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Animal models of pain: Diversity and benefits

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ABSTRACT

Chronic pain is a maladaptive neurological disease that remains a major health problem. A deepening of our knowledge on mechanisms that cause pain is a prerequisite to developing novel treatments. A large variety of animal models of pain has been developed that recapitulate the diverse symptoms of different pain pathologies. These models reproduce different pain phenotypes and remain necessary to examine the multidimensional aspects of pain and understand the cellular and molecular basis underlying pain conditions.

In this review, we propose an overview of animal models, from simple organisms to rodents and non-human primates and the specific traits of pain pathologies they model. We present the main behavioral tests for assessing pain and investing the underpinning mechanisms of chronic pathological pain. The validity of animal models is analysed based on their ability to mimic human clinical diseases and to predict treatment outcomes. Refine characterization of pathological phenotypes also requires to consider pain globally using specific procedures dedicated to study emotional comorbidities of pain. We discuss the limitations of pain models when research findings fail to be translated from animal models to human clinics. But we also point to some recent successes in analgesic drug development that highlight strategies for improving the predictive validity of animal models of pain. Finally, we emphasize the importance of using assortments of preclinical pain models to identify pain subtype mechanisms, and to foster the development of better analgesics.

1. Introduction

Pain is a vital physiological function that protects organisms against potential damage. Acute nociceptive pain is a normal function of the nervous system that provides important sensory information about the environment and reacts to harmful stimuli such as noxious heat, extreme cold, chemical irritants, and mechanical tissue damage. These noxious stimuli activate peripheral nociceptors, triggering action potentials that propagate along sensory axons to the dorsal horn of the spinal cord where nociceptive inputs are processed and relayed to the brain. In turn, the activation of specific brain areas produces a broad array of sensory, emotional, autonomic, and motor responses that shape our experience and perception of pain (Basbaum et al., 2009; Burma et al., 2017).

In contrast to acute pain, chronic pain is a maladaptive disease that heightens the sensitivity to sensory stimulation (Woolf and Salter, 2000; Costigan et al., 2009). Chronic pain results from abnormal functioning of the nervous system, with pain persisting far beyond the resolution of the primary injury. Pain hypersensitivity manifests as spontaneous pain (pain in the absence of an external stimulus), allodynia (pain resulting from an innocuous stimulus), and/or hyperalgesia (an exaggerated pain response to a noxious stimulus). Chronic pain is a major health problem that negatively impacts the quality-of-life of sufferers and exacts enormous socio-economic costs with a prevalence of around 8 % of the general population (Bouhassira et al., 2008). In the European Union, it is estimated that 20 % of the population would suffer from chronic pain during lifespan (Breivik et al., 2006; Alshami, 2014), and it is among the most significant risk factors for suicide.

Chronic pain drastically diminishes quality of life and causes

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enormous socio-economic costs. Besides high costs for disease management, chronic pain is associated with major impacts on daily activities and quality of life (Groenewald and Palermo, 2015) and high productivity losses due to work absences (Mayer et al., 2019) partly due to common co-morbidities such as depression (Phillips, 2006). The estimated direct and indirect healthcare costs for chronic pain disorders in European Member States vary between two and three percent of GDP across the EU (Breivik et al., 2013). For 2016, this estimate would result in up to €441 billion. In the USA, ~100 million people suffer from pain costing ~$600 billion/year in health care and lost productivity (Walker et al., 2014). These costs are reported to exceed those estimated for heart disease, cancer and diabetes (Breivik et al., 2013). However, chronic pain is poorly managed with treatment success rates around 30 % (Ossipov et al., 2014), mainly because chronic pain mechanisms remain poorly understood (Basbaum et al., 2009; Dolique et al., 2010; Corder-o-Erausquin et al., 2016; Kuner and Flor, 2016), and patients often suffer from comorbid disorders such as anxiety and depression (Attal et al., 2011).

It is important to recognize that there is not one overarching, singular condition called chronic pain but rather, there are multiple aetiologies of pain, each resulting from different pathologies and differing in the clinical presentation of signs and symptoms (Burma et al., 2017). Pain is usually subdivided in different categories as a function of the mechanism of injury. Nociceptive pain represents the normal response to noxious insult or injury of tissues such as skin, muscles, visceral organs, joints, tendons, or bones. Inflammatory pain results of activation and sensitization (peripheral and/or central) of the nociceptive pain pathway by a variety of mediators released at a site of tissue inflammation. Neuropathic pain arises from damage to the nervous system itself, central or peripheral, either from disease, injury, or pinching. Other types of pain were characterized, e.g. cancer pain or dysfunctional pain when no biological cause is identified. To address differences in the presentation of pain symptoms across chronic pain conditions, an array of preclinical animal models has been developed to recapitulate the underlying pathology, duration, and comorbidities of pain phenotypes (Mogil, 2009). This variety of preclinical pain models is essential for understanding the molecular and cellular mechanisms that underlie distinct pain conditions. The development of novel and more efficacious therapies requires a thorough understanding of the mechanistic underpinnings of chronic pain and the design and testing of new drugs.

Rodents are employed in an large majority of preclinical pain studies (Mogil, 2009). However, the use of alternate vertebrates and invertebrates, such as zebrafish, fruit flies (Drosophila sp.) and nematodes (*Caenorhabditis elegans*) can also be advantageous for screening assays and for studying the genetic and molecular mechanisms of acute and chronic pain (Way and Chalfie, 1989; Gonzalez-Nunez and Rodríguez, 2009; Milinkeviciute et al., 2012). Each organism confers a distinct advantage for studying pain; the behavioral complexity of the rodents allows the analysis of the affective components of pain (Johansen et al., 2001; Panksepp and Lahvis, 2011), whereas simpler organisms, such as Drosophila, can facilitate the discovery of novel molecular players involved in the detection of noxious stimuli (Caldwell and Tracey, 2010; Mogil et al., 2010).

Another important aspect for designing animal models is to recognize that pain is a multi-dimensional experience. Indeed, pain is processed not only at the peripheral and spinal levels, but also in higher brain structures including cortical areas underlying the affective component of pain (Liu and Chen, 2014). As pain transitions from acute to chronic and becomes pathological, the associated negative emotional state not only exacerbates sensory modalities, but also worsens the comorbidities. Indeed, anxiety is a highly common comorbidity of pain where the interactions between pain and anxiety have been demonstrated in human. In addition, chronic pain and depression are complex disorders that often coexist and increase the risk of one another (Radat et al., 2013; Steel et al., 2014; Zhu et al., 2018a). Investigations of pain and psychiatric disorders are mostly conducted separately, but more knowledge of the overlap and interactions between affective and pain circuits is key to better treatments. Refined analysis of animal models of pain and depression has become mandatory to understand interactions between pain and emotional comorbidities (Kremer et al., 2020).

The present review proposes an overview of rodent and alternate models of pain. A large panel of evaluation devices used to characterize pain-like behavior in animal models has been developed over the years, and a summary description of these tools is presented here. The review focuses mainly on the broadly studied neuropathic and inflammatory types of pain. It also highlights the necessity of specific procedures dedicated to studying emotional comorbidities to pain. Finally, it summarizes the main limitations of using animal models to mimic clinical pain in humans, but also provides examples of successful translational applications of using animal models.

2. Assessment of pain

The classical pain evaluation devices aim to assess the sensory component of pain, usually by measuring a withdrawal reflex. However, more recently, specific efforts have been made to assess pain perception and to evaluate the emotional component of pain and comorbid affections. Unlike humans, animals are incapable of verbally describing pain, therefore a battery of behavioral tests has been developed in order to assess pain-like behavior in animals. These assays can be divided into stimulus-dependent and stimulus independent tests.

2.1. Stimulus-dependent tests

In the evoked tests the latency to or the frequency of paw withdrawal is usually measured after mechanical or thermal stimulation.

2.1.1. Mechanical stimulation

Mechanical hypersensitivity can be of various types, namely dynamic (triggered by brushing), static (triggered by pressure), and punctate (triggered by touch) (Deuis et al., 2017). Dynamic mechanical hypersensitivity is measured by air puffing on the face (Miraucourt et al., 2009) or light stroking (velocity is ~ 2 cm/s) of the external lateral side of the injured hind paw with a paintbrush (Cheng et al., 2017). The typical response of naive rodents to the dynamic mechanical stimulation is a very fast lifting of the stimulated paw aside. In experimental pain models, the response changes into sustained lifting, flinching or even licking behavior. Static mechanical sensitivity can be assessed with a pressure algometer (Deuis et al., 2017). Testing punctate mechanical hypersensitivity generally consists of applying an increasing pressure and measuring nociception in animals. Some tests are more specific to rats (Randall-Selitto Test) and some are common to rats and mice (von Frey). These tests are described more in detail below.

2.1.1.1. Von Frey test. The von Frey test, originally developed by Maximillian von Frey, is used to assess mechanical allodynia in rodents (Piel et al., 2014; Deuis et al., 2017). The manual von Frey test consists of applying pressure of different force using calibrated von Frey filaments (ranged from 0.008 to 300 g) on the plantar surface of the hind paw. The animal is freely moving in a cage, and can rest on a penetrable grid. Once the animal is standing on its 4 legs, the filament is placed perpendicularly and pressed against the paw until it bends.

(i) Three main methods of using von Frey filaments are commonly used. The “up and down” method determines the weight of stimulus that elicits a response 50 % of the times it is applied. It derives of the statistical formula used to determine LD50 s (lethal dose: dose that is lethal for 50 % of the animals in the group) (Dixon, 1980; Chaplan et al., 1994). The methods is based on a series of testing with filament of different forces. The

calculation takes into account six responses around the threshold and assess the 50 % threshold using the formula: 50 % threshold (g) = $10^{(X+kd)}/10^4$, where X = the value (in log units) of the final von Frey filament, k = tabular value for the response pattern (see Appendix 1 in.(Chaplan et al., 1994)) and d = the average increment (in log units) between von Frey filaments (Deuis et al., 2017). Recent refinements of this methods have been published and proposed easier procedures (Bonin et al., 2014; Christensen et al., 2020). A limitation of this method is the repetitive stimulations that is time-consuming and can cause sensitization.

(ii) (In the "percent" method, identical series of stimulations with von Frey filaments of increasing force are applied to all animals and the percentage of withdrawal responses is assessed (Chaplan et al., 1994). Here also the limitation relates to the high number of stimulations applied to one animal.

(iii) In the "ascending" method, filaments with increasing force are used, and nociceptive behavior is considered when the animal retracts the paw, licks it or even shakes it (D'Souza et al., 2011; Papon et al., 2020). The effects of stress are very limited in this test since the animal is unrestrained and is habituated to the environment prior to the test. However, it relies on the experimenter eye and judgment thus a subjective bias has to be taken into consideration. In order to limit this subjectivity, one can use electronic von Frey where a single filament is pressed against the paw and the force is increased automatically until paw withdrawal.

Overall, despite the popularity of the von Frey test, there is no consensus on the sensation that is triggered in rodents, mainly is because the distinction between noxious and innocuous stimuli relies on subjective human judgment and can hardly be applied to an animal. Moreover, pain is an experience that can be different for human and rodents. Therefore, it is assumed that the von Frey test triggers nociception and can be used to assess unpleasantness of the stimulation, rather than pain (Abdus-Saboor et al., 2019).

2.1.1.2. Randall-Selitto Test or paw pressure test. This test is used to assess mechanical hypersensitivity in rats (Randall and Selitto, 1957). The animal is restrained and an increasing pressure is exerted on the hind paw or tail using a dome-shaped plastic tip. When the rat withdraws its paw or vocalizes, threshold is attained and the pressure is stopped (Barrot, 2012). Waiting for the animal to vocalize is not recommended since it is a synonym to great pain which may lead to injuring the animal (Muley et al., 2016). Another limitation is that rats should be habituated to being restrained in order to minimize the stress bias (Santos-Nogueira et al., 2012).

Behavioral tests and readouts must be carefully chosen according to the mechanisms under investigation. Withdrawal reflex is usually seen as a measure of spinal reflex. In contrast, vocalizations are considered as a measure of integrated pain-like behavior (Kayser and Christensen, 2000). Since 22 kHz vocalizations are emitted in response to aversive stimuli, the use of ultrasound has been considered. However, ultrasound vocalization do not correlate to pain-like behavior and cannot be considered as a reliable readout of pain sensation in rodents (Wallace et al., 2005).

2.1.2. Cold stimulation

2.1.2.1. Acetone evaporation test. Acetone evaporation test is used to assess cold allodynia in rodents (Choi et al., 1994; Vissers and Meert, 2005; Colburn et al., 2007). The evaporation of acetone on the hind paw leads to a cold stimulation that is not considered nociceptive in naive animals. Therefore, it is used to evaluate allodynia in neuropathic and inflammatory pain models (Deuis et al., 2017). The test consists of a repetitive application of acetone on the hind paw and a measurement of the latency to withdrawal (Xing et al., 2007). Alternatively, cold allodynia assessment may be achieved by monitoring the duration or the number of nocifensive responses, or scoring the severity of the response. The test is done on one paw, leaving the other as control. However, the smell of acetone can trigger an olfactory stimulus that can overlap the cold stimulation (D'Souza et al., 2011).

2.1.2.2. Cold plate. The cold plate test is used to assess cold allodynia and hyperalgesia. It consists of measuring the latency to paw withdrawal after applying a stick of ice (wet or dry ice) on the floor of a cage just underneath the paw of a freely moving animal (Allchorne et al., 2005). Alternatively, the rodent can be standing on a plate that is cooled down to 5 °C by Pelletier effect. One main disadvantage for this test is that the animal should stay in place until the temperature transfer (Barrot, 2012).

The cold plantar assay has been developed to apply a focal ramping cold stimulus to unrestrained, acclimated mice (Brenner et al., 2012). This assay has the ability to establish a detail evaluation of the nocifensive response as a function of the temperature and to measure both cold allodynia and cold anesthesia with low variability in mice. It is also highly sensitive to experimentally altered pain conditions including CFA-induced inflammation, and SNL-induced nerve injury, or morphine treatment.

2.1.3. Hot stimulation

2.1.3.1. Hot plate. Hot plate test is used to assess thermal nociception in mice and rats (Woolfe and Macdonald, 1944). The test consists of placing a freely moving animal on a hot metallic surface (with a constant temperature at 50−55 °C) and measuring the latency for the animal to exhibit nocifensive behavior (paw withdrawal or jumping). For ethical reasons, it is recommended to stop the test as soon as the animal withdraws the paw. The latency should not be measured on the forepaws since they are more often used to explore and groom. Consequently, it is more reliable to observe hind paw withdrawal. In order to avoid tissue damage, explorers should determine a cut-off time if the animal doesn't respond. Another variant of the hot plate is the dynamic hot plate test where the temperature of the metallic surface increases gradually until pain-like behavior (D'Souza et al., 2011; Barrot, 2012; Burma et al., 2017; Deuis et al., 2017).

The dynamic hot plate (Ogren and Berge, 1984) differs of the classical hot plate test in the sense that the animal is submitted to a ramp of increasing temperatures, usually starting at 42 °C until a nocifensive response is observed. By assessing the response temperature, the dynamic hot plate test gives an estimate of thermal allodynia.

2.1.3.2. Hargreaves or plantar test. Hargreaves test is used to assess heat pain threshold in mice and rats (Hargreaves et al., 1988). The test consists of applying an infrared heat source on the hind paw of an unrestrained animal in a clear box which rests on a glass floor. The latency to withdrawal is automatically measured and displayed. The animal should be acclimatized to the box prior to the experiment to minimize movement not related to nociception. Compared to the hot plate test, the Hargreaves test offers the possibility to address each hind paw and thus using one as control (Hargreaves et al., 1988; Harvey and Dickenson, 2009). In 2013, Banik and Kabadi have developed a modified Hargreaves for rats where they fix the time and measure the temperature at which the paw is withdrawn (Banik and Kabadi, 2013). The authors apply a constant temperature for 10 s, then they increase the temperature by 2.5 °C and apply it for another 10 s until paw withdrawal (with temperature starting at 35 °C up to a maximum of 70 °C).

2.1.3.3. Tail flick test. The tail flick test is used to assess heat pain threshold in mice and rats (D'amour and Smith, 1941). The test consists

of measuring the latency of the tail to flick after a heat stimulation. The tail is either dipped in a hot water bath with a constant water temperature between 46° and 52 °C or the tail is exposed to a light beam. This test is easy and quick to perform if the animal is habituated to being loosely restrained, but there is a risk of jeopardizing animal's thermoregulation since the tail plays an important role in rodents' thermoregulation (Barrot, 2012;Deuis et al., 2017).

