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Temperature and neuronal circuit function: compensation, tuning and tolerance

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Temperature has widespread and diverse effects on different subcellular components of neuronal circuits making it difficult to predict precisely the overall influence on output. Increases in temperature generally increase the output rate in either an exponential or a linear manner. Circuits with a slow output tend to respond exponentially with relatively high Q_{10}s, whereas those with faster outputs tend to respond in a linear fashion with relatively low temperature coefficients. Different attributes of the circuit output can be compensated by virtue of opposing processes with similar temperature coefficients. At the extremes of the temperature range, differences in the temperature coefficients of circuit mechanisms cannot be compensated and the circuit fails, often with a reversible loss of ion homeostasis. Prior experience of temperature extremes activates conserved processes of phenotypic plasticity that tune neuronal circuits to be better able to withstand the effects of temperature and to recover more rapidly from failure.

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The pervasive and fundamental role of temperature in determining organismal physiology via thermodynamic effects is well-recognized and fully described in numerous texts [1–3]. In general, increases in temperature will increase the rates of biochemical processes in ways that can be characterized by the Arrhenius equation and expressed as Q_{10}: the factor by which rates change with a 10 °C increase in temperature (although the use of Q_{10} implies an exponential relationship with temperature, in the neurobiological literature it is often used loosely to describe linear and undefined relationships [4]). In addition, the thermal extremes that limit the viability of different organisms are set, not by membrane collapse, protein denaturation or cell death, but by the inability of nervous systems to control homeostatic mechanisms or generate adaptive behaviours [5–7]. Our discussion will focus mainly on neuronal circuits in poikilotherms both because these organisms typically have lent themselves to detailed intracellular analysis using semi-intact preparations and because their nervous systems are more frequently exposed to large changes in temperature. However, in spite of elaborate mechanisms to regulate body temperature in mammals, their central nervous systems cannot escape temperature variation, usually in a pathological context [8]. There is no reason to suppose that the basic processes of thermosensitivity in neuronal circuits are not equally relevant in human brains or mammalian models.

Whereas it is accepted that the CNS is the living tissue most vulnerable to variation in temperature owing to its complexity and that failure of synaptic function is probably the primary determinant of death at low and high temperatures [2,9], our understanding of the impact of temperature on the operation of neuronal circuits remains limited. It is the complexity of the multiple interdependent mechanisms controlling circuit function that hampers a more complete understanding. Nonetheless, accepting that the idiosyncratic nature of different circuits in diverse organisms will result in idiosyncratic effects of temperature, some general principles are emerging. This review is concerned with general effects of temperature on the operation of neuronal networks, not thermosensation. We note, however, the rich recent literature on the cellular and molecular mechanisms of thermotaxis in two model organisms, the fly and the worm [10••,11–13], and the properties and functional roles of thermosensitive transient receptor potential (TRP) channels [14,15,16•].

Many neuronal mechanisms underlying the central generation of motor patterns underlying behaviour are known in detail. Some general themes provide important context for our consideration of how CPGs are affected by temperature: (1) Whether the circuit is dominated by pacemakers or by network properties, the mechanisms rely on the precisely timed opening and closing of a large variety of different ion channels [17–21]. (2) Functionally appropriate output is generated by circuits with considerable variability in the strength of specific conductances and connections, indicating tolerance to such variability via compensatory mechanisms [22,23•,24,25•]. (3) Glial cells are recognized as contributing to pattern generation by controlling the extracellular microenvironment

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[19,26,27]. In addition, the fact that temperature has profound effects on neuronal processes means that temperature manipulation continues to be a useful tool for dissecting neuronal control systems. Recent technical developments allow localized brain cooling to inactivate regions [28] or to determine the location of areas responsible for temporal dynamics, for example in the vocal pattern generator of *Xenopus* [29] and in the songbird motor pathway [30,31,32•]. A more precise tool capitalizes on the temperature-sensitivity (TS) of proteins in genetic models, particularly *Drosophila*. Numerous TS paralytic mutants have been identified in forward genetic screens and they generally affect the proteins of ion channels or those involved in synaptic transmission [33]. The most productive of these to date has been the gene for a TS dynamin, *shibire^{ts1}*, which is involved in presynaptic vesicle recycling and causes rapid and reversible block of synaptic transmission at restrictive temperatures (>29 °C) [34,35]. Genetic manipulation using *shibire^{ts1}* in combination with the GAL4/UAS procedure for tissue-specific expression [36] permits reversible block of synaptic transmission in a temporally and spatially restricted manner. This has allowed the identification of neurons in the network regulating courtship initiation in *Drosophila* [37] and, by targeting sensory neurons, the demonstration that motor patterns for larval locomotion are centrally generated [38].

