How Can Adaptive Behavioural Plasticity Be Implemented in the Mammalian Brain?*

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The adaptive control of behaviour requires brain mechanisms for the selection (i.e. activation and suppression) of responses, as well as mechanisms for the modulation of the response vigour. The concept of motivation postulates the existence of brain centres that regulate the selection and strength of behavioural responses. The present paper provides examples from the behavioural neurosciences for brain mechanisms that lead to adaptive changes of an organisms responsiveness to external stimuli. The mammalian startle response is a simple defensive behaviour which is mediated by an oligosynaptic pathway located in the lower brainstem. The startle response is enhanced by aversive states (fear, anxiety) and attenuated by appetitive states (pleasure), which can be regarded as an example of motivational priming. Furthermore, the startle response is inhibited by a weak sensory stimulus presented shortly before the startling stimulus. The suppression of startle by a prepulse is an example of sensorimotor gating, a principle that is important for the hierarchical organisation of behaviour. This paper describes the neuronal mechanisms underlying the modulation (prepulse inhibition and fear potentiation) of the startle response in rats, and discusses the possible adaptive significance of these different phenomena of behavioural plasticity.

The behavioural response to a sensory stimulus has to be variable in order to be adaptive. The response vigour depends on previous experiences (learning), as well as on the internal state of an organism. The concept of "motivation" has been developed to account for this kind of response plasticity (Bindra, 1969). Based on this concept it is hypothesised that the sensorimotor information transfer underlying behaviour is under the command of motivational centres of the brain. However, only a few examples in the behavioural literature actually provide a neurobiological substrate for how motivational centres modulate behaviour in mammals. This lack of information is probably due to the fact that the mammalian brain is immensely complex so that it is hard to assess the role of "identified neurones" in behaviour. In contrast, much progress has been in the past in understanding the control of behaviour by the comparatively simple nervous systems of invertebrates (e.g. Huber, 1990; Kandel, 1976). In order to study the contribution of an identified neuronal substrate to behaviour in mammals, it is useful to investigate simple behaviours.

Startle is a fast, defensive and protective response (composed of eyelid-closure, activation of hind-, and forelimb muscles, crouching, stiffening of the neck muscles) to sudden and strong sensory stimulation (e.g. a loud noise pulse), and can be regarded as the initial component of a flight response. The acoustic startle response (ASR) is mediated by a simple neuronal circuitry located in the pontine brainstem. Physiological and behavioural data show that the ASR in rats is mediated by a group of quasi-identified very large ("giant") neurones in the caudal pontine reticular nucleus which receive short-latency acoustic input and project directly onto motor neurones (Koch *et al.*, 1992; Lingenhöhl and Friauf, 1994; Lee *et al.*, 1996; Yeomans and Frankland, 1996). It has been speculated that the ASR in mammals corresponds to the flight response in fish, and that the giant reticulospinal neurones of mammals are equivalent to the

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"brainstem escape network" including the Mauthner cells of fish (Eaton *et al.*, 1991; Koch *et al.*, 1992). Since the ASR has a "non-zero-baseline", i.e. its amplitude can be increased or decreased, the ASR is well suited for the investigation of the mechanisms of response modulation. The most prominent examples of modulation of the ASR in rats and in humans are the inhibition of the ASR by a prepulse and the enhancement, or potentiation of the ASR by fear. Since the neurones of the caudal pontine reticular nucleus are not only the sensorimotor interface of the ASR, but also receive input from a variety of brain areas which modulate the ASR (summarised in Koch and Schnitzler, 1997), these neurones are an ideal target for the study of how behavioural plasticity is implemented in the mammalian brain. The electrophysiological, anatomical and behavioural investigation of the role of the caudal pontine reticular nucleus in mediating and modulating the ASR revealed general principles of sensorimotor integration and provided empirical evidence for the existence of motivational centres of the brain.

A Mechanism of Response Inhibition

The awake organism is permanently under the influence of sensory stimuli. Many of those stimuli may be of behavioural relevance, but the concurrent activation of two or more behavioural programs in a given situation may lead to behavioural interference and is probably not of adaptive value. The sequential and hierarchical organisation of behaviour requires mechanisms that avoid inadvertent responses. In order to suppress inappropriate responding the brain uses inhibitory mechanisms that lead to sensorimotor gating. A simplified model for this aspect of behavioural organisation is depicted in Figure 1: Here, it is assumed that two different types of sensory stimuli elicit two types of behavioural responses. In this example the concurrent activation of these two behaviours would lead to the interference of the two responses and, if their processing pathways in the brain overlap to some extent, to inappropriate or maladaptive responding. Therefore, it is postulated that the behaviour which is activated first triggers an inhibitory, or gating mechanism that suppresses the processing of the later sensory input and prevents the concurrent activation of the other behaviour.

