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Conditioned hormonal responses: A systematic review in animals and humans

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ABSTRACT

In contrast to classical conditioning of physiological responses such as immune responses and drug effects, only a limited number of studies investigated classical conditioning of endocrine responses. The present paper is the first systematic review that integrates evidence from animal and human trials regarding the possibility to condition the endocrine responses. Twenty-six animal and eight human studies were included in the review. We demonstrated that there is accumulating evidence that classical conditioning processes are able to influence specific endocrine responses, such as cortocosterone/cortisol and insulin, while more limited evidence exists for other hormones. Animal and human studies were generally consistent in their findings; however, the limited number of human studies makes it difficult to generalize and translate the results of animal research to humans. Next to methodological recommendations for future studies, we suggest several ways how classically conditioned endocrine responses can be used in clinical practice.

1. Introduction

Classical conditioning is a learning and memory phenomenon that serves as a regulatory adaptive mechanism, helping to prepare the organism for recurrent changes in homeostasis, for example due to food intake (Woods and Ramsay, 2000). Substantial research has been done on this topic looking in various areas: from fear conditioning (e.g., Lissek et al., 2005; Sehlmeyer et al., 2009) to conditioning of immune responses (e.g., Ader, 2003) and drug tolerance effects (Siegel, 1989).

Classical conditioning is a learning process where an association is formed between a physiologically relevant stimulus (unconditioned stimulus, US; e.g., food) and a neutral stimulus (conditioned stimulus, CS; e.g., a sound of a bell). Initially, the biologically relevant stimulus elicits a physiological reaction (unconditioned response, UR, e.g., salivation), while the conditioned stimulus is biologically neutral and elicits no response. However, after repeated contingent pairing of both stimuli, the neutral stimulus will become a conditioned stimulus (CS) and evoke a physiological response (conditioned response, CR; e.g., salivation) in the absence of the US.

Animal, and to a lesser extend human studies, have looked at the effects of classical conditioning on the endocrine system. Hormone secretion can be conceptualized as an UR to various US; for example, drug intake. Stimuli occurring together with the US, for example the process or environment of a drug administration, can be associated with the hormonal responses and can become a CS.

Endocrine responses are involved in a variety of physiological processes, from blood pressure regulation to digestion and stress responsiveness. Moreover, endocrine over- or underproduction underlie various diseases, such as diabetes, thyroid disease, adrenal insufficiency, polycystic ovary syndrome and so on. Therefore, utilizing our understanding of endocrine conditioning to control hormone levels through behavioral manipulation might have widespread clinical implications. Future practice might benefit from enhancing certain endocrine reactions by classical conditioning. Classical conditioning of endocrine parameters may be one of the underlying mechanisms of placebo-controlled dose reduction – a procedure in which a part of the pharmacological treatment is replaced by placebo while maintaining the efficacy of the treatment (Rief et al., 2011). Another possible implication of

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conditioned endocrine responses is reduction of the nocebo effects of medicines, unwanted treatment outcomes that are not due to the treatment mechanism itself, as classical conditioning is hypothesized to trigger this phenomenon (Benedetti et al., 2003). It might be possible to prevent forming unwanted conditioned responses in the endocrine system. For example, prior exposure to the conditioned cue or adding a salient additional cue at the time of conditioning can prevent the development of conditioned responses (Hall et al., 2016; Klosterhalfen et al., 2005). In summary, there are several ways how classical conditioning can be used in practice, however, a comprehensive summary of the knowledge in this field is necessary to draw any clinical conclusions.

Although a few studies have summarized the findings of conditioned endocrine responses, no systematic review covers both animal and human studies on this topic. Several older reviews focus on animal studies in a non-systematic manner (Stanton and Levine, 1988; Woods and Burchfield, 1980); and two papers described human studies, with one non-systematic report from more than a decade ago (Stockhorst, 2005) and one recent systematic review only incorporating human studies (Tekampe et al., 2017). It currently remains unknown whether the results of animal research can be translated to humans. The aims of the current review are to systematically summarize the available knowledge on conditioned endocrine responses in both animal and human studies, to compare the results of animal and human trials, to present an overview of the research designs used in previous studies, to describe methodological caveats of conditioning research, and finally to propose possible implications of using classical conditioning paradigms in modifying hormonal responses.

2. Methods

2.1. Protocol registration

The systematic review was done following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009). The review protocol was registered on PROSPERO (registration number CRD42017058783).

2.2. Inclusion criteria

Original experimental studies were included in which classically conditioned hormonal responses were reported. Classically conditioned hormonal responses were defined as hormonal changes in response to a CS that was previously coupled with a US. The studies had to be written in English, had to be published in a peer-reviewed journal, and had to include a minimum of one control group. Single case studies and conference abstracts were excluded. Furthermore, studies on anticipatory hormone release (incidental learning as a response to naturally occurring stimuli, such as time of the day) were excluded from this review. The current review did not include the studies done on glucose conditioning (e.g., Siegel, 1972; Woods, 1976), as glucose is not a hormone. Even though it was sometimes speculated in these studies that conditioned changes in glucose were triggered by conditioned insulin responses, insulin was not measured directly. Also, studies on fear conditioning were not included in this review even if they measured corticosterone or cortisol. These studies are aimed at conditioning of fear and hormonal responses are measured as indicators of fear and not as a primary CR. No limitations regarding the year of publication were set.

2.3. Data search and study selection

The electronic bibliographic databases PubMed, EMBASE, PsycINFO, and CINAHL were searched from the inception until January 2017, using the key words and connectors *endocrine* OR *hormonal* in combination with *conditioning* OR *associative learning* OR *anticipatory release* and specific names of the hormones such as for example *insulin, cortisol, testosterone*. The full search terms per database are presented in Supplementary material. The search included both human and animal trials that measured hormonal responses to conditioned stimuli. In addition, the search included trials on anticipatory hormone release that will be published separately.

The search was done by two authors (A.S. and I.K.) independently. The two authors screened the search results for eligibility based on the titles, abstracts, and finally full texts of the reports. The results of the search process were compared between the two authors and the final list of the included studies was made. Classification of the studies into intentional conditioning studies or anticipatory incidental learning studies were done by two authors (A.S. and I.K). Studies that employed a two-phase experimental design with acquisition and evocation phases were labeled as intentional conditioning studies and included in the current review. Studies that measured anticipatory hormone release by incidental learning as a response to naturally occurring stimuli (such us time of the day), will be included in another review and discussed elsewhere. The inconsistencies were resolved by consulting with the second author (D.V.).

2.4. Data extraction and risk of bias assessment

The data from the studies were extracted using a standardized data extraction form. The following data were extracted from each eligible study: first author's name, year of publication, journal name, study design, sample characteristics, number of acquisition sessions, number of evocation sessions, US, UR, CS, CR, groups, hormonal outcome, timing of outcome assessment, and main study results.

