawley rats. Sample sizes ranged from 5 to 16 and three experiments utilised a cross-over design. Agonist doses ranged from 10 to 500 pmol and were administered just prior to feeding. Overall food intake and time spent feeding was significantly decreased in the 60 min following agonist administration (all doses). Olson et al. (1991a) reported that rats developed a tolerance to the agonist's inhibitory effects by day three and food intake returned to baseline levels. In one experiment, it was found that pre-treatment with an oxytocin receptor antagonist [$(CH_2)_5^1$, Phe(Me)^2, Thr^4,Orn^8] abolished the inhibitory effects of [e-L-β-MePhe2]oxytocin on food intake (Olson et al., 1991a). Oxytocin agonist administration had an opposite effect on food intake when administered in rodents with hyponeophagia (feeding inhibition induced by a novel environment) (Olszewski et al., 2014). Four experiments, conducted by Olszewski et al. (2014) assessed the effect of IP administered oxytocin agonist (WAY-267,464), on reward and hunger driven food intake in novel and familiar (home cage) environments in BALB/c mice. Sample sizes ranged from ~24 to ~36, and agonist doses administered just prior to feeding ranged from 10 to 500 pmol. Oxytocin agonist administration did not alter food intake in mice fed standard chow in familiar settings, though it reduced the inhibition of feeding produced by a novel environment. This included a reduced latency to approach palatable food (sweetened condensed milk) and an increase in food intake. The decrease in anxiety hyponeophagia was abolished by pre-treatment with an oxytocin receptor antagonist (L-368,899) (Olszewski et al., 2014). In summary, when rodents were fed in a familiar environment, food intake was generally reduced following agonist administration. Whereas when rodents were fed in a novel environment, the usual suppression of food intake induced by an unfamiliar setting was ameliorated, and food intake increased.

3.9. Studies assessing the effect of oxytocin gene deletion on dietary intake and behaviour

Twenty-eight experiments assessed the effect of oxytocin gene deletion on dietary intake and behaviour in male (n = 18) and female mice. Sample sizes ranged from 10 to 28 and the most frequent strain of oxytocin knock out mice (OT KO) used were derived from C57BL/6 mice (n = 24 experiments). Two experiments compared ovariectomised OT KO and wild type mice (WT) to intact controls (Amico et al., 2003). Choice and no-choice feeding paradigms were used and testing durations of experiments ranged from 3 days to 5 weeks. Across the 11 experiments assessing sweet solution intake, OT KO mice displayed a significant increase in and sustained preference for sucrose (n = 9 Amico et al., 2005; Sclafani et al., 2007; Miedlar et al., 2007) and saccharin (n = 2 Billings et al., 2006) compared to WT mice. There was no significant difference in intake between genotypes when fed standard chow alone (n = 2 Camerino, 2009; Rinaman et al., 2005) or high fat vs standard diet (n = 1 Takayanagi et al., 2008). When given a series of two-bottle choice tests, Sclafani et al. (2007) found OT KO mice consumed greater amounts of both sweet and non-sweet carbohydrate solutions (i.e., sucrose, polycose, and cornstarch) compared with WT cohorts, but there was no difference in their intake of a palatable lipid emulsion. In four experiments, Miedlar et al. (2007) found OT KO mice consumed significantly more palatable lipid emulsion than WT on day one only, but there was no difference in overall 3-day intake between genotypes. Similarly, Vollmer et al. (2013) found during a 4-day exposure to a palatable solution, high in sodium and fat, all mice consumed large amounts with no significant differences between genotypes (Vollmer et al., 2013). In two-bottle preference tests (n = 7 Amico et al., 2001; Puryear et al., 2001; Amico et al., 2003; Vollmer et al., 2006, 2013) in which mice could choose between water or a sodium chloride solution (NaCl), OT KO mice consumed significantly greater amounts of NaCl then WT mice in five (Amico et al., 2001; Puryear et al., 2001; Amico et al., 2003) of the seven experiments. In a two-diet choice test (low vs. high sodium chow) there was no difference in intake between OT KO and WT cohorts (Vollmer et al., 2013). In summary, oxytocin KO mice displayed a preference for carbohydrate, saccharin and sodium solutions, compared to their WT counterparts. Oxytocin gene deletion had no significant effect on the consumption of chows, with varying macronutrient profiles, or Intralipid emulsion.

