Inflamm. res. 48 (1999) 417–424
1023-3830/99/080417-08 $ 1.50+0.20/0

Inflammation Research

Commentary

Biotelemetry: an original approach to experimental models of inflammation

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Received 13 March 1998; returned for revision 26 June 1998; returned for final revision 24 August 1998; accepted by R. Day 23 October 1998

Abstract. Biotelemetry is a new biological technology which evaluates continuous spontaneous locomotor activity and body temperature in rodents. The telemetry system comprises a transmitter implanted in the peritoneal cavity of the rodent, and a receiver placed beneath the animal's cage. The receiver detects the radio waves and the activity of the rodents as counts which are registered in the computer system, and the adapter detects the calibrated body temperature. First, we showed that biotelemetric studies of different species (rats, guinea pigs, mice and gerbils) provide substantial information about their circadian rhythms. Second, using the most common examples employed in pharmacology of inflammation (hyperthermia, arthritis, ischemia-reperfusion and so on) biotelemetry has helped us to clarify the pathophysiological significance of the parameters of temperature and mobility in several experimental models in rodents.

Key words: Temperature – Locomotor activity – Rodents – Inflammation

Introduction

Although the pharmacological targets of inflammation are multiple (cyclooxygenases [1], cytokines [2] and their inhibitors [3] or their antagonists [4, 5], neuropeptides [6], cytoplasmic and membrane receptors [7], transduction signals [8], enzymatic systems regulating tissue integrity [9], etc.), in vivo pharmacological studies to establish the validity of these targets are still for the most part the classic ones, as regards both experimental models and the parameters used [10]. Continuous quantitative monitoring of spontaneous locomotor activity and body temperature by biotelemetry is a new concept which complements the standard approaches [11], considerably enriching information derived from assessment of paw edema, arthritic or histological scores and so on.

With this in mind, the newly developed telemetry system, using implanted transmitters, provides an unique opportunity to study body temperature and spontaneous locomotor activity in freely moving conscious rodents over variable periods [12]. Such an original approach makes it possible to evaluate the effects of painful, inflammatory, degenerative, or immune dysfunction processes on the joint function on the one hand, and thermoregulation of the animals studied, particularly in rats and mice, without the stress of handling on the other.

Telemetry thus mimics a clinical approach and changes in physical activity and/or central temperature could be considered as quality-of-life (QOL) measures: it is a fact that measurements of walking time have been an integral part of the clinical assessment of arthritis [14] and algofunctional indexes. Furthermore, biotelemetry takes into account, in a quantitative way, key-indexes widely used for measurements of QOL in rheumatology, e. g. mobility, functionality, pain (influence of drugs) and inflammation (fever) without the influence of handling animals.

In addition, this pharmacological approach allows us to investigate kinetics and duration of effect in acute or in chronic inflammatory phases. The efficacy of new presumed antirheumatic drugs and their influence on degenerative joint process can be evaluated by the assessment of locomotor handicap, joint pain [13] and febrile response in rats. Finally, by coupling simultaneously the study of loss of mobility due to pain (neurogenic transmission, and/or inflammation, and/or dysfunction) and the febrile response inherent to the inflammatory response, biotelemetry may allow us to discriminate articular pain from joint inflammation. For example, intra-articular injection of zymosan or carrageenan induces a febrile reponse and loss of mobility due to acute synovitis, whereas iodoacetate injected similarly causes an apyretic loss of mobility, due to a pure joint pain, without histological signs of synovial inflammation.

Supported by grants from Region Lorraine, Communauté Urbaine du Grand Nancy, Fondation Lorraine pour la Recherche Médicale and Association pour la Recherche contre le Cancer.

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Description of the telemetry system

The telemetry system comprises a transmitter implanted in the peritoneal cavity of the rodent, and a receiver placed beneath the animal's cage. The transmitters consist of sensors or lead wires connected to electronic amplifiers. The amplified signal is used to modulate radio frequency waves which radiate from the animal. The receiver detects the radio waves and reconstructs the original amplified signal. The signals from the transmitter, which include the body temperature and locomotor activity of the animals, are relayed by a consolidation matrix (BCM100 consolidation matrix multiplexes the data from 8 receivers) into a peripheral processor connected to a personal computer (Fig. 1).

The transmitter (model VM-HF disc, Mini-Mitter or model TA10TA-F20 Data Sciences International) implanted in the animal weighs respectively 4.5 and 3.8 grams and has a diameter of 1.8 and 1.75 cm. The receiver (Physiotel Receiver, model RLA 1020, Data Sciences International) detects the radio waves and the activity of the rodents as counts which are registered in the computer system, and the adapter detects the calibrated body temperature. Unlike body temperature, the activity counts are not calibrated, but all the receivers have the same sensitivity. All transmitters work on the same wavelength, and animals are therefore housed singly.