Rate effects

The most striking effect of temperature on the operation of neuronal circuits is the rate increase. Though the neural underpinnings were completely unknown, the consistency of such effects were recognized in the late 19th century when it was suggested that the frequency of cricket chirps could be used as a thermometer [39]. Interestingly, in this brief note Amos Dolbear also suggested that the low temperature limit of 40 chirps/min at 50 °F (10 °C) is set to conserve energy in the cold, that is, that the limit was determined by processes other than the thermosensitivity of the stridulatory mechanism.

Thermodynamic effects on chemical reactions predict an exponential relationship between temperature and the rates of neural processes that can be defined by the Q_{10} and that are well understood [4,40]. However, at the level of the output of neuronal circuits, that is, motor patterns or movements, the temperature relationships can be linear or exponential. In a variety of poikilotherms, linear models gave best fits to temperature relationships and were better predictors for rates in different temperature ranges [41]. It is also a common observation that Q_{10}s tend to be low at higher temperatures [4] suggesting biophysical limits to exponential relationships.

Electrocommunication in electric fish is temperature-sensitive [42,43,44] and the system in *Apternotus leptorhynchus* allows a comparison of linear and exponential temperature relationships in related neuronal circuits. One circuit generates a fast rhythm via electrical synapses (the EOD, electric organ discharge, 500–1000 Hz) and the other generates a slow rhythm via chemical synapses (chirping, a modulation of the EOD, 3-100 chirps/min) [42]. In this case the fast rhythm has a linear relationship with temperature (equivalent Q_{10} = 1.6) whereas the slow rhythm has an exponential relationship (Q_{10} = 3.2) and the difference is ascribed to the different temperature sensitivities of electrical and chemical synapses. A limited survey of mostly recent articles containing information on temperature effects on output rates of rhythmical pattern generators suggests that the nature of the relationship (non-linear or linear) is correlated with the repetition rate of the circuit output (Table 1). Slow rhythms generally have high Q_{10}s and non-linear relationships whereas fast rhythms tend to have low Q_{10}s and linear relationships. Clearly this observation has to be interpreted cautiously because the survey is neither exhaustive nor sophisticated, particularly with respect to judging goodness of fit. In addition, for circuits monitored by examination of behaviour the performance may be limited by the properties of the effectors, usually muscle, rather than the neuronal circuits. In order to power movements above a repetition frequency of around 50 Hz, muscles require special properties such as in asynchronous muscle in many insects [45] and in superfast muscle in acoustic signalling animals [46,47]. Muscle properties (including temperature sensitivities) can thus set maximal repetition rates [48•] and the properties of neuronal circuits will be matched to the constraints of their effectors. Nevertheless there is no obvious correlation of the type of temperature relationship with temperature range or with neural complexity, whereas there is an apparent correlation with base output rate.

The correlation noted in Table 1 might be plausibly explained as follows. At low output rates there is scope for temperature to increase rate in an exponential fashion by speeding activation and inactivation of ion conductances, which are dependent on protein conformational changes: exponential relationship with a Q_{10} of ~3. At high output rates the relationship resembles that for the effect of temperature on electrical conductivity of electrolytes: linear and with a temperature coefficient that converts to a Q_{10} of 1.3 [49], similar to the Q_{10}s of 1.3 and 1.4 for axoplasmic conductance and maximum ion conductance used in the Hodgkin–Huxley formulation [4]. This implies that as output rate increases it becomes limited by circuit constraints other than chemical reaction rate. This remains to be determined but could possibly reflect a requirement for a minimum spiking activity (intraburst frequency or burst length) to effect the transitions between successive phases of the output. The interaction of Q_{10} effects with limits imposed by system structure is nicely demonstrated in a model of neuromuscular modulation in *Aplysia* in which a non-linear dose–response

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Table 1

Characteristics of the response to temperature change of neuronal circuits in a wide variety of different organisms

Neuronal circuit	Base frequency (Hz)	Q_{10}	Range (°C)	Relationship	Reference
Tritonia swimming	0.1	3	6–20	Non-linear	[51]
Mouse respiration	0.28	3.7	30–40	Non-linear	[107]
Drosophila larval crawling	0.5	3.3	20–35	Non-linear	[52]
Frog call	0.76	2.2	18–26	Linear?	[108]
Crab pyloric	1	2.3	5–25	Non-linear	[54••]
Locust ventilation	1	2.3	21–35	Non-linear	[53,64]
Apteronotus chirp rate	3	3	18–32	Non-linear	[42]
Lizard sand-swimming	5	1.84	22–40	Linear	[109]
Tadpole swimming	10	1.5	18–32	Linear	[110]
Locust flight	12	1.15	20–45	Linear	[56,111]
Frog trill	30/70	1.7/1.5	18–26	Linear	[29]
Copepod escape	40	1.6	4–15	Non-linear?	[112]
Fish humming	100	1.5	15–25	Linear	[113]
Apteronotus EOD	650	1.63	18–32	Linear	[42]