2.2. Stimulus-independent tests

When in pain, animals are capable of developing a spontaneous behavior that is not a consequence of thermal nor mechanical stimulation. This type of behavior is believed to be more relevant clinically although it must be kept in mind that rodents being prey animals, they tend to hide states of discomfort. Throughout the years a series of methods have been developed to assess these non-evoked behaviors. In this review the grimace scale, weight bearing, conditioned place preference and burrowing will be discussed (for a more thorough review on spontaneous behavior please refer to Tappe-Theodor and Küner (Tappe-Theodor and Küner, 2014).

2.2.1. Grimace scale and unbiased behavioral analysis

The grimace scale test in rodents consists of observing 5 facial features: orbital tightening, nose bulge, cheek bulge, ear position, and whisker position (Langford et al., 2010; Sotocinal et al., 2011). These features are scored from 0 (normal) to 2 (severe). It is classically used to assess acute pain since animal are capable of adapting to long-lasting pain, and therefore no longer express facial changes (Langford et al., 2010). Moreover, facial expression is being used to asses emotions associated with pain (Dolensek et al., 2020).

Beyond the grimace scale test, high-throughput, unbiased approaches that accurately measure non stimulus-evoked pain are currently under development. Increasing the dimensionality of pain assays has the potential to increase the predictive validity of translational pain therapeutics and the transfer from bench to bed side. The speed of rodent responses to sensory stimulations is in the range of the millisecond and cannot be captured only by the eye experimenter. It requires the development of automated systems to monitor pain-like behavior, possibly coupled with statistical modelling and machine-learning (Abdus-Saboor et al., 2019). Automated behavioral analysis can be performed in a dedicated apparatus (Behavioral Spectrometer, Behavioral Instruments) or in a home cage (HomeCageScan, CleverSys; PhenoTyper, Noldus) and captured a broad array of various motor behaviors. It also computes distance traveled and velocity (Brodkin et al., 2014; Roughan et al., 2016). The challenge is to ensure that the combination of measured behaviors is representative of pain states since each individual behavior is not specific to pain. Comparisons with well-established assays, or series of individual assays, are necessary prior to generalize the use of automated, unbiased paradigms to assess pain conditions in rodents.

2.2.2. Weight bearing

The test consists of measuring weigh repartition on the rodent's hind limbs. In normal conditions the weight is equally distributed on both hind limbs, whereas in inflammatory or neuropathic pain models, the weight is shifted towards the non-painful paw. Weight bearing is assessed either statically (the animal is standing in inclined cage with the 2 paws relying on 2 separate pressure detectors) or dynamically (the animal is freely moving on pressure sensitive floor) (Muley et al., 2016; Burma et al., 2017;Deuis et al., 2017).

2.2.3. Conditioned place-preference (CPP)

CPP test in used to assess ongoing pain in rodents (Leite-Almeida et al., 2015). The original protocol was developed in rats by King et al. (King et al., 2009). The test consists of 2 compartments with identical dimensions but with different floors and walls. One compartment is associated with pain relief and both compartments communicate through a middle chamber (King et al., 2009; Blanco-Gandía et al., 2018). Prior to the test, animals are preconditioned for 3 days where they are left moving freely between both compartments, the ones developing a preference to one compartment are excluded. Afterwards animals are conditioned for 4 days by pairing each of the two compartments with either drug or vehicle administration. The purpose is to associate one compartment with pain and the other one with analgesia. On the test day, animals are left uninjected and moving freely. The time spent in each compartment is recorded (King et al., 2009; Sellmeijer et al., 2018). The animals tend to spend more time in the pain-relief compartment (Vuralli et al., 2019). The test assesses spontaneous pain in an indirect way. To avoid biases in the compartment choice, it is important to maintain the same environment during the whole procedure (Narita et al., 2006).

2.2.4. Burrowing

Burrowing is a spontaneous behavior that has been used in rodents to assess non-evoked pain conditions. A burrow, filled with appropriate substrate, is placed in the home cage and the amount of material displaced by the animal within a predefined time interval is measured by the experimenter (Deacon, 2006). It is a very simple, objective, test, showing a high level of reproducibility. It has been validated for various models of inflammatory and neuropathic pain (Deuis et al., 2017).

2.3. Assessment of pain comorbidities

When chronic pain lasts for more than 3 months and is considered as an illness, it is often associated with emotional or psychiatric comorbidities. In spite of its prevalence and impact on patients quality of life, chronic pain and emotional disorders are still poorly managed and current therapies are often inadequate (Finnerup et al., 2010). Although many reports suggest that typical anti-depressants are successful in treating pain, their success rate remains lower than 50 % (Kroenke et al., 2009). Moreover, anti-depressants have anti-nociceptive effects but are less convincing in preventing the affective component of pain, i.e., pain perception (Boyce-Rustay et al., 2010). Therefore, simply targeting either pain or emotional disorders is not effective and there is a need to identify new common mechanisms. An increased understanding of mechanisms that underlie the overlap of pain with comorbid emotional states are key factors in the development of new therapies (Navratilova et al., 2016). For this purpose, the identification of agents that are active against both pain and emotional pathologies is a priority since these agents are likely to target common mechanisms, engaging overlapping neuronal circuits and underlying both disorders. Such research at the frontier between pain studies and psychiatry requires elaborate animal models and complex analysis to discriminate between the various components of the global pathology. Some highlights on comorbidities between chronic pain and psychiatric disorders are proposed below. A thorough evaluation of pain and anxiety/depression models was recently proposed (Kremer et al., 2020)).

2.3.1. Anxiety-like behavior

In the following tests the time and frequency of staying in one compartment or another is measured.

2.3.1.1. Elevated plus maze test (EPM). The EPM test is considered as the standard test for anxiety-like behavior in rodents (Leite-Almeida et al., 2015). It was first developed in rats by Pellow et al. in 1985 (Pellow et al., 1985) and by Lister et al. in 1987 for mice use (Lister, 1987). The test consists of a cross-shaped maze that is elevated from the floor with 2 open arms that are perpendicular to 2 closed arms (Vuralli et al., 2019). The animal is placed in the centre and left to explore the premises for 5 min (Narita et al., 2006). The test relies on the quandary between the animal innate tendency to explore and its fear of open, lit and elevated

places (Campos et al., 2013). Anxious animals spend less time in open arm. Indeed, inflamed animals exhibit anxious-like behavior just hours after pain induction and lasts for 3–4 weeks, whereas animal models of neuropathic pain develop this kind of behavior 3–4 weeks after the surgery and it lasts for 4 more weeks (Leite-Almeida et al., 2015). It is important to notice that the animal gets familiar with the cross shaped maze, thus introducing some bias (Tucker and McCabe, 2017). Therefore, the elevated zero maze was developed as it consists of a circular-shaped maze (Shepherd et al., 1994). One more pitfall is that the presence of the experimenter interferes with the results. Consequently, animals are videotaped for unbiased data (Vuralli et al., 2019).

2.3.1.2. Open field test (OF). The OF test represents the oldest test to assess anxiety-like behavior in rodents (Leite-Almeida et al., 2015). The test consists of placing the animal in the center of a square with high walls and let the animal explore the area freely for 5 min. The concept of this test is similar to the EPM, as it relies on the dilemma between exploratory behavior and fear of open spaces. Anxious animals tend to stay next to the wall and avoid the center, in fact mouse models of inflammatory pain exhibit anxiety-like behavior from 2 to 28 days after induction of the inflammation whereas neuropathic pain models may develop this kind of behavior 2–8 weeks after surgery or may not. This great variability could be linked to the type of neuropathy or to the test protocol; this is why it is not recommended to use this test as the sole determinant of anxiety-like behavior in neuropathic pain models (Kremer et al., 2020).

2.3.1.3. Light and dark box test (LDB). The LDB test was first developed by Crawley and Goodwin in the 1980's (Crawley and Goodwin, 1980). The box is divided into two compartments, one small and dark and the other big and brightly lit (twice as big as the small dark compartment) (Bourin and Hascoët, 2003). The animal is placed in the light compartment and left to explore the box freely for 5 min (Vuralli et al., 2019). The LDB concept is the same as the EPM and OF, as it is based on the conflict between the animal exploratory behavior and its aversion to light places. Anxious animal tend to avoid the light compartment. In fact mouse models of inflammatory pain exhibit anxiety-like behavior from 1 to 28 days after induction of the inflammation whereas this kind of behavior may develop 4–8 weeks after surgery in neuropathic pain models (Kremer et al., 2020).

2.3.2. Depression-like behavior

2.3.2.1. Forced swim test (FST). The FST is the most commonly used test to assess depression-like behavior in rodents. It was first developed by Porsolt in 1977 (Porsolt et al., 1977a, 1977b). The test consists of dropping the animal in a water filled cylinder for 5 min and measure the total duration of immobility (Leite-Almeida et al., 2015). When faced with the inability to escape (closed water cylinder), the animal stays immobile as a possible manifestation of depression-like behavior. Increased immobility is observed in mouse models of inflammatory pain between 4–35 days post induction and between 4–8 weeks post-surgery in neuropathic pain models (Kremer et al., 2020).

2.3.2.2. Tail suspension test (TST). TST is a depression-like behavior test applicable only in mice and is considered as a more sensitive variant of FST (Steru et al., 1985). It consists of suspending the mice by their tail for 6 min and measuring their duration of immobility. Increased immobility is observed in inflamed mice between 7 days (complete Freund's adjuvant model in mice, see §2) to 41 weeks (osteoarthritis model in mice, see §2) post induction and between 2 weeks to 2 months post-surgery in animal models of neuropathic pain (Kremer et al., 2020).

2.3.2.3. Sucrose preference test (SPT). The SPT developed by Katz (Katz, 1982), is a depression-like behavior test that assesses anhedonia which refers to the inability to feel pleasure. The animal has the freedom to drink either water or a sweet solution. Animal models of depression have a decrease ratio of usage of sweet solution over water. In fact inflammatory pain mouse models have their ratio decreased between 2 days to 4 weeks post induction and between 1 week to 10 weeks post-surgery in neuropathic pain models (Kremer et al., 2020).

3. Models of inflammatory pain

Two important parameters to be considered in animal models of pain are the method of injury and the endpoint measurement. The most appropriate models, whether an injury, application of chemical agents, or other manipulations, should be based on 1) understanding the clinical disease presentation and pathology (i.e. face validity); 2) producing nociception by recapitulating the mechanisms of specific clinical conditions (i.e. construct validity). Measures of nociceptive behavior must not only detect pain-like responses but also do so in a manner consistent with the clinical experience of pain (Gregory et al., 2013). Measures of reflexive behaviors such as withdrawal thresholds to noxious stimuli have been used for decades to examine mechanisms of pain. These have clearly proven useful in advancing our understanding of the physiological basis of nociception, and the identification of neurotransmitters, receptors, intracellular messengers, genes, and circuits implicated in pain-specific mechanisms. They led to better understanding of existing pharmacologic and non-pharmacologic pain treatments (Woolf, 1983, 2011; Basbaum et al., 2009). In addition, past studies in rodent models of acute nociception and chronic pain indicated that the pharmacologic action (i.e. efficacy, potency, duration of action) of a broad spectrum of analgesics to reduce reflexive sensory responses have demonstrated relevance to human analgesia (Yaksh, 2002; Gregory et al., 2013).

Chronic pain can be the consequence of persistent inflammation (Burma et al., 2017). Injured peripheral tissue releases an inflammatory soup made of pro-inflammatory molecules comprising bradykinin, prostaglandin, cytokines and chemokines. This peripheral inflammation stimulates primary afferent neurons and causes peripheral sensitization. This can be accompanied by central sensitization due to the release in the spinal cord of neurotransmitters and neuromodulators such as glutamate, substance P or BD. This sensitization is transient in case of acute inflammation, whereas it becomes long lasting in chronic pain diseases (Ji et al., 2014). In the following, classical animal models of inflammatory pain will be listed first (Table 1) and followed by specific models for specific pathologies. As a matter of fact some animal models are specifically developed for well-defined pathologies. In this review, animal models of pain commonly used for osteoarthritis (which is the most common form of arthritis) and rheumatoid arthritis will be detailed.

3.1. Pain model induced by capsaicin

Capsaicin is a proto-alkaloid present in chili peppers and is considered to be the main irritant responsible for hot sensation (Ilie et al., 2019). Capsaicin induces a neurogenic inflammation. In fact capsaicin binds to transient receptor potential vanilloid 1 (TRPV-1) present on free neuronal endings of primary sensory neurons which will leads to the peripheral release of several inflammatory mediators: calcitonin gene-related peptide (CGRP), neurokinin A/B, somatostatin, vasoactive intestinal peptide (VIP), and substance P (Muley et al., 2016; Ilie et al., 2019). These neuropeptides will thus induce the release of pro-inflammatory cytokines by nearby mast cells, endothelial cells, epithelial cells and immune cells. The local inflammation occurs with hyperalgesia. Administration of capsaicin is accompanied by 2 types of hyperalgesia, a primary one that is believed to be a consequence of peripheral sensitization and responds to thermal and mechanical stimuli, and a secondary one which is a result of central sensitization and responds to mechanical stimulation (Frias and Merighi, 2016; Muley et al., 2016; Ilie et al., 2019). Capsaicin effects are dose dependent. In

Table 1
Classical inflammatory and neuropathic pain models in rodents with notes on companion animals.

	Animal species	Procedure	Clinical relevance	References
Inflammatory pain models				
Pain model induced by capsaicin	Mice Rats	Intra-plantar injection of capsaicin	Mimic skin inflammation and inflammatory bowel disease	Kenins, 1982; Muley et al., 2016
Pain model induced by formalin	Mice Rats	Injection (sub-cutaneous, intra-plantar…) of diluted formaldehyde solution (0.5−5%)	Not specific to a clinical pathology.	Dubuisson and Dennis, 1977; Muley et al., 2016
Pain model induced by complete freund's adjuvant (CFA)	Mice Rats	Subcutaneous injection of CFA in the hind paw or intra-articular	Assess inflammatory pain in mice and rats Robust pain model for the study RA	Stein et al., 1988; Muley et al., 2016
Pain model induced by carrageenan	Mice Rats	Subcutaneously injection of carrageenan	Joint pain inflammation	Winter et al., 1962
Pain model induced by zymosan	Mice	Injection of cell walls of Saccharomyces cerevisiae	Acute inflammation	Doherty et al., 1985
Osteoarthritis pain models	Mice Rats Guinea-Pigs Dogs Cats	• Chemical injections • Joint surgery and ligament manipulation • Streptococcus injection	Musculoskeletal disease and joint inflammation	Kalbhen, 1987; Stoop et al., 2001; Gomis et al., 2007; Knights et al., 2012; van den Broek et al., 1988; McCoy, 2015
Rheumatoid arthritis models	Mice	• Collagen injection • Collagen antibody injection	chronic autoimmune disorder	Courtenay et al., 1980; Nandakumar et al., 2003
Streptococcal cell wall induced arthritis (SCW)	Rats	Intra-articular injection of Streptococcus pyogenes	Mimic RA	van den Broek et al., 1988; Bessis et al., 2017
Centrally induced neuropathic pain models				
Contusive Spinal cord injury	Mice Rats	Weight drop on spinal cord	Clinically relevant model, but not specific to a pathology	Siddall et al., 1995
Spinal hemi-section	Rats	Hemi section of a thoracic segment usually cranial to L1 dorsal root entry	Mimic chronic central pain after spinal cord trauma	Koehler and Endtz, 1986
Photochemical injury	Rats	Ischemia & tissue necrosis of spinal cord	Reproduce a mechanical trauma of the spinal cord without surgery	Watson et al., 1986
Peripherally induced neuropathic pain models				
Sciatic nerve total transection	Mice Rats	Complete sciatic nerve transection	Mimic the clinical symptoms of "phantom limb"	Wall et al., 1979
Chronic constriction injury	Mice Rats	Four loose knots around sciatic nerve or the infra-orbital nerve	Mimic causalgia or complex regional pain syndrome	Bennett and Xie, 1988
Cuffing of sciatic nerve	Mice Rats	Implantation of a polyethylene tubing (cuff) around the common branch of the sciatic nerve	Study anxio-depressive comorbidities associated with NP that lasts for weeks after loss of hypersensitivity to pain	Mosconi and Kruger, 1996 Benbouzid et al., 2008
Partial sciatic nerve injury	Mice Rats	Partial ligation of dorsal third or half of sciatic nerve, peroneal or tibial branch or both	Mimic human causalgia symptoms (injury to the peripheral nerve)	Seltzer et al., 1990 Malmberg and Basbaum, 1998
Spinal Nerve Ligation	Mice Rats	Unilateral ligation of lumbar spinal nerves L5 and L6 distal to dorsal root ganglia	Mimic human causalgia symptoms (injury to the peripheral nerve)	Kim and Chung, 1992. Kiso et al., 2008
Spared nerve injury	Mice Rats	Lesion of two of the three terminal branches of the sciatic nerve	Not specific to a clinical pathology.	Decosterd and Woolf, 2000

fact, a high concentration or a continuous administration can lead to desensitization of TRPV1 resulting in an analgesic effect.