3.10. Studies assessing the effect of dietary intake and behaviour on oxytocin gene expression

Nineteen experiments assessed the effect of dietary intake and behaviour on oxytocin gene expression and hypothalamic oxytocin levels. Short-term exposure (< 24 h) to sucrose (n = 2 Duncko et al., 2003; Mitra et al., 2010) had no effect on gene expression, whereas longer term exposure (≥24 h to 42 days) to sucrose (n = 6 Herisson et al., 2014; Olszewski et al., 2010, 2015; Mitra et al., 2010; Olszewski et al., 2009; Hume et al., 2017), cornstarch (n = 2 Herisson et al., 2014; Mitra et al., 2010) or palatable lipid solutions (n = 1 Olszewski et al., 2010) increased oxytocin mRNA levels (n = 5 Herisson et al., 2014; Olszewski et al., 2010, 2015, 2009) and activated oxytocin neurons (assessed using the Fos-protein marker) (n = 3 Olszewski et al., 2010; Mitra et al., 2010; Hume et al., 2017). Prolonged high fat diet (11 weeks) in ovariectomised mice (n = 1 Pirnik et al., 2012) produced negligible Fos expression in oxytocin neurons in the paraventricular nucleus (PVN) of the hypothalamus. Olszewski et al. (2010) found when mice were grouped according to sucrose or fat preference, baseline oxytocin mRNA levels did not differ between 'sucrose preferrers' and 'fat preferrers'. Further, Olszewski et al. (2010) examined hypothalamic oxytocin gene expression in dominant and subordinate mice (dyads) consuming sugar, and found oxytocin mRNA levels were higher in dominant mice. Forty-eight hour exposure to saccharin had no effect on oxytocin mRNA levels in one experiment, (Herisson et al., 2014) whereas in another experiment a decrease in gene expression was reported (Herisson et al., 2016). Shorter term exposure (2–24 h) to saccharin significantly upregulated oxytocin receptor mRNA expression in the central nuclei of the amygdala (CNA; n = 1 (Klockars et al., 2018), but had no effect on the basolateral nuclei of the amygdala (BLA; n = 1 Klockars et al., 2018); or on ventromedial hypothalamic nuclei (VMH; n = 1 Klockars et al., 2017). Prolonged alcohol exposure (6–10 months) decreased the number of oxytocin neurons, but had no effect on mRNA levels (Silva et al., 2002). Following a fasting-refeeding regime, Uchoa et al. (2009) found refeeding increased the number and percentage of Fos-positive oxytocin neurons in the PVN and supraoptic nucleus (SON) of the hypothalamus, but did not alter oxytocin mRNA expression in these regions (experiment 2). Suyama et al. (2016) found increased synaptic input onto PVN oxytocin neurons in ad libitum fed compared to the fasted state. Oxytocin receptor mRNA was increased by food deprivation in the VMH (n = 1 Klockars et al., 2017) and CNA (n = 1 Klockars et al., 2018), but not in the BLA (n = 1 Klockars et al., 2018). Salt loading (replacement of drinking water with 2% sodium chloride) in rats produced a significant elevation in oxytocin gene expression in the SON (n = 1) (Greenwood et al., 2015). In summary, upregulation of oxytocin mRNA levels occurred largely in response to chronic carbohydrate exposure, compared to standard chow, saccharin or Intralipid emulsions.

3.11. Studies assessing the effect of dietary intake and behaviour on peripheral and central oxytocin concentrations

Eight experiments assessed the effect of dietary or nutrient intake on central (hypothalamic nuclei, n = 3 Burlet et al., 1992; Zhang and Cai, 2011; Morris et al., 1995) and peripheral (plasma, n = 5 Morton et al., 2012; Zhang and Cai, 2011; Bjorkstrand and Eriksson, 1992; Hartley et al., 2003; Greenwood et al., 2015; Morris et al., 1995) oxytocin concentrations. Plasma oxytocin levels were unaltered in rats fed high fat diets compared to controls (n = 1 Morton et al., 2012), whereas the diurnal rhythmicity in 24-hour peak circulating plasma oxytocin levels (n = 1 Zhang and Cai, 2011) and hypothalamic oxytocin release (n = 1 Zhang and Cai, 2011) was abolished in mice fed a high fat diet. Morris et al. (1995) found a high intake of salt (i.e. salt loading) increased plasma oxytocin in baroreceptor-denervated rats, but not in healthy controls (sham operated). In contrast, Greenwood et al. (2015) found salt loading increased plasma oxytocin levels in healthy rats. Exposure to a high soya isoflavone diet had no effect on plasma oxytocin concentrations (n = 1) (Hartley et al., 2003). Food deprivation produced no significant change in oxytocin concentrations in plasma (n = 1 Bjorkstrand and Eriksson, 1992), or in hypothalamic nuclei, with the exception of the median eminence (n = 1 Burlet et al., 1992). This effect in the median eminence was not significantly reversed by refeeding. In summary, alterations in endogenous oxytocin concentrations occurred in response to sodium and chronic high fat diet intakes, and food deprivation.