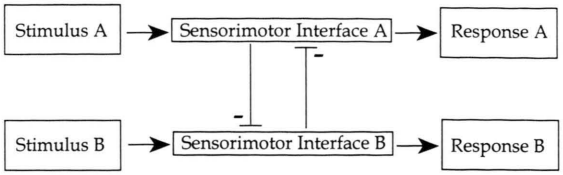

Fig. 1. Hypothetical inhibitory interrelationship between two sensorimotor response systems (A and B). This model predicts that the system which is activated first will inhibit the occurrence of the second response. The term "sensorimotor interface" refers to all the neuronal elements that are interposed between the primary sensory organs and the muscles that mediate the response.

Sensorimotor gating has been operationalised as prepulse inhibition (PPI) of the ASR in a variety of species, including humans. PPI is the reduction of the ASR amplitude that is observed if the startling stimulus is preceded by a weak (non-startling) stimulus which may be of the same or a different (tactile, visual) sensory modality (Fig. 2, upper part). The lead time of the prepulse has to be in a range of 30–500 ms in order to inhibit the ASR (Hoffman and Ison, 1980). PPI is observed in the very first presentation of a prepulse and a startle stimulus, and is therefore not due to learning or habituation. This model postulates that the gating mechanism improves the perceptual and motor performance of an organism by preventing the startle stimulus from disrupting the sensory processing of the prepulse or the motor activities associated with that stimulus.

The mechanisms underlying PPI must not be confused with the non-neuronal mechanisms that avoid overlap of the processing of two stimuli in the auditory system, such as two-tone suppression (Pickles, 1988).

A series of experiments combining electrophysiological, anatomical and behavioural techniques revealed a hypothetical neuronal pathway that mediates PPI (Fig. 2). The brain circuit that mediates the ASR comprises three serial components, the cochlear root nucleus, the caudal pontine reticular nucleus, and finally cranial and spinal motor neurones (summarised in Koch and Schnitzler (1997)). A sudden and intense acoustic stimulus activates this serial oligosynaptic pathway and leads to a short-latency twitch of facial and skeletal muscles. The giant neurones of the caudal pontine reticular nucleus provide the sensorimotor interface of the ASR (Koch *et al.*, 1992; Lingen-

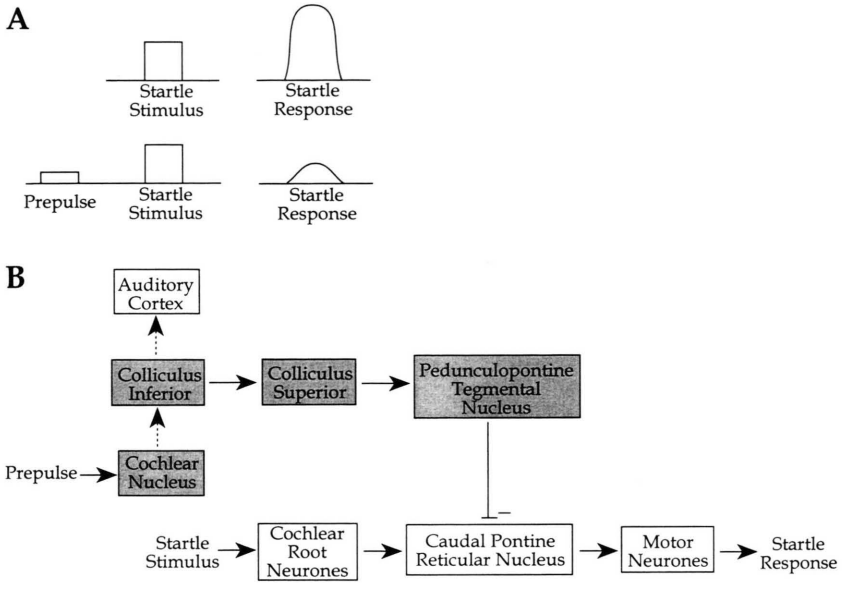

Fig. 2. Schema illustrating prepulse inhibition of the startle response as a model of sensorimotor gating (A). A weak, non-startling stimulus presented some 100 ms before the startling stimulus leads to a strong inhibition of the startle response. The lower part of the figure (B) depicts the brain centres that mediate the acoustic startle response (white boxes), and the PPI-pathway by which the startle response is inhibited (shaded boxes).