This inflammatory induced pain model, obtained after intra-plantar injection of capsaicin, is used in mice and rats (Carter and Francis, 1991; Lynn et al., 1992; Caterina et al., 2000; Laird et al., 2001; Drewes et al., 2003) to mimic skin inflammation and inflammatory bowel disease. It has also been used to assess the efficiency of non-steroid anti-inflammatory drugs (diclofenac) (NSAID), or anti-epileptic drugs (gabapentin) (Muley et al., 2016).

3.2. Pain model induced by formalin

The formalin test is commonly used since it was created in 1977 (Dubuisson and Dennis, 1977). It consists of an injection (sub-cutaneous or intra-plantar) of a diluted solution (0,05−5 %) of formaldehyde (Tjølsen et al., 1992). This pain model is characterized by a biphasic response. A short (0−5 min) first phase, where pain is believed to be a consequence of direct activation of primary sensory neurons, is followed by a second prolonged phase (10−40 min), where pain is the result of spinal cord inflammation within the dorsal horn, leading to central sensitization (Hunskaar and Hole, 1987; Tjølsen et al., 1992; Raboisson and Dallel, 2004). Among the mechanisms involved in this model, it has been shown that formalin activates transient receptor potential ankyrin 1 (TRPA1) (McNamara et al., 2007) more particularly in phase 2. Interleukin-33 and its receptor ST2 are also believed to be involved in inducing pain in both phases. In fact, Il-33/ST2 pathway activation leads to activating mitogen-activated protein kinase (MAPK) signaling pathway cascades that are implicated in central sensitization (McNamara et al., 2007; Han et al., 2015). In phase 1, pain-like behavior (paw licking and lifting, vocalization) can be observed. It is inhibited by lidocaine. In contrast, in phase 2, pain is alleviated by NSAID, morphine and gabapentin (McNamara et al., 2007). The formalin induced model is used in rats (Dubuisson and Dennis, 1977; McNamara et al., 2007) and mice (Hunskaar and Hole, 1987; Han et al., 2013) has largely contributed to better understanding of pain mechanisms (central and peripheral) (Muley et al., 2016).

3.3. Pain model induced by complete Freund's adjuvant (CFA)

CFA is a suspension of heat-killed *Mycobacterium tuberculosis* in

paraffin oil (Barrot, 2012) that is frequently used for inducing inflammatory pain. CFA is injected subcutaneously in the hind paw or intra-articular. When injected in the hind paw, the inflammation occurs 24 h after the injection and lasts for one to two weeks (Ren and Dubner, 1999; Bas et al., 2016). However, after after intra-articular injection, the inflammation takes 7 days to occur (Muley et al., 2016). The mechanisms leading to CFA-induced inflammatory pain are still to be deepened but it is known that the injection of CFA leads to the release of pro-inflammatory mediators (PGE2, TNF alpha, IL-1) that induces synovitis, bone resorption and eventual degeneration. Inflammatory mediators are responsible of neuronal sensitization that is responsible for joint pain (Muley et al., 2016). CFA-induced pain models are frequently used to assess inflammatory pain in mice and rats (Knight et al., 1992; McDougall et al., 1995; Keeble et al., 2005; Simjee et al., 2007; Fernandes et al., 2011; Uematsu et al., 2011; Nisar et al., 2015). For example, the CFA model is considered a robust model to study arthritis, and particularly rheumatic arthritis (RA) since it mimics the synovitis and bone resorption observed in human RA but does not mimic cartilage alteration (Bas et al., 2016).

3.4. Pain model induced by carrageenan

This model is mainly used to study inflammatory pain, more specifically joint inflammation (Mert et al., 2018). Carrageenan is used to induce transient joint inflammation, where hyperalgesia and allodynia are observed (Winter et al., 1962; Fehrenbacher et al., 2012). A carrageenan solution with a concentration centered between 0.5–2 percent is injected subcutaneously, the swelling is observed 3−5 hours after the injection and it lasts for 24 h (Winter et al., 1962; Otterness and Moore, 1988).

3.5. Pain model induced by zymosan

This self-resolving model is used to study acute inflammation (Cash et al., 2009). Indeed, 30 min after injecting zymosan, which is an insoluble polysaccharide component of the cell walls of Saccharomyces cerevisiae, animals develop edema and inflammation as well as thermal and mechanical hyperalgesia (Doherty et al., 1985; Meller and Gebhart, 1997). Thermal and mechanical hyperalgesia are dose dependent, and spontaneous pain is observed with greater doses (Doherty et al., 1985; Meller and Gebhart, 1997).

3.6. Osteoarthritis pain models

Arthritis is a medical condition in which the inflammation of the joint leads to chronic pain and movement limitation. In 2012, 52.5 million USA adults suffered from arthritis (Rice et al., 2019). This number is thought to increase and reach 78.4 million by year 2040 (Hootman et al., 2016). Osteoarthritis (OA) is a progressive musculoskeletal disease that leads to the failure of the entire joint (Teeple et al., 2013; Alshami, 2014). Novel treatment that tackles pain and helps increase activity is of necessity and therefore animal models of pain are needed to deepen the understanding of the underlying physiopathology of OA.

3.6.1. Chemically induced models

A wide range of chemicals are used to induce OA-like models, including papain, trypsin, carrageenan, kaolin, hyaluronidase, collagenase, sodium urate and mono-iodoacetate (MIA) (D'Souza et al., 2011; Fang and Beier, 2014). Notably, MIA is the most commonly used model to assess OA pain and one of the best models to study symptom-modifying OA drugs (D'Souza et al., 2011). MIA injection was first used by Dieter Kalbhen (Kalbhen, 1987). The mechanism of action of MIA consists of inhibiting the glyceradehyde-3-phosphate dehydrogenase in chondrocytes; thus inhibiting the glycolytic pathway and eventually leading to chondrocyte apoptosis, subchondral bone necrosis and cartilage degeneration, consequently mimicking the morphology of end stage OA (D'Souza et al., 2011; Fang and Beier, 2014). Subsequent to MIA injection, there are 2 phases. The first one consists of an early (few days after) inflammation, where pain is reversed by non-steroidal anti-inflammatory drugs (NSAIDs). In the second phase, the joint is destructed and the expression of the nerve injury marker activating transcription factor-3 (ATF-3) is increased in the L5 dorsal root ganglion. The pain during this phase may be lowered by the administration of morphine/gabapentin. MIA injection is used mainly in rats and also in mice and guinea pigs. In rats and mice the clinical outcomes are characterized by mechanical hypersensitivity in hind paw, alteration of sleep, and locomotive deficit, whereas in guinea pig mechanical allodynia is observed with altered weight bearing (D'Souza et al., 2011; Malfait et al., 2013; Fang and Beier, 2014). The intra-articular (knee) injection of the above-listed chemicals is a low-cost procedure that leads to rapid severe joint degeneration. Unfortunately the clinical relevance of this model to model OA is not as accurate as with other procedures.

3.6.2. Surgically induced models

Surgically induced models are obtained after joint surgery that is consequently unstable and altered. The cartilage degeneration, which is proportional to the degree of joint instability, depends on the joint structure. The most common procedures are performed on mice knees and leads to a fast and reproducible disease progression.

3.6.2.1. Anterior cruciate ligament transection (ACLT). It has been used for decades on large animals and nowadays this procedure is performed on rodents (Stoop et al., 2001; Gomis et al., 2007). The post-surgery physiopathology evolves over time with changes in chondrocyte physiology at 4 weeks post-surgery, mild cartilage destruction at 8 weeks, and osteophytes formed at 12 weeks post-surgery. When ACLT is combined to the removal of medial meniscus, the joint destruction and osteophytes formation are observed only at 4 weeks post-surgery. It is important to mention that in human OA, support structures are not all ruptured (D'Souza et al., 2011; Teeple et al., 2013).

3.6.2.2. Meniscectomy. The meniscectomy in rodents could be partial or total, lateral or medial, unilateral or bilateral (Bendele, 1987; Bove et al., 2006; Knights et al., 2012). At 4 weeks post-surgery, the cartilage starts to get damage and OA lesions progressively develop from 8 to 12 weeks post-surgery (Knights et al., 2012). This procedure is questionable since there is no consistency in the amount of meniscus that is being removed (Teeple et al., 2013).

3.6.2.3. Destabilisation of medial meniscus (DMM). The DMM is very common in mice (Glasson et al., 2007). Transection of the medial meniscotibial ligament leads to mild instability with cartilage destruction, subchondrial bone sclerosis and osteophyte formation. Cartilage lesions appear at 2 weeks post-surgery and progress for 16 weeks after this period. This procedure is the most common since it is reliable, reproducible and structurally similar to human OA. Furthermore, pain is reversed by standard analgesics. Finally, the disease progression is slower when compared to others (D'Souza et al., 2011).

3.6.3. Osteoarthritis in companion animals

OA is a natural occurring disease in cats, dogs and horses and appears to be very similar to human disease. Studies in these large animals, although less used than small animal models, are often required in translational research (McCoy, 2015; Lascelles et al., 2018). Dogs are considered as an excellent model to study human OA and remain the most used, especially in preclinical trials (Aragon et al., 2007; Pelletier et al., 2010; McCoy, 2015). However, natural racehorse OA is the best-suited model to investigate the pathophysiology of post-traumatic osteoarthritis in humans, especially in athletes (McIlwraith et al., 2012; McCoy, 2015). In particular, the stifle joints articular cartilage,

the most frequent altered tissue in OA suffering horses, is highly similar to the human knee cartilage. Although some pain research studies have been carried out in induced-OA companion animals, OA-natural companion models are, along with cancer-natural models (see section 4), valid models for modelling human pain (Klinck et al., 2017).

Thermal and mechanical nociception and pain tests commonly used in rodents have been adapted for these large animal models, such as facial expression analysis with the Grimace Scales (Holden et al., 2014; de Grauw and van Loon, 2016). For OA large animal models, subjective lameness scoring and kinetic gait analysis are also a widely method to assess OA pain (Moreau et al., 2014). Clinical metrology instruments (CMIs), questionnaires designed for pet owners, have improved the assessment of sensory and affective effects of pain in companion animals. Several OA CMIs exist for dogs, e.g. The "Canine Brief Pain Inventory" (CBPI) and "Liverpool Ostoearthritis" (LOAD), and cats, e.g. 'The Owner Behavior Watch' (OBW) and 'The Feline Musculoskeletal Pain Index' (FMPI). Although these CMIs are subjective methods to assess pain, they are validated by comparative analysis with objective tests for diagnosis and for outcome measurements in clinical research (Walton et al., 2013; Stadig et al., 2019). The positive therapeutic outcome of the anti-NGF antibodies in OA suffering dogs and cats is a good example of the translational positive values of companion animal models (see § 11; (Gruen et al., 2016; Sanga et al., 2017; Lascelles et al., 2018; Kelly et al., 2019)).

3.7. Rheumatoid arthritis models

An average of 0.5–1 % of the general population suffer from rheumatoid arthritis (RA) (Bas et al., 2016). RA is a chronic autoimmune disorder characterized by T cells' activation of macrophages and release of pro-inflammatory cytokines, e.g. tumour necrosis factor α (TNFα), interleukin (IL) 1, 6 and 17. This results in inflammation of the synovial membrane as well as cartilage and bone erosion (Caplazi et al., 2015; Bas et al., 2016). Immunotherapy is the most commonly used treatment for RA but the underlying cause of T cells reactivation is still unknown. Therefore, animal models are still needed and should new lights on pathophysiological mechanisms.

3.7.1. Collagen-induced arthritis (CIA)

CIA is the most frequently used models for RA since there is a good resemblance with human RA with the presence of rheumatoid factor and anti-citrullinated peptide antibody (Caplazi et al., 2015; Bas et al., 2016). The experimental procedure consists of an intra-dermal (ID) injection of a combination of CFA and collagen II, which constitutes the major form of articular cartilage, leading to chronic polyarthritis in periarticular joints (Courtenay et al., 1980; Caplazi et al., 2015; Bas et al., 2016; Fischer et al., 2017).

3.7.2. Collagen antibody–induced arthritis (CAIA)

CAIA is obtained after intravenous or intraperitoneal injection of a mixture of anti-CII antibodies, followed by lipopolysaccharide (LPS) injection 3 days after (Nandakumar et al., 2003; Caplazi et al., 2015; Bas et al., 2016). Inflammation is at its maximum 8 days after the injection and lasts for a month (Lynn et al., 1992). This model is frequently used because of its histological similarities with human RA. In addition, bone and cartilage degradation as well as synovitis and pannus are observed in CAIA (Fischer et al., 2017). In this model, mechanical and thermal (hot and cold) hypersensitivity are observed. CAIA can be implanted in rodents that are unsuitable for CIA. However the inflammation observed is innate and not related to B cell nor T cell activation (Caplazi et al., 2015; Fischer et al., 2017).

3.7.3. Streptococcal cell wall (SCW)-induced arthritis

This model is used to mimic RA in rats. It consists of an intra-articular injection of Streptococcus pyogenes cell walls. A single injection leads to an acute inflammation within one day, whereas multiple injections lead to chronic RA (van den Broek et al., 1988; Bessis et al., 2017).

4. Models of migraine pain

Migraine has not classically been considered an inflammatory disease probably because it is not obviously associated with heat, redness, and swelling. Instead, a vascular aetiology was proposed and the prevailing theory of migraine for most of the twentieth century, held that pain results from an abnormal dilatation of intracranial blood vessels, leading to mechanical excitation of sensory fibers. However, in recent years, advancements in the neurobiology of migraine headache have shifted the emphasis away from vascular smooth muscle toward mechanisms related to inflammation (Waeber and Moskowitz, 2005). Accumulating data have come, in large part, from basic science research utilizing small animal models of migraine-related pain (Akerman et al., 2017; Harriott et al., 2019; Vuralli et al., 2019). Although the vascular system plays a crucial role in the headache associated with migraine that distinguishes it from somatic or visceral pain, a neuronal involvement in the aetiology of migraine has increasingly been considered (Olesen et al., 2009). Several lines of evidence suggest that activation of trigeminal nociceptors innervating meningeal tissues is central to the initiation of migraine pain. Once activated, trigeminovascular afferents release neuropeptides that, in turn, may mediate additional release of mast cell contents and other immune mediators (Harriott et al., 2019). Exposure of perivascular fibers to inflammatory agents released in the vicinity of sensory fibers alters their sensitivity and leads to the sensation of head pain. Animal models ultimately seek to reproduce the etiology of migraine with various experimental paradigms described below.

4.1. Dural stimulation

Peripheral stimulation of meningeal nerve terminals can be achieved electrically or chemically. The direct electrical stimulation of meningeal nerve terminals (Zagami et al., 1990) derived from the demonstration in human that it results in pain often referred to the face. Such stimulation elicits the polysynaptic activation of the central projection sites of these afferents in the trigeminal nucleus caudalis and ascending projections throughout the brain (Benjamin et al., 2004). These studies have been key in identifying major migraine-related pain processing in preclinical research (Akerman et al., 2013). Direct electrical stimulation is however a nonrecoverable procedure and other protocols are necessary to mimic chronic activation of the dura.

Indeed, direct application of inflammatory soup on the exposed dura mater induces cephalic hypersensitivity (Melo-Carrillo and Lopez-Avila, 2013). This chemical stimulation elicits the expression of pronociceptive markers in the trigeminal ganglia (Lukács et al., 2015). This paradigm authorizes repeated applications producing a long-lasting central sensitization that mimics the pathophysiology of migraine (Munro et al., 2017). Less invasive refinements of this paradigm make it compatible with behavioral testing in conscious freely-moving animals.

Electrophysiology is a common readout for the various procedures of dura mater direct stimulation. It is a powerful assay method that allowed identifying effective mechanisms such as the triptans and CGRP receptor antagonists, while predicting failure of neurokinin (NK)1 receptor antagonists (Akerman et al., 2013).