The two authors (A.S. and I.K.) assessed for risk of bias using the Cochrane Collaboration's tool for assessing risk of bias in human trials (Higgins et al., 2011). For assessing risk of bias in animal studies, the guidelines from O'Connor and Sargeant (2014) and the SYstematic Review Centre for Laboratory animal Experimentation (SYRCLE) (Hooijmans et al., 2014) were used. Selection bias (randomization process and allocation concealment), performance bias (blinding of participants and research personnel), detection bias (blinding of the outcome assessment), attrition bias (reasons for withdrawal in all conditions), and reporting bias (handling of missing data) were assessed by using these guidelines. In case of inconsistencies in the assessment of the two reviewers, the second author (D.V) was consulted. In case no information was provided about a certain bias, unclear risk of bias was chosen. In case the study protocol was not pre-registered, the reporting bias was selected to be unclear as well.

3. Results

3.1. Search results and studies' characteristics

The number of articles found on each step of the systematic search are presented in the Flow Diagram (Fig. 1). In total 108 eligible studies were identified of the 17,899 initially identified unique articles that matched the search criteria; 34 of these were found eligible for inclusion in the current review, whereas 74 studies will be included in a separate review on anticipatory endocrine responses by incidental learning. The overview of the study characteristics and study findings of all included studies is presented in Tables 1 and 2, for animal and human studies separately.

The vast majority of animal studies were performed in males (20 out of 26), two studies- in females, two- in mixed groups and other two studies did not report the gender of the animals. Half of the human studies included only males as participants, two studies included both males and females, and two studies only females. Three (out of 8) human studies were performed in the same lab and written by the same first author (Stockhorst et al., 1999, 2004, 2011). The far majority of both the animal and human studies (31 out of 34) were published

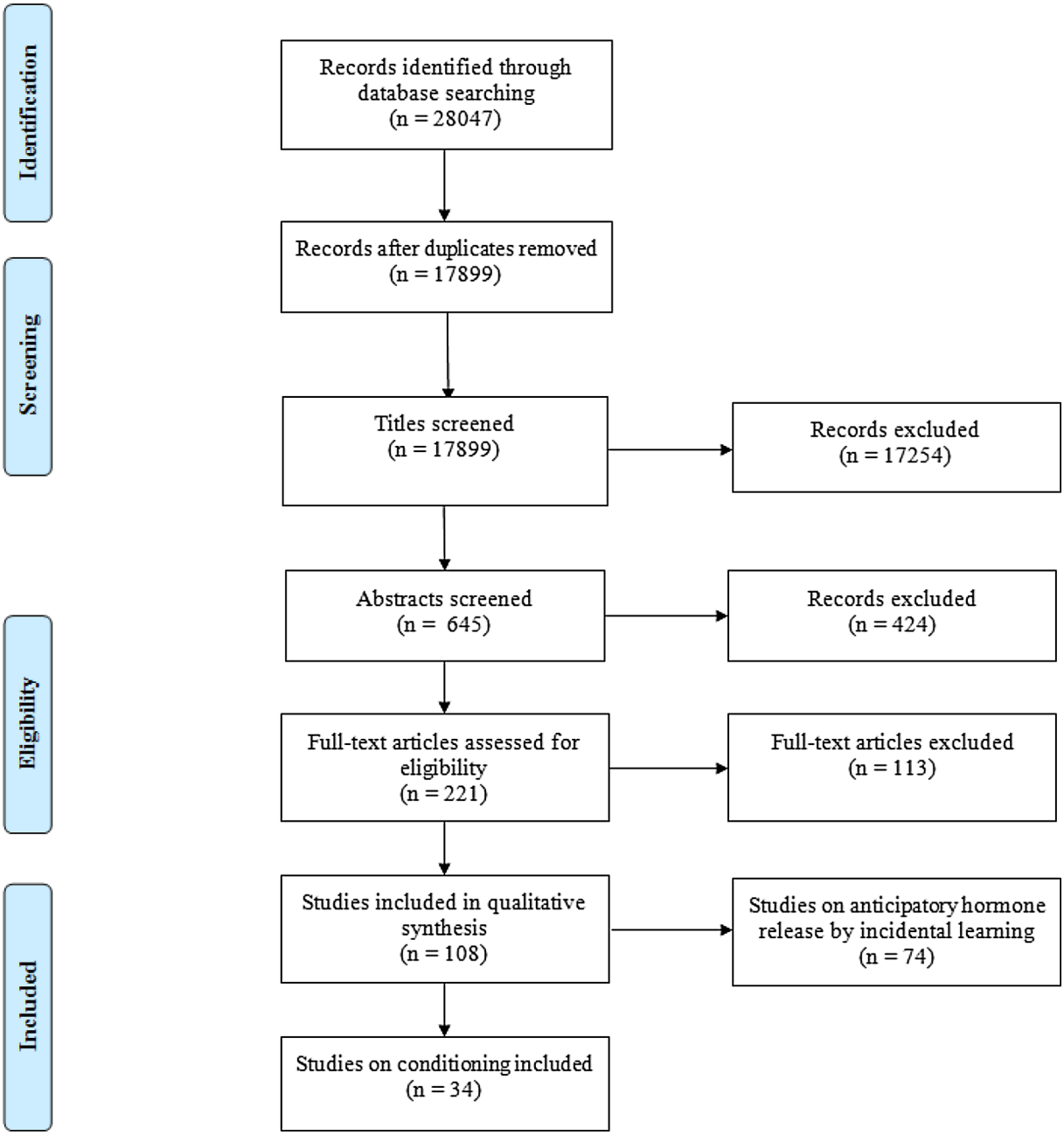

Fig. 1. Flow diagram with the number of included and excluded studies.

before 2008.

3.2. Endocrine parameters

Most commonly measured hormones in the studies involving animals were corticosterone (in rodents) and cortisol (in other species). Over half of animal studies (15 out of 26) measured conditioned changes in either corticosterone or cortisol using various US. Thirteen of these studies found significant changes in the corticosterone or cortisol levels after conditioning (Ader, 1976; Barreto and Volpato, 2007; Buske-Kirschbaum et al., 1996; Coover et al., 1977, 1980; Davis et al., 2005; Dyck et al., 1990; Exton et al., 1995; Janz et al., 1996; Kreutz et al., 1992; Pacheco-Lopez et al., 2004; Smotherman and Levine, 1980; Smotherman et al., 1980), while 2 studies could not demonstrate conditioned corticosterone and cortisol alterations (Janz et al., 1991; Natelson et al., 1984). The studies reported variable conditioned responses: increased or decreased responses were found depending on various factors, including the US used. For example, cyclophosphamide injection as a US (Ader, 1976) led to conditioned corticosterone increase, while food as a US (Coover et al., 1977) led to a conditioned decrease of corticosterone. Six animal studies investigated conditioned insulin release: five of them found significant increases in insulin levels (Detke et al., 1989; Morrell et al., 1988; Roozendaal et al., 1990; Woods, 1972a,b; Woods et al., 1977), while one found null results (Surwit et al., 1985). Oxytocin was investigated in two of animal trials (Onaka and Yagi, 1998; Tancin et al., 2001) of which both found a significant increase in conditioned oxytocin release. There were also single studies that demonstrated conditioned release of adrenaline, noradrenaline, and dopamine (Kassil et al., 1998), testosterone and luteinizing hormone (Graham and Desjardins, 1980) and melatonin (Golombek et al., 1994).