Other configurations are possible, depending on the organ system being studied (mainly cardiovascular and neurological), the parameter being measured (such as heart rate, arterial blood pressure, ECG, EEG, or thirst), and the size of the animals. In the configuration used for the study of models of inflammation in rodents, the frequency of each transmitter, which varies with the ambient temperature, is converted into central temperature according to a conversion algorithm. Each animal's mobility is evaluated by the number of impulses per unit time, each impulse being generated by the animal's movement relative to the antenna beneath its cage. In addition, especially in hamsters, joint function can be evaluated in other ways, such as by measuring the distance it runs per day in its exercise wheel, and the wheel's mean speed [14, 15].

Experimental procedures

In order to create conditions as nearly physiological as possible for telemetry and to avoid causing stress to the animal, a thermoregulated room is necessary (22°C–23°C), with a 12D:12L cycle (lights on from 06:00–18:00) [16]. Animals have free access to water and standard laboratory food to avoid the influence of anorexic behaviour on locomotor activity [17]. The experiment (particularly for studies of the acute phase of inflammation) must be planned so that the beginning of the dark period (corresponding to the beginning of the animal's nocturnal activity) coincides with the pharmacological effect being observed.

The experimental plan has 3 stages after calibration of the transmitters for the study of rodents' temperature (37–40°C):

1. The rodents are anaesthetized intraperitoneally with a mixture of ketamine hydrochloride (50 mg/kg) and acepromazine (1.25 mg/kg). Hair is removed from the abdominal area and the rodents are surgically operated on under sterile conditions; the peritoneal cavity is opened by incisions of the skin and the muscle layers. The sterile transmitters are implanted and the skin and muscles layers closed with non resorbable silk sutures.
2. The rodents are housed in individual plastic cages that are kept on the receiver plates. After the operation, animals are allowed at least 5–6 days for recovery prior to the experimental study where motor activity and body temperature are continuously assessed at different intervals.
3. The experimental phase consists of measures of locomotor activity and body temperature in rodents under various conditions.

The parameters and animals studied

Biotelemetric studies of different species (rats, guinea pigs, mice and gerbils) provide substantial information about their circadian rhythms. First, a normal rat's activity and temperature vary considerably between day-time [18] [period of

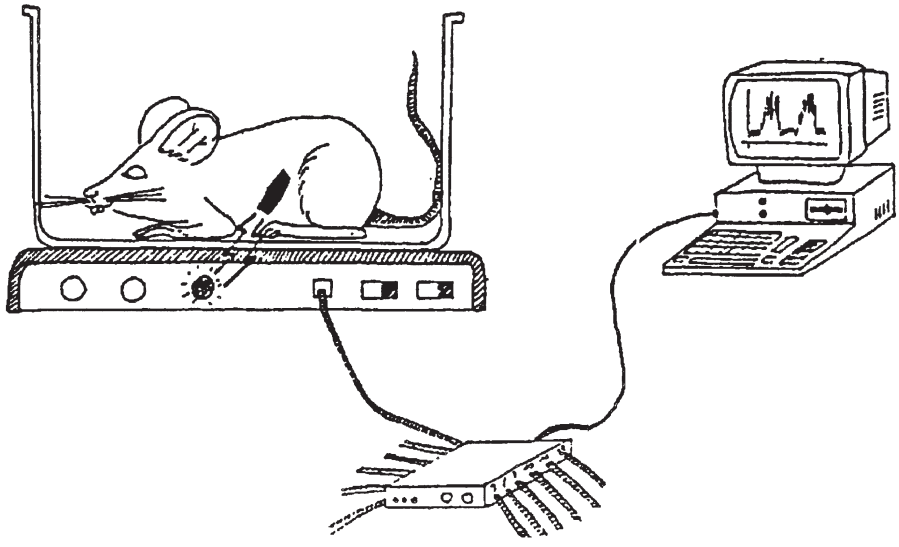

Fig. 1. Organization of a telemetry unit; a transmitter is implanted intraperitoneally in the rat and a receiver is placed beneath the rat's cage. Data (12 cages) are transmitted to a matrix and fed into a personal computer and then integrated with purpose made software.