4.2. Trigeminal neuron stimulation

The stereotaxic insertion of electrodes allows to directly stimulate trigeminal ganglion neurons which causes release of CGRP from perivascular afferent terminals to the dura mater. Short (3−5 min) and long (30 min) stimulation paradigms have been used with the latter inducing morphological changes (Knyihár-Csillik et al., 1997). Notably, neurochemical and morphological changes are sensitive to triptan and dihydroergotamine, thus making the inhibition of peripheral neuropeptide

release a plausible mechanism of anti-nociceptive action (Buzzi et al., 1991).

4.3. In vivo application of algogenic substances

The most widely used models in preclinical migraine research rely on systemic infusion of nitric oxide donors, e.g. glycerol trinitrate (GTN) (Munro et al., 2017). Intraperitoneal administration is replaced in some studies by intravenous infusion that can directly activate the trigeminovascular system (Ramachandran et al., 2014). Beside acute administration, other authors have developed repeated intermittent intraperitoneal administration (Pradhan et al., 2014), or intradermal injection of GTN in the hindpaw (Ferrari et al., 2016). Both variants have clinical relevance, resulting in progressive and sustained basal hyperalgesia and showing sumatriptan sensitivity, repectively. Interestingly in these models, the effects of algogenic substances are not restricted to specific peripheral or central nervous system sites but are likely to act more broadly in migraine-related structures (Harriott et al., 2019).

4.4. Genetic models

Among the rare genetic models of migraine, mouse models expressing gain of function missense mutations of the CACNA1A faithfully recapitulate the symptoms of familial hemiplegic migraine (FHM), a rare monogenic migraine subtype associated with aura. Notably, CACNA1A, as well as other genes implicated in FHM, encode ion channel and transporter subunits that play important roles in neurotransmission.

4.5. Cortical spread depression model

The aura is associated with migraine in up to 30 % of patients. The aura results from a wave of intense excitation across the visual cortex that has been attributed to cortical spreading depression (CSD) process. CSD is a slowly propagating depolarizing wave that can be induced experimentally in rodents where it is initiated by injection of KCl into the cortex (Munro et al., 2017). CSD triggers neuronal activation within the trigeminal ganglion and in higher brain regions (Cui et al., 2015). Moreover, CSD also increased activation of microglia that is a key mechanism relevant to central sensitization and contributing to pain sensitivity.

5. Models of neuropathic pain

Neuropathic pain (NP) is a painful syndrome caused by central or peripheral lesion of the nervous system. It is highly disabling, affecting 7–8 % of general population (Bouhassira et al., 2008). NP elicits sensory alteration including dysesthesia and paresthesia, spontaneous pain, increase pain sensation for innocuous stimuli (allodynia) and increase pain sensation for noxious stimuli (hyperalgesia). Animal models of NP are developed, mainly in rodents, to recapitulate one or several symptoms of NP aiming at deciphering the underlying mechanisms. Larger animals, e.g. cat, have also been used to study NP mechanisms (Koyama et al., 1993). NP models are distinguished according to the localization, central or peripheral, of the nerve injury.

5.1. Models of central NP

Central pain syndrome (CPS) classified as neuropathic pain is defined as “pain initiated or caused by a primary lesion or dysfunction of the central nervous system” (International Association for the Study of the Pain, Merskey and Bogduk, 1994) or more recently as “pain arising as a direct consequence of a lesion or disease affecting the central somatosensory system” (Treede et al., 2008). CPS patients display somatosensory abnormalities (hyposensitivity to thermal and noxious stimuli), which is the universal feature of this syndrome, due to the spinothalamoparietal thermoalgesic pathway dysfunctions (Canavero and Bonicalzi, 2007). CPS patients suffer from dysesthesia and painful burning sensation whose localization in body regions, and intensity and duration, widely differ, depending of the syndrome etiology. CPS onset can be delayed several months after CNS damage but is a lifetime condition in the majority of cases (Berić, 1998; Canavero and Bonicalzi, 2007)CPS is mostly induced by stroke (referred as central post-stroke pain), multiple sclerosis or brain/spinal cord injury (SCI). Diseases displaying a CPS-like component such as Parkinson’s disease are referred as central pain-allied conditions (CPAC). Depending of the origins of the lesions, patients suffer from brain central pain (brain-brainstem lesion) or cord central pain (spinal cord lesion).

CPS has been mostly studied in rodents by performing SCI, either targeting individual fiber tracts, or extensively affecting the cord. Electrolytic lesions (one or two) of the rat spinothalamic tract afferents are performed using tungsten or quartz-insulated platinum or electrodes (Wang and Thompson, 2008; Masri et al., 2009). The electrode is targeted unilaterally to the ventrolateral spinal quadrant in the lower cervical or thoracic vertebral level (Wang and Thompson, 2008; Masri et al., 2009). Demyelinating lesions have also been carried out by the injection of lysophosphatidylcholine solution through a glass pipette inserted into the region of the rat spinothalamic tract (Wang and Thompson, 2008). CCP rodent models allowed to identify the biological bases of this syndrome (Wang and Thompson, 2008; Masri et al., 2009; Quiton et al., 2010; Naseri et al., 2013) and to test therapeutic approaches (Wang and Thompson, 2008; Lucas et al., 2011).

Other models are generated by a more extensive SCI, not only restricted to fiber tracts, e.g. spinal cord compression, partial or complete sections, photo-chemically induced ischemia, spinal cord crushing, contusion, or application of excitatory neurotoxins (Table 1). Even if paralysis is the core symptom of this model due to the lesion of descending motor tracts, other features of SCI impair quality of life such as pain (Simpson et al., 2012; Caplazi et al., 2015; Fischer et al., 2017). Extensive lesions of the spinal cord are associated with spontaneous and evoked pain resulting in both hyperalgesia and allodynia (Campbell and Meyer, 2006; Starkey et al., 2009; Schneider et al., 2017).

Contusive SCI is usually obtained by using a weight-drop technique (Siddall et al., 1995). In this model, rats developed allodynia few days after SCI, that lasts up to 30 days after motor recovery (Siddall et al., 1995). Spinal hemi-section mimics chronic central pain after spinal cord lesion (Christensen et al., 1996). This model offers advantages of maintaining the injured site separate from the intact side. It is obtained by performing a hemi section of a thoracic segment, usually cranial to L1 dorsal root entry. Spinal hemi-section induces changes in withdrawal thresholds in response to both mechanical and thermal stimuli that persist for 5–6 months. In this model, NP develops both below and above the SCI on both sides. This model recapitulates the NP in Brown–Sequard Syndrome, a spinal cord hemi-section injury, where chronic pain also develops on both sides (Koehler and Endtz, 1986).

Photochemical injury, developed by Watson and Colleagues (Watson et al., 1985), presents the advantage to reproduce a mechanical trauma of the spinal cord without surgery. It consists of intravenous injection of the photosensitizing dye, Rose Bengal or erythrosin B, followed by an irradiation. This reaction induces thrombosis leading to ischemia and tissue necrosis of the spinal cord (Gaviria et al., 2002). Injury induces a strong allodynia in different areas innervated by the ischemic spinal segments (caudal trunk, hind limbs, and hind paws) and a hypersensitivity to cold but not to heat stimuli.

5.2. Models of peripherally-induced NP

Various models have been proposed to copy consequences of radiculopathies or post-operative nerve lesions (Table 1). Classical models are obtained by lesioning peripheral nerves, e.g. the infra-orbital nerve (face neuropathy) or the sciatic nerve (hindlimb neuropathy). Peripheral NP models elicit peripheral but also central effects, including

spontaneous discharges from afferent neurons, nociceptor sensitization and spinal and cortical reorganization.

5.2.1. Nerve transection

The sciatic nerve total transection is achieved by a complete axotomy of the sciatic nerve removing approximately 5 mm of the sciatic nerve in rats or mice. This model mimics the clinical symptoms of "phantom limb" that occur in humans after transversal spinal lesion. The limitation of this axotomy model is the motor impairment, which hampers behavioral evaluation by testing withdrawal latencies, and causes frequent autotomy. For ethical considerations, these axotomy models are now replaced by partial nerve injury in which autotomy is strongly reduced or totally suppressed.

5.2.2. Partial nerve lesion

Several partial nerve lesion models have been developed over the last 20 years. These models differ according to their procedure, their reproducibility, the inflammatory component and the duration of NP symptoms. Chronic constriction injury (CCI) (Bennett and Xie, 1988) consists of four loose knots around the sciatic nerve or the infra-orbital nerve. This model involves both neuropathic and inflammatory components triggered by suture thread (Costa et al., 2005). CCI elicits spontaneous pain and pain hypersensitivity that occurs 24 h after surgery and persists for a duration of at least 7 weeks. Variability in responses occurs upon variation in the tightness of ligature and thread used. Cuffing of sciatic nerve ("cuff" model) allows a standardized and reproducible chronic constriction injury; it is obtained by the implantation of a section of polyethylene tubing placed around the common branch of the sciatic nerve of rats or mice (Pitcher et al., 1999; Benbouzid et al., 2008; Yalcin et al., 2014). Animals develop heat-hyperalgesia lasting for 3 weeks and mechanical allodynia for at least 2 months (Benbouzid et al., 2008). This model is of interest to study anxio-depressive comorbidities associated with NP that lasts for weeks after removal of hypersensitivity to pain (Yalcin et al., 2014). Partial sciatic nerve injury (PNI), developed in rats by Seltzer and colleagues (Seltzer et al., 1990), consists of tight partial ligation of the dorsal third or half of sciatic nerve, peroneal or tibial branch or both. Pain symptoms occur within 1 week after surgery and continue up to 6 weeks post-injury. PNI has been adapted in mice by Malmberg and Basbaum (Malmberg and Basbaum, 1998) and showed pain symptoms one day after injury. The thermal allodynia resolves by 49 days, but the mechanical allodynia persists for the duration of the study (70 days). Spinal Nerve Ligation (SNL) was developed in rats by Kim and Chung (Kim and Chung, 1992). It consists of a unilateral and tight ligation of lumbar spinal nerves L5 and L6 distal to dorsal root ganglia. Within 24–48 h after surgery, this model develops a mechanical allodynia, thermal hyperalgesia and spontaneous pain that persist for 4 months without any autotomy. Although the surgery is complex, it is a highly reproducible method with little damage to surrounding tissue (Kim and Chung, 1992; Dobremez et al., 2005; LaBuda and Little, 2005; Fossat et al., 2010; Laffray et al., 2012). SNL model is also available in mice (Kiso et al., 2008) where mechanical allodynia started at day 1 and lasted for at least 2 months after surgery. Spared nerve injury (SNI) corresponds to the lesion of two of the three terminal branches of the sciatic nerve that is obtained by the ligation of common peroneal and tibial nerves leaving the remaining sural nerve intact (Decosterd and Woolf, 2000; Bourquin et al., 2006). Mechanical and thermal responsiveness is increased in the territory of spared sural nerve. SNI model displays early and persistent pain-like behaviors; it is easy to perform and highly reproducible. Caudal trunk resection is performed by lesioning the caudal trunk in rat or mice (Na et al., 1994; Sung et al., 2000). Allodynia and hyperalgesia appear within a day of nerve injury and last for weeks (Back et al., 2003). In rats and mice, this model offers several advantages by allowing behavioral tests, thermal and mechanical stimuli to be easily performed at the same spot on the tail.

These models of peripheral neuropathy induce pain-like behavior as a direct consequence of nerve lesion (i.e. sciatic nerve for the hindlimb or infra-orbital nerve for the face). These models have the ability to recapitulate some particular neuropathic syndromes in human. For instance, CCI, SNI and PNI targeting the sciatic nerve are models of complex regional pain syndromes type II (CRPS) that same sensory disorders similar to those described in patients, e.g. touch hypersensitivity, mechanical hyperalgesia, spontaneous pain, and pain irradiatio. Moreover, in the case of CCI, the strong inflammatory component mimics some features of the chronic low back pain syndromes in human. Finally, SNL that targets dorsal roots of the sciatic nerve models sciatica or radiculopathy (defined as pain resulting from injury or disease of the cervical, thoracic, lumbar or sacral nerve roots). Although these models present interesting features, there is still today a large gap between the number of molecules effective in preclinical studies and their poor outcome in clinical trials. Several explanations can be evoked such as the genetic homogeneity of the models (inbred mouse/rat), the low diversity of the behavioral tests generally used (i.e. withdrawal reflexes), the similarities between the different preclinical models (nerve injury modelling mononeuropathy) and the almost exclusive use of male rodents. Future challenges will be to determine precisely which mechanisms is targeted by a given drug, and which patients will be relevant for treatment (Rice et al., 2018). For this purpose, the relevance of pain assessment in animal models, and the similarities between animal behavior and human symptoms are critical.

5.3. Models of poly-neuropathy (PN)

Notably, studies on animal models of mononeuropathic pain most largely report sensory gain (Rice et al., 2018). However, traumatic nerve injury is most often characterized by a loss of sensitivity to non-painful stimuli, and a moderate sensory gain to painful stimuli (Gierthmühlen et al., 2012). In addition, most of clinical trials involve patients with polyneuropathy (Rice et al., 2019). In human clinics, polyneuropathies (peripheral neuropathies) are the most common type of disorder of the peripheral nervous system in adults, and specifically in the elderly, with an estimated prevalence of 5–8%, depending on age. A sensory loss profile is reported in the majority of patients with common polyneuropathies for example: chemotherapy-induced (Ventzel et al., 2018), diabetic (Raputova et al., 2017) and HIV-associated associated (Phillips et al., 2014) polyneuropathies, and spinal cord injury (Finnerup et al., 2003) or postherpetic neuralgia (Fields et al., 1998). Recently, relevant disease models have been developed and validated, especially those related to drug-induced neuropathy, diabetic and HIV-associated neuropathy and autoimmune neuropathy. Some examples of these models are briefly discussed in the following.

5.3.1. Chemotherapy-induced neuropathy

Peripheral neuropathy is a dose-limiting side effect for a number of chemotherapeutic agents including platinum analogues, microtubule-directed agents (taxol, vincaalkaloids), suramin or thalidomide. Cisplatin neurotoxicity is very common and can be mimicked in in mice and rats by repeated injections of platinum for several weeks. Mechanical and thermal hyperalgesia and allodynia appear in the 2–4 weeks following the beginning of treatment (Authier et al., 2003). Oxaliplatin is another chemotherapeutic drug used for the treatment of gastrointestinal tract tumours, especially in colorectal cancer (Ibrahim et al., 2004). Oxaliplatin induces acute side effects in 80 % of the patients, and can evolve to a long-term neuropathy in a fraction of the affected patients (around 15–20 %). Mouse models of chemotherapy-induced neuropathy are generated by repeated (e.g. twice a week for 4 weeks) intravenous injection of oxaliplatin in the tail vein (Marmiroli et al., 2017). Chronic treatment with oxaliplatin has been reported to induce shrinkage of Dorsal Root Ganglia (DRG) neurons and axonopathy of myelinated fibres in animal models (Renn et al., 2011), and impairs sensory neuron arborisation, indicating that oxaliplatin neurotoxicity occurs mainly in sensory neurons (López-González et al., 2018).

5.3.2. Diabetic neuropathy

Diabetic neuropathy is a progressive disease that leads to structural changes in the nerve causing hyperalgesia. Various animal models, with possible different pathogenesis underlying mechanisms, exist and highlight the importance of establishing clear criteria for models of diabetic neuropathy in rodents.

The most common metabolic models are the streptozotocin (STZ) diabetic rats and mice (mainly Swiss, C57/Bl6 or CD1) (Biessels et al., 2014). Depending on the severity of anticipated disease, diabetes is induced by a single intraperitoneal or intravenous dose of 40–80 mg STZ/kg (rat), or 150–200 mg STZ/kg (mouse) body weight, or of lower doses given to mouse over consecutive days. STZ neurotoxicity was reported to induce early behavioral and electro-physiological changes followed by distal nerve fiber loss, axonal atrophy and myelin thinning after many months of diabetes. However, STZ toxicity may be indirectly responsible for neuropathy (Davidson et al., 2009).

A large variety of genetic model have been also proposed to recapitulate the pathophysiology of diabetes. The BB/Wor and BBZDR/Wor rats model type 1 and type 2 diabetes respectively. The BB/Wor rats lack T lymphocytes expressing the RT6 alloantigen, and develop autoimmune attack of the pancreas and spontaneous onset of type 1 diabetes in males between the ages of 70–80 days (Yang and Santamaria, 2006). The BBZDR/Wor-rat spontaneously develops insulin resistance that is preceded by obesity and these animals model type 2 diabetes (Tirabassi et al., 2004). In mouse, there are two common genetic models of type 1 diabetes: the non-obese diabetic (NOD) mouse and the Akita mouse, representing spontaneous auto-immune type 1 diabetes (NOD) and a mutation of the insulin-2 gene, respectively. There is currently relatively little consistent information on the neuropathy in these animal models (Biessels et al., 2014). Models of type 2 diabetes, such as db/db (leptin receptor mutation) and ob/ob (leptin mutation) mice, have been available for many years (Wang et al., 2014). Both models develop diabetes at 4–6 weeks of age with hyperinsulinemia and hyperlipidemia. Early electrophysiological changes, and later structural abnormalities have been reported during the progression of the disease. The main limitation of both the db/db and ob/ob models is that death occurs at 24–30 weeks of diabetes in the absence of insulin supplementation.

