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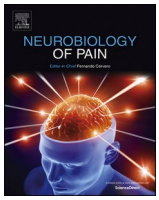

Review

Diet, body weight and pain susceptibility – A systematic review of preclinical studies

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ABSTRACT

Obesity has been associated with increased chronic pain susceptibility but causes are unclear. In this review, we systematize and analyze pain outcomes in rodent models of obesity as these can be important tools for mechanistic studies. Studies were identified using MEDLINE/PubMed and Scopus databases using the following search query: (((pain) OR (nociception)) AND (obesity)) AND (rat OR (mouse) OR (rodent))). From each eligible record we extracted the following data: species, strain, sex, pain/obesity model and main behavioral readouts. Out of 695 records 33 were selected for inclusion. 27 studies assessed nociception/acute pain and 17 studies assessed subacute or chronic pain. Overall genetic and dietary models overlapped in pain-related outcomes. Most acute pain studies reported either decreased or unaltered responses to noxious painful stimuli. However, decreased thresholds to mechanical innocuous stimuli, i.e. allodynia, were frequently reported. In most studies using subacute and chronic pain models, namely of subcutaneous inflammation, arthritis and perineural inflammation, decreased thresholds and/or prolonged pain manifestations were reported in obesity models. Strain comparisons and longitudinal observations indicate that genetic factors and the time course of the pathology might account for some of the discrepancies observed across studies. Two studies reported increased pain in animals subjected to high fat diet in the absence of weight gain. Pain-related outcomes in experimental models and clinical obesity are aligned indicating that the rodent can be an useful tool to study the interplay between diet, obesity and pain. In both cases weight gain might represent only a minor contribution to abnormal pain manifestation.

Introduction

Obesity is defined by the World Health Organization as an abnormal or excessive fat accumulation that presents risk to health. Once considered a problem only in high income countries, it is now dramatically on the rise all over the world, particularly in urban settings. Obesity has been associated with multiple complications including chronic pain – i.e. pain lasting for more than 3 or 6 months (Treede et al., 2015). Excessive weight was considered a major factor leading to pain. Obese individuals are indeed more commonly affected by chronic painful musculoskeletal conditions such as osteoarthritis (Grotle et al., 2008; Rydberg et al., 2020) but they are also more prone to other painful pathologies such as headaches and migraine (Chai et al., 2014; Razeghi Jahromi et al., 2019) – see for review (Chin et al., 2020; May and Schulte, 2016; Stokes et al., 2020) – which indicates that other pathophysiological mechanisms might be involved other than the mechanical stress caused by weight in the skeletal tissues.

Indeed, obesity has long been considered a low-grade inflammatory condition (Bastard et al., 2006; Das, 2001; Eichwald and Talbot, 2020; Ellulu et al., 2017) associated with leukocytosis (Perfetto et al., 2002), increased levels of IL-6 (Yudkin et al., 2000), TNFα (Dandona et al., 1998), acute phase proteins (van Dielen et al., 2001; Visser et al., 1999) and markers of endothelial cell dysfunction and activation (Ferri et al., 1999) – see also(Asghar and Sheikh, 2017; Das, 2001; Schachter et al., 2018; Varghese et al., 2017). Many of these inflammatory mediators have a pronociceptive influence acting at both peripheral and central nervous systems (O'Brien et al., 2017; Rahman et al., 2018). Increased IL-6 has been observed in both animal models (DeLeo et al., 1996) and clinical (Geiss et al., 1997) chronic pain conditions. Intracerebroventricular injections of interleukin-6 (Oka et al., 1995) decreased nociceptive thresholds in otherwise naïve animals and intrathecal injection of IL-6 neutralizing antibodies reduced allodynia in

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neuropathic rats (Arruda et al., 2000) – see for a recent review (Atzeni et al., 2019). Similarly, transgenic mice expressing the human TNF-α gene developed chronic inflammatory polyarthritis (Keffer et al., 1991). Endoneurial injections of TNF-α caused hyperalgesia and allodynia (Wagner and Myers, 1996) and epineural application of TNF-α neutralizing antibodies reduced these effects (Lindenlaub et al., 2000). In humans arthritic patients intravenous injection of the TNF-α blocker infliximab reduced pain and pain-related CNS activity in a fMRI study (Hess et al., 2011) – see for review (Leung and Cahill, 2010). Also, metabolic alterations can contribute to the manifestation of painful conditions. Both hyperglycemia and dyslipidemia have been associated with endoplasmic reticulum stress, DNA damage and mitochondrial dysfunction in neurons and myelinating cells that can lead to neuropathies and pain (Feldman et al., 2019, 2017).

The delineation of these mechanisms underlying the association between pain and obesity prompted a number of studies in rodents. Most commonly reaction thresholds and/or latencies to both innocuous and noxious mechanical (e.g. von Frey monofilaments) and thermal (e.g. radiant heat paw) stimuli have been used as pain proxies (Barrot, 2012; Tappe-Theodor et al., 2019; Tappe-Theodor and Kuner, 2014). In subacute and chronic pain models these are frequently complemented with additional behavioral readouts like protection of the affected areas, flinches, poorer grooming and even displays of anxiety and depressive-like behaviors (Cunha et al., 2020b; Leite-Almeida et al., 2015). To our knowledge, there has been no previous attempt to systematize nociceptive and pain related readouts in obesity models. We have therefore performed a systematic review of the literature regarding pain testing in obese or high-fat fed rodents aiming to identify potential associations.

Methods

This systematic review adhered to the PRISMA (Moher et al., 2009) checklist for the reporting of systematic reviews.

Search strategy

Studies were identified using the MEDLINE/PubMed and Scopus databases on March 2020. The arrangement of keywords used for the search was the following: (((pain) OR (nociception)) AND (obesity)) AND (rat OR (mouse) OR (rodent))). The keywords pain and nociception were used to widen our data search as far as the selection process was concerned regarding the models used to test pain. The search was not temporally limited.

Inclusion/exclusion criteria and study selection

Upon removal of duplicated entries, titles and abstracts of the remaining records were reviewed independently by CMM and MLC (discrepancies were resolved by HLA). All studies evaluating pain related behaviors in rodent models of obesity (high-fat diet and genetic models) were considered including nociceptive tests in naïve animals as well as in models of subacute and chronic pain. In order to be eligible, a non-obese control group (e.g. rodents fed a regular diet) was a mandatory requirement. Exclusion criteria were: i. absence of pain-related readouts, ii. absence of control groups, iii. language (only studies published in English were included), iv. type of study (only experimental studies were included), v. experimental subjects (only students using rodents were included) and vi. studies using additional experimental manipulations (other than the pain model) were excluded.

Reporting quality assessment

The quality of the eligible records was assessed using the Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines (Kilkenny et al., 2010). The ARRIVE recommendations are organized in a 20 item checklist divided in 6 categories: Title/abstract (1–2), Introduction (3–4), Methods (5–13), Results (14–17) and Discussion (18–20).

Data extraction and synthesis

Data from the selected studies was collected to an extraction spreadsheet. Collected data was independently verified by the authors. Divergences were resolved in group meetings. From each eligible record the following data was extracted: species, strain, sex, model used to study pain/nociception, obesity/high-fat diet model and main readouts. A narrative synthesis of pain related effects associated with diet and/or obesity was then performed.