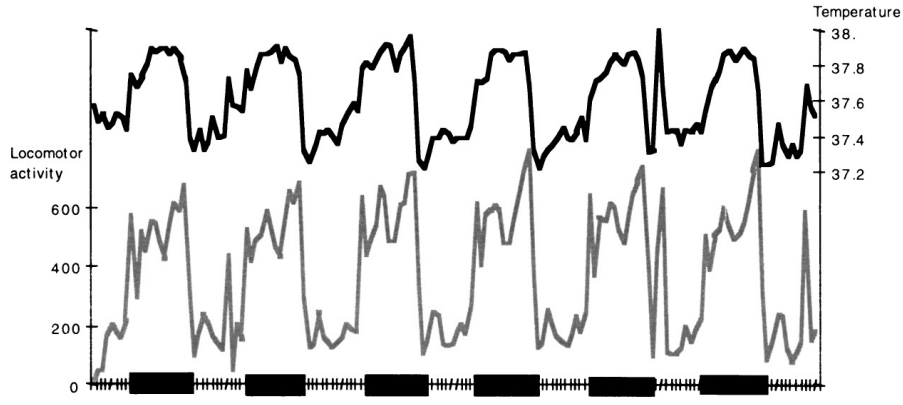

Fig. 2. Normal circadian variation of body temperature (°C) and locomotor activity (counts/hour) in Wistar rats (180 g, Charles River Laboratories). Each point is the mean of 2 observations of 40 conscious rats. For the sake of clarity, standard deviations have not been depicted. Dark bars represent light off period (5:30 p.m.–5:30 a.m.). Light on 5:30 a.m.–5:30 p.m.

light: low activity and normal temperature, about 37–37.2°C] and night-time [period of darkness: high activity and high temperature, about 37.8–38°C]. The day-time temperature is usually 1°C lower than the nocturnal temperature, reflecting the rat's widely recognised circadian rhythm (Fig. 2). This regular diurnal cycle is reached from the fourth day after surgical transmitter implantation and this period of recuperation should therefore always be instituted before the experiment is started.

The rat's environment is also important, as simply changing the litter temporarily modifies the rat's spontaneous mobility, especially during the day-time loss of mobility phase which represents the 'exploratory phase'. This phenomenon, which is well known in psychopharmacology [19, 20], lasts about 45 min and provokes hypermobility, which is accompanied by stress and a transitory rise in temperature. The same thing happens when the animals themselves or their neighbors are handled in any way (during force-feeding, weighing, or parenteral injections for example), which may necessitate conditioning of the animals during the acclimatization stage.

Mice are also nocturnal animals (Fig. 3) and show some diurnal variation in activity and temperature. While the rat's diurnal cycle is strictly defined and stops immediately with the light, the period of mice's hyperactivity is longer in our experimental conditions. The body temperature of mice followed the same pattern with the same quantitative variations (37°C during the light period and 38°C during darkness).

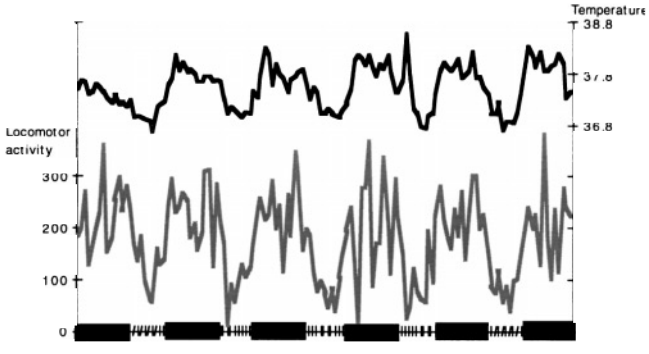

Fig. 3. Normal rhythm in body temperature (°C) and locomotor activity (counts/hour) in CD1 mice (20 g, Charles River, Laboratories). Each point is the mean of 2 observations of 8 conscious mice during 6 days. For the sake of clarity, standard deviations have not been depicted. Dark bars represent light-off period (5:30 p.m.–5:30 a.m.). Light-on 5:30 a.m.–5:30 p.m.

On the other hand, the study of locomotor activity and temperature in gerbils (Fig. 4) and guinea pigs (Fig. 5) demonstrates that any circadian rhythm is obvious. Locomotor activity is highly irregular and sometimes shows large variations. Normal temperatures in guinea pigs are higher and vary between 39°C and 39.8°C, therefore temperature of gerbils are similar to the temperature of rats. These significant variations in temperature and activity, along with the absence of a diurnal cycle in gerbils and guinea pigs, make their biotelemetric studies more difficult to interpret.

Analysis of results

To quantify the biotelemetric changes, as well as the influence of drugs, data continuously generated by a telemetry system capable of reliably collecting and storing vast amounts of data can be compared with different control values [21]:

- *individual* control values (collected at the end of the equilibration phase), each animal serving as its own control;
- *collective* values from a control group of animals subjected to similar experimental conditions. They can also be compared to an 'absolute' control group in order to follow the effect of external phenomena or manipulation stress.
- *initial* values collected just before the stage of pharmacological treatment (at T0) such as a dose-effect study of NSAIDs, or a kinetic study of an antipyretic effect during an induced fever, which assumes that control and experimental values will be obtained in the same experiment.