A major limitation of the STZ and genetic models is that they do not replicate the evolution of the metabolic imbalance and the natural progression from obesity to diabetes (Preguiça et al., 2020). High fat, or high fat and high sugar diets, alone or associated with low or moderate doses of STZ, more closely model the disease progression. These paradigms induce the hallmarks of diabetic neuropathy and are key in the progressive development of symptoms including behavioural alterations, nerve conduction velocity deficits and nerve structural impairments (O'Brien et al., 2014).

In these different models of diabetic peripheral neuropathy, evoked nociception is not correlated to ongoing pain that remains present whatever the hypo- or hyperalgesic status and the possible loss intraepidermal nerve fibre endings (Agarwal et al., 2018; Gao et al;, 2019).

5.3.3. Autoimmune neuropathy

Autoimmune neuropathies comprise a diverse group of conditions resulting from an immune attack on the peripheral nervous system. The prototypic immune neuropathy is the heterogeneous Guillain-Barré syndrome (GBS), the most common acute paralytic disorder in industrialized countries. It is classically considered as an acute inflammatory demyelinating polyneuropathy (Fricker et al., 2008). The pathological substrate for GBS has been well established with immune cell infiltration, demyelination with or without axonal damage in the peripheral nervous system (PNS), nevertheless molecular and cellular mechanisms require adapted animal models to be fully understood. In the classical models of experimental allergic neuritis (EAN), the auto-immune aetiology of GBS was reinforced using homogenate of peripheral nerve tissue in adjuvant (Waksman and Adams, 1956). Classical EAN is induced in susceptible rats (the Lewis rat strain is the most sensitive to auto-immune conditions) or mice by active immunization (complete Freund's adjuvant) with peripheral myelin extract, or the whole or partial purified P2 myelin protein (Hahn, 1996). Adoptive transfer EAN is induced by injection into naive animals of antigen-specific T cells obtained from lymph nodes of EAN syngenic animals (Toyka, 1999). Although EAN has provided valuable information, it has been criticized for its artificial manipulation (Yang et al., 2014). Therefore, genetic models have been raised that develop spontaneous autoimmune peripheral polyneuropathy caused by B7-2 (Salomon et al., 2001) or CD4 (Yang et al., 2014) depletion in mouse.

5.3.4. Infectious neuropathy

Infectious neuropathies include several diseases associated with infectious micro-organisms targeting the central (e.g. neurosyphilis, viral meningitis) or the peripheral (e.g. leprosy, HIV, Lyme disease, hepatitis C) nervous system. Here we provide examples of animal models of the two most common neuropathies induced by an infectious agent, leprosy and HIV-associated neuropathy. Leprosy is the most common sensory multiple mononeuropathy, still largely present in developing countries. Leprosy is caused by the non-toxic non-cytolytic Mycobacterium *leprae*, an obligate intracellular parasite. The proliferation of M. *leprae* in the mouse footpad (MFP) has been widely used to test bactericidal activity (Ji et al., 2006) and to define the role of immunity in leprosy after MFP infection in immune-deficient mice (Rambukkana et al., 2002; Fricker et al., 2008). However, the development of more representative models of human leprosy is still necessary to better account for a real leprosy neuropathy.

In HIV-associated neuropathy, peripheral sensory structures (DRG, peripheral nerves and cutaneous terminals) are affected. Distal sensory polyneuropathy (DSP) is the most common HIV-associated neuropathy and is present in one third of HIV-infected patients. Classical animal models rely on the postulated direct toxicity of secreted viral proteins (gp120 and Tat) on DRG and axons leading to degeneration and the development of DSP. Gp120 can be delivered acutely through an intradermal injection, or chronically, directly to the sciatic nerve, with a carrier matrix, thus inducing allodynia and hyperalgesia (Herzberg and Sagen, 2001). HIV infection may also heightens the vulnerability to antiretrovirus-induced neurotoxicity. Indeed, in transgenic mice continuously releasing gp120 from astrocytes and Schwann cells, food supplementation with the antiretroviral agent didanosine results in small unmyelinated fiber degeneration and hyperalgesia (Keswani et al., 2006). Similarly, the intravenous injection of a common protease inhibitor, indinavir, triggers hindpaw mechanical hypersensitivity in rats (Huang et al., 2017). Notably, DSP in these models is responsive to analgesic compounds, e.g. gabapentin.

6. Models of cancer pain

Several mammalian and non-mammalian animal models have been developed to improve our understanding of cancer biology (Schachtschneider et al., 2017). However, cancer pain, which is experienced by human patients and animals in advanced stages of cancer, has only been addressed in some of these models.

Immunocompromised and immunocompetent rodents (mouse and rat) are commonly used to study cancer pain. Because of its large size, rat model is better suited for manipulations and injections into bones compared to mouse. However, mice are more widely used compared to rats mostly due to the possibility to address cancer pain in transgenic mice either in knock-out or -in overexpressing gene mice (Ghilardi et al., 2005; Lindsay et al., 2005). Larger animals also used are dogs and less commonly cats as they develop spontaneous tumors such as mammary, prostate, head and neck squamous cell carcinoma (HNSCC), squamous cell carcinoma (SCC). In dogs, cancer is the number one cause of mortality with osteosarcoma (OSA) being the most common primary bone tumor, and a painful one. Dogs and cats display similar cancer biology when compared with humans and are therefore appropriate models for

Table 2
Animal Models of Cancer Pain. Canine BPI: Canine Brief Pain Inventory; ET-1: Endothelin-1 ; n.a: not applicable; QoL: Quality of Life; QST: quantitative sensory testing; VAL; Visual analog scale; VMR: Visceromotor responses.

	Animal Species	Procedure	Cancer cell line	Pain Tests	References
Bone Cancer Induced Pain (CIBP)	Mice	Intraosseous Injection Cancer Cells into	66.1 or 4T1-Luc2 mammary adenocarcinoma	Flinching Guarding von Frey Test	Schwei et al., 1999; Wacnik et al., 2001;
		Femur	NTCT2472 Fibrosarcoma	Limb use	Grenald et al., 2017; Sabino et al., 2003; Vermeirsch et al., 2004
		Humerus	B16 melanoma	Tail Flick Assay Dynamic weight bearing Palpation (light touching)	Elramah et al., 2017; Appel et al., 2019
		Calcaneus bone of hindpaw	C26 colon adenocarcinoma		
		Transgenic mice	n.a.	Flinching Guarding	Ghilardi et al., 2005
	Rat	Intraosseous Injection Cancer Cells into Tibia	MRMT-1 murine mammary carcinoma	von Frey Test	Medhurst et al., 2002;
			Walker 256 rat mammary carcinoma	Limb use	Wu et al., 2012; Zhu et al., 2018 Wang et al., 2018;
		Femur	MLL rat prostate adenocarcinoma	Weight-bearing test	Falk, 2018
	Dog	Naturally-Occurring Bone Cancer	n.a.	Lameness Canine BPI QST VAL QoL	Brown et al., 2015; Sapio et al., 2018: Monteiro et al., 2018
Breakthrough Cancer pain (BTcP)	Mice	Injection of Cancer Cells into Femur + ET-1 injection into tumor cells	Lewis Lung carcinoma	von Frey Test Limb use	Tang et al., 2016;
Metastasis Bone Cancer Pain	Mice/rat	Injection of Cancer Cells into: Tail vein Intracardiac Intraosseous Orthotopic	ACE-1 canine prostate carcinoma R3327 Mat LyLu cells rat prostatic adenocarcinoma	Flinching Guarding Thermal Paw stimulator Posture changes, movement limitations	Liepe et al., 2005; Halvorson et al., 2005
Breast Cancer Pain	Mice	Injection of cancer cells into mammary fat pad	4T1 murine breast cancer	von Frey Test Acetone drop grimace scale	de Almeida et al., 2019
Pancreatic Cancer Pain	Mice	Injection of cancer cells into pancreas	SW1990 human pancreatic cancer	Abdominal withdrawal threshold Hunching VMR	Wang et al., 2017
		Transgenic mice	n.a.	Hunching Vocalization	Lindsay et al., 2005
Peritoneal carcinomatosis	Mice	Injection of cancer cells into abdominal cavity	60As6Luc derived from HSC60 human gastric scirrhous carcinoma	von Frey test licking Abdominal withdrawal threshold Hunching	Suzuki et al., 2012

human cancer (MacEwen, 1990; Simmons et al., 2015). Methods used to quantify cancer pain are various and dependent of the animal species used. In rodents, the von Frey assay remains most widely used although non-evoked pain tests are also applied (Table 2). Cancer pain in dogs is addressed mostly using owner-completed questionnaires and activity sensory function measure assays (Brown et al., 2015; Monteiro et al., 2018) (Table 2).

Bone cancer leads to the most painful conditions with patients suffering from chronic pain and breakthrough pain. Moreover, as bone is the major site of metastasis in advanced stage cancer, e.g. mammary and prostate cancers, it is expected that bone cancer induced pain (CIBP) models are the first cancer pain models to be developed. Metastastic bone cancer pain models were developed via intravenous, intra-cardiac (left ventricule of the heart), or orthotopic injections of cancer cells (Arguello et al., 1988; Yoneda et al., 1994; Liepe et al., 2005). However, assessment of bone induced pain cancer has been proven difficult in these models due to the differences in size, tissue/organ localization of the metastases. The first primary bone cancer pain model was developed in 1998 by injection of NCTC 2472 fibrosarcoma cells into mouse intramedullary space of long bone, i.e. femur (Schwei et al., 1999). The first rat model was developed a few years later by injection of MRMT1 mammary carcinoma into the intramedullary space of tibia (Medhurst et al., 2002). A model of breakthrough cancer pain defined as an intermittent episode of extreme pain has been recently developed (Tang et al., 2016). Non-bone cancer models were also developed using orthotopic injections (see Table 2). The differences between these different rodent models depend on the site of injection and the type of cancer cell injected (Table 2). Development of these diverse models allowed pharmacological interventions with preclinical positive outcome (reviewed in (Slosky et al., 2015)). Indeed, analgesic effects of resiniferatoxin, a TRPV1 activator, were demonstrated on intractable osteosarcoma suffering dogs and in phase I clinical trials on patients with intractable cancer (Brown et al., 2015). Moreover, the use of various animal models has validated the anti-NGF therapy for cancer pain management (Sevcik et al., 2005; Jimenez-Andrade et al., 2011). Tanezumab and Fulranumab, two NGF antibodies, safety and efficiency have been tested in phase I and phase II clinical trials (Sopata et al., 2015; Slatkin et al., 2016). A phase III trial using Tanezumab is currently in progress to determine whether Tanezumab is effective in the treatment of cancer pain due to bone metastasis in patients already taking background opioid therapy (see ClinicalTrials.gov).

The use of these different models has provided insight into the mechanisms involved in cancer pain (reviewed in (Falk and Dickenson, 2014)) and brought *in vivo* evidence of the implication of tumor secreting proteins, e.g. endothelin 1, (Wacnik et al., 2001; Tang et al., 2016)), microRNAs (Bali et al., 2013; Elramah et al., 2017),

neurotrophins, receptors (e.g. osteoprotegerin, (Honore et al., 2002)), and TRPV1 (Ghilardi et al., 2005; Sapio et al., 2018). In particular, the implication of the purinergic P2X receptor family and purinergic pathway in cancer pain has been shown using these rodent models (Gilchrist et al., 2005; Wu et al., 2012; Guedon et al., 2016; Falk et al., 2019).

7. Models of visceral pain

Visceral pain includes pain emanating from organs localized into the thoracic, pelvic and abdominal regions. This type of pain is poorly localized, often affecting two or more visceral organs. In particular, gastrointestinal (GI) pain is common in various disorders including irritable bowel syndrome, inflammatory bowel diseases (IBD) (Crohn's disease and ulcerative colitis), pancreatitis, kidney stones, biliary disorders or associated with cancer. Several factors have been identified as contributing to visceral pain, such as stress, early life influence, microbiota, genetic predispositions, epigenetic changes and miRNA regulation ((Larauche et al., 2012; Zhang and Banerjee, 2015; Fuentes and Christianson, 2018; Lomax et al., 2019; Louwies et al., 2019; van Thiel et al., 2020). However, the mechanisms of visceral pain are complex and identifying its cause and the correct treatments for patient remains a challenge (Drewes et al., 2020). Numerous animal models, mostly rodent models, have been developed to mimic GI diseases (reviewed in (Larauche et al., 2012; Goyal et al., 2014; Greenwood-Van Meerveld and Johnson, 2017)). However, visceral pain has only been investigated in a small number of these available models (Schwartz and Gebhart, 2014). Some examples of naturally occurring or induced visceral pain are given in the Table 3.

Visceral pain associated diseases naturally occur in dogs, and

Table 3
Visceral pain models. AWR: Abdominal Withdrawal Reflex; CRD: Colorectal distension; EAP: Experimental autoimmune prostatitis; IBD: Inflammatory Bowel Disease; IBS: Irritable Bowel syndrome; IBS-D: Irritable Bowel syndrome - diarrhea-predominant; NMS: Neonatal Maternal Separation; PRS: Partial restraint stress; VMR: Visceromotor responses, WAR: Water avoidance stress.

	Animal Species	Procedure	Clinical relevance	Pain/Nociceptive tests	References
Abdominal Viscera	Mice	Intraperitoneal injection of chemicals	Visceral Pain	Writhing Test Responses	Alonso-Castro et al., 2017
		Colorectal distension (CRD)		VMR	Kamp et al., 2003
	Rat	Colorectal distension		Passive avoidance behavioral paradigm AWR	Ness and Gebhart, 1988; Ness, 1999;
	Dog	Colorectal distension		VMR	Lyubashina et al., 2017
Digestive Tract	Mice	Intracolorectal injection of chemicals	IBD	"up and down" method von Frey Test	Hou et al., 2019
		Oral ingestion of chemicals	IBD Ulcerative colitis	Intracolonical administration of allyl isithiocyanate (mustard oil) (0,5%) VMR	Lapointe et al., 2015
	Rat	Intracolorectal injection of chemicals	IBD	VMR AWR	Huang et al., 2019; Parisio et al., 2020
Colon-Bowel	Mice	Castor-oil induced diarrhea	*IBS-D*	Intracolonical administration of allyl isithiocyanate (mustard oil)	Sobczak et al., 2014
		Repeated WAS	*IBS*	Writhing Test AWR	Zhu et al., 2019
		NMS PRS		VMR	Miquel et al., 2016
	Rat	Colorectal injection of inflamogens or irritants	PI-IBS Ulcerative colitis	AWR	Zhu et al., 2018b
		Intragastric Parasite infection Subcutaneous LPS injection		VMR	Zhang et al., 2019 Nozu et al., 2019
		Repeated WAS	IBS		Nozu et al., 2019
Stomach		Hollow stomach distention Gastric injection/Oral injection of irritant chemical	Gastric hyperalgesia	VMR Passive Avoidance Behavior paradigm	Ozaki et al., 2002
Ureter	Rat	Intraureteral injection of dental cement	Ureteric calculi (Kidney stones)	vocalization to electrical stimulation	Giamberardino et al., 1995
Pancreas	Mice	oral injection of DBTC	Chronic pancreatitis	von Frey Test animal posture gait disturbances	Oz, 2016
	Rat	High fat (65 %)/ethanol (6%) diet (10 weeks)	Chronic pancreatitis	von Frey Test up-down method Hot plate	McIlwrath and Westlund, 2015
		Intraductal infusion of a bile salt + Intraperitoneal injection of aCCK analogue	Acute pancreatitis	Exploratory activity	Zhang et al., 2004
		Intravenous injection of chemical		von Frey Test abdominal withdrawal to heat stimulus	Vera-Portocarrero and Westlund, 2004
	Dog	Naturally-Occurring	Pancreatitis	Glasgow Composite Pain Scale	Mansfield and Beths, 2015 Catanzaro et al., 2016
Prostate	Mice	Infection with *E.coli* bacteria isolate from patient EAP induction	Chronic prostatitis/ chronic pelvic pain syndrome (CP/CPPS)	von Frey Test	Quick et al., 2013Liu et al., 2019
Biliary system	Mice	Injection of solvents into bile duct	Cholangiopathy	Grimace face Parameters activity	Berntsen et al., 2018
	Rat	Bile duct resection	Cholestasis	Tail-flick latency	Hasanein, 2010
Referred visceral pain	Mice	Intracolonic capsaicin instillation	Prolonged referred hyperalgesia	Von frey test	Laird et al., 2001
	Rats				Sanoja et al., 2010

pancreatitis is the most frequent visceral pain condition (Catanzaro et al., 2016). Pain is addressed by posture, movement, behavioral, physiological changes and reaction to abdominal palpation (Mansfield and Beths, 2015; Catanzaro et al., 2016).