Results

Study selection

The search results are detailed in the PRISMA flow chart (Fig. 1). A total of 692 articles were retrieved from our searches, including 185 duplicate entries that were removed. Title and abstract of the remaining 507 were screened resulting in the inclusion of 30 articles (469 excluded) overall of high quality according to the ARRIVE guidelines (Kilkenny et al., 2010) (Table 1). In subsequent searches 3 additional articles of interest were found and included in the analysis. Excluded articles failed to meet the following criteria: experimental study (44), pain model (89), pain evaluation in obesity models (297) and rodents as experimental subjects (39).

The characteristics of the studies are summarized in Table 2. The majority used in mice (21/33) particularly the C57BL/6J strain; Sprague-Dawley was the most frequently used rat strain. Of interest in this context, 3 studies used Zucker rats (Iannitti et al., 2012; Roane and Porter, 1986; Sugimoto et al., 2008), the first and one of the most widely used model of genetic obesity. Other genetic models were also used, namely the ob/ob mice but, for most studies, high fat diets (HFD) were the preferred approach to experimentally induce obesity – see for review on experimental obesity models (Aleixandre de Artinano and Miguel Castro, 2009; Preguica et al., 2020). Concerning pain models, 27 studies tested for acute nociception, mainly response thresholds/latencies to thermal and mechanical stimuli and 17 tested for pain in subacute and chronic pain models which included skin incision, transient local inflammation, diabetic neuropathy, traumatic neuropathy and arthritis models. Finally, regarding sex the majority (23/33) exclusively used males and a small part of the studies (4/33) females; 6 articles assessed potential sex-related effects in the evaluated outcomes.

Models and readouts of nociception, subacute and chronic pain

We divided the synthesis in acute pain (Table 3.) and subacute/chronic pain (Table 4). In the former, studies measuring response latencies/thresholds to nociceptive/noxious stimuli (nociception assays) in non-injured animals were considered. In these cases, there is no tissue injury and/or inflammation and pain resolves soon after the termination of the stimulus. The remaining studies were classified as subacute and chronic pain. These included very heterogenous tests and/or models in which the duration of pain-related manifestations can be highly variable, in some cases disappearing in hours/days with the resolution of the injury (subacute) while in others being sustained over time (chronic). In a general way, all involved a challenge with substances triggering inflammatory reactions – e.g. capsaicin (Iannitti et al., 2012; Rossi et al., 2016, 2019), formalin (Cooper et al., 2018; Hu et al., 2018) or carrageenan (Iannitti et al., 2012; Wang et al., 2014b) – or a lesion – e.g. paw incision (Guillemot-Legris et al., 2018; Iannitti et al., 2012; Song et al., 2018). In the specific case of neuropathy models, most commonly lesions in the peripheral nervous system were used to model neuropathic pain like in the spared nerve injury (SNI; Decosterd and Woolf, 2000) model –(Cristino et al., 2016; Guo et al., 2019) – but 1 model of perineural inflammation was also used (Song et al., 2017). It should be noted

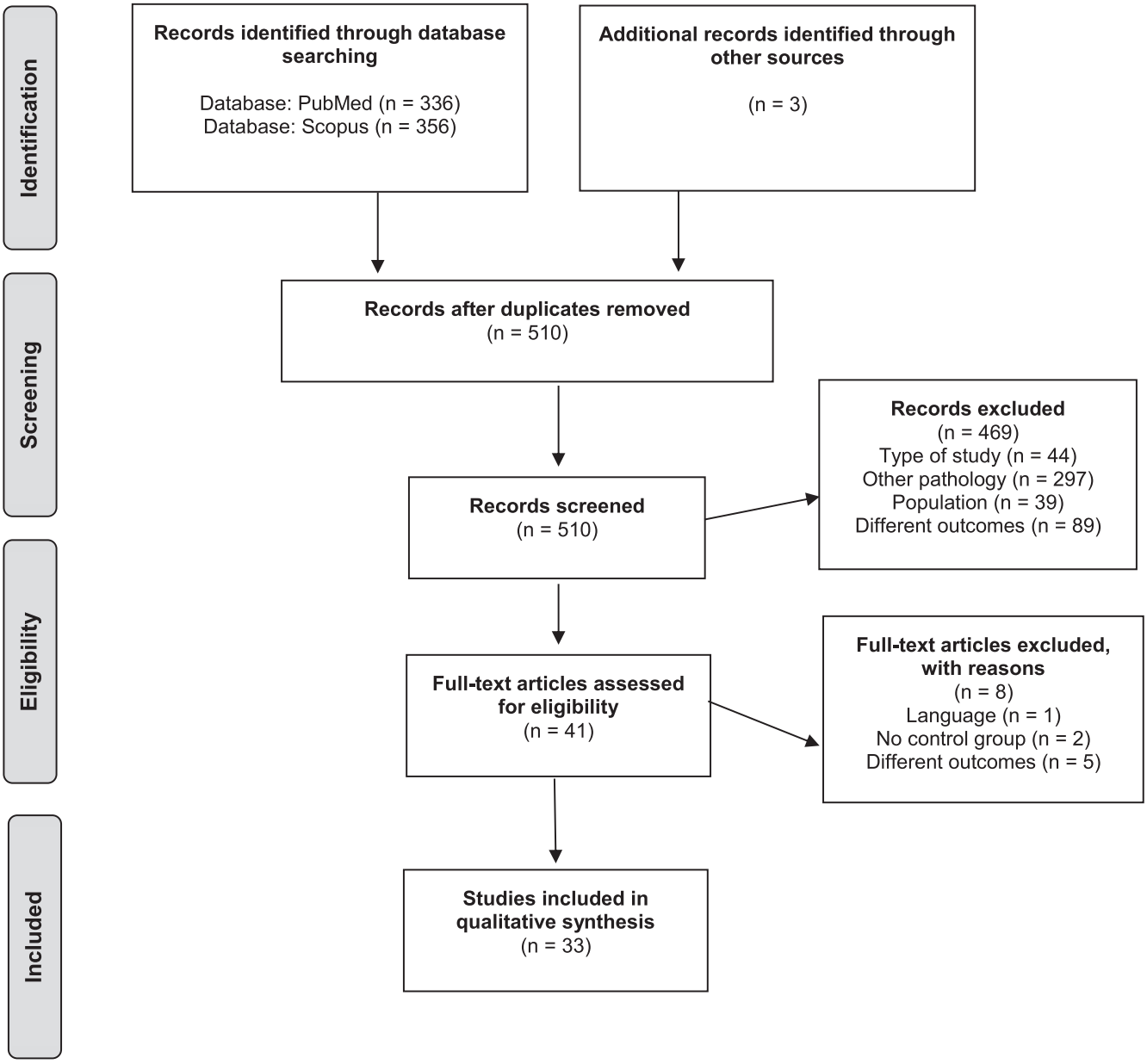

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Moher et al., 2009) flow diagram of literature search and selection. From a total of 692 records obtained from 2 combined searches using the search query (((pain) OR (nociception)) AND (obesity)) AND (rat OR (mouse) OR (rodent))), 30 were selected for data extraction and synthesis. 3 additional records identified through other sources were also added.

that, while neuropathies and neuropathic pain are a common event in obesity models – see for review (Islam et al., 2013; Jolivalt et al., 2016; O'Brien et al., 2014; Preguica et al., 2020) – only models with an effective lesion in neuronal tissues were considered in this section. The manifestation of hyperalgesia – increased pain from a stimulus that normally provokes pain – or allodynia – pain due to a stimulus that does not normally provoke pain – were used as pain proxies (terminology from the International Association for the Study of Pain (IASP)).

Pain in models of obesity

Pain-related readouts are presented below for the 2 types of obesity models – dietary and genetic (see discussion) – used in the selected studies.