Basal parameters

The use of telemetry in the pharmacology of inflammation is still not widespread and is not fully understood. Using several examples, we here try to clarify the pathophysiological significance of the parameters of temperature and mobility in experimental arthropathies in rats.

- Temperature can be measured during the nocturnal or the day-time phase, where different regulation pathways interfere; it is interesting that a NSAID such as indomethacin lowers the nocturnal temperature of a normal rat without significantly changing its day-time temperature.

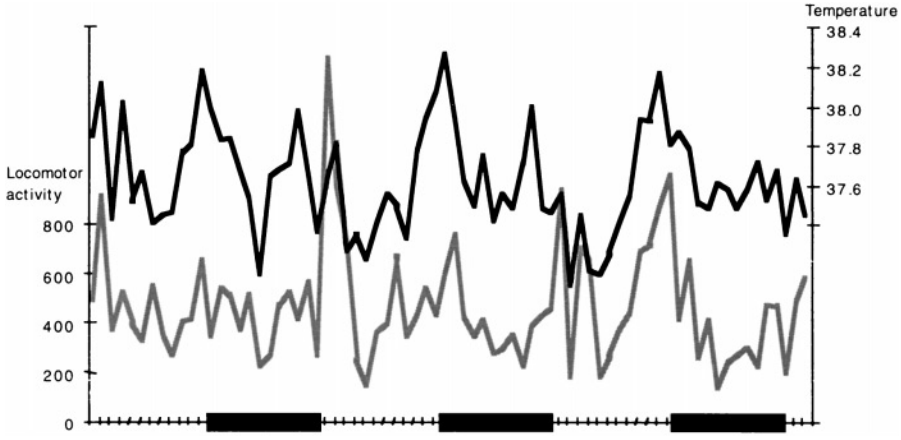

Fig. 4. Normal rhythm in body temperature (°C) and locomotor activity (counts/hours) in gerbils (Rj/MON, 70 g, CERJanvier). Each point is the mean of 10 conscious gerbils during 3 days. For the sake of clarity, standard deviations have not been depicted. Dark bar represents lights off period: 5:30 p.m.–5:30 a.m. Light on 5:30 a.m.–5:30 p.m. No evident circadian rhythm is noticed in gerbils.

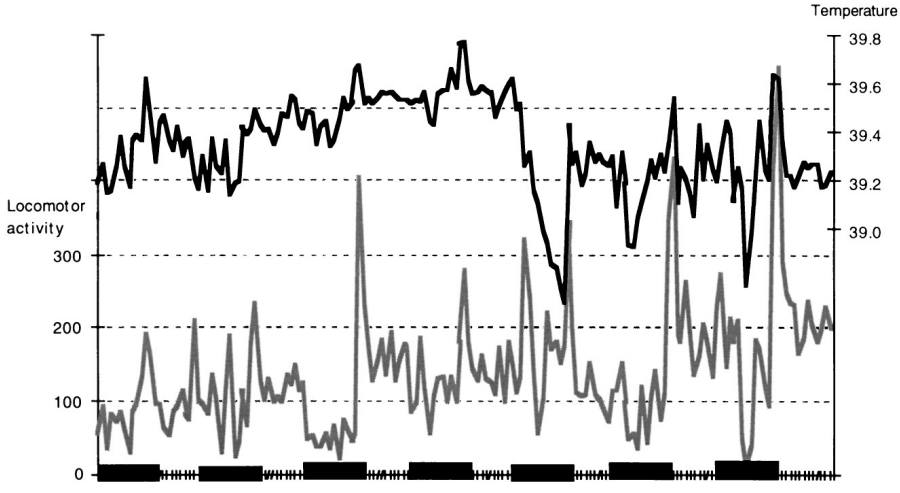

Fig. 5. Normal rhythm in body temperature and locomotor activity in guinea pigs (Hartley, 170 g, Charles River Laboratories). Each point is the mean of 18 conscious guinea pigs during 7 days. For the sake of clarity, standard deviations have not been depicted. Dark bar represents lights off period: 5:30 p.m.–5:30 a.m. Light on 5:30 a.m.–5:30 p.m. Note that guinea pigs' body temperature (39.2 °C) is higher than in rats.

– The nocturnal phase (06:00 h–18:00 h) is to some extent characterized by an increase in the rats' temperature related to an increase in mobility. Hyperthermia accompanied by a decrease of activity signifies that the febrile process reflects a pathological process, probably inflammatory or infectious. Conversely, anaesthesia or a toxic effect (of a drug) can lead to severe hypomobility and hypothermia.