Human trials measured conditioned responses of several hormonal

Table 1
Animal studies (n = 26).

	Subjects Species (N, sex)[#]	Study design	Conditioned stimulus	Unconditioned stimulus Nature, Dose, Administration route	Conditioning protocol			Endocrine conditioned responses	Result
					Acquisition trials	Rest days	Evocation trials		
Ader, 1976; experiment 1	rats (9–12 per group, M)	between-subject, randomized; 10 groups: control (nondeprived, deprived, saccharine, cyclophosphamide), conditioned (saccharine, H_2O, deprived), nonconditioned (saccharine, H_2O, deprived)	0.1% saccharine solution	50 mg/kg cyclophosphamide injection	1	3	2	corticosterone in conditioned group	↑
Ader, 1976; experiment 2	rats (55, M)	between-subject, randomized; 4 groups: conditioned (saccharine, H_2O, deprived), nonconditioned (saccharine)	0.1% saccharine solution	50 mg/kg cyclophosphamide injection	1	3	1	corticosterone in conditioned group	↑
Barreto and Volpato, 2007	nile tilapia fish (75, mixed sex)	between-subject, randomized; 5 groups: conditioned, undisturbed control, CS only, US control (daily US except on the final day), US last day (daily US including the final day)	aeration off for 30 s	air emersion	10	1	1	cortisol in conditioned group	↑
Buske-Kirschbaum et al., 1996	rats (26, M)	between-subject, randomized; 3 groups: conditioned, unpaired, control (saline)	peppermint odor	0.1 mg/kg nicotine bitartrate injection	4	2	1	corticosterone	↑
Coover et al., 1977; experiment 1	rats (60, M)	between-subject, randomized; 2 × 5 design: food (fed, not fed) × sample time (0, 5, 10, 20, 50 min after CS)	experimenter entering the room	food	14	1	1	corticosterone in not fed group 50 min after CS	↓
Coover et al., 1977; experiment 2	rats (270, M)	between-subject, randomized; 3 × 4 × 3 design: food (conditioned fed, conditioned not fed, pseudoconditioned not fed) × trials number (1, 6, 14, 24) × sample time (0, 10, 20 min after the CS)	placing the animal in sound attenuating chamber	food	1, 6, 14, 24	1	1	corticosterone in conditioned not fed 1 trial corticosterone in conditioned not fed 6 trials corticosterone in conditioned not fed 14, 24 trials	↑ n.s. ↓
Coover et al., 1977; experiment 3	rats (120, M)	between-subject, randomized; 2 × 4 × 3 design: food (conditioned fed, conditioned not fed, pseudoconditioned not fed) × trials number (1, 14) × sample time (0, 10, 20 min after the CS)	placing the animal in sound attenuating chamber	food	1, 14	1	1	corticosterone in conditioned not fed 1 trial corticosterone in conditioned not fed 14 trials	n.s. ↓
Coover et al., 1980; experiment 1	rats (68, M)	between-subject, randomized; 2 groups: fed, unfed	experimenter entering the room	food	14	1	1	corticosterone in conditioned unfed 10 min after CS corticosterone in conditioned unfed 20 and 40 min after CS	↓ ↑
Coover et al., 1980; experiment 2	rats (92, M)	between-subject, randomized; 3 × 3 design: surgery (operated with ventromedial hypothalamus lesions, control operated, not operated) × group (decapitated immediately, fed, unfed)	placing the animal in sound attenuating chamber	food	14	1	1	corticosterone in operated unfed corticosterone in unfed 10 min after CS	n.s. ↓
Davis et al., 2005	rats (140, M)	between-subject, randomized; 2 × 2 × 2 design: sessions (5, 10) × CS (distinctive context, home cage) × test (nicotine test, saline test)	distinctive context room	1.0 ml/kg of body weight nicotine bitartrate	5, 10	1	1	corticosterone in distinctive context group	↑
Detke et al., 1989;	rats (8, M)	within-subject, pseudo-randomized order of trials.	long CS (A or B)- 35 sec noise; short CS (x)- 10 sec noise. The presentation of the US took place on Ax but not Bx trials	1 ml of 12.5% glucose solution	28 trials per session, several sessions		8 in replication 1 and 7 in replication 2	insulin in Ax condition	↑

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Table 1 (*continued*)

	Subjects Species (N, sex)[#]	Study design	Conditioned stimulus	Unconditioned stimulus Nature, Dose, Administration route	Conditioning protocol			Endocrine conditioned responses	Result
					Acquisition trials	Rest days	Evocation trials		
Dyck et al., 1990; experiment 1	mice (30, F)	between-subject, randomized; 5 groups: IL-1, IL-1 conditioned, IL-1 conditioned (no cues, not re-exposed), unconditioned, negative control	0.35% saccharine solution + injection of LiCl	0.2–0.5 mg of recombinant interleukin 1-beta injection	2	2	1	corticosterone in conditioned group	↑
Dyck et al., 1990; experiment 2	mice (50, F)	between-subject, randomized; 5 groups: IL-1, IL-1 conditioned (saccharine + LiCl); IL-1 conditioned (saccharine), IL-1 conditioned (no cues, not re-exposed), cue control unconditioned	0.35% saccharine solution + injection of LiCl	0.5 mg of recombinant interleukin 1-beta injection	1	1	1	corticosterone in conditioned group	↑
Dyck et al., 1990; experiment 3	mice (27, F)	between-subject, randomized; 3 groups: IL-1 conditioned, IL-1 conditioned (no cues, not re-exposed), negative control	peppermint odor	0.2 mg of recombinant interleukin 1-beta injection	4	7	1	corticosterone in conditioned group	↑
Exton et al., 1995	rats (58 first analysis, 28 control study, M)	between-subject, randomized; 4 groups: conditioned with saccharine, conditioned with water, saccharine only, water only	1% saccharine solution	1 ml intraperitoneal injection of lipopolysaccharide	1	7	1	corticosterone in conditioned group with saccharine	↓
Golombek et al., 1994	rats (60, M)	between-subject, randomized; 6 groups: US for training & no treatment at the day of trial, US for training & US for trial, CS + US for training & CS for trial, CS + US for training & no treatment on day of trial, CS + US for training, CS + US for trial, CS + US for treatment & US for trial	restricted water availability	lights off	7	1	1	pineal melatonin in CS + US for training & CS for trial	↑
Graham and Desjardins, 1980; experiment 1	rats (M)	between-subject, randomized; 5 groups: CS followed immediately by US, CS alone, CS followed by a 6-hour delay US, US alone, removal from the home cage and being handled	vapors of methyl salicylate	placing in a cage with a sexually receptive female	14	1	1	luteinizing hormone in conditioned group	↑
Graham and Desjardins, 1980; experiment 2	rats (M)	between-subject, randomized; 5 groups: CS followed immediately by US, CS alone, CS followed by a 6-hour delay US, US alone, removal from the home cage and being handled	vapors of methyl salicylate	placing in a cage with a sexually receptive female	14	1	1	testosterone in conditioned group	↑
Janz et al., 1991	rats (72, M)	between-subject, randomized; 5 groups: conditioned reexposed to saccharin, conditioned not reexposed, water followed by IL-1 on the training day, negative control (saline injection, and saccharin), US only group (drug on the test)	0.1% saccharine solution	5 ng interleukin	1	1	1	corticosterone in conditioned group	n.s.
Janz et al., 1996	rats (38, M)	between-subject, randomized; 4 groups: paired reexposed to saccharin, paired group not reexposed, the unpaired group received plain water followed by an LPS injection, the injection, cue, and water deprivation control group received saccharin followed by a saline injection	0.15% saccharine solution	ip injection of 50 µg lipopolysaccharide	1	5	1	corticosterone in conditioned group	↑
Kassil et al., 1998	rats (58, MF)	between-subject, randomized; 2 groups: experimental (conditioning: saccharine + rotation; test: saccharine); control (conditioning: water + rotation; test: saccharine)	2 ml of 0.2% saccharine solution	angular acceleration (rotation)	1	5, 10 and 15 days	3	adrenaline, noradrenaline, dopamine in conditioned group	↑