Acute pain

In this section we included tests involving innocuous and noxious (and potentially tissue damaging) stimuli that evoke a pain-like reaction in the animal, typically a withdraw from the stimuli, in the absence of a lesion. Noxious mechanical (Randall-Sellito, tail-pinch) and thermal (Hargreaves, tail-flick) stimuli were amongst the most used as well as Von Frey monofilaments for innocuous allodynia. In all cases the behavioral response ceased with the termination of the stimuli.

Nociception in high-fat diet fed rodents. Most studies used noxious heat to assess nociception in alimentary models of obesity, particularly the Hargreaves' and the tail-flick tests (Table 3). In such conditions, rodents presented either decreased (i.e. longer response latencies) or unaltered responses to noxious painful thermal stimuli in comparison to lean controls. However, 3 studies, both in mice, found the opposite effect (Bonomo et al., 2020; Gavini et al., 2018; Xu et al., 2014). In part, these differences across studies might result from the periods chosen for pain evaluation. Totsch and colleagues reported a sustained increase in latencies across time (Totsch et al., 2018, 2017, 2016). On the other hand,

Table 1
Quality appraisal of the selected studies using the Animal Research: Reporting of In Vivo Experiments (ARRIVE; Kilkenny et al., 2010) checklist.

Studies	Title, Abstract	Introduction	Methods	Results	Discussion
(Bonomo et al., 2020)					
(Brandao et al., 2019)					
(Choucair-Jaafar et al., 2014)					
(Cooper et al., 2018)					
(Cristino et al., 2016)					
(Croci and Zarini, 2007)					
(Davidson et al., 2014)					
(Gavini et al., 2018)					
(Guilford et al., 2011)					
(Guillemot-Legris et al., 2018)					
(Guo et al., 2019)					
(Holmes et al., 2015)					
(Hu et al., 2018)					
(Iannitti et al., 2012)					
(Latham et al., 2009)					
(Burnett et al., 2019)					
(Loredo-Perez et al., 2016)					
(Ramzan et al., 1993)					
(Roane and Porter, 1986)					
(Rodgers et al., 2014)					
(Rossi et al., 2013)					
(Rossi et al., 2016)					
(Rossi et al., 2019)					
(Song et al., 2017)					
(Song et al., 2018)					
(Sugimoto et al., 2008)					
(Totsch et al., 2016)					
(Totsch et al., 2017)					
(Totsch et al., 2018)					
(Tramullas et al., 2016)					
(Wang et al., 2014b)					
(Watson et al., 2014)					
(Xu et al., 2014)					

Liang and colleagues reported no significative alteration in thermal hyperalgesia however, in weeks 6 and 8 post HFD, a reduction in the latencies was reported (Liang et al., 2019). Only 1 study assessed visceral nociception – colorectal distention (CDR) – and reported increased visceromotor response and decreased threshold which indicates increased pain perception in obese animals (Tramullas et al.,

Table 2
Characteristics of the studies and respective subjects that met the inclusion criteria; "-" – not mentioned/explicit; g.m. – genetic model; LE – Long-Evans; M – male; SD – Sprague-Dawley; wn – weaning; [1]Age (in weeks) when animals started the diet/when the experiments started; [2]the number of subjects given corresponds to that used in the main experiments; [3]pain models were classified in acute if no lesion was involved, subacute when a spontaneously resolving lesion or challenge with an irritant/pungent substance was used and chronic when a permanent lesion was induced. Note that despite alimentary and genetic obesity models being commonly associated with the development of peripheral neuropathies, neuropathological evidence was not always investigated/reported and for that reason only studies that used direct lesions to the nervous system were classified as neuropathic.

Study	Species	Strain/ subtrain	Sex	Age[1]	N[2]	Pain model[3]
(Bonomo et al., 2020)	Mice	C57BL/6J	M	7/21	12–14	acute
(Bonomo et al., 2020)	Mice	C57BL/6J	M	6/16	40	subacute
(Choucair-Jaafar et al., 2014)	Mice	C57BL/6J	M	g.m./7	30	acute
(Cooper et al., 2018)	Mice	C57BL/6J, C57BL/6NIH and C57BL/6CR	M	8/15	60	acute; subacute
(Cristino et al., 2016)	Mice	C57BL/6J	M	g.m.; 9–11 (HFD)/ 16–18	–	acute; chronic
(Croci and Zarini, 2007)	Rat	SD Crl:CD	F	4/40	15–36	acute; chronic
(Davidson et al., 2014)	Rat	SD	M	12/28	20–24	acute
(Gavini et al., 2018)	Mice	C57BL/6J	M	wn/wn + 12	16	acute
(Guilford et al., 2011)	Mice	C57BL/6	M	7/16	30–42	acute
(Guillemot-Legris et al., 2018)	Mice	C57BL/6J	M	10/19	40	subacute
(Guo et al., 2019)	Rat	SD	M	4/14	20	acute; chronic
(Holmes et al., 2015)	Rat	SD	M	12/24	33	acute
(Hu et al., 2018)	Mice	C57BL/6	M	g.m.;7/ 8–12; 12	16	acute; subacute
(Iannitti et al., 2012)	Rat	Zucker	M	g.m./12–14	96	acute; subacute
(Latham et al., 2009)	Mice	C57BL/ 65 J	F	g.m./4–30	24–48	acute
(Liang et al., 2019)	Mice	C57BL/6CR	M	4/12	38	acute
(Loredo-Perez et al., 2016)	Mice	ICR	M	3/17	59	chronic
(Ramzan et al., 1993)	Rat	SD	M	-/(20w HFD)	25	acute
(Roane and Porter, 1986)	Rat	Zucker	F	g.m./17–21	15	acute

(continued on next page)

Table 2 (*continued*)

Study	Species	Strain/ subtrain	Sex	Age[1]	N[2]	Pain model[3]
(Rodgers et al., 2014)	Mice	C57BL/6	F/ M	g.m./12–42	48	acute
(Rossi et al., 2013)	Mice	C57BL/ 6J, SKH1-E (SK)	F/ M	wn/20	37	acute
(Rossi et al., 2016)	Mice	C57BL/6J	M	g.m.; wn (HFD)/6–8; 8–11 (pre-obese HFD); 20–25 (obese HFD)	83	subacute
(Rossi et al., 2019)	Mice	C57BL/6J	M	g.m.; -/5–9; 20 (HFD)	99	acute; subacute
(Song et al., 2017)	Rat	LE, SD	F/ M	-/(6w HFD)	32	subacute
(Song et al., 2018)	Rat	LE	F/ M	-/(6w HFD)	44	subacute
(Sugimoto et al., 2008)	Rat	Zucker and Wistar	M	g.m./8–36	120	acute
(Totsch et al., 2016)	Mice	CD1	M	-/(13w HFD)	18	acute; subacute
(Totsch et al., 2017)	Rat	SD	F/ M	-/(20w SAD)	35	acute; subacute
(Totsch et al., 2018)	Mice	CD1	F/ M	8/12	60	acute; subacute
(Tramullas et al., 2016)	Mice	C57BL/6J	M	3/19	80	acute
(Wang et al., 2014b)	Rat	SD	M	-/(12w HFD)	16–36	acute, subacute
(Watson et al., 2014)	Mice	C57BL/6	M	g.m./8–10	24	acute
(Xu et al., 2014)	Mice	C57BL/6J	F	4/10	30	acute

2016).