There is a tendency for pattern generators with a low output frequency to have high Q_{10}s and non-linear relationships with temperature. Also, the locust deafferented flight CPG (in red) stands out as being remarkably temperature compensated. Some values were estimated and/or recalculated from the data provided in the references. Unlike a previous analysis [41], characterization of relationships as non-linear or linear is based on the original authors' preferences or the current authors' examination of the data and there has been no attempt to assess goodness of fit. The temperature relationship for frog calls is indicated as linear because the article presented linear regressions, however the individual data points underlying the regressions were not given. The temperature relationship for copepod escape is indicated as non-linear because the authors fitted the data with a non-linear function, however the data were relatively few and scattered and could have been fitted with a linear regression.

curve provides a level of temperature compensation; that is, the effect of a neuromodulator is initially relatively insensitive to the exponential drop in neuromodulator concentration caused by a temperature increase [50].

Temperature compensation

In the patterned output of a neuronal circuit, whether this is rhythmical or not, there are transitions between distinct phases of activity. For the output to remain effective as temperature increases, appropriate phase relationships within the pattern must be maintained in spite of overall rate increases. Arguably it is not surprising that this occurs because the processes that effect phase transitions will be affected in parallel by temperature; it is controlled phase transition that generates the pattern. For example, temperature-compensated phase (or duty cycle of a single phase) with variable output rate is evident for the CPGs of *Tritonia* swimming [51], *Drosophila* larval crawling [52] (see, e.g. Figure 2a, b, c), locust ventilation [53] and the crab pyloric rhythm [54••]. The last example deserves special mention because of the remarkable precision with which phase is temperature-compensated during a 4-fold increase in output frequency (Figure 1a). It is also notable because it is described in the pre-eminent model CPG that permits detailed electrophysiological and computational analyses of the mechanisms involved. The timing of LP onset phase is determined predominantly by two currents that oppose each other, I_A and I_h (Figure 1b), and temperature compensation arises when opposing processes have similar Q_{10}s. The computational analyses demonstrate nicely that the measured Q_{10}s of I_A and I_h are appropriate for this and reinforce the notion that despite considerable variability in system parameters they are matched to allow normal function and precise compensatory reactions to environmental perturbations [23•].

Temperature compensation of overall rate is a rarer phenomenon and possibly more difficult to achieve for neuronal circuits. The general mechanism for temperature compensation of rate in biochemical networks is similar to the one described above for phase: automatic compensation via opposing reactions with equivalent temperature sensitivities [55]. Table 1 suggests that there is little temperature compensation of rate for those CPG circuits with low base frequencies. If we accept that there is some property of neuronal circuits, based on their fundamental nature, which is rate-limiting in spite of Q_{10} effects on chemical reactions, for example [50], then the linear temperature relationships of circuits with high base frequencies also show little temperature compensation. The alternative explanation would be that rapid output is temperature-compensated, independently of the nature of the output or the complexity of the nervous system. The exception in this list is the flight CPG of the migratory locust (*L. migratoria*) with a Q_{10} of 1.15, which becomes even more insensitive to temperature changes after prior heat exposure [56]. Flight performance of the desert locust (*S. gregaria*) was originally described as being perfectly temperature-compensated [57] and the wing-stroke frequency of dragonflies and other insects with synchronous flight muscles also have distinctly low Q_{10}s [58] suggesting that the strict aerodynamic requirements of flapping flight require a high degree of temperature compensation in the neuronal control circuits. Temperature compensation in the flight CPG has been attributed to the inhibitory effects of membrane hyperpolarization and reduced input resistance opposing the excitatory