(*continued on next page*)

Table 1 (*continued*)

	Subjects Species (N, sex)[#]	Study design	Conditioned stimulus	Unconditioned stimulus Nature, Dose, Administration route	Conditioning protocol			Endocrine conditioned responses	Result
					Acquisition trials	Rest days	Evocation trials		
Kreutz et al., 1992	rats (11, M)	within-subject comparison:4 conditioning trials, 4 control trials (injection of saline and injection of Ringer solution), 2 test trials (injection of sodium saccharine and Ringer solution)	an intraarterial injection of 0.25 ml sodium saccharin solution	injection of 0.154 pmol corticotrophin-releasing factor dissolved in Ringer solution	4	2	2	corticosterone during test trials	↑
Morrell et al., 1988	mice (M)	between-subject, randomized; 4 groups: lean conditioned, lean control (US and CS not contingent), obese conditioned, obese control (US and CS not contingent)	odor of mentholatum for 5 min prior to feeding and 3 min during the feeding	food	21 days and 4 additional days	1 day and 2 weeks	2	insulin in the obese conditioned group	↑
Natelson et al., 1984	rhesus monkeys (6, M)	within-subject; test sessions (presentation of CS) and control sessions (no CS)	30-min tone	food	at least 1 month daily			cortisol during test trials	n.s.
Onaka and Yagi, 1998	rats (32, M)	between-subject, randomized; 3 groups: conditioned, control 1 (vehicle + US), control 2 (US + CS 2 h after)	sucrose solution (0.75–2.0 M) or NaCl	cholecystokinin octapeptide 20 mg/kg	1	3 h	1	oxytocin in conditioned group	↑
Pacheco-Lopez et al., 2004	rats (32, M)	between-subject, randomized; 4 groups: conditioned, conditioned not re-exposed, placebo, unconditioned	0.2% saccharin solution	2.0 mg/kg staphylococcal enterotoxin B, injection	1	6	1	corticosterone	↑
Roozendaal et al., 1990	rats (34, M)	within-subject, time points comparison; groups: control, central amygdala lesioned, sham-lesioned	sound of the door opening	food	5	2	1	insulin after the CS in sham-operated group and control groups	↑
Smotherman and Levine, 1980	rats (48, M)	between-subject; randomized; 6 groups: conditioned ACTH + milk, conditioned ACTH + water, conditioned saline + milk, conditioned saline + water, conditioned not injected + milk, not injected not conditioned + milk	sweetened milk solution	ip injections of lithium chloride (0.40 M, 7.5 ml/kg)	1		1	corticosterone in milk conditioned groups	↑
Smotherman et al., 1980; experiment 1	rats (37, M)	between-subject, randomized; 2 groups: conditioned and saline	sweetened milk solution	ip injections of lithium chloride (0.40 M, 7.5 ml/kg)	1		1	corticosterone in conditioned group	↑
Smotherman et al., 1980; experiment 2	rats (60, M)	between-subject; randomized; 2 × 3 design: treatments (conditioned, saline) × preexposures to CS (2, 5, 10)	sweetened milk solution	ip injections of lithium chloride (0.40 M, 7.5 ml/kg)	1		1	corticosterone in conditioned 2 and 5 preexposures groups	↑
Smotherman et al., 1980, experiment 4	rats (60, M)	between-subject; randomized; 6 groups: control, conditioned (with 5, 6, 7, 8, 9 or 10 preexposures)	sweetened milk solution	ip injections of lithium chloride (0.40 M, 7.5 ml/kg)	1		1	corticosterone in conditioned 5 and 6 preexposures groups	↑
Surwit et al., 1985	mice (24)	between-subject design, randomized; 2 × 3 design: group (obese, control) × conditioning (conditioned, CS without US, noncontingent CS and US)	metronome sound	shaking	7	1	1	insulin in conditioned group	n.s.
Tancin et al., 2001	cows (20, F)	within-subject comparison: milking and suckling in known and unknown surrounding	known surroundings	milking and suckling				oxytocin in unknown surroundings	↓
Woods et al., 1972	rats	between-subject, randomized; 3 groups: conditioned, control 1 (water on test trial), control 2 (US on test trial)	smell of menthol	300 mg/kg of tolbutamide	6		1	insulin in conditioned group	↑
Woods et al., 1977	rats (48, M)	between-subject, 6 groups: CS & US at 11:30, US at 11:30 & CS at random, CS at 11:25 & US at random, US & CS together but at a random time; ad libitum food & CS at random; ad libitum food & CS the random interval prior to the time the appropriate meal-fed rats received their food.	5 min of odor of mentholatum	food	21	1	1	insulin in meal fed groups	↑

[#] Number of species and sex reported if this information is available; M – males; F – females; US – unconditioned stimulus, CS – conditioned stimulus.