höhl and Friauf, 1994; Lee *et al.,* 1996). In this model, the auditory prepulse that precedes the startling stimulus by some 100 ms is processed within the auditory system and activates neurones in various parts of the cochlear nucleus, as well as in other relay neurones of the ascending auditory pathway (dashed arrow), including the colliculus inferior. Lesion studies suggest that the pathway mediating PPI is activated by the inferior colliculus and comprises the superior colliculus and the pedunculopontine tegmental nucleus, from where an inhibitory projection to the primary startle pathway arises (summarised in Koch and Schnitzler (1997)). In functional terms, it is hypothesised that while the auditory prepulse is being processed within the ascending auditory pathway, this inhibitory circuitry is activated and, in turn, reduces the activity of other brain systems (including the startle-mediating brain structures) so as to minimise the disruption of the neuronal system engaged in processing the prepulse. Neurones of the pedunculopontine tegmental nucleus release the neurotransmitter acetylcholine, which inhibits the auditory responsive neurones of the caudal pontine reticular nucleus (Koch *et al.,* 1993), so that a startling noise pulse presented shortly after activating the PPI circuit will be much less effective in inducing a full-blown ASR.

PPI is an example for sensorimotor gating and it is assumed that the activation of an inhibitory loop of brain structures that reduces concurrently activated behaviour reflects a general principle of behavioural control in mammals. The mechanisms leading to PPI are located in the lower brainstem, so that higher mental functions are unlikely to contribute to the mediation of PPI, although a modulatory effect of various forebrain areas on PPI has been shown (Swerdlow *et al.,* 1992; Koch and Schnitzler, 1997). The adaptive benefits of sensorimotor gating are probably to prevent the brain from sensory overload and to optimise the sequential information processing in an environment rich of sensory stimuli. This kind of response suppression is one of the basic requirements for the selection and execution of a behaviour in a given situation.

A Mechanism of Response Potentiation

Adaptive behaviour is characterised by a high degree of plasticity, i.e. the strength of the response to a stimulus is variable according to the motivational state of the organism. For example, the potentiation of protective or defensive responses (behavioural, endocrine and cardiovascular stress responses) by an aversive motivational

state is adaptive in a dangerous situation, because it prepares the organism for fight or flight. In the simple schema shown in figure 3, it is assumed that a brain area which is not part of the system that mediates the response, acts as a motivational centre and excites a given sensorimotor system. Furthermore, this model predicts that this motivational centre exerts its influence on the response at the sensorimotor interface, rather than in the sensory periphery, or at the level of the motor neurones, for this would compromise the behavioural specificity of the modulation.

Drawing on ideas developed by Konorski (1967) and by Dickinson and Dearing (1979), Peter Lang proposed a theory of emotional priming, which predicts that the vigour of a response is determined by the affective value of the stimulus (aversive, appetitive) and by the affective category of this response (protective: fight or flight, or procreative: sexual, parental or consummatory behaviour). In support of his theory, Lang and his coworkers showed in humans that the defensive ASR is enhanced in an aversive motivational state (fear, apprehension) and attenuated in a pleasant or hedonic state (Lang, 1995). Similar results have been found in the rat (Davis, 1992; Schmid *et al.*, 1995). The following paragraph focuses on the brain mechanisms leading to an enhancement of the ASR by fear in the rat.

Fear is one of the most powerful determinants of human and animal behaviour. The term fear refers to a hypothetical motivational state of the brain, which facilitates the occurrence of protective, defensive behaviours and which helps to avoid danger and harm. Most of the physiological responses to threatening of fearful stimuli are similar in rats and humans, so that it is conceivable that these responses have similar neuronal substrates. It is important to emphasise, though, that emotions did probably not evolve as conscious feelings, rather they should be regarded as by-products of physiological and behavioural adaptations for the purpose of survival (protection) of the organism. The assumption of a conscious state of fear in animals is therefore not necessary to explain the behavioural and physiological effects of adverse situations (Le Doux, 1996).

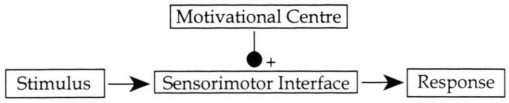

Fig. 3. Simplified illustration of the enhancement of a response by a specific motivation. In this model, the response to a sensory stimulus is potentiated, because neurones of the sensorimotor interface (neurones that translate the sensory input into a motor response) are excited by neurones from a motivational brain centre.