3.12. Studies assessing other measures of oxytocin on dietary intake and behaviour

Of the 11 experiments assessing other measures of oxytocin, two experiments conducted by Bahi et al. (2016) examined the effect of increased expression of the oxytocin receptor, in the nucleus accumbens, on voluntary alcohol consumption and taste sensitivity. Oxytocin receptor overexpression, relative to sham controls, led to a decrease in voluntary alcohol consumption. The same mice, when exposed to sweet and bitter tastants (i.e. saccharin and quinine), showed similar intake and preference for both tastants. Ryan et al. (2017) found chemogenetic activation of oxytocin receptor neurons (n = 2) in the parabrachial nucleus of the pons in mice did not decrease usual food intake, or food intake (standard chow or liquid diet) after fasting, but did decrease sodium intake in dehydrated mice. Overall, Ong et al.

(2015) found virally mediated oxytocin receptor knockdown had no significant effect on food intake in fasted or satiated rats (n = 3). Wu et al. (2012) found oxytocin neuron ablation had no significant effect on food intake in rats fed a high fat or standard diet (n = 1). Morris et al. (1995) found PVN injection of oxytocin antisense significantly decreased salt intake in baroreceptor-denervated rats, but not in healthy controls.

4. Discussion

This systematic review provides a summary of preclinical studies investigating oxytocin in relation to dietary intake and feeding behaviours. A total of 246 experiments in rats and mice from 75 published papers were reviewed. Various oxytocin measures were reported with the most common examining the effects of exogenous oxytocin administration on food intake (grams, g/kg BW, mL or kcal). In addition to physical dietary intake a range of feeding behaviours were also assessed. The majority of studies (87%) were carried out in male rodents. While male rodents are often preferred in research studies over females, due to the potential effect of hormonal variations on food intake associated with the female oestrous cycle, 32 experiments included female rodents. Of the thirteen experiments (Sinclair et al., 2015; Zhou et al., 2015; Benelli et al., 1991; Amico et al., 2005; Bjorkstrand and Uvnas-Moberg, 1996; Cox et al., 2013; Bjorkstrand and Eriksson, 1992; Maejima et al., 2017) that included both sexes, in all but two (Bjorkstrand and Uvnas-Moberg, 1996; Maejima et al., 2017), exogenous oxytocin had similar effects in males and females. However, two studies found females were more sensitive to lower doses of oxytocin than males in reducing sucrose and food intake (Zhou et al., 2015; Benelli et al., 1991). Notably, ten of the 19 experiments carried out exclusively in females were conducted in oxytocin KO mice. This may be attributed to the tendency for male mice lacking oxytocin to develop late-onset obesity (Takayanagi et al., 2008; Leng et al., 2008).

The majority of studies in this review investigated the effect of acute or chronic exogenous oxytocin via central (brain delivery) or systemic administration (n = 125 experiments). In 55% of studies, food intake or feeding behaviour was assessed over a relatively short duration (< 24 h) and food or nutrient intake was most often reported as grams consumed. Collectively the majority of studies reported a decrease in food intake, sucrose and alcohol intake, in addition to decreased feeding duration and increased latency to the first meal. Notably, chronic doses of oxytocin produced a stronger anorexigenic effect in DIO and obese leptin resistant rodents than lean controls. Acute doses of oxytocin were given up to two hours prior to feeding. For the majority of studies with earlier administration times (30–120 min prior to feeding) oxytocin still produced positive effects on intake outcomes. This is an advantage of animal studies, allowing for a more controlled environment where food intake can be closely monitored, in contrast to human studies where feeding often can occur more spontaneously without prompting or time to administer oxytocin. Few studies reported raw data to demonstrate a reduction in food intake, but rather reported the direction and quantification of the result. Results of the meta-analysis in mice and rats show there was a systematic difference in the cumulative amount of food eaten in the early time periods following oxytocin or vehicle administration (1–4 h in rats; 1–6 h in mice) between oxytocin treated rodents and controls. The early decrease in food intake was no longer significant 24 h post-administration in either mice or rats, indicative of oxytocin's declining effectiveness over time. Of the experiments included in the meta-analysis, for three conducted in rats (Arletti et al., 1989; Benelli et al., 1991; Ibragimov et al., 1988) and 10 conducted in mice (Maejima et al., 2015, 2011), food was not provided immediately (within 10 min) following oxytocin/vehicle administration. Rats will commonly consume up to ~ 15–30 g of standard chow per day, and mice up to ~5–8 g, depending on their strain and body weight (Lab Diet, 2017). Whilst these numbers appear small, the oxytocin post-administration reduction in food intake can be represented as a ~ 4–9% decrease in rats and a ~ 18–29% decrease in mice over two hours, which contextually is a significant reduction. Importantly, not all exogenous oxytocin administration experiments (n = 4) (Bjorkstrand and Uvnas-Moberg, 1996) showed a reduction in food intake after oxytocin. The reasons for these differences are not immediately apparent and highlights a need to consider interactions between hormones (e.g. oxytocin + cholecystokinin Blevins et al., 2003, oxytocin + leptin Blevins et al., 2004). Making between study comparisons difficult is the tendency of preclinical studies to report only minimal information regarding housing conditions which may be highly influential. Indeed, standardising housing, light cycle and other laboratory conditions would make comparisons far easier. For this review many of the experimental results included in the meta-analysis were extracted from a graphical data using a web digitiser. The WebPlotDigitizer (Rohatgi, 2017) is considered accurate and has been used widely for previously published reviews, however also acknowledged as a limitation of this review (Diah et al., 2014; Hoogeboom et al., 2012; Mukherjee et al., 2013). To allow for a more detailed meta-analysis in the future, an important recommendation arising from this review is that publications should report outcome data, including means and standard deviation, and group changes in addition to the direction which was more often reported.