Classically, visceral pain can be induced by hollow organ isobaric distension using latex balloon inserted into the esophagus or colon that is distended over a certain period of (Ness and Gebhart, 1988; Ozaki et al., 2002; O'Mahony et al., 2012). Colonic sensitivity is then measured by behavior analysis, e.g. abdominal withdrawal reflex (AWR) and/or monitoring abdominal muscles contraction (visceromotor responses, VMR). This method is mostly used in rodents but has been adapted to bigger animals, such as dogs or horses (Ness, 1999).

One widely used technique consists of inducing GI irritation, in order to copy IBD, by intra-colorectal injection or oral ingestion of irritant chemicals such as trinitrobenzene sulphonic acid, dextran sulfate sodium, dibutyltin dichloride (Vera-Portocarrero and Westlund, 2004; Lapointe et al., 2015; Zhu et al., 2018b; Hou et al., 2019). This technique derives from the writhing test developed in 1957. In this method, intraperitoneal injection of chemical irritant, such as acetic acid or phenylquinone, induced writhing responses and has been used as pharmaceutical screening tool (reviewed in (Schwartz and Gebhart, 2014)). However, its use needs to be reconsidered due to limitations and ethical issues. GI inflammation can also be induced by parasite or E.coli infection or lipopolysaccharide (LPS) injection (Quick et al., 2013; Nozu et al., 2018; Nozu et al., 2019; Zhang et al., 2019).

More disease-specific models, such as experimental autoimmune pancreatitis induced by mice immunization with rat prostate extracts antigen, or kidney stones obtained by the injection of dental cement into rat ureter, have been generated (Giamberardino et al., 1995; Liu et al., 2019).

Animal models have also been developed to evaluate stress-induced visceral pain. They rely on inducing stress in adult rodents by repeated water avoidance stress, partial restraint stress or in early life of mice by neonatal maternal separation (Miquel et al., 2016; Nozu et al., 2018 ; Zhu et al., 2019).

In all of these disease models, visceral pain is then measured using abdominal withdrawal reflex, visceromotor responses, mustard oil test, von Frey assay or "up and down" method, or animal behavior analysis such as grimace face (see Table 3).

The use of different rodent strains is a plus to address the importance of individual's sensitivity to stress into the induction and maintenance of GI pain (O'Malley et al., 2014). Furthermore, these assays to induce visceral nociception/pain can be carried out in transgenic mice, enabling to highlight the implications of factors, or signaling pathways, e.g. purinergic signaling pathway in the mechanisms of visceral pain and/or to address the effects of analgesics and probiotics/prebiotics on visceral pain (Trimble et al., 2007; Ochoa-Cortes et al., 2014; Pusceddu and Gareau, 2018).

Visceral pain can also be felt in other somatic regions than the affected one, therefore it is called referred visceral pain (Giamberardino et al., 2010). For example left shoulder, jaw and neck pain are typically observed in case of a cardiac ischemia. The physiopathology underlying referred visceral pain lies in the presence of viscerosomatic convergence at spinal cord level. In fact the dorsal horn of the spinal cord receives a visceral input that converges with a somatic input leading to the sensation of pain (Gebhart and Bielefeldt, 2016). Referred visceral pain is first felt within the deep tissue walls but with persistent stimulation and secondary hyperalgesia the pain is extended to superficial layers (Sikandar and Dickenson, 2012). Laird et al. developed an animal model for referred visceral pain in mice, it consists of an intracolonic capsaicin instillation (ICI). In fact 50 µl of capsaicin were injected in the colon via a cannula inserted in the anus. Von frey filaments were applied to the abdomen before the instillation and 20 min after, and the difference in the frequency to withdrawal was tested (Laird et al., 2001). ICI was also adapted for rats, in this case 200 µl of capsaicin were injected (Sanoja et al., 2010).

8. Models of musculoskeletal pain

Similarly to cancer pain or visceral pain, muscle pain results in a diffuse, aching pain that contrasts with sharp and localized cutaneous pain. Models specific to studying muscle pain are scarce in the literature although muscle pain is a major clinical problem. Indeed, musculoskeletal pain is a chronic widespread pain manifestation that affect between one quarter and one third of the US population (Gaskin and Richard, 2012). In chronic conditions like lowback pain, myositis, myofascial pain, and fibromyalgia, muscle pain is one of the major clinical manifestations. Therefore, animal models obtained after muscle insult more reliably replicate many clinical pain syndromes when compared to models of cutaneous pain (Lesnak and Sluka, 2019).

Models of chronic muscle pain include inflammatory and non-inflammatory components. Musculoskeletal hyperalgesia is classically generated by intramuscular injection of either carrageenan (inflammatory) or acidic saline (noninflammatory) (Sluka et al., 2001; Radhakrishnan et al., 2003). The inflammatory pain models mimic a wide range of painful muscular disorders with an inflammatory component such as myositis and tendonitis. The pain behaviors are sensitive to anti-inflammatory drugs (Kehl et al., 2000). The inflammatory model of musculoskeletal pain in rodents is obtained by carrageenan injection in the gastrocnemius muscle and produces hyperalgesia to heat stimuli (Chopade et al., 2014). This carrageenan-induced pain model has been suggested to have greater face validity to pain of musculoskeletal origin in humans.

The non-inflammatory model mimics painful muscle disorders such as fibromyalgia, where inflammation is not present. This model is not sensitive to anti-inflammatory agents (Radhakrishnan et al., 2003). The most common and well-characterized models of fibromyalgia-like pain involve repeated insults to the muscle. A non-inflammatory pain model is induced by repeated injections of acid saline (pH 4.0) into the same gastrocnemius muscle. It results in widespread hyperalgesia of the skin, muscle and viscera without observable tissue damage or inflammation (Sluka and Clauw, 2016).

In both inflammatory and non-inflammatory animal models, the findings nicely corroborate clinical observations and contributed to demonstrate that chronic widespread pain is multifactorial. Peripheral alterations are partly responsible of the symptoms through the involvement of the immune system or impaired nociceptor sensitivity, in particular in the induction of hyperalgesia. However, emerging evidence suggest that the central nervous system maintains the hyperalgesia. In inflammatory musculoskeletal pain, recent observations indicate the importance of a spinal COX-2 mechanism, and the spinal site of action of systemically delivered drugs that alleviate hyperalgesia (Chopade et al., 2014). Central excitatory mechanisms have also been implicated in the pathophysiology of fibromyalgia (Sluka and Clauw, 2016). In addition, the inhibitory effects of central pain modulation are decreased in human patients with fibromyalgia and animal model studies point to reduced serotoninergic transmission in the brain stem that projects to the spinal dorsal horn (Bobinski et al., 2015).

9. The particular case of non-human primates

Although rodents are mammals, their behavior and the organization of their nervous system remains different from humans. In contrast, studying pain in non-human primates offers the opportunity to investigate mechanisms, and response to analgesic treatment, that are close to what is expected in humans. However, using non-human primates undoubtedly poses acute ethical problems and little exploration of pain-related mechanisms has been done in non-human primates as compared to rodent.

Few attempts have been made to develop NP models in non-human primates. The most classical approach was the ligation of the L7 spinal nerve in rhesus monkeys. At 14 days post lesion, this resulted in the alteration in the activity of spinothalamic tract neurons that displayed

increased activity in response to mechanical and thermal stimuli (Palecek et al., 1992). Accordingly, the animals exhibited behavioral responses consistent with mechanical and thermal allodynia (Carlton et al., 1994). Recently, *Macaca fascicularis* has been used to establish a model of mild injury of the sciatic nerve. This does not involve nerve transection, so that nerve transduction can still take place. Under these conditions, behavioral and physiological outcomes model the chronic and long-term nature of sciatic nerve neuropathy that is observed in clinics more closely than in classical rodent models (Guo and Gu, 2014). Sciatic nerve retained the ability of nerve signal transduction, and showed a firing rate profile consistent with injury induced-sensitization of sensory fibres. This model may serve as a non-human primate model to study functional changes of traumatic injury to the sciatic nerve. In a macaque model of chemotherapy-induced neuropathic pain, functional magnetic resonance imaging (fMRI) reported abnormal activation of pain-related brain regions including insular and secondary somatosensory cortices, suggesting that fMRI measurement combined with behavioral outcomes in macaque models could be used to test therapeutic treatments for neuropathic pain and document their modes of action (Nagasaka et al., 2020).

Interestingly, a procedure similar to the rodent CCI model failed to induce symptoms of neuropathic pain in non-human primates (Palecek et al., 1992), likely because of the thicker protective sheath of the primate spinal nerve that prevented rodent-like pathology to develop. This example highlights that specific pain-inducing procedures must be adapted for every species studied.

The use of large animal models is more common to study acute or chronic inflammatory pain (Henze and Urban, 2010). In non-human primates, the formalin test has been used as a tonic pain model with good objectivity, validity, reproducibility and quantification. Moreover, this model exhibits good predictive validity by recapitulating the analgesic effects of morphine and pethidine (Alreja et al., 1984). Similarly, topical application of capsaicin proved to be efficient in inducing transient hyperalgesia and can serve as a model to test analgesic treatments in primates (Kupers et al., 1997). Spontaneous osteoarthritis exists in rhesus monkeys but despite a good face validity, it has never been used to test effectiveness of analgesics, perhaps because it would require preliminary reliable methods to assess pain in these free-range animals (Henze and Urban, 2010). Another painful affection that develops spontaneously in non-human primates is endometriosis (Braundmeier and Fazleabas, 2009). Such spontaneous endometriosis in *cynomolgus* monkeys displays similar clinic-pathological characteristics to the human disease and was useful as an experimental model (Nishimoto--Kakiuchi et al., 2018). *Cynomolgus* monkeys have similar lesions to those in humans as revealed with MRI studies (Nishimoto-Kakiuchi et al., 2018). The implications of these findings are that well established conventional laboratory methods and parameters for assessment can be applied for evaluating disease progress and drug efficacy in this model.

10. Pain models in simple organisms

To reduce the use of rodents in pain studies and carry out high-throughput screening studies, new models have started to appear in pain research, using lower vertebrate species such as zebrafish or *Xenopus* and invertebrates such as Drosophila and *Caenorhabditis elegans (C. elegans)*.

The shared advantages of these models reside in their simplicity of use including low cost and easy maintenance, large brood and egg size and rapid external development. They are genetically similar to humans and genome manipulation (random or directed mutagenesis, transgenesis, Crisp/Cas9...) or gene expression alteration (knock-down or over-expression) can be easily and quickly carried out (St Johnston, 2013; Sassen and Köster, 2015; Chen et al., 2016; Tandon et al., 2017). Genetic, chemical and behavioral screening can also be performed in multiwell-format screening (Jorgensen and Mango, 2002; Wheeler and Brändli, 2009; Giacomotto and Ségalat, 2010; Venken and Bellen, 2014). These diverse and efficient technologies together with online resources make them powerful model to human neuropathologies (Jeibmann and Paulus, 2009; Bessa et al., 2013; Pratt and Khakhalin, 2013; Fontana et al., 2018; Abreu et al., 2020; Vaz et al., 2019; Markaki and Tavernarakis, 2020). Furthermore, the lower level of ethical constraints for *Drosophila* and *C. elegans* and zebrafish and *Xenopus* embryos and larvae under European and USA legislation places them as a replacement approach in animal experimentation and alternative promising models to study nocifensive reactions, in respect of the 3R principles (Sneddon et al., 2017).

There are numerous debates regarding the capacities of non-mammals to experience pain (Sneddon et al., 2014; Brown, 2015; Key, 2015; Sneddon, 2018, 2019; Williams et al., 2019). Indeed these species are quite distant phylogenetically from humans and their nervous system is indeed not organized as in mammals (White et al., 1986; Rein et al., 2002; Pratt and Khakhalin, 2013; Lee-Liu et al., 2017; Zheng et al., 2018; Vaz et al., 2019). The simplicity of nervous system and the lack of neocortex in zebrafish and somatocortex in *Xenopus* is one of the main arguments for no possible pain experience in these species. However, it has been established that nociceptive pathways in these four animals are similar to mammalian ones (Tobin and Bargmann, 2004; Kahn-Kirby and Bargmann, 2006; Smith and Lewin, 2009; Stevens, 2011, 2015; Khuong and Neely, 2013; Demin et al., 2018b, 2018a; Sneddon, 2018; Walters, 2018). This includes (1) nociceptors with morphological and functional resemblance to vertebrate ones, (2) ions channels which, based on their sequence and structure homology and functional assays, are orthologous to the mammalian TRP channels, (3) opioid system and (4) neurotransmitters of primary afferents (Table 4). These four species are capable of sensing mechanical, chemical and thermal noxious stimuli although only amphibians can sense cold stimuli (Sneddon, 2018).

Stereotypical behavioral responses to a noxious stimulus have been well described in these simple organisms and helped to develop numerous assays to study thermal, mechanical and chemical nociception and also neuropathic and chronic pain models (Table 5). In *Drosophila*, the classical response of larvae to heat or mechanical noxious stimuli is the rolling (corkscrew-like) response (Milinkeviciute et al., 2012). *C.elegans* respond to a heat stimulus with the stereotypical escape behavior called Tav (thermal avoidance), which includes a stop movement followed by reversal, reposition and a forward movement to another new direction (Wittenburg and Baumeister, 1999). However, new heat avoidance assays rely on other behavior responses such as crossing a thermal barrier or distance travelled on heated assay plate (Glauser et al., 2011; Nkambeu et al., 2019). *Xenopus* nociceptive response to the application of acetic acid test (AAT) drops of dilute acetic drops (5%) to the hindlimb, a pain model developed by Pezalla in 1983 (Pezalla, 1983), is called “wipping response”. In zebrafish, nociception has been assessed by changes in behavior, such as reduction of activity, swimming distance and space use, physiological changes (opercular beat rate) or more recently by abdominal constriction like response (Costa et al., 2019; Sneddon, 2019). Some of these assays such as the hotplate or von Frey test, successfully implemented in *Drosophila* larvae and adults, are similar to the mammalian ones (Milinkeviciute et al., 2012). These nociception like assays based on behavioral responses coupled to the ease of genomic manipulation allowed the discovery of new molecular mechanisms involved in nociception and pain. As an example, painless, a TRP channel related to the TRPA1 channel subfamily, was identified in the first nociception study though a forward genetic screen for *Drosophila* mutants defective in heat stimulus response (Tracey et al., 2003).

It is now admitted that these four animals can be used as alternatives to mammalian models to study nocifensive behaviors. However, it remains unclear if they can be used to improve our understanding of pain integration. Pain models, such as neuropathic pain, have been developed in *Drosophila* and zebrafish (Malafoglia et al., 2014; Khuong et al., 2019) (Table 5). The ATT test, performed in *Xenopus* and zebrafish have

Table 4
The nociceptive pathways in invertebrates (*C.elegans* and Drosophila) and lower vertebrates (*Xenopus* and Zebrafish). Some examples of neurotransmitters or TRP channels are given; only TRPM, TRPA and TRPV channels are indicated for *Xenopus* and Zebrafish, *demonstrated in amphibian class (Rana).