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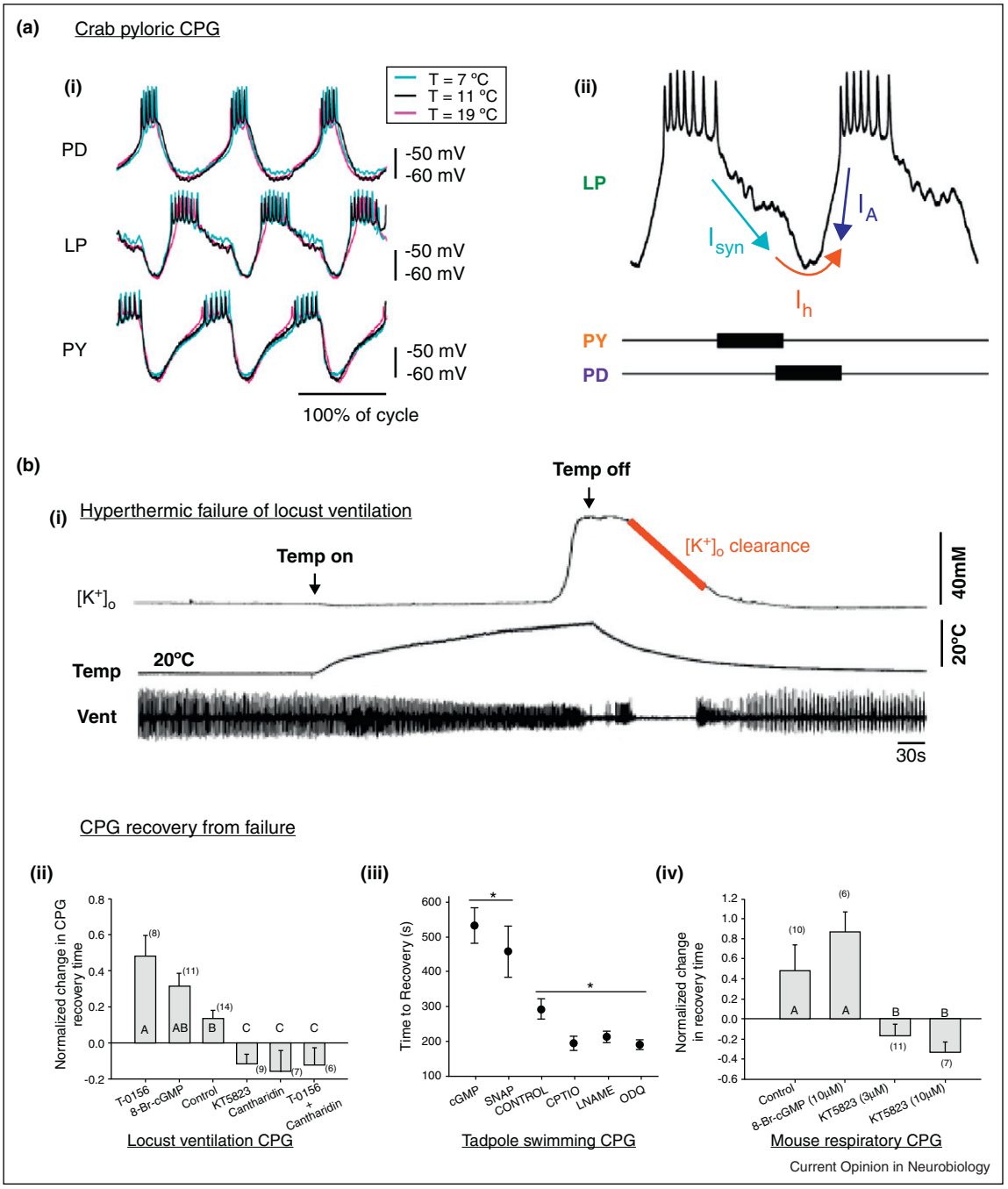
Figure 1



Temperature effects on central pattern generators. **(a)** Precise temperature compensation of phase: **(i)** Superimposed intracellular recordings of neuronal activity during motor pattern generation of the pyloric motor pattern of the crab, *Cancer borealis*, at three different temperatures. The time scales of the recordings have been manipulated to normalize cycle period (approximately 1.3 s at 7 °C, 0.8 s at 11 °C, 0.4 s at 19 °C). The precise matching of burst onset and offset in successive cycles of overlaid traces indicates accurate temperature compensation of phase in spite of the >3 fold increase in network frequency. **(ii)** Diagram illustrating the currents (I_{syn}, I_h, I_A) contributing to setting phase in the LP neurons. The effects of increasing temperature to increase the rates of opposing forces will tend to balance each other out and compensation will be optimized when the temperature coefficients of all the currents controlling phase are close in value. Panels **a** and **b** adapted from [54••]. **(b)** Motor pattern arrest owing to failure of ion homeostasis can be modulated by pretreatments in diverse organisms: **(i)** Extracellular recordings of ventilator motor activity (Vent) in the locust, *Locusta migratoria*, during an increasing temperature ramp (Temp). Note that individual bursts of ventilator muscle activity are difficult to discern owing to compression of the time base. Arrest of motor patterning with hyperthermia is associated with an abrupt surge in extracellular potassium concentration ($[K^+]_o$) indicating a failure of ion homeostasis. On return to room temperature motor pattern recovery is associated with a return to normal $[K^+]_o$ and the time to recover is determined by the rate of $[K^+]_o$ clearance. **(ii)** Normalized change in the time to recover ventilator motor

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effects of increased conduction velocity and decreased membrane time constant [59,60] with the amplitude of postsynaptic potentials having no influence [61], though confirmation of these ideas via modelling has not been undertaken.