Given the short half-life of oxytocin (approximately 1–6 min Romano et al., 2016; Szeto et al., 2011) and the demonstrated 1–24 h reduction in food intake post-administration, exogenous oxytocin may activate an indirect peripheral pathway triggering increased central release of endogenous oxytocin via increased basal activity of oxytocin cells in which oxytocin secretion increases. Assessing intake at regular intervals post-administration throughout the experimental period, rather than a one off measure, may be beneficial to address this possibility. As suggested by Leslie et al. (2018) longer study durations, with a regime of intermittent oxytocin administration of differing dosing schedules, are needed to determine if the reduction in appetite induced by oxytocin can be maintained over the longer-term (i.e. > 3 weeks). This would assist in the translation to human studies and enable oxytocin's effect on longer durations of habitual food intake to be measured. Consideration should be given to the timing of experimental protocols and data collection. Rodents, when housed under a standard 12 h light/12 h dark cycle, will consume the majority of their daily food intake (~70%) during the dark cycle, with shorter bouts of feeding during the light phase (Ellacott et al., 2010). As many of the shorter duration experiments (< 12 h) were conducted during the light phase, it is possible that differences in dietary intake were not detected. Interestingly it was reported in two studies (Herisson et al., 2016) that the oxytocin-induced decrease in food intake was diminished when animals were placed into a social context. This warrants further consideration given the known role for oxytocin in social bonding and interactions in animals and humans, and may suggest that the effect of oxytocin on food intake is context specific. To increase the relevance of animal to human investigations, further studies observing more naturalistic feeding behaviours, such as the frequency and length of meal bouts, would be worthwhile. Measuring food or nutrient intake as kilojoules consumed or percent of baseline intake may provide a better understanding of the interaction between oxytocin and dietary intake or behaviours, making results more comparable across studies.

The oxytocin gene deletion studies examined in our review highlight the importance of oxytocin in reducing food intake, especially for highly palatable foods. This is further supported by most oxytocin receptor antagonist and agonist studies. Oxytocin receptor antagonists stimulated food intake by increasing meal size and feeding duration. Additionally, the central (lateral ventricle, fourth ventricle and nucleus accumbens core) and peripheral (IP and IV) administration of oxytocin receptor antagonists blocked the hypophagic action induced by exogenous oxytocin (Herisson et al., 2016; Arletti et al., 1989, 1990; Ho et al., 2014; Rinaman and Rothe, 2002; Olson et al., 1991a; Klockars et al., 2017a, 2018, 2017b). With the exception of two experiments (Ho

et al., 2014), oxytocin was administered via the same route as the antagonist. The administration of an oxytocin agonist was found to have a similar effect to oxytocin on food intake. Further studies examining oxytocin gene expression found sucrose and sodium consumption enhanced oxytocin mRNA levels, whereas high fat diets and prolonged alcohol exposure did not change oxytocin mRNA levels. Only one of two studies found fasting as well as overfeeding led to changes in mRNA expression levels of oxytocin. Oxytocin concentrations in hypothalamic nuclei (PVN and SON) were generally unaltered by food deprivation and refeeding, with the exception of the median eminence. With respect to plasma oxytocin, the consumption of standard chow did not significantly alter plasma levels of oxytocin. Whereas, plasma levels were found to be lowered in rodents fed chow higher in fat, and elevated in those consuming liquids high in sodium. Furthermore, chronic exposure to high fat diet disrupted diurnal oxytocin release correlated with a feeding circadian pattern.

