**Table 1** Study characteristics: design characteristics of included studies.

| **Study** | **Method** | **Materials** | **Groups** | **Outcome** |
| --- | --- | --- | --- | --- |
| **Endocrine** | **Immune** | **Other** |
| Albring 2014, Experiment A[[23](#_ENREF_23)] | **Participants:** Healthy male volunteers (18-40yrs, mean age 26.0; sd 4.5)**N acquisition trial(s):** 4 (in 3 days)**N evocation trial(s):** 14 (in 7 days)5-day interval between last acquisition and first evocation | **CS:** 150 ml strawberry milk with 1 drop of lavender oil, dyed green**UCS:** CsA, 2.5mg/kg capsulated per os (p.o.)CS and UCS administered at same time**Measurement type:** Blood | **Conditioning:**1) taste + CsA (N=20)**Control:**2) taste + placebo (N=15) | plasma cortisolplasma epinephrine plasma norepinephrine  | **IL-2 production by peripheral blood mononuclear cells**IL-2 mRNA expression, CD3+ and CD3+CD4+ lymphocyte numbers | heart rate systolic blood pressurediastolic blood pressureSTAI |
| Albring 2012Experiment B[[19](#_ENREF_19)] | **Participants:** Healthy male volunteers (18-40yrs, mean age 26.9; sd 0.9)**N acquisition trial(s):** 4 (in 3 days)**N evocation trial(s):** 1 8-day interval between last acquisition and evocation | **CS:** 150 ml strawberry milk with 1 drop of lavender oil, dyed green**UCS:** CsA, 2.5mg/kg capsulated per os (p.o.)CS and UCS administered at same time**Measurement type:** Blood | **Conditioning:**1) taste + CsA (N=10)**Control:**2) taste + placebo (N=9) |  | **IL-2 production by peripheral blood mononuclear cells** |  |
| Barrett 2000Experiment 1[[27](#_ENREF_27)] | **Participants:** Patients with allergic rhinitis (age range N.A.; mean age N.A.; sd N.A.; sex N.A.)**N acquisition trial(s):** 1 **N evocation trial(s):** 2 (in approx. 2 weeks)Approx. 1-week interval between last acquisition and first evocation, approx. 1-week interval between the two evocations | **CS:** 10ml benzoaldehyde**UCS:** seasonal grass allergen intranasallyCS before UCS**Measurement type:** Nasal release, self-report | **Conditioning:**1) smell + allergen (N=15)**Control:**2) smell + placebo (N=15),3) no smell + allergen (N=15), 4) no smell + placebo (N=15) |  | **histamine release** | PNIF,Allergic symptoms |
| Buske-Kirschbaum 1992[[24](#_ENREF_24)] | **Participants:** Healthy volunteers (age range N.A.; mean age N.A.; sd N.A.; sex N.A.)**N acquisition trial(s):** 4 (on 4 consecutive days)**N evocation trial(s):** 1Evocation on day after last acquisition | **CS:** sherbet sweet**UCS:** Epinephrine, 0.2mg subcutaneouslyCS immediately before UCS**Measurement type:** Blood | **Conditioning:**1) taste/tactile + epinephrine (N=6)**Control:**2) taste/tactile + saline (N=6)3) taste/tactile + epinephrine (non-contingent) (N=6),4) taste/tactile + epinephrine (also in evocation) (N=6) | plasma epinephrine | **natural killer cell activity** |  |
| Gauci 1994[[28](#_ENREF_28)] | **Participants:** patients with house dust mite allergy (16f, 5m; 19-55yrs; mean age N.A.; sd N.A.)**N acquisition trial(s):** 1**N evocation trial(s):** 1Evocation 2 days after acquisition | **CS:** 200ml soda water with methyl anthranilate and benzaldehyde dyed blue**UCS:** house dust mite allergen intranasallyCS immediately before UCS**Measurement type:** Nasal release, self-report | **Conditioning:**1) taste+ allergen (N=9)**Control:**2) taste + saline (N=5)3) water + allergen (N=8) |  | **tryptase release** | Allergic symptoms |