Tuning

Neuronal circuits have high and low temperature limits for successful operation. The fact that these limits, particularly the upper limit, are not near the physical limits imposed by protein stability and function [62,63•] suggests that failure results from a mismatch in the temperature sensitivities of important components. This is borne out by the modelling analysis of the crab pyloric system in which 40% of 1027 computational models with varying maximal conductances were unable to operate throughout the test temperature range, and independently varying the Q_{10}s of just two parameters (I_A and I_h) perturbed phasing of the pattern [54••]. Hyperthermic failure has been investigated in the locust CNS using the ventilatory CPG as a monitor of neuronal circuit operation [53,64–66]. A critical feature is a dramatic, but reversible, loss of ion homeostasis manifest by a surge in extracellular potassium concentration, $[K^+]_o$ (Figure 1c), at the point of neuronal circuit failure (insect [66]; mammal [67]). This is also evident during failure induced by other means [66], including hypothermia [68•]. The working model to explain this event centres on ionic balance in the relatively small volume of the extracellular space [69]. Any mismatch between rates of ionic disturbance, for example by the increased activity during hyperthermia, that is not matched by an increased rate of ionic clearance mechanisms will eventually cause a generalized depolarization that triggers a positive feedback cycle leading to depression of electrical activity that spreads throughout the neuropile. Thus, during a functional range of temperatures the Q_{10}s of neuronal processes leading to ion disturbance and ion homeostasis are approximately matched, however, at the limits, ion homeostatic mechanisms cannot keep up and the result is a rapid and widespread depolarization and failure. In the case of hyperthermia, increasing temperature past this point evokes a larger and irreversible ionic disturbance suggestive of membrane collapse [66]. Not surprisingly, if the hyperthermia is localized, the disturbance of the extracellular environment blocks conduction in axons of passage [70] reinforcing the notion that consideration of glia and the control of extracellular ionic concentrations is increasingly important in understanding the operation of neuronal circuits [19,27].

An interesting recent observation is that the hyperthermic limit of neuronal circuits can be modulated by the NO/cGMP/PKG second messenger pathway. The first demonstration of this was with *Drosophila* having allelic variation at the *foraging* gene, which encodes a cGMP-dependent protein kinase (PKG) and which is associated with reduced K^+ currents in neurons [71,72]. Also, pharmacological manipulation of PKG levels modulates the hyperthermic failure temperature for neuromuscular transmission in flies and the ventilatory CPG in locusts. In locusts, hyperthermia increases NO production in the thoracic ganglia and manipulating the NO/cGMP/PKG pathway at different levels modulates the duration of circuit failure caused by an experimentally induced loss of ion homeostasis (Figure 1d; [69]). Recovery from hyperthermia can be similarly manipulated for the tadpole swimming CPG (Figure 1e; [73]) and the respiratory CPG in the neonatal mouse brainstem (Figure 1f; [74•]) suggesting an evolutionarily conserved mechanism. Under control conditions there is a tone of activity in the pathway allowing the hyperthermic limit to be increased or decreased, indicating that properties of the neuronal circuits can be tuned via this pathway to be appropriate for varying environmental conditions. The fact that the operation of the locust ventilatory CPG and its sensitivity to perturbations of ion homeostasis can be modulated via the AMP-activated protein kinase (AMPK) pathway [75••], which responds to energetic status, takes us back to Amos Dolbear [39] and the idea that the effects of temperature on a neuronal circuit can be determined by mechanisms other than simple tolerance to temperature.

Phenotypic plasticity and thermotolerance

It has long been known that organismal performance and neuronal properties can be acclimated by prior exposure to different temperatures [76] and the modification of synaptosomal membranes in a relatively slow process of homeoviscous adaptation remains an excellent example of this [77]. Upregulation of chaperone proteins during the heat shock response is also well established as a neural protective mechanism [78]. In particular, induced HSP70 is located at synapses in the mammalian brain after hyperthermia [79] where it has several protective roles