systems and almost all of them included measurements of several hormones at the same time. Consistent with animal trials, most of the human trials looked at conditioned responses of cortisol (5 out of 8). Four of these studies found significant conditioned decreased or increased cortisol levels (Benedetti et al., 2003; Hall et al., 2016; Sabbioni et al., 1997; Stockhorst et al., 2004) and one study had null results (Stockhorst et al., 1999). Insulin conditioning was the subject of interest in four the human studies: 2 of these studies demonstrated conditioned insulin increases (Stockhorst et al., 2004, 2011), while 2 found no conditioned changes in insulin (Overduin and Jansen, 1997; Stockhorst et al., 1999). Two human studies measured noradrenaline: one of these demonstrated a significant conditioned increase in noradrenaline (Stockhorst et al., 2004), while the other reported null results (Stockhorst et al., 1999). Significant increases in growth hormone was reported in two the studies (Benedetti et al., 2003; Stockhorst et al., 2004). Two human studies measured glucagon and both of them failed to find conditioned glucagon release (Stockhorst et al., 1999, 2004). One human study demonstrated significant conditioned decreases in adrenaline (epinephrine) (Stockhorst et al., 2011), and one study failed to find conditioned changes in endocrine indicators of nausea (adrenocorticotrophic hormone, antidiuretic hormone, pancreatic polypeptide) (Klosterhalfen et al., 2000). In general, there were more null results found in human studies than in animal studies.

3.3. Study designs

The two-phase conditioning design of the studies included acquisition and evocation trials. In acquisition trials, a US that triggered certain hormonal changes (UR) was associated with an initially neutral stimulus (becoming the CS). In the evocation trial(s), only the CS was presented and conditioned hormonal responses (CR) were measured.

The number of acquisition and evocation trials varied across the studies. Animal trials in general had many acquisition trials, varying from 1 (e.g. Ader, 1976; Pacheco-Lopez et al., 2004) up to 28 (Detke et al., 1989), while human studies had between 1 (Klosterhalfen et al., 2000) and 6 (Overduin and Jansen, 1997; Stockhorst et al., 2011) acquisition trials. In contrast, the majority of studies included only 1 evocation trial: 19 animal studies (e.g., Barreto and Volpato, 2007; Buske-Kirschbaum et al., 1996) and 7 human studies (e.g., Benedetti et al., 2003; Hall et al., 2016). The maximum number of evocation trials in animal studies was 8 (Detke et al., 1989) and in human studies 6 (Stockhorst et al., 2011).

Most of the studies employed a between-subject design: 21 of animal studies (e.g., Ader, 1976; Barreto and Volpato, 2007) and 7 human studies (e.g., Benedetti et al., 2003; Klosterhalfen et al., 2000; Overduin and Jansen, 1997). In general, animal studies included multiple control groups, including an undisturbed control (no manipulations done) (Barreto and Volpato, 2007), a CS only (Barreto and Volpato, 2007), a US only (Janz et al., 1991), an unpaired (US and CS are presented in an uncoupled manner) (Janz et al., 1996), a conditioned not re-exposed (CS is not presented during the evocation) (Pacheco-Lopez et al., 2004), or a placebo control group (a placebo was used instead of a US) (Dyck et al., 1990). Most human studies (6 out of 8) included a placebo control group (Benedetti et al., 2003; Overduin and Jansen, 1997; Sabbioni et al., 1997; Stockhorst et al., 1999, 2004, 2011). One other study included a control group in which the CS was given an hour before the US (Klosterhalfen et al., 2000) and one study employed a within-group comparison (Hall et al., 2016).

The US used to elicit hormonal changes varied between the studies. For example, food was often used as a US in order to elicit insulin release (e.g., Coover et al., 1977; Natelson et al., 1984), while administration of various agents including cyclophosphamide (Ader, 1976), nicotine bitartrate (Buske-Kirschbaum et al., 1996; Davis et al., 2005), and corticotrophin-releasing factor (Kreutz et al., 1992) were used for the conditioning of hormone release (e.g., corticosterone).

The CS also varied across the studies. Most of the animal studies used taste (10 out of 26) (e.g., Ader, 1976; Dyck et al., 1990), smell (6 out of 26) (e.g., Buske-Kirschbaum et al., 1996; Dyck et al., 1990), or sound (6 out of 26) (e.g., Coover et al., 1977; Detke et al., 1989) as a CS. In two animal studies, distinctive surroundings, such as placing animal in an unknown room, were used as a CS (Davis et al., 2005; Tancin et al., 2001). Single animal studies used other CS such as restricting water availability (Golombek et al., 1994), switching off the aeration in the fish tank (Barreto and Volpato, 2007) and intra-arterial injection of sodium saccharin solution (Kreutz et al., 1992). Among human studies, also smell (3 out of 8) (Stockhorst et al., 1999, 2004, 2011) and taste (2 out of 8) (Klosterhalfen et al., 2000; Sabbioni et al., 1997) were the most commonly used CS. Single human studies used other CS: both smell and taste (Overduin and Jansen, 1997), an injection procedure (Benedetti et al., 2003) and an experimental context (Hall et al., 2016).

3.4. Risk of bias assessment

The results of the risk of bias assessment are presented in Figs. 2 and 3, for animal and human studies separately. Most animal studies lack important information to evaluate risk of bias and were assigned an unclear risk of bias. Human studies provide more details regarding the procedures and, therefore, in general have lower risk of bias. The results of the studies with the higher risk of bias did not differ from the results of the studies with the lower risk of bias: several studies that demonstrated null results (Janz et al., 1991; Klosterhalfen et al., 2000; Natelson et al., 1984; Overduin and Jansen, 1997; Stockhorst et al., 1999; Surwit et al., 1985) had the same risk of bias as other studies that reported significant findings.

4. Discussion

This is the first review systematically summarizing findings of studies on intentional conditioning of the endocrine system in both animals and humans. Findings of classical conditioning studies using a two-phase design incorporating acquisition and evocation trials were systematically reviewed. This review demonstrates that there is an accumulating evidence from both animal and human studies that classical conditioning processes are able to influence specific endocrine responses. Some endocrine responses have been more thoroughly studied, such as corticosterone/cortisol and insulin, while fewer studies looked at other hormones, such as testosterone, luteinizing hormone, oxytocin, growth hormone, glucagon and melatonin, adrenaline, and noradrenaline. Most notably, animal and human studies were generally consistent in their findings: conditioned responses were found in the same endocrine systems in both animal and human trials. Nevertheless, some methodological caveats exist that need attention in future research.

The present review demonstrated that not all endocrine systems were investigated equally in the context of classical conditioning. The majority of the studies focused on hypothalamus-pituitaryadrenal axis and on insulin responses, while evidence for other hormones is very limited or absent. Future studies should focus on other endocrine parameters, especially those that play a possible role in the treatment of diseases, such as thyroid hormone, growth hormone, prolactin, adrenocorticotropic hormone etc.

Additionally, the majority of the studies were performed in males and none of them looked at the possible moderation of the conditioned response by gender. So far there is no evidence that gender moderates placebo effects (Weimer et al., 2015). Nevertheless, considering the gender specificity of the endocrine responses, future research should examine possible differences in endocrine conditioning between males and females.

