Chapter 10
Central Effects of Efferent Activation

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10.1 Introduction

The action of the medial olivocochlear system (MOCS) in the auditory periphery is well established and is described in detail elsewhere in this volume (Guinan, Chap. 3; Sewell, Chap. 4; Katz et al., Chap. 5). The major peripheral effect of activation of the MOCS is a reduction in gain of the outer hair cell (OHC) cochlear amplifier and a consequent reduction in sensitivity of the primary afferent neurons to tones at their most sensitive, or characteristic frequency (CF). This action on the OHCs has different functional consequences for the responses of primary afferent neurons to tone stimuli, depending on whether these are observed in quiet or in the presence of background noise.

In quiet, the MOCS action generally results in a simple rightward shift of the single afferent input–output curves to CF tones (Fig. 10.1 left). There is little effect on the maximum discharge rate. This is because the OHC mechanical amplifier has a limited operating range, and therefore its contribution to basilar membrane vibration (and hence neural firing) is saturated more than about 60 dB above neural threshold (Patuzzi et al. 1984; Patuzzi and Rajan 1992; Rajan and Patuzzi 1992). In a small proportion of the most sensitive neurons, medial efferent activation results in a minor reduction in spontaneous firing rate of primary afferents, probably because of the small (maximum of 3 mV) drop in endocochlear potential that results from the MOCS-induced increase in the basolateral wall conductance of the OHCs (Fex 1967; Desmedt and Robertson 1975). The reduction in the endocochlear potential reduces the standing current through the inner hair cells, hyperpolarizing them and lowering the basal rate of neurotransmitter release (Sewell 1984).

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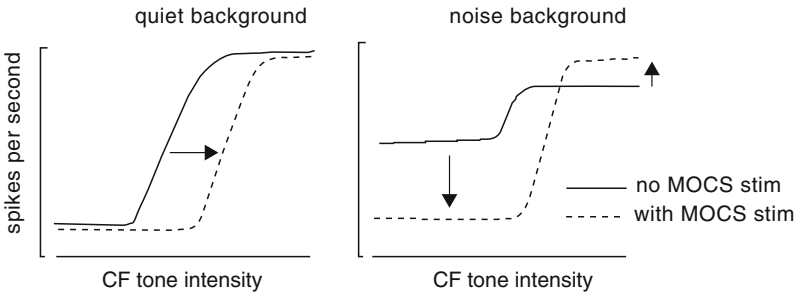

Fig. 10.1 Idealized representation of effects of MOCS activation on input–output responses of single primary afferent neuron to a range of CF tone intensities. *Left*, responses in quiet background; *right*, responses in presence of continuous background noise. Note elevated basal firing rate and reduced maximum rate in noise without MOCS stimulation

In the presence of background noise, the input–output functions of primary afferents to CF tones are compressed for several reasons (Fig. 10.1right). The continuous response to the background noise raises the primary afferent neurons' basal firing rate. In addition, the resulting adaptation reduces the maximum discharge rate. These two effects of the background noise lead to a reduced range of output firing rates. In addition, there is a "jamming" effect of the noise on the cochlear amplifier function of the OHCs and this shifts the input–output function to the right. It has been elegantly shown (Winslow and Sachs 1987; Kawase et al. 1993) that these effects cause a reduced ability of the primary afferents to encode intensity differences in the tonal stimuli. When the MOCS is stimulated, there is a preferential, level-dependent suppression of the response to the background noise and less effect on responses to higher level tonal stimuli. The reduced rate of background firing results in a release from adaptation, so the maximum discharge rate returns towards normal, and the net result is a partial restoration of the dynamic range of the response to CF tones. This "antimasking" effect of the MOCS has received much attention because of its potentially important role in enhancing auditory signal detection (Winslow and Sachs 1987; Kawase et al. 1993; Mulders et al. 2008; Seluakumaran et al. 2008b).