There has been considerable progress in understanding the neuronal basis of fear in mammals. Conditioned fear is due to an association between an aversive event and a neutral stimulus, and can be assessed in rats and humans by measuring the physiological or behavioural changes after presentation of the aversive CS. We and others have studied the enhancement of the ASR by fear in rats (reviewed in: Davis, 1992; Koch and Schnitzler, 1997). Recent important work has shown that the association between an aversive stimulus (US, e.g. an electric foot shock, mediated by spinal and thalamic brain centres that process noxious stimuli) and a neutral stimulus (prospective CS, e.g. a light, mediated by sensory thalamic and cortical structures) occurs due to long-term potentiation in the lateral/basolateral amygdala (McKernan and Shinnick-Gallagher, 1997; Rogan *et al.*, 1997). Intraamygdaloid projections connect the lateral/basolateral amygdaloid nuclei with the most prominent output structure of the amygdala, the central nucleus. Electrophysiological studies have shown that the acoustically induced single unit activity of neurones in the caudal pontine reticular nucleus, which mediates the ASR, is potently enhanced by electrical stimulation of the central amygdala. Moreover, the ASR is enhanced by electrical or chemical stimulation of the central amygdala in awake rats (Koch and Ebert, 1993). Finally, it has been shown that fear potentiation of the ASR can be blocked by lesions of the amygdala. There is evidence for a direct excitatory projection from the central amygdala to the caudal pontine reticular nucleus that uses glutamate and the neuropeptide corticotropin releasing factor as transmitters. The pharmacological blockade of these transmitters in the caudal pontine reticular nucleus reduces the potentiation of the ASR by fear (Fendt *et al.*, 1996a; Fendt *et al.*, 1997). Additionally, an indirect descending projection connects the central amygdala via relay neurones in the central gray and different tegmental nuclei with the sensorimotor interface of the pathway that mediates the ASR

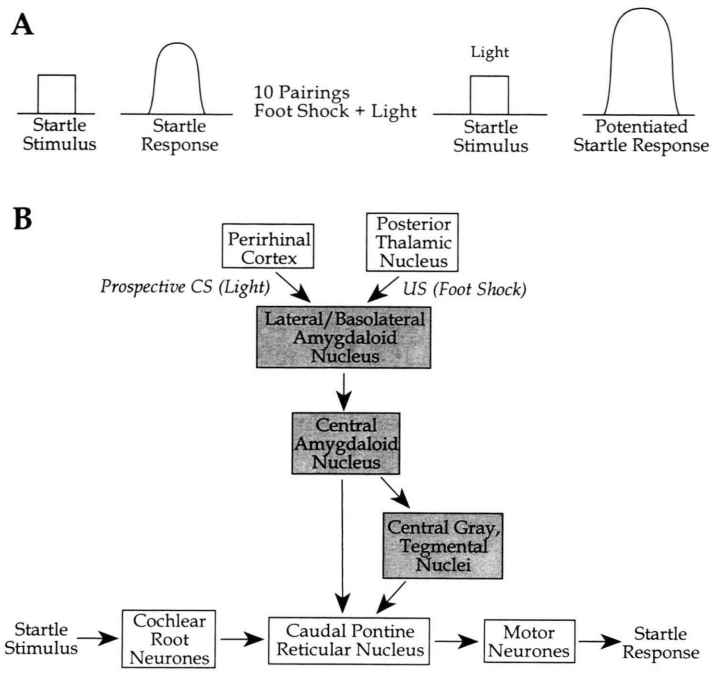

Fig. 4. The startle response is enhanced in the presence of a conditioned stimulus (say a light) that predicts the occurrence of an aversive event (A). The lower part of the figure (B) depicts pathways mediating the startle response (white boxes) and potentiating the startle response (shaded boxes). Pavlovian fear conditioning (pairing a foot shock with a light) leads to an association between the prospective CS and the US in the lateral/basolateral amygdaloid complex, where the CS- and the US-pathways coincide. Fear-conditioning is based on long-term potentiation in amygdala neurones. After conditioning the CS (light) activates neurones in the central amygdaloid nucleus which leads to an enhancement of the startle response, by an activation of neurones of the primary startle pathway.

(Fendt *et al.*, 1996b). These relay nuclei also modulate the ASR and are probably responsible for the fine-tuning of the fear-induced potentiation of the ASR. The direct and indirect modulatory afferents to the caudal pontine reticular nucleus enhance the excitability of the giant neurones probably via axo-dendritic and axo-somatic synaptic contacts (Koch and Ebert, 1993), although a presynaptic enhancement of transmitter release of the auditory afferents cannot be excluded.

Taken together, these findings indicate that the neuronal systems responsible for the enhancement of the defensive ASR by an aversive motivational state (fear), and those responsible for the inhibition of the ASR can readily be explained by anatomically and physiologically characterised pathways in the rats brain. The investigation of the mediation and modulation of the ASR gave insights into the principles of the neurobehavioural organisation of the mammalian brain.

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