Regarding innocuous mechanical stimuli, assessed in a high number of studies with Von Frey monofilaments, the large majority of the studies found either no alterations (Cooper et al., 2018; Croci and Zarini, 2007; Totsch et al., 2018, 2017, 2016; Wang et al., 2014b) or decreased response thresholds, i.e. allodynia (Bonomo et al., 2020; Cooper et al., 2018; Gavini et al., 2018; Guo et al., 2019; Liang et al., 2019). Again, a number of factors including the time course of the pathology might explain differences across studies. For instance, Cooper and colleagues compared 3 C57BL/6 substrains and observed while obese C57BL/6CR presented allodynia and C57BL/6NJ presented a reduction (not statistically significative) in mechanical thresholds, C57BL/6J presented no alterations at HFD week 7 (Cooper et al., 2018). Interestingly, these phenotypes were related with diet impact on glucose tolerance, C57BL/6CR presenting significantly reduced, C57BL/6NJ moderately reduced and C57BL/6J unaltered glucose tolerance despite all presenting hyperinsulinemia at fasting – see also 3.5.2. for nociception in genetic models of obesity. Two studies reported a decreased response (i.e. increased thresholds) to innocuous mechanical stimulation in obese animals, one specifically in later assessments (after TWD week 9) (Totsch et al., 2016) and in other after corneal stimulation (Davidson et al., 2014).

While there is compiling evidence that obesity is associated with a predisposition for chronic pain development and indeed in some of the above-mentioned studies animals manifested allodynia no evidence on spontaneous pain manifestations in obese mice was found when the rodent grimace scale was used as a pain proxy (Totsch et al., 2017).

Nociception in genetic models of obesity. Genetic models of obesity present similar phenotypes to those described in alimentary obesity models (3.5.1). For noxious heat, both increased (Cristino et al., 2016; Rodgers et al., 2014; Rossi et al., 2019; Sugimoto et al., 2008), unaltered (Iannitti et al., 2012; Sugimoto et al., 2008; Watson et al., 2014) and decreased (Latham et al., 2009; Roane and Porter, 1986; Sugimoto et al., 2008) latencies were reported. Again, differences across studies might be explained, at least in part, by the time course of the pathology. For instance, using obese Zucker (*fa/fa*) rats, Sugimoto and colleagues followed threshold evolution between 8 and 36 weeks-old and observed that while in early time points obese *fa/fa* rats tended to have faster response latencies than lean controls, after the 28th week response latencies become progressively higher than controls (Sugimoto et al., 2008). Similarly, Rodgers and colleagues reported a sustained increase in response latencies in *ob/ob* mice with age (Rodgers et al., 2014).

Regarding innocuous mechanical stimulation, findings with genetic obesity models overlap those obtained with caloric diets with most studies reporting no alterations (Choucair-Jaafar et al., 2014; Iannitti et al., 2012; Latham et al., 2009) or decreased thresholds/allodynia (Choucair-Jaafar et al., 2014; Latham et al., 2009). In line with what has been described so far, Latham and colleagues observed that allodynia was more pronounced in 8–20 week time window (Latham et al., 2009). In noxious mechanical testing, both no alterations (Randall-Selitto test; Sugimoto et al., 2008) or decreased latencies/increased pain perception (tail-pich test; Roane and Porter, 1986) were reported, which despite the reduced number of studies, suggests a similar pattern to that observed in noxious thermal tests.

Subacute and chronic pain models

In this section we included pain models of persistent pain, typically induced by a challenge with an irritant/pungent substance (e.g. capsaicin or formalin) or by a lesion. Pain manifestation varies substantially across models, in some cases the display of evident nocifensive behaviors (e.g. protection, flinches or biting of the affected area) and in other cases by an alteration of the response to sensory stimulation including hyperalgesia – increased pain to a noxious stimulus – and allodynia – pain caused by a normally innocuous stimulus – which in non-human pain models manifest as a reduced latency/threshold to stimulation. In subacute models these manifestations are transient, typically resolving in hours or few days, as the tissue repairs but in chronic models they typically are sustained over several weeks.

Inflammatory pain models. Overall studies reported that alimentary and genetic models of obesity took more time to recover after a challenge with an irritant/pungent substance when compared to the respective controls. Because these models vary substantially, each will be discussed separately despite the small number of studies in each category.

Capsaicin. Capsaicin is the pungent ingredient of chili peppers and acts on the transient receptor potential cation channel vanilloid subfamily member 1 (TRPV1) (Braga Ferreira et al., 2020; Yang and Zheng, 2017); it has long been used to model somatic and visceral inflammatory pain.

No evident differences were observed between obese and lean controls after capsaicin challenges both displaying nocifensive behaviors and increased nociception/hyperalgesia (Iannitti et al., 2012; Rossi et al., 2016, 2019); such was the case for both dietary and genetic obesity models. When injected in the whisker pad, capsaicin was associated with photophobia in obese, but not in lean animals (Rossi et al., 2016).

Carrageenan. Carrageenan is a polysaccharide present in red algea. Subcutaneous injections of this substance has long been used in rodents as an inflammatory pain model (Winter et al., 1962). Intraarticular

Table 3
Characterization of the studies testing acute pain. CBE – Cochet-Bonnet esthesiometer; CRD – colorectal distension; DPA – dynamic plantar esthesiometer; HFD – high fat diet; w(s) – week(s); RGS – rat grimace scale; SAD – standard American diet; TWD – total western diet; WD – western diet;