From a simplistic perspective, both of these peripheral effects of MOCS activation might be expected to result in comparable "upstream" changes in the activity of central nervous neurons in quiet and in background noise. If, for example, the sensitivity of primary afferents to CF tones in quiet were reduced by 20 dB, one might expect that a central neuron with the same CF would show a comparable reduction in sensitivity. This question was addressed many years ago by Desmedt (1962), who measured click-evoked field potentials in anesthetized cats at several stages of the central auditory pathways and compared the effects of MOCS activation on these central responses with those produced on the cochlear compound action potential to the same stimuli. Desmedt quantified the MOCS effect by titrating the amount of suppression as an equivalent reduction in acoustic stimulus intensity, using the amplitude/intensity function for the evoked potentials. Using this method, the amount of suppression was found to be very similar at all stages of the pathway

and also very similar to the equivalent suppression of the cochlear nerve action potential.

However, there are several reasons why this issue of the central consequences of efferent activation has been revisited by others and why it still remains a matter deserving further investigation. The broadband clicks employed in the early study by Desmedt (1962) tell us little about the nature of responses to tones of particular frequency, for example, at the neurons' CF. In addition, field potential recordings may obscure subtle effects on neuronal subpopulations. The ascending pathways are highly complex, with a bewildering range of neuronal subtypes and circuitry involving multiple interneuronal connections, both excitatory and inhibitory, that shape each neuron's dynamic range and response area. A simple reduction in afferent drive from the cochlea caused by MOCS stimulation might not necessarily be translated faithfully as a linear reduction in the operation of all elements of this complex central circuitry. Finally, it needs to be borne in mind that the olivocochlear neurons terminate not only within the cochlea, but as shown in Brown (Chap. 2), they also send collaterals to other auditory brainstem regions, notably the cochlear nucleus (CN) and superior olivary complex (SOC). As discussed further in this chapter, the precise action of these collateral pathways is still contentious, but their very existence opens up the possibility that MOCS activation may produce a variety of peripheral and central actions that may interact in ways that produce surprising outcomes for central neuronal firing behavior.

For several reasons, it of interest to know more about the central effects of olivocochlear activation, and in particular, to know if they differ from those predicted simply from the effects on the primary afferent neurons. First, the postulated role of olivocochlear neurons in auditory signal processing (antimasking) is based to a large extent on their effects documented in primary afferents. To be meaningful in terms of behavioral output, it is a necessary condition that these effects are also apparent in the behavior of at least some of the higher order neurons of the pathway. Second, a detailed study of variations in the effects of olivocochlear activation on the diverse neuronal response types in the central pathways could generate insights into the various roles that these different neurons may play in signal processing.

This chapter reviews the evidence for effects of olivocochlear activation on neurons in central auditory structures of the more common animal models. The broad questions addressed are:

1. Are effects seen in central neurons that are not readily predictable from peripheral afferent changes? (Sect. 10.2)
2. What mechanisms might be responsible for such "nonclassic" effects? (Sects. 10.3– 10.5)
3. What are the implications of central effects for understanding auditory signal processing and the role of the olivocochlear efferents? (Sect. 10.6)

In addressing these questions, the chapter considers only the effects of activation of the MOCS on single-neuron responses in the cochlear nucleus (CN) and inferior colliculus (IC). Some of the technical obstacles to obtaining clear answers as to the origin of these effects are highlighted. The effects of lateral olivocochlear system

activation (LOCS) will not be discussed in view of the paucity of data and the difficulties of achieving selective and reliable activation of this component of the olivocochlear system. A number of other aspects of central efferent effects are not considered, such as the role of other efferent systems innervating the brain stem (see, e.g., Pickles 1976a; Klepper and Herbert 1991; Thompson et al. 1995; Ebert 1996; Mulders and Robertson 2001; Shore et al. 2003; Mulders and Robertson 2005). Aspects of corticofugal pathways and detailed overarching anatomy of the efferent pathways from cortex to cochlea are considered elsewhere in this volume (Brown, Chap. 2; Schofield, Chap. 9; Suga et al., Chap. 11).

A number of methods have been employed to study the effects of MOCS activation on central neurons. These can be broadly classified as follows:

1. Single-neuron recordings in vivo while activating MOCS. Both intra- and extracellular recording methods have been used.
2. Single-neuron recordings in vitro (brain slices) while applying putative MOCS agonists and antagonists.
3. Behavioral experiments of auditory processing while manipulating MOCS function.