	Nociception	Nociceptors	TRP-like channels	Neuromodulators	Opioid system	References
C.elegans	Thermal, chemical and mechanical	ASH pair of neurons DRG polymodal nociceptors	Osm-9 and ocr-2 (=TRPV)	SubstanceP, calcitonin, Glutamate FLP18/ FLP-21/NRP-1	μ-opioid like receptor	Bargmann and Kaplan, 1998; Glauser et al., 2011; Kahn-Kirby and Bargmann, 2006; Mills et al., 2016; Nkambeu et al., 2019; Venkatachalam et al., 2014; Wittenburg and Baumeister, 1999
Drosophila	Thermal, chemical and mechanical	Multidendritic (Md) class IV and class III neurons	Painless, TRPA1, pyrexia (≈ TRPA) Pkd2, NompC, and Trpm Inactive (≈ TPRV)	NRP1 Neuropeptide F Amnesiac	μ-opioid like receptor	Aldrich et al., 2010; Hu et al., 2017; Hwang et al., 2007; Khuong and Neely, 2013; Kwon et al., 2010; Lee et al., 2005; Neely et al., 2011; Tracey et al., 2003; Turner et al., 2016; Walters, 2018
Zebrafish	Thermal, chemical and mechanical	Polymodal nociceptors Un-myelinated C-fiber and Myelinated Aδ−fibres	10 TRP channels (TRPV, TRPM, TRPA)	Substance P, Glutamate,	14 opioid (μ,δ,κ and opioid-like) receptors	Demin et al., 2018; Saito and Shingai, 2006; Sneddon, 2019; Williams et al., 2019 Demin et al., 2018; Stevens, 2015;
Xenopus	Thermal, chemical and mechanical	Polymodal nociceptors Un-myelinated C-fiber and myelinated Aδ−fibres	14 TRP channels (TRPV, TRPM, TRPA)	Substance P, CGRP, Glutamate*	4 opioid (μ,δ,κ and opioid-like) receptors	Saito and Shingai, 2006; Stevens, 2009, 2011; Williams et al., 2019

been considered as a pain model, mimicking the rodent visceral pain protocol when injected intraperitoneally (Costa et al., 2019). These animals have also been used in analgesia and anaesthesia research and it has been proven that negative effects of noxious stimulus are blocked by the use of anaesthetics (Morgan et al., 2007; Stevens, 2011; Lopez-Luna et al., 2017). To access pain events is complicated in these four organisms, but it has shown they display cognitive processes such as memory, learning, active avoidance learning, punishment learning, pain-relief

Table 5
Examples of assays to study nociception performed in *C. elegans, Drosophila*, Zebrafish and *Xenopus*.

	Age	Thermal assay	Mechanical assay	Chemical assay	Chronic pain-like assay	Neuropathic pain-like assay	References
C. elegans		Heated metal pen tip or laser diode Thermal barrier assay Noxious heat thermogradient assay and four quadrants assay	Harsh touch assay	Octanol avoidance assay Thrashing assay	N.T.	N.T.	Cohen et al., 2014; Glauser et al., 2011; Mills et al., 2016; Nkambeu et al., 2019; Tobin and Bargmann, 2004; Wang et al., 2019; Wittenburg and Baumeister, 1999
Drosophila	Larvae	Soldering iron heated to 46 °C Heated Water Droplet Cold probe contact	von Frey fibres assay	HCl (quick exposure or incubation)	N.T.	N.T.	Calvo et al., 2019; Im and Galko, 2012; Khuong et al., 2019; Lopez-Bellido et al., 2019; Milinkeviciute et al., 2012; Turner et al., 2017
	Adult	Water-tight chamber surrounded by hot water ‘Jump’ reflex assay ‘Hotplate’ assay The light-driven heat avoidance test	N.T.	Feeding session Direct contact with food/liquid laced with noxious compound	‘Sunburn’ UV radiation	Nerve injury (Middle leg amputation)	
Zebrafish	Embryo/ Larvae	Thermal challenge (warm water bath) Temperature aversion assay Cold and warm water tank	N.T.	Acetic Acid exposure	Acetic acid test (exposure)	Extreme Thermal exposure	Malafoglia et al., 2014; Curtright et al., 2015; Taylor et al., 2017; Deakin et al., 2019; Ellis et al., 2018; Yang et al., 2018; Costa et al., 2019; Sneddon, 2018
	Adult	N.T.	Electric shock	Acetic acid test (exposure or subcutaneous injection) Algogen injections	Acetic acid test (exposure or subcutaneous injection)	N.T.	
Xenopus	Adult	Hargreaves test	Pinch by a bulldog clamp in the dactyls of the forelimbs Pull of the ovaries Electric shock	Acetic acid test (exposure)	Acetic acid test (exposure)	N.T.	Millhr et al., 1974; Stevens, 2011

learning and if trained, opioids self-administration (Millhr et al., 1974; Ardiel and Rankin, 2010; Gerber et al., 2014; Rothman et al., 2016; Bossé and Peterson, 2017; Yang et al., 2018).

The large number of *Drosophila*, *C.elegans* and zebrafish and *Xenopus* larvae obtained from one mating combined to the absence of ethical issues for these individuals made them very attractive for large genetic and chemical screenings. Teratogenecity assays in zebrafish and *Xenopus* embryos and larvae have been used to address toxicity of pain drugs and herbal remedies and could be powerful tests for future analgesics and anaesthetics development (Chae et al., 2015; Jayasinghe and Jayawardena, 2019). High-throughput screenings have already been implemented with the aim to identify new pain drugs (Ellis et al., 2018). *Xenopus* wild type or overexpressing human proteins related to chronic pain oocytes are frequently used to screen libraries of compounds and test their specificity using electrophysiology or voltage-clamp fluorometry (Zeng et al., 2020). In particular, inhibitors of the P2 × 7 purinergic receptor or an ion channel involved in chemotherapy induced peripheral neuropathy have been identified using *Xenopus* oocytes (Zeng et al., 2020). *Straightjacket*, member of the voltage-gated calcium channel family involved in acute and chronic pain in humans, and the thermoreceptor TRPA1 were identified among 580 new pain genes in a 10,000 knockdown adult flies screen (Neely et al., 2010, 2011). Recently, a forward behavioral genetic screen allowed testing more than 600,000 transgenic tgMOR *C.elegans* mutants and identifying a novel and conserved orphan-opioid system (Wang et al., 2019). The recent development of novel behavioral assays with large numbers of animals, automated behavioral tool (such as the Fish Behavior index (FBI)), tracking software (AnyMaze®) and quantitative models should become very useful tools for assessing nociceptive responses high-throughput screening (Curtright et al., 2015; Leung et al., 2016; Taylor et al., 2017; Deakin et al., 2019). Indeed, the Multi-Worm Tracker software (Swierczek et al., 2011) was used to record the animal movement and identify *C.elegans* mutants displaying behavioral changes to opioids (Wang et al., 2019). Finally, habituation alterations have been successfully tested in these high-throughput models for neurodevelopmental disorders (Kepler et al., 2020). Such assay could be a promising approach to provide insight into nociception and pain.

The easiness of these four organisms, the ethical issues and the development of recent automated methodologies have contributed to the increase of studies on nociception and pain research. Although these animals feel nociception and can be used to test behavioral responses to thermal, chemical and mechanical noxious stimuli with a great potential for pharmacological research, for molecular mechanisms understanding and for the 3R respect, there is some limitations to their use. One of these limitations is their phylogenetic distance to humans and therefore to some molecular and cellular mechanisms differences. For example, the P2 × 3 receptor involved in pain is not found in *Xenopus* genome (Burnstock, 2016; Bernier et al., 2018; Blanchard et al., 2019). The main limitation resides in the difficulty to assess pain perception, if any. However, the use of these models, especially in high-throughput screening, could be the first *in vivo* step before any experimentation on rodents or other mammals.

11. Limitations of animal models of pain

The study of pain always relied on preclinical animal models that attempted to explore the complex physiological and sensory implications of the condition. Various animal models of chronic pain aim to emulate different types of pain and they have been instrumental in the discovery and development of analgesic agents. While there is no doubt about the necessity of such models in chronic pain research, there are several limitations to their use. This is especially true when considering their failure to facilitate the translation of basic science data into effective and commercially available therapies. This is supported by the fact that there is a high rate of translational failures associated with preclinical animal models (Le Bars et al., 2001; Negus et al., 2006). One well-known failure is that of the neurokinin-1 receptor antagonists (substance P) (Hill, 2000). Several reasons have been suggested for these failures (Mogil, 2009). This debate focuses partly on the utility of animal models of pain and behavioral measures for screening new potential analgesics. One concern is the reliance of studies on reflexive measures, and it has been suggested that additional measures of supraspinal integration that use non-reflexive pain-like behaviors should be included, such as operant learning measures, spontaneous nocifensive behaviors and quality of life or physical activity measures. Another concern is the use of animal models of disease that do not reflect the clinical condition the experimenter is trying to model, such as using inflammatory pain in animals to study chronic low back pain. Finally, the insufficiency of the knowledge on fundamental neuronal mechanisms must be also emphasized. In particular, recent studies pointed to the importance of NK1 receptor signaling along the endocytotic pathway, and not only at the plasma membrane, in the transduction of nociceptive information (Jensen et al., 2017). Therefore, classical NK1 antagonists that target membrane NK1 may not be able to prevent atypical intracellular NK1 signaling.

Most molecules that successfully demonstrated analgesic effects in preclinical studies fail to produce similar effects when tested on a clinical level. One of the reasons this might occur relies on the genetic and molecular neurochemical differences between humans and animals. This makes it difficult to predict the pharmacological effect of a molecule on the clinical level. In contrast, after clinical validation, most approved drugs have proven good efficiency in reverse translational studies in animals. The difficult translatability of pain across species and transfer to clinical settings could also be due to non-optimal translational research conditions and not directly related to the failure of the model to simulate human pain mechanisms (Le Bars et al., 2001; Henze and Urban, 2010). In fact, failure in translational approaches can be due to the presence of severe side effects that appear in clinics but are not detected in preclinical studies (Mogil, 2009).

Another major cause is likely to be the heterogeneous nature of human chronic pain which can have a multitude of aetiologies. This heterogeneity clashes with the controlled environment often used in animal studies that might interfere with the translation of the research to a human population. In particular, a vast majority of animal studies utilize inbred animal. While some injury models are available, most studies only use sensory-evoked thresholds (e.g., von Frey filaments) in order to assess nociceptive sensitivity; whereas the evaluation of ongoing pain based on non-evoked stimulus (such as the grimace scale, weight bearing, CPP…) may be clinically more relevant (Negus et al., 2006; Deuis et al., 2017). Other challenges researchers are facing include the replication of the transitional process of pain from acute to chronic in animal models. The complexity of pain mechanisms and differences between pain types (i.e. neuropathic vs. inflammatory) indicates a lack of a mechanistic delineation between conditions (Le Bars et al., 2001; Ferrari et al., 2015).

In addition, several demographic factors are implicated in pain mechanisms in humans including age. Pain mechanisms are often considered independent from age in animals, which lead to the predominant use of young mice in preclinical studies. This is questioned by the increasing evidence of the involvement of an age-dependent mechanism (Mogil, 2009). Sexual dimorphism is another demographic factor that might lead to the misrepresentation of chronic pain in animal models. This is apparent through the overuse of male subjects in studies which is a clear contrast to the high prevalence of chronic pain in females. The underutilization of female subjects in preclinical trials might provide an explanation to the lack of effective analgesic therapies for the human global population (Le Bars et al., 2001; Negus et al., 2006; Henze and Urban, 2010). Pain perception differs between female and male; with female perceiving more pain perhaps due to high levels of estrogen and progesterone, and low testosterone levels. In fact, pain perception is modulated by the immune system that is under the control of gonadal hormones (Mogil, 2009). This difference has been highlighted in a study

that indicated only male mice developed acute thermal hypersensitivity when tested in an environment linked to a painful memory (Martin et al., 2019). Furthermore it has been showed that T-cell deficient female mice needed 2–3 times the morphine dose administered to male mice (Rosen et al., 2019). Another example pointed that the hypersensitivity induced by nerve injury is different between male and female mice since the spinal mechanisms differ between the two genders (Mapplebeck et al., 2018).

Interstrain animal genotypic variabilities can also account for the failure of human chronic pain modelling in animals (Le Bars et al., 2001; Negus et al., 2006; Henze and Urban, 2010). The example of the gene encoding sodium channel Nav1.7 is illustrative. This gene is present on adrenal and pituitary gland of rodents, and its mutation is lethal. However, the situation is different in primates where this gene mutation leads to pain insensitivity (Mogil, 2009). Notably, recent studies pointed that Nav1.7 may not be critical for survival even in rodents, but appears as an key molecular component for transmitting high-threshold noxious stimuli (Gingras et al., 2014). There is also genetic variability among rodents that is also to blame for clinical failure. In fact, mice show an increase of morphine analgesia when isolated in a cage, whereas it decreases with rats. Furthermore chronic pain was shown to modulate 43 genes in rats versus only 10 in mice (Mogil, 2009).

12. Translational lessons learned from animal model studies

Translation is defined by the National center for advancing translation science as “the process of turning observations in the laboratory, clinic, and community into interventions that improve the health of individuals and populations – from diagnostics and therapeutics to medical procedures and behavioral interventions” (Nakao, 2019). It is worth noting that despite the aforementioned limitations, a growing number of examples demonstrate the potential to convert new agents into widely used analgesics through pre-clinical testing in animal models. The following will consider such examples for treating neuropathic or inflammatory pain, as well as low back pain and post-operative pain.

12.1. Targeting purinergic signalling

ATP induces acute pain when applied to human skin (Bleehen and Keele, 1977; Hamilton et al., 2000) where it activates ATP-gated channels (P2X receptors), mainly P2 × 3 receptors that are almost exclusively expressed in nociceptive sensory neurons. P2 × 3 and heteromeric P2 × 2/3 play a key role in pain sensing and in various sensory transduction such as taste and visceral afferent sensation. Several P2X receptors expressed in neurons and/or microglia, including P2 × 3 and P2 × 4 or P2 × 7, are also involved in the chronic nociceptive behavior that follow nerve injury or inflammation indicating that P2X receptors represent therapeutic targets for pain syndrome (Khakh and North, 2006).

Nerve injury mouse models recently allowed the understanding of a spinal mechanism in which the purinergic receptor P2 × 4 expressed in microglia plays a critical role specifically in neuropathic pain but not in acute or inflammatory pain. Using a spinal nerve ligation rat model of neuropathic pain, a pioneered work showed that the increase of P2 × 4 expression specifically in reactive microglia within the dorsal horn of the spinal cord is determinant in tactile allodynia (Tsuda et al., 2003). The authors also showed that the pharmacological blockade of P2 × 4 or the expression knock-down using siRNA dramatically reduced pain-like behavior indicating that P2 × 4 activation is required to maintain pain hypersensitivity. The key role of P2 × 4 was confirmed in P2 × 4 knockout mice (P2 × 4KO) in which tactile allodynia after peripheral nerve ligation was drastically reduced (Ulmann et al., 2008). Several studies established that activation of microglial P2 × 4 by ambient ATP increases nociceptive signaling within the spinal cord by reducing inhibitory currents within the spinal cord. This neuronal disinhibition results from a rise in the intracellular concentration of chloride ions that suppresses GABA or Glycine mediated-inhibitory responses. This phenomenon may eventually convert inhibition into excitation in a subset of neurons, sufficient to induce hypersensitivity of spinal neurons and tactile allodynia (Coull et al., 2005; Trang et al., 2009). These changes in chloride concentration are triggered by the potassium-chloride co-transporter (KCC2) downregulation, which is mediated by the extracellular release of BDNF and the activation of Trk-B receptor located at the surface of inhibitory neurons. The neuronal hyper-excitability mediated by microglial P2 × 4 signaling may account for the main symptoms of neuropathic pain suggesting that the blockade of P2 × 4 expression or function alleviates this debilitating condition in human. Although no commercially available P2 × 4-derived pain killer exists, the therapeutic potential of targeting this system is well recognized, and current research efforts are made for P2 × 4 drug development. TNP-ATP or 5-BDBD are P2 × 4 antagonists that have been commonly used to show the involvement of P2 × 4 in rodent nervous tissue but they are not very selective (Suurväli et al., 2017). New antagonists of rodent P2 × 4 (BAY-1797 or NP-1815-PX) and a highly selective human P2 × 4 antagonist (BX430) with no effect on rodent P2 × 4 were recently identified (Ase et al., 2015; Matsumura et al., 2016). Kyushu University and Nippon Chemiphar Co., Ltd. initiated a phase 1 clinical trial of the NC2600 P2 × 4 antagonist but no data is available since then (Bhattacharya, 2016).

An alternative to P2 × 4 blockade could be the enhancement of KCC2. Actually, chloride extrusion enhancers have been proposed as novel therapeutics for pain alleviation (Gagnon et al., 2013). Chloride enhancers could also be used in synergy with other pharmacological agents. Indeed, a recent study pointed to the benefit of rescuing chloride homeostasis with the KCC2-enhancer CLP25728 on the analgesic action of the benzodiazepine site ligand L838,417. This combination produced an efficient analgesia even with high doses of benzodiazepine, whereas they remained otherwise ineffective when administered alone (Lorenzo et al., 2020).