We have also documented that the results of the animal studies are more extensive than the results of the human studies and most of the animal studies found coherent conditioned endocrine responses. The human studies vary more in this respect. Only two human studies

Table 2
Human studies (n = 8).

Authors, year of publication	Subjects N (sex)[#]	Study design	Conditioned stimulus	Unconditioned stimulus Nature, Dose, Administration route	Conditioning protocol			Endocrine conditioned responses	Result
					Acquisition trials	Rest days	Evocation trials		
Benedetti et al., 2003	95 (47 M, 48F)	between- subject, randomized; 9 groups: conditioned and control groups with various suggestions	injection procedure	sumatriptan injection	2	1	1	growth hormone levels in the conditioned groups cortisol levels in the conditioned groups	↑ ↓
Hall et al., 2016	32 (F)	within-group comparison for cortisol, 4 conditioned groups: latent inhibition with overshadowing, latent inhibition, overshadowing, control	context of rotation	rotation	2	1	1	cortisol after the CS presentation in all groups	↑
Klosterhalfen et al., 2000	90 (42 M, 48F)	between-subject, randomized; 2 groups: conditioned, control (CS 1 h before US)	100 ml elder-berry juice	rotation procedure	1	7	1	adrenocorticotrophic hormone, antidiuretic hormone, pancreatic polypeptide in conditioned group	n.s.
Overduin and Jansen, 1997	20 (F)	between-group, randomized; 2 groups: conditioned, placebo	peppermint flavor	50 g ad lib glucose	6	2	1	insulin levels in conditioned group	n.s.
Sabbioni et al., 1997	25 (M)	between-subject, randomized; 2 groups: conditioned, placebo	lemon-lime with bitter tonic beverage	5 ml dexamethasone ad lib	3	7	1	plasma cortisol levels in conditioned group	↑
Stockhorst et al., 1999	20 (M)	between- subject, randomized; 2 groups: conditioned, placebo	rosewood–peppermint oil smell	intravenous insulin injection (0.035 units/kg)	4	1	1	insulin in conditioned group glucagon in conditioned group noradrenaline in conditioned group cortisol in conditioned group	n.s. n.s. n.s. n.s.
Stockhorst et al., 2004	30 (M)	between-subject, randomized; 3 groups: insulin conditioned, glucose conditioned, placebo	rosewood-peppermint oil smell	intravenous insulin injection (0.05 IU/kg) or intravenous glucose injection (15%, 0.5 g/kg)	4	2	1	cortisol, insulin in the glucose conditioned group glucagon in the glucose conditioned group noradrenaline, growth hormone in the insulin conditioned group	↑ n.s. ↑
Stockhorst et al., 2011	32 (M)	between-subject, randomized; 2 groups: conditioned, placebo	smell of meta-cresol	soluble H-insulin intranasal spray (20U[0.2 ml])	6	1	6	peripheral insulin in conditioned group epinephrine in conditioned group	↑ ↓

[#] Number of species and sex reported if this information is available; M – males; F – females; US – unconditioned stimulus, CS – conditioned stimulus.

reviewed here found conditioned cortisol changes and since the review search was done, one newly appeared study failed to condition the cortisol response in humans (Petrakova et al., 2017). Also conditioning of insulin responses was less successful in human studies compared to animal studies. Possibly, conditionability of insulin responses in humans depends more on the US Stockhorst et al. (2011) demonstrated that it is possible to condition insulin release using intranasal insulin spray as a US, but not when using an intravenous insulin injection (Stockhorst et al., 1999). Another difference between animal and human research that might lead to different findings, is the number of acquisition trials. Animal studies in general have more acquisition trials than human studies. Possibly, a low number of acquisition trials in human research might lead to more contradictory results, as a small number of acquisition trials might not always be enough to establish the association between the US and the CS.

In general, the limited number of human studies makes it difficult to generalize the results of the animal research to humans. Several methodological limitations exist that complicate human endocrine conditioning experiments. First of all, application of a two-phase design is time consuming, since it implies several sessions with the administration of pharmacological agents and acquiring biological samples, which is done easier in animals than in humans. Moreover, the environment in animal studies is more controllable in comparison to human studies. Various factors that are difficult to strictly control in humans over a period of time, such as food consumption, physical activity, and psychogenic stressors, can confound human research, potentially creating noise in the outcomes. Finally, cognitions and expectations might play an additional role in the conditioned hormone release in humans. Although Benedetti et al. (2003) showed that giving verbal suggestions regarding the change of cortisol and growth hormone levels did not influence the secretion of these hormones, other studies with an experimental classical conditioning design did not take the expectations of the participants in consideration. Presentation of the CS can trigger cognitive expectations that have to be taken into account while interpreting the results. For future research, it is important to further identify the role of expectancies and cognitions in the classically conditioned hormone release, because these can be possibly manipulated in clinical practice.

It is also important to point out that there was no consistency in the reviewed studies regarding the exact study design or procedures that were used to condition endocrine responses. Different number of acquisition and evocation trials were used in different studies. To date it is unclear what number of acquisition trials is optimal to develop conditioned responses in the endocrine system, and whether this is dependent on the species that is being examined, the conditioned drug of interest, or other factors such as the context of conditioning. Only two studies included in this review compared the effectiveness of different numbers of acquisition trials in eliciting conditioned endocrine responses and both of them concerned conditioned corticosterone. Coover et al. (1977) showed that conditioned corticosterone decreased in response to a CS associated with feeding after 14 acquisition trials, but that 6 trials were not enough to demonstrate this response. Davis et al. (2005) demonstrated that conditioned corticosterone release already developed after 5 pairing of nicotine bitartrate with a distinctive context and this release increased marginally after 10 acquisition trials. These results are generally in line with the research on conditioned immune responses that demonstrated that more acquisition trials may lead to a stronger conditioned response (Barrett et al., 2000), however more research in the endocrine system is needed to confirm this proposition in relation to the nature and intensity of the US. The number of evocation trials was significantly lower than the number of acquisition trials: the majority of studies used only 1 evocation trial to test whether conditioning took place. This general use of only 1 evocation trial makes it unfortunately impossible to study the extinction process in the endocrine system, since more evocation trials are needed to see how fast the classically conditioned endocrine responses disappear.

A wide variety was found regarding the different types of the CS that were used in the different studies. Most of the animal and human trials used either gustatory (e.g.: Buske-Kirschbaum et al., 1992; Sabbioni et al., 1997) or olfactory (e.g.: Overduin and Jansen, 1997; Stockhorst et al., 2004) conditioned stimuli. It was previously reported that gustatory and olfactory CS associate with visceral US stronger than other types of CS (Domjan, 1973, 2005; Pacheco-Lopez et al., 2007). This can be explained by the naturalistic association and biological importance of such stimuli, because they are associated with food intake and are important for survival. However, other types of CS were also employed in a few studies and were successfully associated with endocrine changes. For example, Benedetti et al. (2003) used an injection procedure as a CS to condition changes in cortisol. Speculatively, the nature of the CS seems of marginal significance since conditioned effects were found with both biologically relevant and other types of CS, but future studies may investigate this further and compare the efficiency of various CSs.