Measurement of mobility, which depends greatly upon joint function, is also affected by many other factors that must be taken into account. Thus, the circadian rhythm of the rat means that its spontaneous nocturnal mobility can be only interpreted in the context of physiological locomotor activity. However, its day-time exploratory activity can be used to evaluate the impact of stress. So, biotelemetric studies are dependent on the time of day when experiments are carried out.

Whichever parameter is chosen – spontaneous or provoked mobility – the locomotor activity of the rat can be influenced by various other factors:

– local, articular, periarticular, neurophysiological, or circulatory changes related, for example, to painful, inflammatory, or degenerative processes;
– a systemic reaction, to some extent related to an inflammatory or dysimmune reaction, provoking sleep or drowsiness, fever, cachexia, or stress, such as the general and central effects of the cytokines involved in the inflammatory process [interleukin 1 (IL-1) [22], tumor necrosis factor (TNF) [23], interleukin 6 (IL-6), interferons, etc.);
– pharmacodynamic effects, whether beneficial or harmful, principal or ancillary, of the drugs used (dose-effect relation), which can ameliorate or aggravate hypomobility. Thus whereas an anti-inflammatory drug can ameliorate hypomobility due to arthritis of the knees, a psychotropic drug can affect locomotor function through its sedative [24] or stimulant properties [25, 26].

Interpretation of the results thus requires that many elements be taken into account, including the following:

– the animal studied and the nature of the model used, as well as the pathological process that the model is intended

to reproduce (inflammation, pain, dysimmunity, degenerative joint disease, etc.);
– the degree of concordance between decreased mobility and hyperthermia.
– the route of administration, whether local, for example, intra-articular (knee, ankle, etc.) or systemic (oral or parenteral); and the nature of the pharmacological agent (whether it is pain-producing or inflammation-producing or both).

Nature of the inflammatory response

The animals' response, whether painful or inflammatory or both, varies distinctly with the phlogistic agent used and the injection site. Thus the effect of carrageenan will depend on the site of injection, intraperitoneal, subcutaneous, or intra-articular. The use of pro-inflammatory mediators such as IL-1 (Fig. 6) or TNF could be more complex to analyze. For example in rats, IL-1 has as many central effects [27, 28] (fever, drowsiness, loss of appetite, etc.) as it has peripheral effects (chemotaxis, inflammation at the injection site, etc.) or mixed effects (induction of PGE2 [29], pain, etc.).

The study of routes of administration shows that intra-articular injection of a low dose of IL-1β provokes hypomobility which reflects more its local articular action (pain and inflammation) than central effects on drowsiness and feeding behaviour. Interestingly, the study of effects of IL-1, continuously administered by intraperitoneal minipump for 7 days, clearly shows that decreased mobility and degenerative effect on articular structures remain, whereas central effects (fever, feeding behaviour) are regulated after 3 days (Fig. 7).

Telemetric measurements of temperature and mobility, whether they are of interest as components of the inflammatory process or as a means of studying drugs, can thus be put into practice under very diverse circumstances, such as the following:

– after injection of a mediator, e.g. a pro-inflammatory cytokine (IL-1α, IL-1β, TNFα);
– after injection of a cytokine inducer: endotoxin, Poly IC, muramyl dipeptide, etc;
– after induction of an acute inflammatory process, either local (carrageenan- or zymosan-induced edema) or systemic (by the use of brewer's yeast) and even chronic (Freund's complete adjuvant, subcutaneous or intra-articular).