| Goebel 2002[[20](#_ENREF_20)] | **Participants:** Healthy male volunteers (age range N.A.; mean age 26.7; sd 4.2)**N acquisition trial(s):** 4 (in 3 days)**N evocation trial(s):** 4 (in 3 days)Evocation 5 days after acquisition | **CS:** 150 ml strawberry milk with 1 drop of lavender oil, dyed green**UCS:** CsA, 2.5mg/kg capsulated per os (p.o.)CS and UCS at same time**Measurement type:** Blood | **Conditioning:**1) taste + CsA (N=18)**Control:**2) taste + Placebo (N=16) |  | **IL-2 and IFN-γ production by CD3+CD4+ lymphocytes**IL-2 and IFN-γ mRNA expression,IL-2 and IFN-γ in vitro release, Lymphocyte proliferation |  |
| Grigoleit 2012[[25](#_ENREF_25)] | **Participants:** Healthy male volunteers (age range N.A.; mean age 26.6; sd 4.9)**N acquisition trial(s):** 1**N evocation trial(s):** 1Evocation 5 days after acquisition | **CS:** 150 ml strawberry milk with 1 drop of lavender oil, dyed green**UCS:** Lipolpolysaccharide 0.4mg/kg intravenousCS immediately after UCS**Measurement type:** Blood, body temperature, self-report | **Conditioning:**1) taste + liposaccharide (N=10) **Control:**2) taste + saline (N=10) |  | plasma concentrations of TNF-α, IL-6, IL-10 | STAI, POMS,body temperature,taste and odor rating of the CS |
| Longo 1999[[26](#_ENREF_26)] | **Participants:** Healthy volunteers (18-50 years; mean age N.A.; sd N.A.; 17 f, 14 m)**Intermittent treatment design****Acquisition trial(s):** 7(in two sets of 4 and 3 across two weeks; second set took place 4 days after the first set)**Evocation trials:** 7(across two weeks interrupted by two booster trials)First evocation on day after last acquisition; booster trials after first and second evocation | **CS:** 0.5ml propylene glycol**UCS:** rhIFN-γ 0.1mg/m2 sub cutaneousCS 1 – 5 minutes before UCS**Measurement type:** Blood | **Conditioning:**1) taste + rhIFN-γ (n=10)**Control:**2) taste + normal saline (n=10)3) rhIFN-γ only (n=11) | early morning serum cortisol | **quinolinic acid****neopterin**CD14, CD64, HLA-A,-B,-C, -DR antigen expression on mononuclear cells |  |
| Ober 2012[[21](#_ENREF_21)] | **Participants:** Healthy male volunteers (age range 18-33; mean age 25.3; sd 3.9)**N acquisition trial(s):**  4 (in 3 days)**N evocation trial(s):** 4 (in 3 days)Evocation 5 days after acquisition | **CS:** 150 ml strawberry milk with 1 drop of lavender oil, dyed green**UCS:** CsA, 2.5mg/kg capsulated per os (p.o.)CS and UCS at the same time**Measurement type:** Blood, self-report | **Conditioning:**1) taste+ CsA (N=32)**Control:**2) taste + placebo (N=14) |  | **IL-2 production by peripheral blood mononuclear cells**  | taste of the CS |
| Overduin 1997[[31](#_ENREF_31)] | **Participants:** Healthy female volunteers (age range N.A.; mean age 19.9; sd 1.9)**N acquisition trial(s):** 6 (in three sets of 2 interrupted by two “non-conditioning” sessions and a 2 day weekend break)**N evocation trial(s):** 1 Evocation trial on day after last acquisition | **CS:** smell of peppermint/mentholatum, taste of peppermint/mentholatum flavor**UCS:** glucose 50g dissolved in 30cl water per os (p.o.)CS before UCS**Measurement type:** Blood, self-report | **Conditioning:**1) smell, taste + glucose (n=10)**Control:**2) smell, taste + placebo (n=10)Subsequently run plain water condition:3) smell, taste + water (n=9) Healthy female volunteers (age range N.A.; mean age=23.1 sd=2.9) | **blood glucose**serum insulinserum c-peptideplasma glucagon |  | hunger, thirst, tension, craving for salty/sweet food |
| Sabbioni 1997[[33](#_ENREF_33)] | **Participants:** Healthy male volunteers (age range 20-43; mean age 30.5; sd 7.6)**N acquisition trial(s):** 3 in 3 weeks, one trial every week)**N evocation trial(s):** 1Evocation trial one or two weeks after last acquisition | **CS:** mix of lime Kool Aid and Bitter Tonic**UCS:** dexamethasone 5mg capsulated per os (p.o.)CS-UCS sequence not reported**Measurement type:** Blood | **Conditioning:**1) taste + 5 mg dexamethasone (N=8)**Control:**2) taste + placebo (N=7) | **plasma cortisol** |  | plasma dexamethasone |