Each of these experimental approaches yields different levels of understanding of the problem, and each suffers from particular advantages and disadvantages that are discussed in turn in the text that follows.

10.2 Single-Neuron Recordings In Vivo

10.2.1 Technical Issues

The most commonly used experimental approach to activate the MOCS, illustrated schematically in Fig. 10.2, involves electrical stimulation of the olivocochlear efferents by placing stimulating electrodes at the point of decussation of the medial axons at the floor of the IVth ventricle. This activation of the efferents is combined with single-neuron recording from different central nuclei, using either extracellular recording of action potential firing, or intracellular recordings that enable direct observation of inhibitory and excitatory synaptic events. Electrical stimulation has the virtue of conceptual simplicity, and it guarantees activation of the olivocochlear efferents that can be verified by monitoring the signature peripheral changes: suppression of the cochlear nerve action potential and an increase in the externally recorded cochlear microphonic potential (Mulders and Robertson 2000). Collateral pathways of MOCS axons to CN and elsewhere will also be activated at the same time as the axons traveling to the cochlea.

However, this method has some serious limitations and potential sources of error. First, electrical stimulation at the floor of the IVth ventricle generally results in activation of the entire olivocochlear bundle, which courses as compact fascicles at

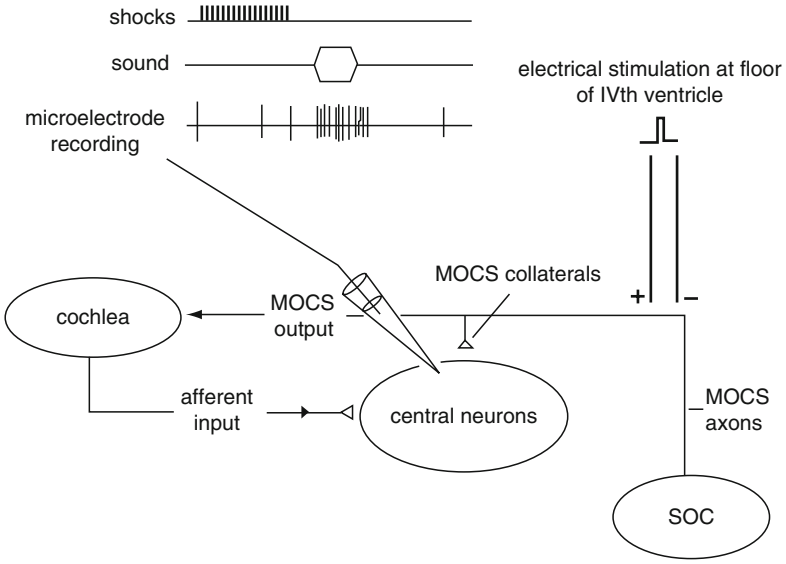

Fig. 10.2 Schematic representation of the basic stimulation and recording arrangement used to study central effects of MOCS activation in vivo. Typical relationship between acoustic stimulus and shock train to MOCS shown in upper part of figure

the level of the facial genua. Thus the effects on cochlear neural output span a frequency range limited only by the extent of efferent innervation of the organ of Corti. This may mimic to a reasonable degree, the efferent activation resulting from physiological stimuli such as broadband noise, but it is not routinely possible with this method to measure the effects on central neural responses of more limited activation of smaller numbers of efferents innervating limited cochlear regions. It is conceivable that very focal stimulation might be able to be used to activate small fascicles of the MOCS axons, but so far this has not been achieved (see Suga et al., Chap. 11, with regard to the application of this technique to selective activation of corticofugal pathways).

Second, the electrical stimulation regimen used makes a detailed investigation of the time course of efferent effects difficult. In the classic paradigm for studying MOCS effects, test acoustic stimuli are usually delivered 5–10 ms after the end of a train of shocks delivered to the MOCS axons (Fig. 10.2). This is because the peripheral effect of MOCS activation caused by single shocks is immeasurably small, and because the size of electrical shock artifacts picked up by the recording microelectrode often makes accurate recording of physiological responses difficult during the shock train itself. As a consequence, the precise onset of effects during the shock train often cannot be accurately estimated, and rapid, short-lasting effects may be missed altogether. In addition, probing for effects after stimulation has ceased means that one is measuring effects that are generally in the process of dissipating. This poses problems for quantifying effects when test stimuli of appreciable duration are used, as is usually the case in studies of central neurons.