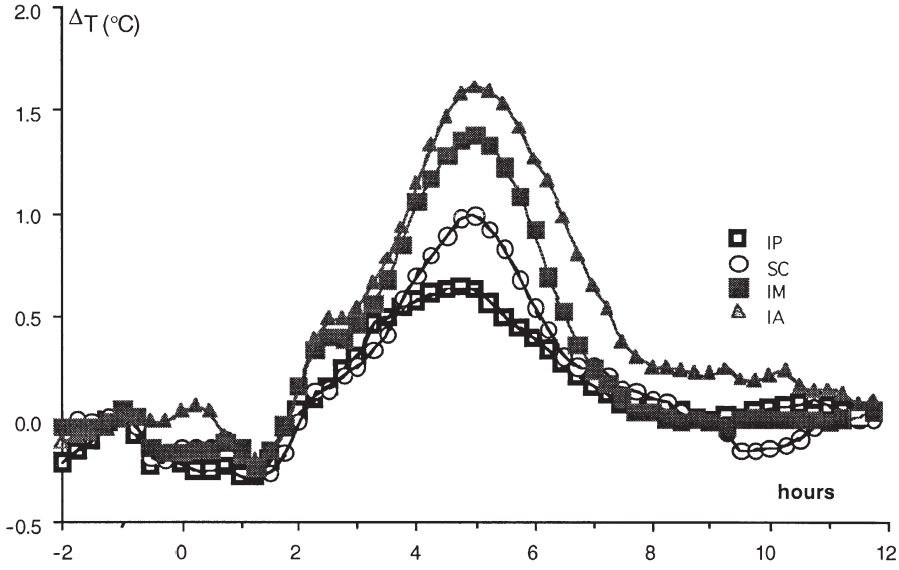

Fig. 6. Kinetic profile of febrile response (nocturnal temperature) after parenteral injections of 500 ng of human recombinant IL-1β (IP, intraperitoneal; SC, subcutaneous, IM, intramuscular; IA, intra-articular). Values (n = 6 rats/group) are recorded each 15′ and expressed as differences in body temperature just before the experiment began (personal communication).

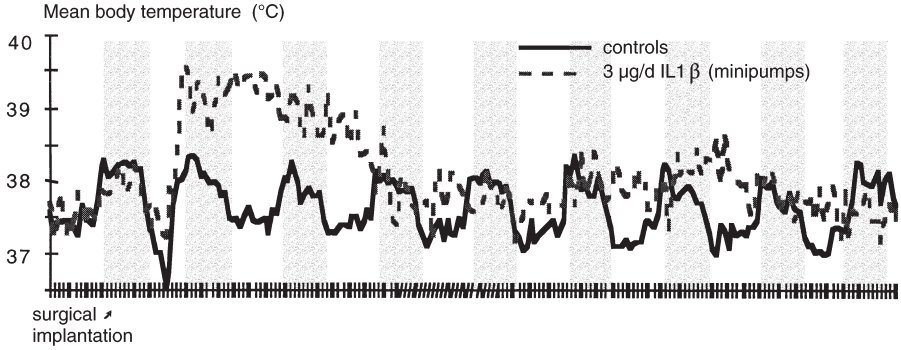

Fig. 7. Effects of continuous administration over 8 days of human recombinant Interleukin-1β (3.0 µg/day by Alzet's osmotic minipumps) on body temperature. Grey and white bands represent respectively lights-off and lights-on period. Data are means (n = 4 in two groups). A downregulation of fever is present 3 days after IL-1β perfusion. (*Inflammation Research 1995; 44: S256*).

Telemetry and experimental models of inflammation

In the pharmacology of inflammation, in vivo experimentation can help to achieve extremely diverse goals: analysis of the various phases of a model, or verification of mediator effects (e.g. IL-1) or of antagonistic effects [30] with respect to a target and the antagonist's efficacy, or drug effects in a given experimental model. In each case, telemetry provides pertinent information, while permitting at the same time the use of traditional parameters (edema, body weight, arthritic score, etc). This is particularly useful for the study of mediators or the effects of anti-inflammatory drugs (in terms of kinetics and potency), in the classic models such as carrageenan or zymosan-induced edema, hyperthermia induced by brewer's yeast or turpentine, and experimental arthritides like adjuvant or type II collagen induced arthritides among others.

Models of hyperthermia

The use of telemetry in experimental thermoregulation can help to clarify the mechanisms of the febrile reaction, as well as the mediators involved [31], by verification of the effects of various antagonists [32] or of endogenous feedback [33, 34]. Thus a drug's kinetics, duration of effect, maximum effect, area under the (effects) curve, and dose-effect relations can all be evaluated. This makes it possible to analyse the animals' response both to the particular action of an agent and as a function of the site of injection, without handling the animals [35], which is not the case for example of measuring repeated colonic temperature [36]. A febrile reaction induced in the rat by subcutaneous injection of brewer's yeast is one of the most widely used models: this model makes it possible to study the effects of increasing doses of NSAIDs, which increases the C_{max} in a dose-dependent fashion and with longer and longer duration of effect. The injection of turpentine oil into rodents, as well as LPS [37, 38], provokes high fever, possibly in relation to its potent induction of IL-6, this effect possibly being modulated by endogenous glucocorticoids [39].

Models of inflammation

The use of numerous in vivo models is required to demonstrate the anti-inflammatory properties of antirheumatic drugs, particularly if the action on a precise target is to be verified. Thus for example, in a model of inflammation induced by IL-1, the drug effect can be verified in that model, as its predictive value regarding a particular disease process has previously been established, e.g. carrageenan-induced edema and adjuvant-induced arthritis, etc.