(Figure 1 Legend Continued) patterns after KCl-induced $[K^+]_o$ surges used as a proxy for hyperthermia-induced surges measured before and after treatment with: T-0156 (phosphodiesterase inhibitor) or 8-Br-cGMP (phosphodiesterase resistant analog of cGMP) to increase levels of cGMP and PKG; and KT5823 (PKG inhibitor) or Cantharadin (protein phosphatase 2A inhibitor) to decrease effects of PKG. Combining T-0156 and Cantharadin shows that PP2A is downstream of cGMP. **(iii)** Time to recover swimming motor patterns generated by the spinal cord of *Xenopus* tadpoles in control preparations and after treatment with cGMP or SNAP (NO donor) to activate the NO/cGMP pathway; and CPTIO (NO scavenger) or LNAME (NO synthase inhibitor) or ODQ (guanylyl cyclase inhibitor) to inhibit the NO/cGMP pathway. **(iv)** Time to recover respiratory motor patterns generated in brainstem slices of neonatal mice in control preparations and after activating PKG with 8-Br-cGMP or inhibiting PKG with two concentrations of KT5823. Note that in all three cases activation of the NO/cGMP/PKG signalling pathway slowed recovery whereas inhibition of the pathway speeded recovery. In phylogenetically distant organisms acute manipulation of an evolutionarily conserved signalling pathway tunes the temperature sensitivity of central pattern generators illustrated here using the time to recover from motor pattern failure as a measure. Panels **ii**–**iv** adapted with permission from [66,69,73,74•].

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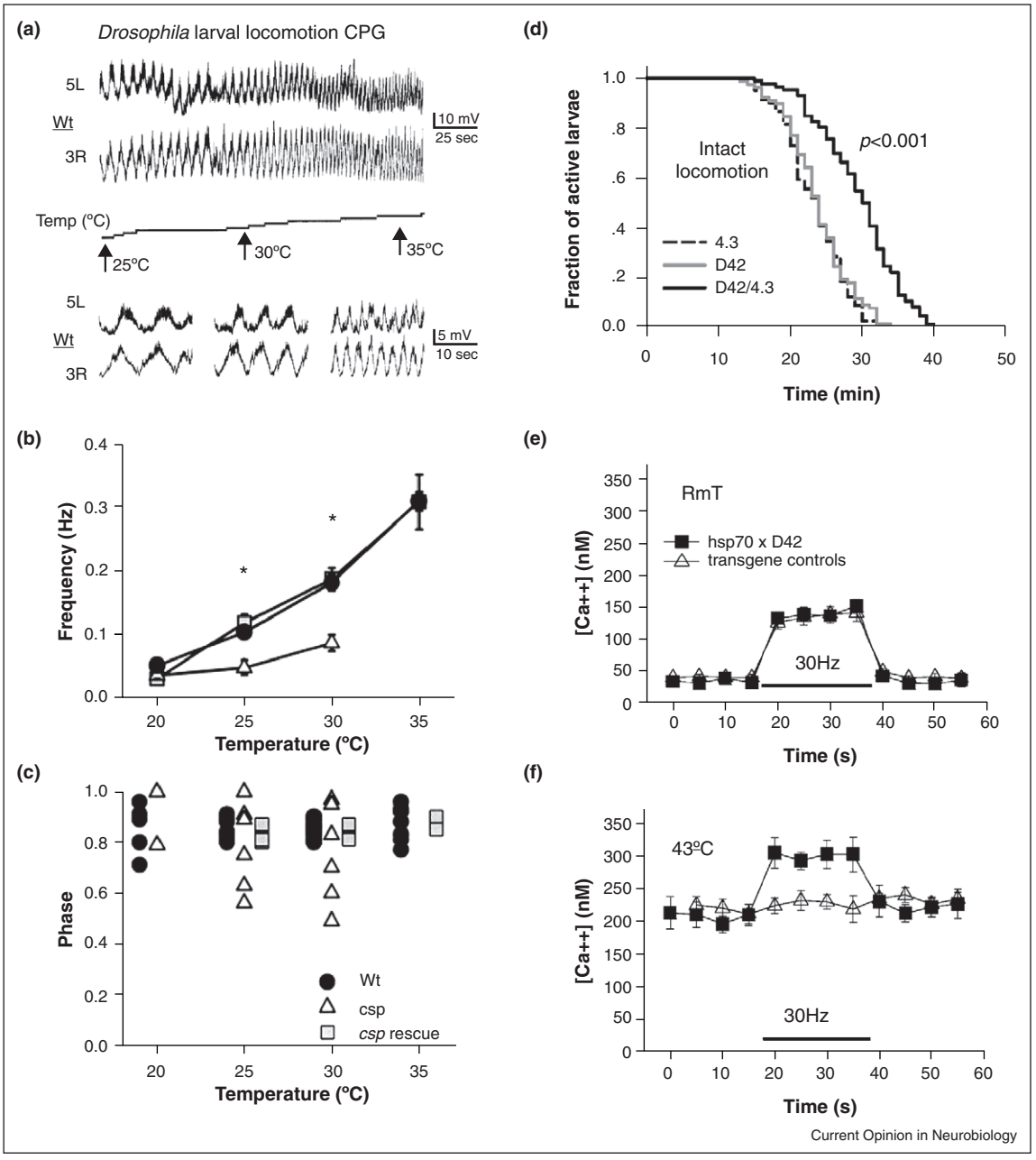
Figure 2