Nociceptive assay	Obesity model	Weight variation	Main results	References
Spontaneous pain				
Grimace (RGS)	SAD	Increased weight in female but not male SAD rats;	No differences were observed related with diet and sex;	(Totsch et al., 2017)
Innocuous mechanical				
Allodynia (VF)	WD	Significantly higher weight from w10 on;	WD mice had significantly lower thresholds;	(Bonomo et al., 2020)
Allodynia (VF)	HFD	Increased body weight at HFD w3. C57BL/6CR presented the greatest difference to controls at HFD w8;	C57BL/6CR presented allodynia; C57BL/6NJ presented a reduction (not statistically significative) in mechanical thresholds; C57BL/6J presented no alterations in mechanical sensitivity at HFD w 7;	(Cooper et al., 2018)
Allodynia (VF)	HFD	HFD presented a significantly higher weight at the beginning of the protocol;	Lean and obese presented similar responses to innocuous mechanical stimuli;	(Croci and Zarini, 2007)
Allodynia (VF)	*ob/ob*	All ob/ob mice became overweight;	Diabetic ob/ob mice developed mechanical allodynia starting at w 12; 28% of ob/ob did not develop allodynia (nor hyperglycemia);	(Choucair-Jaafar et al., 2014)
Allodynia (CBE)	HFD	Significantly increased weight on HFD w26 and w40;	HFD rats presented decreased corneal sensitivity;	(Davidson et al., 2014)
Allodynia (VF)	WD	Significantly higher from WD w5;	WD mice had significantly lower thresholds;	(Gavini et al., 2018)
	HFD		Increased response to a 1.4 g VF monofilament	(Guilford et al., 2011)
Allodynia (VF)	HFD	HFD weighted nearly 2x more controls by w10;	Lower thresholds at HFD 10 w; this trend persisted until 12 w;	(Guo et al., 2019)
Allodynia (DPA)	*fa/fa*	*fa/fa* presented significantly increased weight compared to *fa/-* (14 ws);	No threshold differences between obese (*fa/fa*) and lean (*fa/-*) rats;	(Iannitti et al., 2012)
Allodynia (VF)	*ob/ob*	*ob/ob* body weight doubled 10 ws of age and tripled by 20 ws; weight gain in wild type mice was less than 55%;	*ob/ob* presented mechanical hypersensitivity starting at 6 ws until 20 ws of age; in the remaining assessment until 30 ws *ob/ob* and controls presented similar responses;	(Latham et al., 2009)
Allodynia (VF)	HFD	Significantly higher weight from w5 on;	Reduced thresholds to VF on HFD w6 and w8;	(Liang et al., 2019)
Allodynia (VF)	TWD	No effect of diet on body weight though TWD presented increased fat mass;	Thresholds elevated over 13 ws and starting on w 9 they significantly differed from controls;	(Totsch et al., 2016)
Allodynia (VF)	SAD	Increased weight in female but not male SAD rats;	SAD increased thresholds over a 20 w period but no significative differences were observed between the 2 groups; no sex differences were observed;	(Totsch et al., 2017)
Allodynia (VF)	SAD	SAD increased body weight in both female in male rats over 17 ws;	Thresholds increased over a 15 ws period on both SAD and controls; females presented higher thresholds;	(Totsch et al., 2018)
Dynamic plantar aesthesiometer	HFD	HFD gained significantly more weight in a 12 ws period, significantly at 4 ws;	No differences between HFD and controls;	(Wang et al., 2014b)
Response frequency (VF)	HFD	Significantly higher weight from w4 on;	Increased response frequency to a 1.4 g VF monofilament;	(Guilford et al., 2011)
Noxious mechanical				
Randall-Selitto	*fa/fa*	*fa/fa* rats developed early-onset (8 w) and sustained obesity (36 w).	No differences between *fa/fa* and respective age-matched controls in all time points analyzed;	(Sugimoto et al., 2008)
Tail-pinch	*fa/fa*	*fa/fa* weighted nearly twice than *fa/-*	Obese (*fa/fa*) presented shorter latencies than lean (*fa/-*);	(Roane and Porter, 1986)
Noxious heat				
Hargreaves	WD	Significantly higher weight from w10 on.	WD mice had significantly lower latencies;	(Bonomo et al., 2020)
Hargreaves	HFD	Increased body weight at HFD w 3. C57BL/6CR presented the greatest difference to controls at HFD w 8.	No alterations across 7 ws on HFD;	(Cooper et al., 2018)
Hargreaves	HFD	HFD presented a significantly higher weight at the beginning of the protocol;	Lean and obese presented similar responses to noxious thermal;	(Croci and Zarini, 2007)
Hargreaves	HFD	Significantly increased weight on HFD ws 26 and 40;	HFD rats presented increased latencies to noxious heat;	(Davidson et al., 2014)
Hargreaves	WD	Significantly higher from WD w 5;	WD mice had significantly lower withdraw latencies;	(Gavini et al., 2018)
Hargreaves	HFD	Significantly higher weight from w4 on;	No differences in withdrawal latencies;	(Guilford et al., 2011)

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Table 3 (*continued*)

Nociceptive assay	Obesity model	Weight variation	Main results	References
Hargreaves	HFD	HFD weighed significantly more than control rats after 24 ws;	HFD presented significantly higher response latencies; diet switch normalized weight and reduced response latencies;	(Holmes et al., 2015)
Hargreaves	HFD	HFD gained significantly more body weight and fat than the control group;	No differences in withdrawal latencies;	(Hu et al., 2018)
Hargreaves	*fa/fa*	*fa/fa* presented significantly increased weight compared to *fa/-* (14 ws);	No latency differences between obese (*fa/fa*) and lean (*fa/-*) rats;	(Iannitti et al., 2012)
Hargreaves	*ob/ob*	*ob/ob* body weight doubled 10 ws of age and tripled by 20 ws; weight gain in wild type mice was less than 55%;	*ob/ob* developed hyperalgesia starting at w 6; this phenotype was stronger between ws 8 and 16;	(Latham et al., 2009)
Hargreaves	HFD	Significantly higher weight from w5 on;	Reduced latencies on HFD w6 and w8;	(Liang et al., 2019)
Hargreaves	TWD	No effect of diet on body weight though TWD presented increased fat mass;	Thresholds elevated over 13 ws and starting on 8 w they significantly differed form controls;	(Totsch et al., 2016)
Hargreaves	SAD	SAD increased body weight in female but not in male rats;	Thresholds increased over 20 ws for SAD and controls; no diet or sex differences were observed;	(Totsch et al., 2017)
Hargreaves	SAD	SAD increased body weight in both female in male rats over 17 ws;	Thresholds increased over a 15 ws period on both SAD and controls; no diet or sex effects were observed;	(Totsch et al., 2018)
Hargreaves	HFD	HFD gained significantly more weight in a 12 ws period, significantly at 4 ws;	No differences between HFD and controls;	(Wang et al., 2014b)
Hargreaves	*ob/ob*	–	No differences between *ob/ob* and controls;	(Watson et al., 2014)
Hargreaves	HFD	HFD presented increased body weight (after 14 w);	HFD displayed thermal hyperalgesia;	(Xu et al., 2014)
Operant facial pain assay	HFD	C57BL/6J presented increased body weight at HFD w 12(M) and 18(F); HDF SKH1(M) weight gain was less pronounced;	The number of licks and its duration reduced with increasing temperature in both C57BL/6J and SKH1 males; HFD C57BL/6J (but not SKH1) presented decreased licking in both innocuous and noxious temperatures when compared to control diet; overall no sex effects were found in C57BL/6J;	(Rossi et al., 2013)
Operant facial pain assay	*ob/ob*	–	*ob/ob* presented a marked decrease in thermal facial nociception;	(Rossi et al., 2019)
Tail-flick	HFD; *ob/ob*	Increased body weight at HFD ws 2–7;	ob/ob presented higher latencies; no differences between HFD and standard diet/wildtype;	(Cristino et al., 2016)
Tail-flick	HFD	HFD gained significantly more body weight and fat than the control group;	No differences in tail-flick latencies;	(Hu et al., 2018)
Tail-flick	HFD	HFD presented increased body weight;	HFD presented increased response latencies (approximately 30% higher than controls); a positive correlation with body weight was reported;	(Ramzan et al., 1993)
Tail-flick	*fa/fa*	*fa/fa* weighted nearly twice than *fa/-*	Obese (*fa/fa*) presented shorter latencies than lean (*fa/-*);	(Roane and Porter, 1986)
Tail-flick	*ob/ob*	*ob/ob* presented increased body weight which was corrected by leptin administration;	*ob/ob* had longer tail-flick latencies; response time was further increased with age (15, 23 and > 42 ws); no sex-related effects;	(Rodgers et al., 2014)
Tail-flick	*fa/fa*	*fa/fa* rats developed early-onset (8 w) and sustained obesity (36w);	*fa/fa* presented shorter latencies when young (8–12 w) and longer when mid-aged (26–36 w);	(Sugimoto et al., 2008)
Visceral nociception				
CRD	HFD	HFD presented increased body weight, a higher percentage of adipose mass and a relative proportional decrease in lean mass;	HFD over 16 ws presented increased visceromotor responses to CRD and decreased pressure threshold;	(Tramullas et al., 2016)

Table 4
Characterization of the studies testing subacute and chronic pain. CFA – complete Freund's adjuvant; DRG – dorsal root ganglia; F – females; HFD – high fat diet; LE – Long-Evans; M – males; PGE2 – prostaglandin E2; SD – Sprague-Dawley; SNI – spared nerve injury; VF – von Frey monofilaments; *wt* – wildtype;