| Stockhorst 1999[[29](#_ENREF_29)] | **Participants:** Healthy male volunteers (age range20-30yrs; mean age G1: 25.2; SEM=0.7; G2: 24.3; SEM=0.7) **N acquisition trial(s):** 4(on 4 consecutive days)**N evocation trial(s):** 1Evocation on the day after last acquisition | **CS:** rosewood and peppermint oil**UCS:** insulin, 0.035IU/kg intravenouslyCS before and during UCS**Measurement type:** Blood, self-report | **Conditioning:**1) smell +insulin (N=10)**Control:**2) smell + placebo (N=10) | **blood glucose**serum insulinplasma glucagon plasma epinephrineplasma norepinephrine serum cortisol |  | Neuroglycopenic symptoms |
| Stockhorst 2004[[30](#_ENREF_30)] | **Participants:** Healthy male volunteers ( age range 20-30yrs; mean age G1: 25.2; SEM=0.9; G2: 24.4; SEM=0.8G3: 25.0; SEM=1.0)**N acquisition trial(s):** 4(on 4 days separated by 48h)**N evocation trial(s):** 1Evocation trial 48h after last acquisition | **CS:** rosewood and peppermint oil**UCS:** inulin, 0.05IU/kg intravenously or glucose 0.5g/kg intravenouslyCS before and during UCS**Measurement type:** Blood, self-report | **Conditioning:**1) smell +insulin (N=10)2) smell +glucose (N=10)**Control:**3) smell + placebo (N=10) | **blood glucose**serum insulin, plasma glucagon, plasma epinephrine plasma norepinephrine serum cortisol serum growth hormone |  | Neuroglycopenic symptoms |
| Stockhorst 2011[[32](#_ENREF_32)] | **Participants:** Healthy male volunteers (age range N.A.; mean age=24.2; SEM=0.5)**N acquisition trial(s):** 6 (in one day, 15 min apart)**N evocation trial(s):** 6 (in one day, 15 min apart)Evocation on day after acquisition | **CS:** Meta-cresol (stabilizing vehicle agent of the insulin nose-spay)**UCS:** insulin 20U (0.2ml) intranasally, 0.1ml/nostrilCS and UCS at same time**Measurement type:** Blood | **Conditioning:**1) smell + nasal insulin (N=16)**Control:**2) smell + nasal placebo (N=16) | **blood glucose**serum insulinplasma leptinplasma epinephrine plasma norepinephrineserum cortisol |  |  |
| Vits 2013[[9](#_ENREF_9)] | **Participants:** Patients with house dust mite allergy (age range N.A.; mean age 30.3; sd 8.6; 37 f, 25 m)**N acquisition trial(s):** 5**N evocation trial(s):** 5Evocation 9 days after acquisition  | **CS:** 150 ml strawberry milk with 1 drop of lavender oil, dyed green**UCS:** desloratadine 0.5mg per os (p.o.)CS and UCS at the same time**Measurement type:** Skin prick, nasal provocation | **Conditioning:**1) taste + desloratadine (5mg) (N=25)**Control:**2) taste + placebo (N= 25)3) natural history (N=12) |  | **wheal size** | Allergic symptoms |
| Wirth 2011Experiment 2[[22](#_ENREF_22)] | **Participants:** Healthy male volunteers (age range 18-40; mean age 25.7; sd 4.2)**N acquisition trial(s):** 4 (in 3 days)**N evocation trial(s):** 8 (in 2 sets of 4, each in 3 days)5-day interval between last acquisition and first evocation set 1, 11 day interval between last evocation set 1 and first evocation set 2 | CS: 150 ml strawberry milk with 1 drop of lavender oil, dyed greenUCS: CsA, 2.5mg/kg capsulated per os (p.o.)CS and UCS at the same timeMeasurement type: Blood, autonomic, self-report | Conditioning:1) taste + CsA (2,5mg/kg) (N=17) Control:2) taste + placebo (N=15) | norepinephrine, epinephrine, cortisol plasma levels | IL-2 and IFN-γ production by peripheral blood mononuclear cells CD3+ cells, CD4+ cells | taste of the CS |