During carrageenan edema [40], it is easy to detect the influence of a NSAID on phlogistic response and simultaneously on fever, both being prostaglandin-dependent parameters. On the other hand, study of the arthritic score in adjuvant-induced polyarthritis allows identification of a primary phase, corresponding to the acute inflammatory phase, which can be crudely distinguished from an immunological phase, considered to be secondary. Telemetric monitoring of the rodents for 30 days leads to improved definition of the different phases of the arthritic process [41]. Inspection of the temperature and mobility curves reveals 4 phases (Fig. 8), with quite distinct characteristics of fever and handicap: the local acute inflammatory

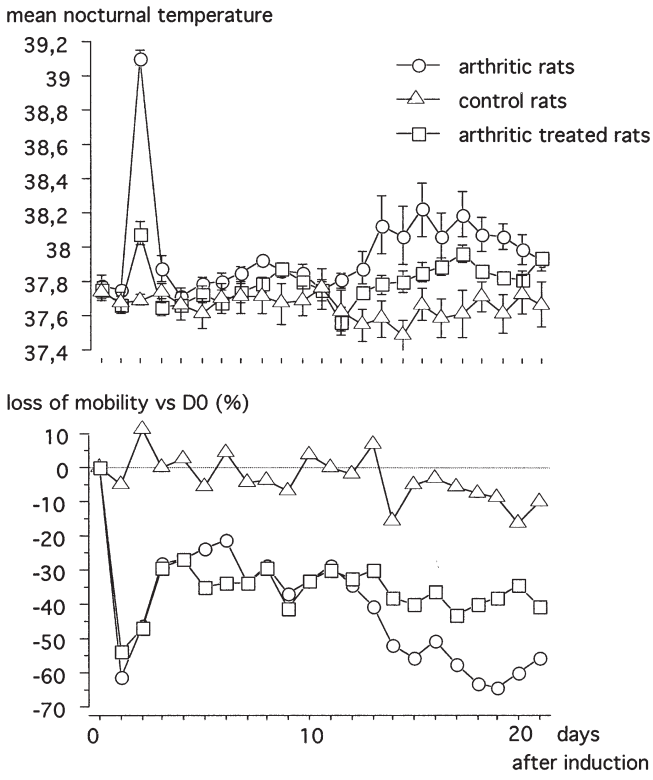

Fig. 8. Variation of nocturnal body temperature and locomotor activity during adjuvant arthritis in Lewis rats; data are means ± SE (n = 6). Note the biphasic response of both parameters and the benefical effect ($p < 0.05$, ANOVA) of nimesulide (5 mg/k/day given orally from D0 to D21).

response (day 1 to day 3), the silent phase (day 4 to day 9), the systemic immunological phase (day 10 to day 13) and the established arthritic phase (day 14 to day 28). In this way, telemetry can distinguish the effects of drugs and other factors on these phases, other issues such as drug dosage, mode of delivery and timing of administration, and whether the drug has preventive or curative properties, either on febrile response or loss of mobility can be evaluated.

Telemetry also makes it possible to use experimental models of inflammation other than the classic ones – for example, models in which inflammation is induced in the joint itself (e.g. IL-1, carrageenan, zymosan, turpentine), with obvious physiopathological significance for inflammatory or even degenerative arthritides. The contribution of telemetry in this circumstance is all the greater if the usual parameters in these models are limited to measurements of knee edema, which do not provide much information about the various phenomena involved.

NSAIDs and paracetamol, both powerful antipyretics, are known to have very different anti-inflammatory properties and telemetry clearly confirms this difference. After injection of IL-1 in rats, NSAIDs (such as ketoprofen) diminish both IL-1-dependent locomotor handicap and IL-1 induced fever, and the effects are dose-dependent. In contrast, paracetamol exerts mainly antipyretic properties. This drug exerts only a modest effect on the handicap, and only at the highest subtoxic dose (300 mg/kg/d given orally) – so high as to be useless in predicting the actual benefits of using paracetamol as an anti-inflammatory drug.