	Pain model	Pain assessment	Obesity model	Weight variation	Main results	References
Inflammatory						
	Capsaicin	dynamic plantar aesthesiometer; Hargreaves	*fa/fa*	*fa/fa* presented significantly increased weight compared to *fa/-* (14 ws);	Obese (*fa/fa*) and lean (*fa/-*) rats presented decreased mechanical thresholds and thermal hyperalgesia; no differences were observed between the 2 groups;	(Iannitti et al., 2012)
	Capsaicin (whisker pad)	Nocifensive behaviors; photophobia	HFD; *ob/ob*	HFD and *ob/ob* presented significantly higher weight than respective controls at testing;	Increased ipsilateral facial wipes and decreased rearings in HFD and controls; capsaicin increased photophobia in obese HFD but not in lean HFD or controls; *ob/ob* presented baseline photophobia further intensified by capsaicin;	(Rossi et al., 2016)
	Capsaicin (corneal; whisker pad)	Nocifensive behaviors; conditioned place aversion;	HFD; *ob/ob*	–	*ob/ob* presented normal nocifensive response to corneal and facial capsaicin though in the latter *ob/ob* presented a significantly higher immobility (partially mimicked in HFD); capsaicin-related aversion was similar between ob/ob and controls;	(Rossi et al., 2019)
	Carrageenan	Dynamic plantar aesthesiometer; Hargreaves	*fa/fa*	*fa/fa* presented significantly increased weight compared to *fa/-* (14 ws);	Both obese (*fa/fa*) and lean (*fa/-*) rats presented decreased mechanical thresholds however in obese rats it developed faster (2 h) and lasted longer (still present at 8 h); thermal hyperalgesia evolved in a similar fashion;	(Iannitti et al., 2012)
	Carrageenan	Dynamic plantar aesthesiometer; Hargreaves	HFD	HFD gained significantly more weight in a 12 ws period, significantly at 4 ws.	HFD presented a more intense and prolonged response to carrageenan with decreased thresholds/latencies;	(Wang et al., 2014b)
	Formalin	Nocifensive behaviors	HFD	Increased body weight at HFD w 3. C57BL/6CR presented the greatest difference to controls at HFD w 8;	HFD C57BL/6CR displayed increased nocifensive behaviors in the acute phase of the formalin test; no alterations were observed in tonic phase in all strains;	(Cooper et al., 2018)
	Formalin	Nocifensive behaviors	HFD; *ob/ob*; *db/db*	HFD gained significantly more body weight and fat than the control group;	HFD presented reduced nocifensive behavior (paw flinches) in both acute and tonic phases of the test (diet switch for 3 ws rescued the phenotype); similar results for the *ob/ob* and *db/db* models;	(Hu et al., 2018)
	PGE2	Mechanical allodynia (VF)	HFD; voluntary physical activity	Significantly higher body mass in HFD;	PGE decreased thresholds (increased delta); this effect was sustained in HFD but not controls; voluntary physical activity counteracted this effect however physical activity was significantly higher in controls;	(Brandao et al., 2019)
Postoperative pain						
	Hindpaw incision	Mechanical allodynia (VF)	HFD	HFD-fed mice (60 day protocol) developed an obese phenotype characterized by increased body weight and fat depots;	Thresholds decreased after incision in both HFD and controls recovering in the latter after 14 days; allodynia lasted at least 162 days in HFD however diet switch rescued post-operative pain;	(Guillemot-Legris et al., 2018)
	Hindpaw incision	dynamic plantar aesthesiometer; Hargreaves	*fa/fa*	*fa/fa* presented significantly increased weight compared to *fa/-* (14 ws);	Both obese (*fa/fa*) and lean (*fa/-*) rats presented decreased mechanical thresholds and thermal hyperalgesia; no differences were observed between the 2 groups;	(Iannitti et al., 2012)
	Hindpaw incision	Mechanical allodynia (VF); nocifensive behaviors	HFD	There was obvious weight gain in high-fat-fed rodents.	Paw incision induced robust allodynia and spontaneous pain behaviors in both males and females; HFD intensified the phenotype particularly in males; diet switch lessened HFD effects; a short, 1 w HFD, produced similar pain-related behaviors though in a smaller magnitude (males);	(Song et al., 2018)
Inflammatory (arthritis)						
	CFA (intraplantar)	Arthritic score	HFD	HFD presented a significantly higher weight at the beginning of the protocol; CFA induced a marginal decrease in body weight in both lean and obese animals;	Increased arthritis score in both HFD and lean animals at 7, 10 14 post CFA; significantly higher in HFD vs lean at day 7; both developed edema which was significantly higher in HFD at day 7;	(Croci and Zarini, 2007)
	CFA (intraplantar)	Static (VF) and dynamic mechanical allodynia; cold allodynia (acetone test); nocifensive behaviors	HFD	8 ws on HFD significantly increased body weight in LE but not SD rats;	Baseline readout similar between HFD and controls; both LE and SD on HFD presented a stronger and long lasting static/dynamic mechanical and cold allodynia as well as paw edema than controls; only males were evaluated;	(Song et al., 2017)
	CFA (intraplantar)	Mechanical allodynia (VF); Hargreaves	TWD	No effect of diet on body weight though TWD presented increased fat mass;	TWD presented prolonged mechanical and thermal hypersensitivity following CFA;	(Totsch et al., 2016)
	CFA (intraplantar)	Allodynia (VF)	SAD	SAD increased body weight in female but not in male rats;	SAD presented prolonged mechanical allodynia following CFA; no sex-related differences observed;	(Totsch et al., 2017)

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Table 4 (*continued*)

	Pain model	Pain assessment	Obesity model	Weight variation	Main results	References
	CFA (intraplantar)	Allodynia (VF)	SAD	SAD increased body weight in both female in male rats over 17 ws;	Following CFA, SAD took 13(F)/11(M) days to return to baseline while controls took 7 days; diet switch at the time of CFA challenge improved recovery to 7(F)/9(M) days;	(Totsch et al., 2018)
	CFA (intra-articular)	Spontaneous pain-related behaviors; weight-bearing	HFD	HFD displayed significantly higher body weight;	Increased spontaneous pain-like behaviors, flinches and guarding, as well as abnormal weight-bearing in both HFD and lean controls; these are however exacerbated in the former; no differences in knee edema;	(Loredo-Perez et al., 2016)
Neuropathic (trauma)						
	SNI	Mechanical allodynia (VF)	*ob/ob*	Matched to 7w HFD *wt* with same age;	*ob/ob* mice did not develop tactile allodynia;	(Cristino et al., 2016)
	SNI	Mechanical allodynia (VF)	HFD	HFD weighted nearly 2x more controls by w 10;	HFD and controls presented allodynia after SNI but thresholds were significantly lower in the former up to 14 days post-SNI;	(Guo et al., 2019)
Neuropathic (perineural inflammation)						
	Zymosan (L5, DRG) /radicular pain.	Static (VF) and dynamic mechanical allodynia; cold allodynia (acetone test); nocifensive behaviors	HFD	HFD consumption for 8 ws affected body weight in LE but not SD rats;	Baseline readout similar between HFD and controls; both LE and SD on HFD presented a stronger and long lasting mechanical/cold allodynia and guarding behaviors; no sex differences observed; a short, 1 w HFD, produced similar pain-related behaviors though in a smaller magnitude;	(Song et al., 2017)

injection of carrageenan (frequently with kaolin) has also been used as a knee joint monoarthritic model (Neugebauer et al., 2007).