Primary outcomes are printed boldly; sd = standard deviation, N.A. = not available, IL = Interleukin, (mRNA), STAI= State trait anxiety inventory, CsA = Cyclosporine A, IFN-γ = interferon gamma,

CS = conditioned stimulus, PNIF = peak nasal inspiratory flow, TNF-α = tumor necrosis factor alpha, POMS = profile of mood states.

**Table 2** Study outcomes: effects of conditioning found by included studies.

| **Unconditioned Stimulus** | **Study** | **Outcome measure** |  | **Result** |
| --- | --- | --- | --- | --- |
|  |  |  |  |  |
| **Cyclosporine A** |  |  |  |  |
|  | Albring 2014 [[23](#_ENREF_23)] | IL-2 production by pbmcIL-2 mRNA expression CD3+ and CD3+CD4+ lymphocyte numbersplasma cortisol, plasma epinephrine, plasma norepinephrineheart rate, systolic blood pressure, diastolic blood pressure, STAI |  | ↓\*↓\*n.s. |
|  | Albring 2012 [[19](#_ENREF_19)] | stimulated in vitro release of IL-2 |  | n.s. |
|  | Goebel 2002 [[20](#_ENREF_20)] | IL-2 mRNA expressionproduction of IL-2 by CD3+CD4+ lymphocytesin vitro release of IL-2IFN-γ mRNA expressionproduction of IFN-γ by CD3+CD4+ lymphocytesin vitro release of IFN-γlymphocyte proliferation |  | ↓\*↓\*\*↓\*↓\*↓\*\*↓\*↓\*\* |
|  | Ober 2012 [[21](#_ENREF_21)] | IL-2 production by pbmctaste of the CS |  | ↓\*\*n.s. |
|  | Wirth 2011 [[22](#_ENREF_22)] | IL-2 production by pbmcIFN-γ production by pbmcnumber of CD3+ and CD3+CD4+ cells plasma cortisol, plasma epinephrine, plasma norepinephrine taste of the CS |  | ↓\*\*↓\*n.s.n.s.↓\*\* |
|  |  |  |  |  |
| **Allergens** |  |  |  |  |
|  | Barrett 2000 [[27](#_ENREF_27)] | histamine releasePNIFsymptoms |  | ↑\*\*↓\*\*(only 1st evoc)n.s. |
|  | Gauci 1996 [[28](#_ENREF_28)] | tryptase releasesymptoms |  | ↑\*n.s. |
|  |  |  |  |  |
| **Desloratadine** |  |  |  |  |
|  | Vits 2013 [[9](#_ENREF_9)] | wheal sizesymptoms |  | n.s.n.s. |
|  |  |  |  |  |
| **Epinephrine** |  |  |  |  |
|  | Buske-Kirschbaum 1992 [[24](#_ENREF_24)] | natural killer cell activity |  | ↑\*\* |
|  |  |  |  |  |
| **Lipopolysaccharide** |  |  |  |  |
|  | Grigoleit 2012 [[25](#_ENREF_25)] | plasma IL-6, IL-10, TNF-αPOMS, STAI, body temperaturetaste of the CSodor of the CS |  | n.s.n.s.n.s.↓\*\* |
| **IFN-γ** |  |  |  |  |
|  | Longo 1999 [[26](#_ENREF_26)] | serum Qinolinic acidserum NeopterinCD64 antigen expressionearly morning serum cortisolCD14, HLA-A,-B,-C, -DR antigen expression  |  | ↑\*\*↑\*↑\*n.s.n.s. |
|  |  |  |  |  |
| **Insulin** |  |  |  |  |
|  | Stockhorst 1999 [[29](#_ENREF_29)] | blood glucoseserum insulinplasma glucagon, plasma epinephrine, plasma norepinephrine, serum cortisolsymptoms |  | ↓\*n.s.n.s.n.s. |
|  | Stockhorst 2004 [[30](#_ENREF_30)] | blood glucoseserum insulin plasma glucagon, plasma epinephrine, plasma norepinephrine, serum cortisol serum growth hormonesymptoms |  | ↓\*n.s.n.s.↑\*n.s.↑\*↑\* |
|  | Stockhorst 2011 [[32](#_ENREF_32)] | blood glucoseserum insulinplasma epinephrineplasma leptin, plasma norepinephrine, serum cortisol  |  | n.s.↑\*↓\*n.s. |
|  |  |  |  |  |
| **Glucose** |  |  |  |  |
|  | Stockhorst 2004 [[30](#_ENREF_30)] | blood glucoseserum insulin plasma glucagon, plasma epinephrine, plasma norepinephrine, serum cortisol serum growth hormonesymptoms |  | n.s.n.s.n.s.↑\*\*n.s.↑\* |
|  | Overduin 1997 [[31](#_ENREF_31)] | blood glucoseserum insulinserum C-peptidePlasma glucagonhunger, thirst, tension, craving for salty/sweet food |  | n.s.n.s.n.s.n.s.n.s. |
|  |  |  |  |  |
| **Dexamethasone** |  |  |  |  |
|  | Sabbioni 1997 [[33](#_ENREF_33)] | plasma cortisol |  | n.s. |