Finally, only one of the reviewed studies looked into the neuronal mechanisms of the conditioned endocrine responses. Roozendaal et al. (1990) demonstrated that the central nucleus of the amygdala was involved in the conditioned insulin release and its lesioning abolished this conditioned response in rats. The most well-investigated neural pathways of conditioning are the mechanisms involved in the conditioning of pain responses: it was demonstrated that the descending pain control system gets activated during placebo analgesia (Eippert et al., 2009). Possibly, these findings can be extended to endocrine conditioning in that brain regions responsible for endocrine regulation are also responsible for the release of hormones during conditioning. Nevertheless, this remains only a speculation and future research should focus on further identifying the neural pathways that underlie conditioned endocrine responses in both animals and humans.

The main limitation of this review is heterogeneity of the included studies that makes it difficult to compare them and make definitive conclusions. There is no standard conditioning design established and,

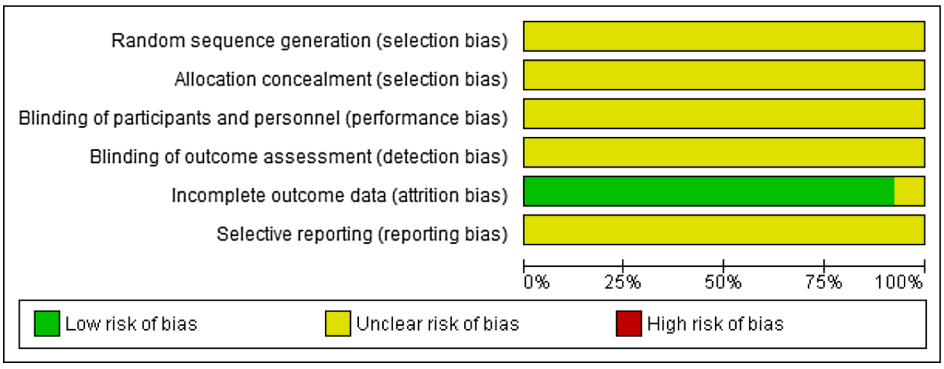

Fig. 2. Risk of bias for animal studies. Risk of bias is presented as a percentage across all included studies and for each separate study.

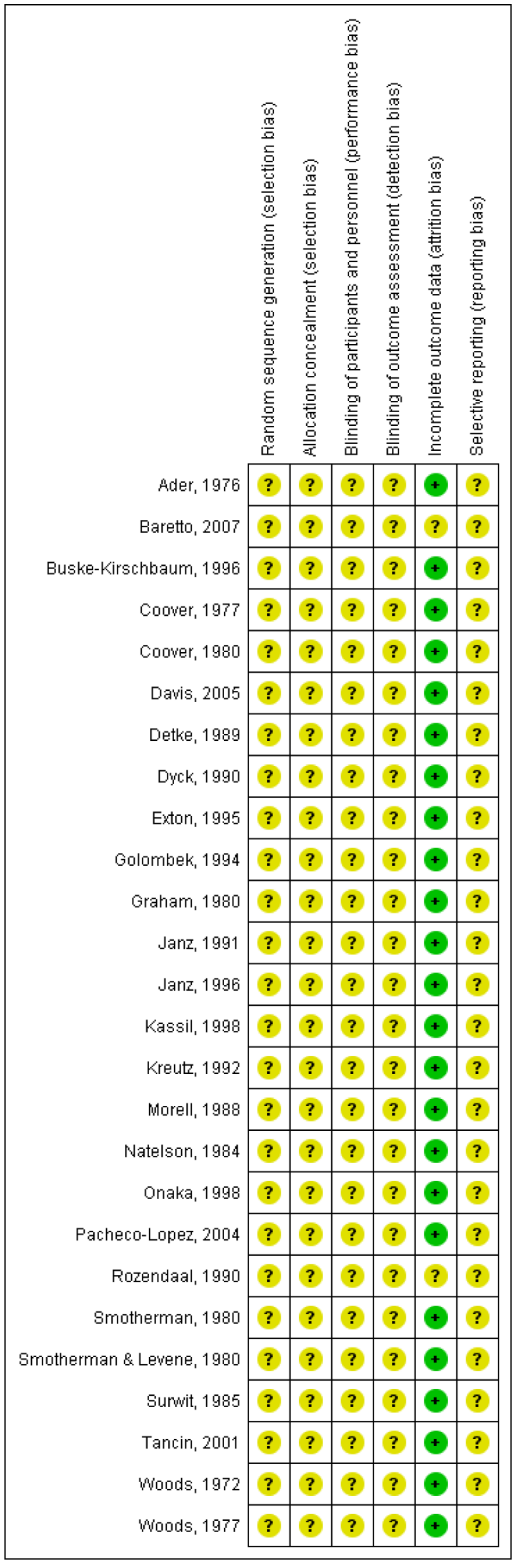

Fig. 2. (*continued*)

therefore, every experiment recruited a different procedure for the conditioning of endocrine responses. In case of null results, such variability in procedures makes it difficult to conclude whether the failure to find conditioned responses was caused by an unappropriated experimental design or by the fact that the certain endocrine system is not malleable to conditioning.

Several methodological aspects of the present review have to be mentioned. The review has not included studies on anticipatory hormone release induced by incidental learning: that is considered to be a conditioned response to naturally occurring conditioned stimuli such as a particular time of the day, called "Zeitgeber" (Ehlers et al., 1988). Incidental classical conditioning in this case is established naturally already before the start of the experiment, as for example, increase in insulin levels in response to a food taste without the food ingestion (e.g., Berthoud et al., 1981). Instead, in this review we focused on intentional conditioning studies that included acquisition and evocation phases and established a connection between initially neutral stimulus and an US. Additionally, the present review did not include glucose conditioning studies (e.g., Siegel, 1972; Woods, 1976) even though conditioned changes in glucose levels might indicate conditioned insulin response. This link between conditioned insulin and glucose responses not always seem to exist, as for example, Stockhorst et al. (1999) found a conditioned glucose decrease during conditioning with intravenous insulin but no conditioned changes in insulin levels. As it is not possible to prove that conditioned changes in glucose are triggered by conditioned insulin response, studies that measured only glucose – and therefore no hormonal outcomes – were not included in this review.