In the 2 studies selected, an intraplantar carrageenan injection was used in genetic (Iannitti et al., 2012) and HFD (Wang et al., 2014b) obesity models. In both cases, pain-related phenotypes/hyperalgesia were more intense and more prolonged in obese compared to lean animals (Iannitti et al., 2012; Wang et al., 2014b).

Formalin. Formalin has long been used as a model of inflammatory pain (Dubuisson and Dennis, 1977). It produces a characteristic biphasic response that starts soon after formalin injection and that is followed by a second pain-related activity peak minutes later – e.g. (Fischer et al., 2014; Sotiropoulos et al., 2014). Acute (0′-5′) and tonic (20′-40′) phases are characterized by intense nocifensive activity including paw biting, flinching and protection. These 2 phases are thought to be mechanistically distinct, the former resulting from a direct nociceptive activation and the second to result from inflammation and/or sensitization (Hunskaar and Hole, 1987).

Cooper and colleagues reported increased nocifensive behaviors in C57BL/6CR HFD mice (but not C57BL/6NJ or C57BL/6J, substrains) specifically in the acute phase (Cooper et al., 2018); no alterations were observed in the tonic phase for any of the substrains analyzed. On the contrary, a different study observed a reduction in nocifensive behaviors in both phases of the formalin test in HFD, *ob/ob* and *db/db* mice (Hu et al., 2018). No obvious experimental differences exist between the 2 studies.

Prostaglandin E2. The inflammatory prostaglandin E2 (PGE2)-induced persistent hyperalgesia model (Ferreira et al., 1990) was used in only 1 study (Brandao et al., 2019). It differs from the previous inflammatory models as it makes use of an endogenous proinflammatory molecule (Nakanishi and Rosenberg, 2013).

Intraplantar injections of PGE2 lead to a decrease in the thresholds to innocuous mechanical stimuli. In HFD mice the effect was sustained at least for 7 days after the last PGE2 injection, while in the standard diet group recovered to baseline values in the same period (Brandao et al., 2019).

Postoperative pain. Postoperative pain can be modeled by an incision in the skin and underlying tissues. Such procedure normally results in the development of hypersensitivity in the lesioned and in adjacent areas (Brennan et al., 1996).

This was the case in all selected studies with animals presenting allodynia and hyperalgesia as well as increased nocifensive behaviors (Guillemot-Legris et al., 2018; Iannitti et al., 2012; Song et al., 2018) however, the effects were prolonged over time in HFD models (Guillemot-Legris et al., 2018; Song et al., 2018) but not in genetic models (Iannitti et al., 2012); in both HDF studies, diet switch improved pain-related outcomes. Diet impact was particularly evident in male rats (Song et al., 2018).

Arthritis models. Arthritis is an inflammation of 1 or more joints. This pathology has been modeled in a number of different ways all ultimately leading to inflammation and/or joint tissue damage – consult for instance (Fang and Beier, 2014; Gregory et al., 2013; Hong et al., 2020; Neugebauer et al., 2007).

Despite the diversity of models available, in our pool of studies the vast majority used an intraplantar Complete Freund Adjuvant (CFA) injection (Croci and Zarini, 2007; Song et al., 2017; Totsch et al., 2018, 2017, 2016), a model of poly-arthritis/rheumatoid arthritis and 1 used an intra-articular CFA injection (Loredo-Perez et al., 2016), a model of mono-arthritis osteoarthritis. In all studies caloric diets were associated with either an exacerbation of pain-related behaviors and/or a prolonged manifestation. No studies were performed in genetic models.

Neuropathic pain models. Neuropathic pain is defined as pain resulting from a lesion or disease of the somatosensory system (Scholz et al., 2019). Numerous neuropathic pain rodent models have been developed of both central and peripheral neuropathies – see for review (Coderre and Laferriere, 2020; Leite-Almeida et al., 2015), and references within. Despite the diversity of models and its widespread use in different experimental contexts they are clearly underrepresented in the pool of selected articles.

Amongst the trauma models only the spared nerve ligation (SNI; Decosterd and Woolf, 2000) was used in 2 studies both using mechanical allodynia, a hallmark of peripheral neuropathies, as final readout. Interestingly, Cristino and colleagues reported that *ob/ob* mice did not developed such characteristic phenotype after SNI (Cristino et al., 2016). On the contrary, using the same model, Guo and colleagues observed that both HFD and control diet SNI animals presented a significant reduction in the thresholds to innocuous mechanical stimuli, although this was more severe in the former (Guo et al., 2019). Note that, starting around HFD week 6, HFD already presented a threshold decrease in comparison to control feed animals (statistically significative from week 10 onwards; see also 3.5.1.1). HFD was also associated with stronger and long lasting mechanical and cold allodynia in a radicular pain model induced perineural inflammation in the dorsal root ganglia L5 in 2 strains of rats (Song et al., 2017).

Discussion

A potential relation between obesity and pain has been for a long time a matter of debate (Bigand et al., 2018; Narouze and Souzdalnitski, 2015; Okifuji and Hare, 2015; Taylor et al., 2014; Wright et al., 2010). Human studies comparing nociception in obese and lean individuals have been inconclusive, some studies reporting lower thresholds – e.g. (Miscio et al., 2005; Pradalier et al., 1981) – while others reporting obesity-associated hypoalgesia – e.g. (Torensma et al., 2017) – see also for review (Torensma et al., 2016). Regarding chronic pain, literature is more consensual, showing an increased risk/susceptibility for chronic pain development in obese subjects – see (Okifuji and Hare, 2015) and references within. Such has been in part attributed to weight-related increased mechanical stress in skeletal tissues but there is overwhelming evidence that other factors may play an important role. For instances, obese women are more susceptible to develop knee osteoarthritis than obese men (King et al., 2013). Also, obesity has also been associated with increased osteoarthritis hands (Grotle et al., 2008; Oliveria et al., 1999) i.e. in joints that are submitted to considerable less mechanical stress. Finally, obesity has also been associated with chronic pain conditions other than musculoskeletal as for instance migraine (May and Schulte, 2016) altogether suggesting a multifactorial pathophysiology.

Rodent models can potentially be of interest to study the association and to provide mechanistic explanations. We therefore reviewed and systematized information regarding pain-related behaviors in rodent models of obesity. Nociceptive assays included Hargreaves (Hargreaves et al., 1988), tail-flick (D'Amour and Smith, 1941), tail-pinch (Haffner, 1929), hotplate (Woolfe and MacDonald, 1944), Randall-Selitto/paw pressure test (Randall and Selitto, 1957), Von Frey monofilaments (von Frey, 1896) and colorectal distension (Ness and Gebhart, 1988) – included in the acute pain section (3.3.1) as in the specific study (Tramullas et al., 2016), animals had no additional condition (e.g. colitis). Additionally, nocifensive behaviors like protection, licking, flinching (Guimaraes et al., 2019; Sotiropoulos et al., 2014) were also used in some studies to assess pain, for instance in the formalin test or in neuropathic conditions. On the contrary, readouts like the grimace scale (Langford et al., 2010) or ultrasonic vocalizations (Smith et al., 2020) as well as more complex emotional and cognitive behaviors – e.g. anxiety/depression (Guimaraes et al., 2021, 2019), impulsivity (Cunha et al., 2020a), attentional set-shifting (Leite-Almeida et al., 2014); see also for review (Cunha et al., 2020b; Leite-Almeida et al., 2015) – were absent in the works selected for this systematic review. Regarding obesity, both dietary and genetic models were used. Generically, dietary obesity