In the context of this review, very few studies investigated the effect of altered diet on endogenous oxytocin levels (n = 8 endogenous studies vs. n = 126 exogenous studies), in contrast to studies of oxytocin in humans. The difference may be accounted for by the fact that exogenous administration of oxytocin in humans is relatively new and more substantial ethical implications apply in human studies. Similar to the review of human studies, plasma values varied markedly across studies, consequently oxytocin concentrations cannot be compared directly between studies. A criticism that has been raised regarding the measurement of plasma oxytocin is the use of unextracted serum in enzyme immunoassay and radioimmunoassay procedures (Szeto et al., 2011; Leng and Sabatier, 2016). It has been reported that values generated for oxytocin levels in unextracted plasma can be "impossibly high and wholly erroneous measurements" (Leng and Sabatier, 2016). To resolve existing controversies further validation studies are needed, and as previously suggested, a gold-standard methodology for oxytocin measurement would be beneficial.

Within this review, the method of exogenous oxytocin administration was distinctly different to that found in human studies. Many of the included studies administered oxytocin by invasive procedures that are not possible in humans. While not directly translatable to human based studies it does provide valuable evidence of the influence of oxytocin on dietary intake. Pharmacotherapeutic drugs for the treatment of several neuropsychiatric states, including addiction and eating disorders, often require repeated administration of the prescribed drug for treatment. However, of the 126 exogenous studies reviewed here, only 25 experiments used repeated or continuous administration of oxytocin. In approximately half of these experiments (52%) study durations were ≤ 2 weeks. Single dose administration is less likely than repeated administrations to elicit adverse effects (Kramer et al., 2003; Macdonald and Feifel, 2013). Several off-target effects have been reported in human trials (e.g. anti-social behaviours such as increased aggression (De Dreu et al., 2010), decreased trust and co-operation Bartz et al., 2011) following acute oxytocin administration. These effects are yet to be monitored following the chronic administration of oxytocin in either human or animals. Examining these effects will greatly improve understanding of the oxytocin system for future therapeutic targets. Furthermore, it is still unclear how the effects of exogenous oxytocin produces its effects on feeding behaviour. Current thinking is that exogenous (high dose) oxytocin may signal to the brain via actions at areas with porous blood brain barrier permeability (e.g. the area postrema, nucleus of the solitary tract) or actions on the vagus nerve (Blevins and Ho, 2013; Gimpl and Fahrenholz, 2001). Oxytocin may also act on peripheral oxytocin receptors expressed in the gastrointestinal tract (Blevins and Ho, 2013; Ohlsson et al., 2006).

Limitations of the present systematic review need to be acknowledged. Firstly, the review included only published studies in English, and was limited to mice and rats. Overall samples were predominantly made up of male rodents and sample sizes were small, potentially limiting the generalisability of the results. However, the small sample sizes may be attributable to ethical considerations to minimise animal usage. Secondly, heterogeneity (e.g. differing feeding protocols and experimental durations) among the majority of the included experiments limited the opportunity for meta-analytic synthesis of all the experiments in this systematic review. With regard to the meta-analysis, it is possible that reporting bias may have arisen due to the small sample sizes of the included studies, or potentially publication bias. Thirdly, unlike human-based studies, exact numbers of animals were often not reported or the same animals were used across experiments, potentially confounding the results. Lastly, the quality of the included articles were assessed as having an unclear risk of bias for many of the domains due to missing information. Providing detailed information regarding allocation concealment, housing, and blinding of assessors to interventions and outcomes would help improve the methodological quality of future studies. The use of ARRIVE (Animals in Research: Reporting In Vivo Experiments) (Kilkenny et al., 2010) guidelines provide a practical resource to improve the standardisation of experimental and reporting procedures.

5. Conclusion

This review identified a large number of studies investigating the regulatory effects of oxytocin on dietary intakes in mice and rats. Exogenous studies formed the majority of included studies and it was found that the central and systemic administration of oxytocin significantly reduced food intakes in both lean and obese rodents. The greatest effects on food intake were observed in the short term, 1 h post-administration. The underlying neural mechanisms with respect to the behavioural aspects of diet and eating warrant further investigation.

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Declaration of interest

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Appendix A. Supplementary material

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