P2 × 7 is expressed in most of the immune cells and regulate the inflammation, thus representing a valuable therapeutic target for many diseases involving inflammation, including persistent pain (Burnstock and Knight, 2018). P2 × 7 antagonists such as AZ106006120 or nanobodies that are small single chain antibodies blocking or modulating P2 × 7 functions have been proposed as drug candidates for inflammatory disorders (Danquah et al., 2016; Mishra et al., 2016). P2 × 7 knockout mice showed reduced behaviorral responses to inflammation or tactile allodynia (Chessell et al., 2005). These effects seem to be mediated by the decrease of the pro-inflammatory interleukin-1 release from microglia. P2 × 7 is abundantly expressed in reactive microglia after CNS injury, and neuropathic pain is reduced by P2 × 7 antagonist such as A-740003 and A-438079. These data suggest that targeting microglial P2 × 7 may be useful for the treatment of chronic pain (Tsuda, 2017).

Antagonist selective of P2 × 3 or P2 × 2/3 receptors have also been shown to have anti-inflammatory and anti-nociceptive effects in different models of neuropathy and peripheral inflammation when expressed in sensory neurons (Jarvis et al., 2002; Kuan and Shyu, 2016). Mechanical allodynia in animal models was also reduced in mouse with deletion of P2 × 3 gene (Cockayne et al., 2000; Souslova et al., 2000). In addition, P2 × 3 knockout mice exhibited a marked urinary bladder hyporeflexia and it has been showed that ATP released by the distension of the urothelium activates P2 × 3 expression in afferent nerves. A similar link have been established for the taste buds, the wall intestine and reflexes such as cough, indicating that P2 × 3 and/or P2 × 2/3 receptors have a more widespread role in sensory transduction. Therefore, they represent attractive targets for drugs, and not only for pain. Among the numerous selective antagonists of P2 × 3 discovered, some of them have been studied in clinical trials for pain-related disorders but also for other diseases such as overactive bladder, irritable bowel syndrome, or chronic cough. Gefapixant (MK-7264) significantly reduced cough frequency in patients with refractory chronic cough or unexplained chronic cough (Smith et al., 2020) and is one of the most

promising P2 × 3 antagonists in phase 3 clinical trials for the treatment of chronic cough.

12.2. Targeting 5-HT receptors

Lumbar disc herniation is a well known aetiology of chronic lower back pain. A herniated disc induces pain by a mechanical deformation (in addition to a biochemical irritation) to the dorsal root ganglion and the nerve root. Many substances such as proinflammatory cytokines and monoamines play a role in the biochemical irritation of the nerve. Serotonin (5-HT) is one of the monoamine participating in pain modulation mainly *via* 5-HT_{2A} receptors. Nowadays, scientists are using animal models to understand the complexity of chronic pain pathways, aiming to project these hypothesis and find a curative treatment for chronic pain, and especially low back pain in humans (Kato et al., 2015).

In their paper, Hashizume H et al. evaluated the effect of a 5-HT_{2A} receptor antagonist (sarpogrelate) on lumbar disc herniation pain (Hashizume et al., 2007). They performed a study on rats that underwent surgery to place an autologous nucleus pulposus at the 4th and 5th left lumbar nerve roots in order to mimic lumbar disc herniation pain. After studying pain related behaviors, researchers found that sarpogrelate treatment considerably reduced mechanical allodynia at 5 and 8 days after drug administration (Hashizume et al., 2007). In a related experiment, the same surgical model of rats was used to study the effect of a similar 5-HT_{2A} receptor antagonist (saprogrelate hydrochloride) on pain related behavior, and on the expression of 5-HT_{2A} receptors in dorsal root ganglia. The results confirmed that saprogrelate used at high doses (10 mg/kg) dramatically reduced mechanical withdrawal threshold evaluated by von Frey tests. In addition to decreasing nociceptive transmisison, researchers confirmed that this 5-HT_{2A} antagonist down-regulates 5-HT_{2A} receptor expression in dorsal root ganglia (Kato et al., 2015). Furthermore, the effect of the serotonin noradrenaline reuptake inhibitor (SNRI) duloxetine was evaluated on radiculopathy in the same rat model of lumbar disc herniation pain (Handa et al., 2016). Rats received duloxetine at different doses (low dose 0.4 mg/kg, high dose 1.2 mg/kg). Results confirmed that duloxetine had a positive impact on neuropathic pain in rats probably by down regulating the expression of tumor necrosis factor alpha and nerve growth factor and microglia activation (Handa et al., 2016).

These preclinical data obtained on animal models drove clinical trials in order to demonstrate SNRI drug efficacy on chronic back pain in humans. A recent meta-analysis reported the results of 3 randomized double blind clinical studies of patients taking duloxetine or placebo for chronic low back pain (Enomoto et al., 2017). Duloxetine-treated patients (n = 400) and placebos (n = 451) were considered and the statistical analysis revealed that duloxetine considerably alleviated pain. Duloxetine-induced analgesic effect was mainly modulated by interaction with the pain pathway rather than with the anti-depressive effect of the drug, indicating that duloxetine primarily targeted pain-specific mechanisms and not comorbid disorders (Enomoto et al., 2017). The effectiveness and safety of duloxetine monotherapy was assessed in a Japanese population suffering from chronic low back pain. Duloxetine (60 mg daily) was effective in pain management. Moreover, duloxetine was well tolerated with mild side effects that may resolve and improve with the course of the treatment (Konno et al., 2016). These results were confirmed by independent studies with randomized, double-blind trials on chronic low back pain patients (Skljarevski et al., 2010a, 2010b).

Taken together, these studies have led to the recommendation of duloxetine in the management of chronic low back pain as a second line therapy by the American college of physicians in 2017 (Qaseem et al., 2017).

In addition, a novel dual antagonist of the GlyT2 glycine transporter and 5-HT_{2A} receptor (VVZ-149) is being tested in healthy volunteers for future applications in the management of post-operative pain (Oh et al., 2018). In case of success, the therapeutic indication for this drug may be extended beyond post-operative pain to other pain pathologies.

12.3. Targeting TRPV1 receptors

Capsaicin is a TRPV1 receptor agonist (see §2.) with anaesthetic effects that is approved as a pain killer and proved to be efficient in various types of pain. Although the analgesic properties of capsaicin were empirically known for long, animal model studies allowed to determine its mechanisms of action. Early evidence, back in the 1980s, indicated that capsaicin treatment causes an alteration of the synthesis and storage of substance P in the dorsal horn and primary afferent neurons, thus affecting nociceptive transmission (Gamse et al., 1980; Lembeck and Donnerer, 1981). Subsequently, capsaicin-mediated thermal anti-nociceptive effects were demonstrated, and the suggested mechanisms pointed to a possible suppression of axoplasmic impulses in sensory neurons (Yaksh et al., 1979; Buck et al., 1981; Gamse et al., 1982). More recent studies revealed that capsaicin alleviates pain in various animal models including post-surgical pain (Hamalainen et al., 2009) and bone cancer pain (Ghilardi et al., 2005).

Based on animal model studies, the use of topical capsaicin for the management of human chronic pain became increasingly popular (Wagner et al., 2013; Blair, 2018). The effect of an 8% capsaicin patch were assessed on peripheral neuropathic pain in comparison with oral Pregabalin (Haanpää et al., 2016). Capsaicin treatment contributed to remarkable pain alleviation at 8 weeks in comparison with optimal Pregabalin doses. Patches are associated with less systemic side effect, rapid action and greater treatment satisfaction (Haanpää et al., 2016). Another study also indicated the superiority of 8% capsaicin patches over Pregabalin on mechanical allodynia in patients suffering from peripheral neuropathic pain (Cruccu et al., 2018). These findings were confirmed by a network meta-analysis of 25 randomized controlled trials (van Nooten et al., 2017). Consequently, Capsaicin patch is indicated in treating neuropathic and skeletomuscular pain (Chang and Quick, 2020). In addition, a recent paper supported the use of capsaicin patches to attenuate chemotherapy-induced peripheral neuropathy that may occur in cancer patients (Anand et al., 2019).

Prolonged application of capsaicin results in the desensitization of TRPV1 channel. As a consequence, the nociceptive afferent becomes functionally silent (Zhang et al., 1994; Lambert, 2009). The efficacy of capsaicin-induced desensitization in treating pain pushed pharmaceutical companies to develop TRPV1 antagonists (Dray, 2008). Moreover, TRPV1 was shown to play a role in neural sensitization (Ramsey et al., 2006), and preclinical studies suggested TRPV1 antagonists may exhibit analgesic effects in inflammatory conditions (García-Martinez et al., 2002). These findings paved the way for clinical research, and at least seven orally active TRPV1 antagonist substances were under development in 2009, with many more in preclinical development (Gunthorpe and Chizh, 2009). In the same period, phase II clinical trials were performed for compounds such as GRC 6211 (Lilly/Glenmark), NDG6243 (Merck/Neurogen) and AZD1386 (AstraZeneca). However, to date, no TRPV1 antagonists are available for the clinician.

The main reasons for this failure relies in the lack of precise and rigorous preclinical evidence for using TRPV1 antagonists in pain treatment. Hence, it is necessary to optimize preclinical pharmacology to define precisely pain profiles sensitive to the compounds tested. Alternatively, refinements in preclinical studies may avoid making overenthusiastic assumptions, and help in a timely manner not to pursue clinical developments, thus saving money and resources for the pharmaceutical industry (M Keppel Hesselink, 2016).

12.4. Targeting nerve growth factor

Evidence for a contribution of locally produced nerve growth factor (NGF) to joint pathology, as well as pain in arthritic joints has emerged from animal model studies. A single intraarticular (IA) injection of NGF into normal rat knees produced a direct sensitisation of nociceptors

through dose-dependent, long-lasting increases in pain-like behavior, joint swelling and synovial macrophage infiltration (Ashraf et al., 2014). Other work provided evidence that NGF is released by damaged cells in arthritic joints, and elevated NGF is detected in synovium of murine OA model (Kc et al., 2016). Elevated levels of NGF has been also found in synovial fluid in dogs with naturally occurring OA (Isola et al., 2011). Administration of an anti-NGF/TrkA signalling molecule significantly decreased pain-like behaviors in a murine model of OA (McNamee et al., 2010). In particular, anti-NGF monoclonal antibody (mAb) produced a robust analgesia that is equal to or greater than current analgesics in animal models (Xu et al., 2016; Enomoto et al., 2019).

In view of experimental preclinical findings on the role of NGF in pain, clinical trials have been initiated to demonstrate the effectiveness of the strategy targeting the NGF system (Takasusuki and Yaksh, 2011; Bannwarth and Kostine, 2014, 2017). Anti-NGF mAbs are in development as treatments for several pain conditions and three NGF-blocking drugs have been developed: tanezumab (humanised mAb; Pfizer, in collaboration with Eli Lilly), fulranumab (fully human mAb; Amgen) and fasinumab (fully human mAb; Regeneron Pharmaceuticals, in collaboration with Sanofi). The first attempts to develop clinical trials aimed at evaluating the efficacy of anti NGF antibodies on osteoarthritis pain (Ishikawa et al., 2015; Miyagi et al., 2017). Tanezumab prevents NGF binding to its TrkA receptor resulting in pain alleviation. Although many studies emphasized Tanezumab positive effects against osteoarthritis pain, Tanezumab exhibits also serious adverse effects such as arthralgia, paraesthesias and osteonecrosis that question Tanezumab approval to treat chronic pain conditions in humans (Schnitzer et al., 2015; Walicke et al., 2018; Webb et al., 2018). After being put on a clinical hold between 2010 and 2012, trials for the development of anti-NGF mAbs in human restarted in 2015, and Tanezumab received fast track designation by the Food and Drug Administration in 2017. Tanezumab is currently in phase III studies in patients with OA of the hip and knee, chronic lower back pain, and bone cancer pain trials (Enomoto et al., 2019). Other companies are developing TrkA antagonist (Sanofi, GZ389988; Glenmark Pharmaceuticals Ltd., GBR 900). Comparisons with anti-NGF antibodies in animal models of inflammatory pain demonstrated that GBR 900's efficacy is similar as that of anti-NGF antibodies

Since OA naturally occurs in cats, dogs and horses (see §2), companies are developing canine and feline anti-NGF mAbs (NexVet, Ranevetmab and Frunevetmab, respectively). Overall, significant improvement has been seen in both dogs and cats following administration of anti-NGF mAbs. Assessment was made in dogs with OA through the subjective (owned completed questionnaire) and objective (activity) measures. These results suggested a positive analgesic effect possibly greater than that expected with NSAIDs (Webster et al., 2014). Anti-NGF mAB effectiveness was also demonstrated in dogs with pain artificially induced by kaolin injection (Gearing et al., 2013).

12.5. *Targeting calcium channels*

Conopeptides are interesting candidates to design novel drugs for alleviating chronic neuropathic pain. Conopeptides are extracted from the venoms of marine snails and have an effect on calcium channels in modulating pain (Schroeder and Craik, 2012; Patel et al., 2018). Efficiency of conopeptides were first assessed in animal models of pain and then transferred to human clinic (Nielsen et al., 2005). Among conopeptides, a peptide blocker of CA_V 2.2 channels (synthetic version of W-conotoxin MVIIA, named Ziconotide) has attracted much attention (Patel et al., 2018). Intrathecal administration of Ziconotide for refractory chronic pain (e.g. neuropathic pain) has proved antiallodynic and antihyperalgesic effects (Wermeling and Berger, 2006; McDowell and Pope, 2016). Ziconotide however show severe drawbacks, and various alarming side effects have been monitored, e.g. sedation, confusion, ataxia, memory impairment, vertigo, gait imbalance, hallucinations, nausea and vomiting, that limit its indications (Wermeling and Berger, 2006). Actually Ziconotide is approved as a non-opioid analgesic but it must be administered intrathecally in refractory chronic pain cases, allowing patients to benefit from a potent long lasting analgesic effect related to malignant and non-malignant aetiologies (McGivern, 2007; Wie and Derian, 2020). To facilitate the use of Ziconotide, recent studies are evaluating the possibility of administrating the drug intranasally (Manda et al., 2016).

13. Conclusion

Animal models of pain were historically viewed as reliable tools that have served to advance research in the field over the past decades. They have been instrumental in constructing a global picture of how key proteins, signalling systems, and neural circuits contribute to pain-like behaviors. However, there are limitations and caveats to these models that must be acknowledged when considering the translation of research findings from the bench to the bedside. There is not one "best model" for the study of pain. Instead, the use of different organisms has been instrumental for integrating a comprehensive array of genetic, molecular, cellular, and behavioral data on normal and pathological pain processing in the central and peripheral nervous systems.

Classical rodent models usually display good face validity. However, it is still needed to improve construct validity by choosing refine animal models that mimic faithfully the human diseases. In particular, considering sex-differences, genetic variations, or comorbid interactions will contribute to describe a greater diversity of mechanisms that accurately account for clinical situations. In addition, defining more accurate behavioral measures will assist investigators in developing an appropriate set of experiments to better test mechanisms and potential treatments.

In contrast, using simpler organisms provides an efficient mean to achieve high throughput screening of possible key players in pain processes. These approaches are based on alterations of aversive behaviors that are considered surrogates of aberrant pain processes. Although far from the human clinics, these assays are likely to inform the construct of specific rodent models, or the design of protocols dedicated to test the actual role of these candidates.

The combination of distinct animal models may be the alternative to the lack of good predictive validity of animal models that basic research is facing so far. As long as the interpretation of the results remains constrained by their intrinsic limitations, integrating data obtained from different animal models is a powerful method to build up a comprehensive understanding of pain mechanisms and for the identification of potentially more relevant therapeutic targets.

Developing clinical assessment of pain is another important path to help defining more accurate animal models. Quantitative sensory testing, assessment of evoked *vs* resting pain, are parameters that are needed to understand how pain develops in humans. Clinical trials may also be designed to test outcomes and mechanisms derived from animal studies. Finally, an open dialogue between basic research results and clinical challenges posed by human studies is necessary to improve the translation of findings from bench to the bedside and to ensure the development of better pain therapies and pain management strategies.

CRediT authorship contribution statement

Cynthia Abboud: Writing - original draft. **Alexia Duveau:** Writing - original draft. **Rabia Bouali-Benazzouz:** Writing - original draft. **Karine Massé:** Writing - original draft. **Joseph Mattar:** Writing - original draft. **Louison Brochoire:** Writing - original draft, Writing - review & editing. **Pascal Fossat:** Writing - original draft. **Eric Boué-Grabot:** Writing - original draft. **Walid Hleihel:** Funding acquisition, Supervision, Writing - original draft. **Marc Landry:** Funding acquisition, Supervision, Conceptualization, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare they have no competing interests.

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