models rely on diets that have more kcal/g which is normally achieved with an increased fat content (e.g. HFD). However, high-carbohydrate diets like the western (WD; Gavini et al., 2018), total western (TWD; Totsch et al., 2016) and the standard American (SAD; Totsch et al., 2017) diets were also used in the selected studies. No study compared the impact of each of these diets in pain related outcomes. Obesity genetic models included the *ob/ob* mice (Ingalls et al., 1950), the db/db mice (Hummel et al., 1966) and the fa/fa rat (Zucker "fatty" rat; Zucker and Zucker, 1961). The mutation, named fa ("fatty") was firstly reported in 1961 (Zucker and Zucker, 1961) and manifested in crossings between the Sherman strain and Merck stock 13 M strain. It was later characterized as a missense mutation in the leptin receptor gene (Chua et al., 1996a, 1996b; Phillips et al., 1996). Indeed, all genetic models above rely on the disruption of leptin signaling a critical hormone for energy homeostasis (Pan and Myers, 2018). They have similar phenotypes, particularly excessive weight, but while the *ob/ob* mice is a leptin deficiency model, db/db mice and the fa/fa rat are leptin receptor-deficient being therefore resistant to its effect (Chua et al., 1996a) – see for review (Wang et al., 2014a).

The first observation of altered nociception in these models of obesity dates back to the 1980′s in an abstract reporting higher response thresholds in *ob/ob* mice; a possible relation with elevated pituitary endorphins levels was hypothesized (Roy et al., 1980). The majority of the studies included in this systematic review aligned with this early finding showing either increased response latencies or thresholds to noxious stimuli or no differences between obese and control animals. Time-dependent effects most certainly due to the normal development of the pathology and/or aging were reported (Liang et al., 2019; Rodgers et al., 2014; Sugimoto et al., 2008; Totsch et al., 2016) and might in part explain some divergence across studies. Interestingly, no sex-related effects were observed in any of the studies (Rodgers et al., 2014; Rossi et al., 2013; Totsch et al., 2018, 2017). Overall, data obtained in experimental models of obesity greatly overlap those reported in human studies (reference above). The most used tests in rodents were the Hargreaves (Hargreaves et al., 1988) and tail-flick (D'Amour and Smith, 1941) both using noxious heat stimuli applied in the plantar surface of the hind paws and tail, respectively. It is not therefore expected that fat accumulation provides a reasonable explanation for this outcome as suggested in human studies. Instead, hypoalgesia is more likely to result from structural and functional alterations in the peripheral nerves. Intraepidermal nerve fiber density was found to be decreased in obese animal as well as decreased nerve conduction velocity (Guilford et al., 2011; Holmes et al., 2015; Xu et al., 2014) – confront with (Cooper et al., 2018). It is therefore not a surprise that some studies observed allodynia, a hallmark of peripheral neuropathies, in obese subjects (Choucair-Jaafar et al., 2014; Cooper et al., 2018; Gavini et al., 2018; Guo et al., 2019; Latham et al., 2009). This set of studies provide good hints on the diversity of outcomes observed which could be strain-dependent (Cooper et al., 2018) and/or time-dependent (Latham et al., 2009). Choucair-Jaafar and colleagues reported that by the 8th week all *ob/ob* were obese but 28% had not developed obesity-related diabetes nor mechanical allodynia (Choucair-Jaafar et al., 2014).

In models of subacute and chronic pain conditions, obese animals frequently presented an exacerbation of nocifensive behaviors and/or pain-related phenotypes were sustained over longer periods of time. Such was particularly evident in models with an obvious inflammatory component such as subcutaneous inflammation (carrageenan and PGE2; Brandao et al., 2019; Iannitti et al., 2012; Wang et al., 2014b), post-operative pain (skin incision; Guillemot-Legris et al., 2018; Iannitti et al., 2012; Song et al., 2018), arthritis (Croci and Zarini, 2007; Loredo-Perez et al., 2016; Song et al., 2017; Totsch et al., 2018, 2017, 2016) and radicular pain (perineural inflammation; Song et al., 2017) most certainly reflecting the proinflammatory state that has been associated with obesity (Bastard et al., 2006; Das, 2001; Eichwald and Talbot, 2020; Ellulu et al., 2017). In diet-induced obesity preclinical studies, it was demonstrated a spontaneous development of arthritis (Griffin et al., 2012) or an aggravation in induced models (collagen-induced arthritis; Jhun et al., 2012), although pain-related outcomes were not directly measured – see for review (Fang and Beier, 2014). In these 2 examples, obesity-associated inflammation was shown to be essential underlying mechanism. Curiously, in fast resolving inflammatory models like the capsaicin (Iannitti et al., 2012; Rossi et al., 2016, 2019) and formalin (Cooper et al., 2018; Hu et al., 2018) no alterations or conflicting findings were reported, respectively. Similarly, discrepancies were observed in the two studies assessing pain in traumatic neuropathies (Cristino et al., 2016; Guo et al., 2019). It is important to note that the spontaneous development of neuropathies in obese subjects might be a confounder and therefore the differences between the 2 studies might simply reflect different stages of the pathophysiology.

In addition to the underrepresentation of some pain models several other limitations need to be mentioned. First, the number of studies using females to investigate potential sex-related differences was limited. Although in general no sex discrepancy was observed – e.g. (Rodgers et al., 2014; Rossi et al., 2013; Totsch et al., 2018, 2017) – HFD impact on pain in an hind paw incision model was lower in females (Song et al., 2018). Such reinforces the pertinence of the inclusion of this group in all experimental studies – (Mogil, 2020). Next, the mutations found in *ob/ob* mice (Ingalls et al., 1950), db/db mice (Hummel et al., 1966) and fa/fa rat (Zucker "fatty" rat; Zucker and Zucker, 1961) are rarely found in humans. While these models are interesting from a mechanistic point of view, most forms of human obesity, although associated with reduced hypothalamic leptin receptor activity and subsequent elevated leptin production from the adipose tissue (Munzberg and Morrison, 2015), are primarily due to environmental factors, particularly decreased physical activity and increased consumption of high-caloric foods (Hill and Peters, 1998; Ledikwe et al., 2006; Zobel et al., 2016). In the same line, alterations in nociception and pain susceptibility were observed in the absence of weight gain (e.g. Song et al., 2017) indicating that the diet itself can have an impact – see for review (Elma et al., 2020; Mendonça et al., 2020; Totsch et al., 2015). One study in mice even showed a positive association between HFD duration and longer recovery periods to basal pain thresholds after diet normalization (Guillemot-Legris et al., 2018). Altogether, this raises the question on whether other biochemical models should also be studied concerning diet/obesity influence on pain. For instance, a recent study demonstrates an interesting relation between fecal microbiome and WD related pain which was rescued after a fecal transplantation (Bonomo et al., 2020).

Conclusion

In general high caloric diets and a genetic models of obesity were associated with decreased nociception and manifestations of allodynia. Also, particularly in inflammatory conditions, pain-related behaviors were more pronounced and sustained over time. While the overall quality of the selected studies was high, some limitations were found, of notice the small number of studies assessing sex-related effects. On the other hand, experimental and clinical obesity studies are in general aligned regarding pain-related outcomes, indicating that rodent models might be a valuable tool to uncover the underlying pathogenesis of abnormal pain processing in obesity and to unravel diet's contribution to the phenomena.

Author contributions

HLA conceived the study. CMM and MLC collected and organized information. All authors contributed to data analysis and interpretation. CMM and MLC wrote the first draft of the manuscript. All authors contributed to the following versions of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

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