This review shows promising results for applying mechanisms of classical conditioning in clinical practice. For instance, it was demonstrated that cortisol levels can be increased (Sabbioni et al., 1997) using the classical conditioning procedures. Administration of cortisone (a prodrug of cortisol) can have fear-reducing effects in phobic patients (Soravia et al., 2006) and might prevent the occurrence or reduce the severity of post-traumatic stress disorder after a traumatic event (Amos et al., 2014). Therefore, speculatively, using the classical conditioning procedure to elicit endogenous cortisol release might be beneficial for these groups of patients. Another clinically relevant example could be applying classical conditioning of insulin responses as demonstrated by Stockhorst et al (2011) in healthy control subjects to patients with diabetes type-2 who suffer from dysfunctional insulin system and heightened glucose levels.

Also, placebo-controlled dose reduction is based on the principles of classical conditioning (Rief et al., 2011). It was demonstrated that placebo-controlled dose reduction can be as efficient as full treatment for ADHD and psoriasis (Ader et al., 2010; Sandler et al., 2010). Although these two studies did not measure endocrine parameters and the mechanisms of the symptoms reduction remain therefore unclear, it might be possible that the classical conditioning procedure triggered endocrine changes that lead to the reduction of symptoms.

Finally, unwanted side effects of medications, nocebo effects, can be triggered by classically conditioned endocrine and other pharmacological responses (Benedetti et al., 2003). For example, Hall et al. (2016) showed that nausea as well as cortisol release can be simultaneously classically conditioned and that there effects can be diminished using overshadowing (presentation of a salient additional cue at the time of conditioning). This principle could be applied to other unwanted side effects, for example, nausea caused by chemotherapy in cancer patients, that has been proposed to be triggered by classical conditioning and shown to be related to heightened cortisol levels (Stockhorst et al., 1998). Presenting a salient cue such as a distinctive drink along with chemotherapy, might decrease the conditioned nausea and cortisol levels. It would be also worthwhile for future studies to look into possibilities of using overshadowing for the modification of other endocrine conditioned responses.

Overall, despite the heterogeneity of the described studies, this systematic review delivers supportive evidence that endocrine levels can be influenced by classical conditioning mechanisms, at least for certain endocrine parameters (e.g., insulin and cortisol) in animal studies and to a lesser extent in human studies. Nevertheless, to be able to use classical conditioning in clinical practice, several concrete questions still have to be answered by future research. First, it is important to investigate if all hormones can be influenced by conditioning and how

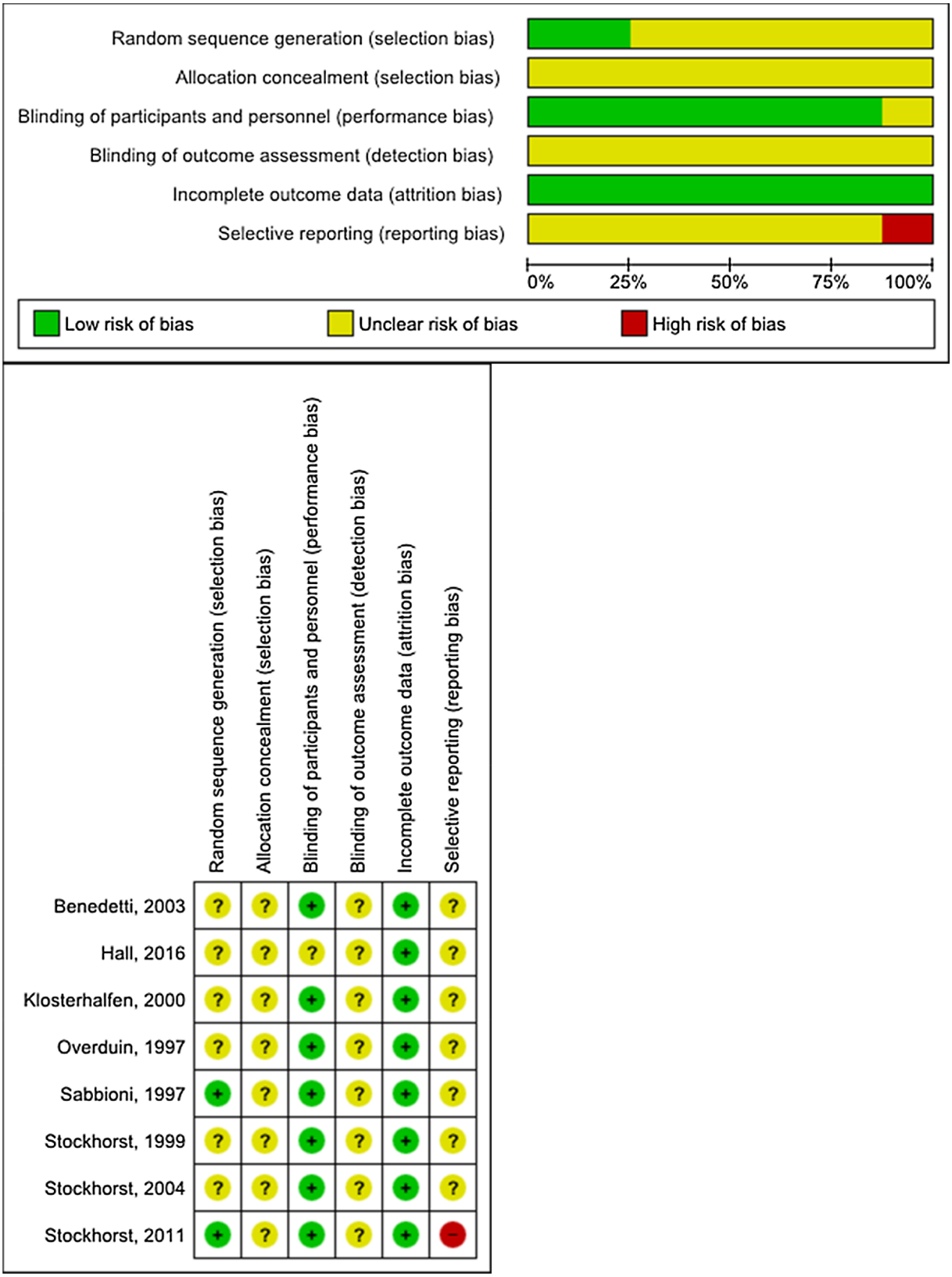

Fig. 3. Risk of bias for human studies. Risk of bias is presented as a percentage across all included studies and for each separate study.

conditioned hormone responses generalize to the other hormonal and immune parameters. Second, more insight is needed in the extinction of the conditioned hormonal responses and the optimal way to reinforce them. Moreover, individual differences and possible predictors of endocrine responses remain underexplored. Finally, more knowledge is needed about how the conditioned responses influence various health outcomes and behavior. It is important that laboratory studies focus on investigating classical conditioning phenomena in various hormonal systems and use controlled designs of high methodological quality. Clinical trials may further explore the possibilities of applying the conditioning paradigms in clinical settings for dose reductions, enhancements of treatment favorable endocrine parameters, and reduction of unfavorable conditioned endocrine responses.

Conflict of interest

None.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yfrne.2018.12.005.

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