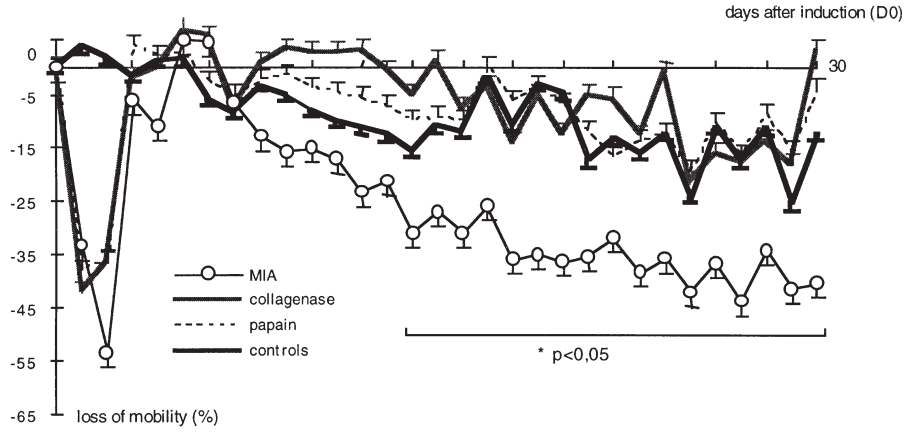

Fig. 9. Effects of intra-articular injection (day 0) in both knees of monoiodoacetate (MIA 0.3 mg/50 µl), collagenase (3 mg/50 µl) and papain (1 mg/50 µl) versus saline (controls; 50 µl) on spontaneous nocturnal activity in normal Wistar rats. Data are means ± SEM (n = 12 in each group). Statistical significance of differences from the control group as determined by ANOVA comparisons; * $p < 0.05$. Note that no febrile response was detected throughout the experiment.

Model of osteoarthritis

Osteoarthritis (OA) is a degenerative joint disease in which the articular cartilage is progressively remodelled (narrowing of the joint space, subchondral cysts) and affected joints undergo cicatricial remodelling (condensation of subchondral bone and osteophytosis). In humans, OA comprises an initial, silent phase, followed by a symptomatic phase that proceeds to handicap and pain. Telemetry is also very powerful in experimental models of OA, particularly for identifying the chronology of the appearance of such handicap.

Among the various experimental models of OA applicable to rats, it is well established that injection of iodoacetate into rats' knees provokes a rapid joint disease with many histological and biochemical similarities to OA [42]. Biotelemetric study of the animals (Fig. 9) shows a transitory primary loss of mobility related to the pain secondary to intra-articular injection, followed by a gradually appearing handicap that mimics osteoarthritic joint disease (pain and loss of function) [43]. This process is purely degenerative, because no hyperthermia appears during the OA course, suggesting an absence of local or systemic inflammatory reaction. Other models, like papain-, or collagenase-induced OA in rats (Fig. 9), as well as anterior cruciate ligament section do not provoke a similar secondary loss of mobility under our experimental conditions.

Model of ischemia reperfusion

In the model in which the rat's hind paw undergoes local hypoxia and is then reperfused, many mediators can be generated, such as free radicals, cytokines, nitric oxide and adhesion molecule receptors [44]. The model can be produced by applying a tourniquet to the knee or the ankle and releasing it after 1 to 3 h. A telemetric study of the animals during the ischemic and reperfusion phases reveals an initial stress-induced hyperthermia and transitory hypermobility (inherent to pain), followed by a hypoactive phase, the degree of which is relative to the duration of the hypoxia. Study of analgesic or anti-inflammatory drugs under these conditions may provide substantial evidence about their therapeutic potential.

Conclusion

The use of telemetry in a configuration adapted to experimental models can provide the basis for progress in the study of experimental inflammation, particularly joint inflammation, adding to the available knowledge about anti-inflammatory drugs and new molecules with new pharmacological targets. Biotelemetry will make finer monitoring of the pathophysiological mechanisms that contribute to the inflammatory and degenerative reactions, e.g. with knock-out models in mice [45] or transgenic animals, providing continuous data about both central and peripheral functions. Studies of animal locomotion [46] will also greatly contribute to classical pharmacology [47] and toxicology [48], and is a unique tool in assessing experimental models of articular pain (inflammatory and/or degenerative), as well as neurological diseases, such as experimental auto-immune encephalomyelitis (in which telemetry detects transient acute hypomobilities and remnant phenomena) in a more comprehensive and seemingly clinical relevant way.

Implantable telemetry compared to the conventional methods, has a number of advantages such as elimination of stress from tethers, handling, restraint and human contact, as well as elimination of the influence of disturbed emotional state and sleep. Furthermore, maintenance is not recquired once telemetry devices are implanted. The method allows for automated continuous monitoring for days, weeks, or months. Measurements are free from the effect of anesthesia and data obtained by telemetry do not contain 'cable' or 'commutator' artifacts common in tether systems.

Our studies revealed that rats and mice are the most useful for biotelemetric monitoring especially due to their regular circadian rhythm. Furthermore, biotelemetry enhances the value of in vivo experimentation by allowing minimal constraints of the animals being studied and more ethical and rational use of the animals studied. Finally, the technique has rich potential, as regards both the technology itself and the experimental model in which it is used, permitting new pharmacological and pathophysiological concepts to be addressed and explored.

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