Temperature sensitivity of pattern generation and synaptic physiology in a genetic model organism. **(a)** The CPG for larval locomotion recorded in a dissected preparation of *Drosophila melanogaster* is temperature-sensitive. Recordings from different segments on either side of the preparation (5th segment on the right and 3rd on the left) indicate that patterning is conserved at different temperatures. **(b and c)** The frequency of motor patterning has a Q_{10} around 3 whereas the phase relationship of activity in different segments is temperature-compensated in wild type (Wt). Compared with Wt, mutants for cysteine string protein (*csp*: a synaptic protein that can interact with HSP70) have a disturbed temperature sensitivity phenotype, with respect to frequency and phase, that can be genetically rescued (*csp* rescue). **(d)** Transgenic expression of HSP70 in motoneurons using the GAL4/UAS tissue-specific gene targeting system increases the length of time that intact larvae are able to locomote in a hyperthermic environment (40 °C; 4.3 – UAS-HSP70 control, D42 – GAL4 specific for motoneurons control, D42/4.3 experimental line with increased expression of HSP70 targeted to motoneurons). **(e and f)** Temperature sensitivity of a model synapse (the larval neuromuscular junction) is associated with disturbance of calcium handling in the presynaptic bouton. Ca^{2+}-sensitive imaging indicates that $[Ca^{2+}]$ in the presynaptic bouton increases with increasing temperature and above 200 nM the ability to increase in response to 30 Hz stimulation is impaired. Calcium dynamics at high temperature is maintained with presynaptic targeting of HSP70 (hsp70 × D42) compared with transgene controls. Figure adapted with permission from [52,91–93].

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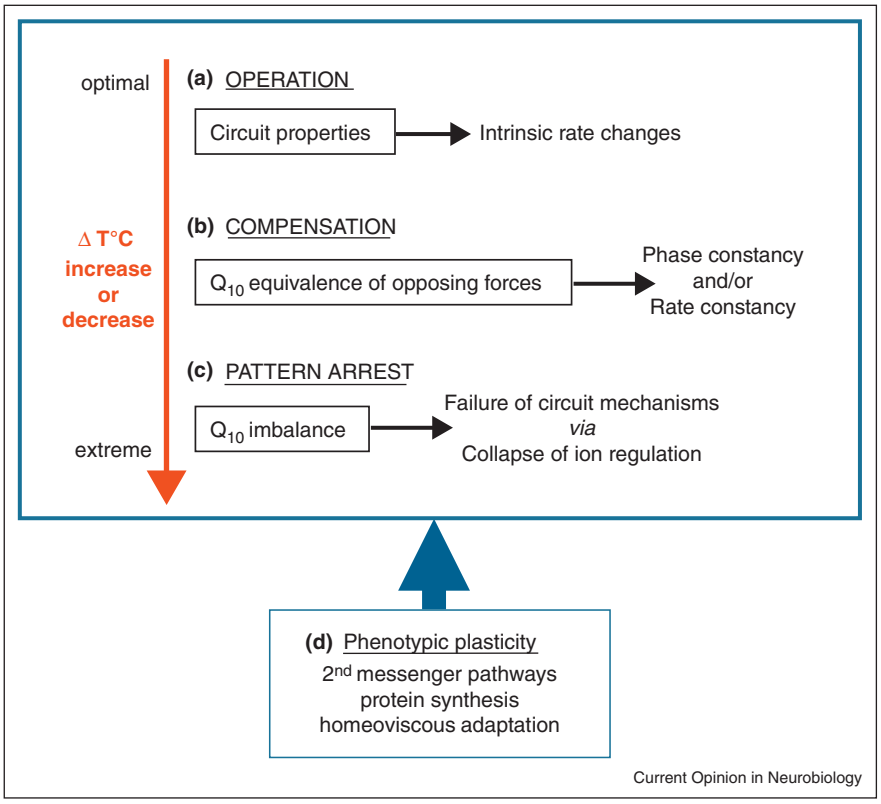
[80,81]. Although the ventilatory CPG in locusts can be protected by prior heat shock [66], which also has effects on the temperature sensitivity of K^+ conductances [82], action potentials [83,84], and synaptic potentials [85,86], there does not seem to be a role for HSP70 because its upregulation after heat pretreatments is undetectable in thoracic ganglia [87•]. Current evidence points to a heat shock-induced increase in the activity of the Na^+/K^+-ATPase as a means of maintaining ion homeostasis during hyperthermia in this system [66], mediated by octopamine and a cAMP/PKA pathway [53] and involving the cytoskeleton [88,89].