Level of significance: n.s.: not significant, \* : p ≤ .05, \*\*p ≤ .01; direction of effect: ↑: increase, ↓: decrease; IL = Interleukin, pmbc = peripheral blood mononuclear cells, (mRNA), STAI= State trait anxiety inventory, CsA = Cyclosporine A, IFN-γ = interferon gamma, CS = conditioned stimulus, PNIF = peak nasal inspiratory flow, TNF-α = tumor necrosis factor alpha, POMS = profile of mood states.

|  |
| --- |
| (((“Association Learning”[Mesh] OR “Avoidance Learning”[Mesh] OR “Discrimination Learning”[Mesh] OR “Reinforcement (Psychology)”[Mesh] OR “Conditioning (Psychology)”[Mesh:NoExp] OR “Conditioning, Classical”[Mesh] OR “Conditioning, Operant”[Mesh] OR conditioning [tw] OR conditioned [tw] OR unconditioned [tw] OR acquisition [tw] OR evocation [tw])) AND (physiology[MeSH Subheading] OR drug therapy[MeSH Subheading] OR AD[MeSH Subheading] OR drug effects[MeSH Subheading] OR pharmacology[MeSH Subheading] OR "Drug-Related Side Effects and Adverse Reactions"[Mesh] OR "adverse effects" [Subheading] OR "Metabolic Side Effects of Drugs and Substances"[Mesh] OR drug [tw] OR medication [tw] OR administration [tw] OR dose [tw] OR treatment [tw] OR side effect [tw] OR side effects [tw] OR adverse reaction [tw] OR adverse reactions [tw])) AND (“Placebos”[Mesh] OR “Placebo Effect”[Mesh] OR placebo [tw] OR saline [tw]) |

**Figure 1.** Search term for electronic search in PubMed.

Number of relevant articles:

**153**

Number of articles excluded:

**141**

|  |  |
| --- | --- |
| 55 | animal studies |
| 32 | not presenting (new) data |
| 20 | no biochemical outcome |
| 10 | no defined CS |
| 7 | no pharmacological UCS |
| 6 | no placebo-controlled design |
| 6 | full text not available |
| 5 | not written in English |

Number of articles included:

**12**

|  |  |
| --- | --- |
| 6 | based on abstract |
| 4 | based on full text |
| 2 | after discussion with third rater |

New studies based on screening reference lists and citing articles:

**4**

Total number of included articles:

**16**

Unduplicated search results:

**12.016**

Not thematically relevant articles:

**11.863**

**Figure 2.** Number of included and excluded articles.



**Figure 3.** Risk of bias graph: judgements about each risk of bias item presented as percentages across all included studies.



**Figure 4.** Risk of bias summary: judgements about each risk of bias item for each included study.