HSP70 does, however, have a role in thermoprotection of the larval locomotory CPG in *Drosophila*. Larval locomotion can be conditioned by prior heat shock [38] and output of this neuronal circuit can be monitored in functionally deafferented preparations, which show a strong temperature sensitivity with a Q_{10} of 3.3 (Figure 2a, b, c; [52]). Disrupting synaptic function with a TS-mutant (null for *cysteine string protein* that interacts with the cognate form of HSP70 in a synaptic chaperone machine [90]) disrupts temperature sensitivity of the circuit and the ability to maintain proper phase relationships. Targeting transgenic HSP70 to motoneurons in the absence of heat shock protects locomotion (Figure 2d; [91]) probably by protecting presynaptic calcium handling at high temperatures (Figure 2e, f; [92]). In this case the best current explanation for the thermoprotective effect of heat shock is that HSP70 stabilizes presynaptic Ca^{2+}-ATPase, which is perturbed during hyperthermia [93], to maintain ion homeostasis at synapses.

Neuronal circuits show phenotypic plasticity and can be conditioned to continue operating at higher temperatures by activating diverse mechanisms that primarily target processes of ion homeostasis, which should not be too surprising given that regulating ion flow and storage is at the heart of neuronal circuit operation.

Figure 3



Schematic summary of the effects of temperature on the operation of neuronal circuits. **(A)** As temperature changes, the modulation of kinetic energy in neural systems has predictable effects on the rates of intrinsic circuit properties. **(B)** If the temperature coefficients (Q_{10}s) of circuit mechanisms having opposing effects are approximately balanced then some measure of phase constancy and rate constancy of the overall output pattern is possible. **(C)** With increasing divergence from the normal operating range of temperatures any differences in the Q_{10}s of circuit mechanisms become accentuated and the resulting mismatch of rates causes the failure of circuit mechanisms, the loss of appropriate ion regulation and consequent arrest of patterning. Note that this will occur with increasing and decreasing temperature change. **(D)** All these properties and mechanisms are continuously modulated by processes of phenotypic plasticity, mediated by signalling pathways and gene regulation, which tune neuronal circuits for their changing environments.

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A neuroecological perspective

Neuroecology is concerned with the fit of an organism's neural control systems with its ecological niche [94–96]. This embraces considerations of the ecological function of behaviours as an approach to understanding existing circuitry, the matching of neural parameters to particular ecological niches [97,98] and the long-term effects of abiotic factors on neural function. There is little doubt that the temperature sensitivity of an organism's neuronal circuits will determine its ecological range and its success within that range. In insects, optimal neuronal performance often depends on high operating temperatures [99,100]. Also, low temperatures considerably increase the energetic demand of signalling [101•]. Which animals are most vulnerable? Where will they end up as climate changes? How fast could they adapt to change, if at all? With the growing interest in predicting the ecological effects of global climate change there is increasing awareness that comparative and evolutionary physiological approaches may provide some answers [102–104,105•,106]. Neuronal circuits are particularly vulnerable to acute extreme temperatures because of the complexity of the biochemical underpinnings of neural function. A better understanding of the short and long-term effects of temperature on neuronal circuits will help to predict how ecological niches will change.

Conclusions

There will be wide variation in the details of how neuronal circuits respond to and cope with temperature change. Some of this variability is noted above. Nevertheless, the effect of temperature change can be described in general terms as follows (Figure 3). A change in temperature changes the amount of kinetic energy in the system and affects the rates of the protein conformational changes and chemical reactions that underlie neural function. If the temperature coefficients of linked processes are reasonably well matched then the system can continue to operate, though usually at a different rate. Temperature compensation is possible if opposing processes have similar Q_{10}s, however, as the temperature changes become extreme, any discrepancy between rates becomes accentuated and the circuit falters and fails. Circuit failure may arise primarily when energy-dependent, ion homeostatic processes are unable to maintain the correct ionic environment for proper function. The excitable properties of nervous systems that are necessary for them to operate become a liability as positive feedback exacerbates the condition with the end result that widespread depolarization shuts down neuronal circuits and results in coma. This is before cellular damage and is thus reversible if conditions return to normothermia. Experience of extreme temperatures activates processes of phenotypic plasticity with short and long time courses that feedback to tune the circuit parameters and the homeostatic processes such that subsequent exposures can be tolerated more easily.

Future research could be directed towards finding out what determines whether the output rate of a neuronal circuit shows an exponential or a linear relationship with temperature. Similarly we have little understanding of the molecular mechanisms by which second messenger pathways or chaperone proteins tune neuronal circuits to be more appropriate for the thermal environments they are likely to encounter. It will also be important to integrate what is known about temperature effects on specific neural processes with consideration of glial contributions and the role of cellular metabolism and energetic constraints.

Acknowledgements

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Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

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