The final and most important limitation is that the placement of electrical stimulating electrodes at the floor of the IVth ventricle is dangerously close to major fiber tracts other than the MOCS axons (Fig. 10.3). These are the ascending fiber tracts (dorsal and intermediate acoustic striae) emanating from the dorsal and posteroventral cochlear nuclei, as well as the commissural pathway between the cochlear nuclei. The ascending tracts project to the nuclei of the lateral lemniscus and to the IC. The commissural pathway is believed to comprise principally the axons of large glycinergic multipolar neurons in the cochlear nucleus that correspond to neurons described physiologically as "onset choppers." These glycinergic neurons mediate inhibition in the contralateral cochlear nucleus and elsewhere. Unless great care is taken to limit the spread of electrical stimulation to the olivocochlear bundle, activation of these other tracts can confound the effects seen. As indicated in Fig. 10.3, these confounding effects can arise from orthodromic propagation of impulses providing synaptic direct input to the IC, which in turn could activate descending projections to the SOC or CN. Antidromic and/or orthodromic activation of recurrent collateral circuitry within the CN regions constitutes a further possible complication. In either case, the effects on single neurons from which recordings are being obtained might be wrongly concluded to arise from MOCS activation.

Because of this problem of inappropriate activation of non-olivocochlear tracts, considerable care has to be exercised with the choice of stimulating electrodes and their placement. Bipolar stimulating electrodes with close separation between the

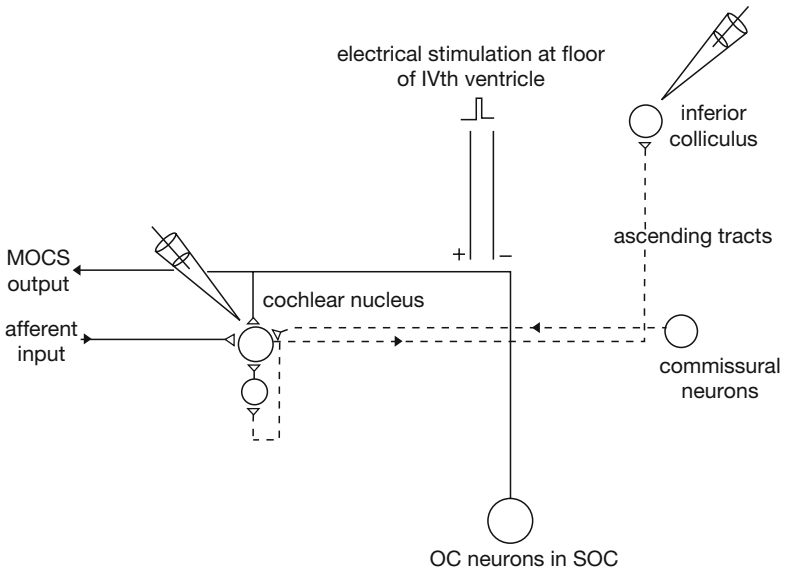

Fig. 10.3 Schematic representation showing ascending and commissural fiber tracts that run close to MOCS axons and are at risk of uncontrolled stimulation by shocks to MOCS. *Dotted lines*, tracts whose activation could give rise to spurious effects in cochlear nucleus and/or inferior colliculus, either by orthodromic or antidromic conduction of action potentials. *Arrows* indicate direction of action potential conduction

bipolar pair, with good insulation and small exposed tips, are required. Some sense of the spatial spread of current can be obtained by eliciting medial olivocochlear (MOCS) effects in the cochlea and observing the impact of raising or lowering the electrodes relative to the floor of the IVth ventricle. To ensure correct electrode placement, careful mapping of the sensitivity of facial nerve signs (whisker and eyebrow twitch) to shocks delivered through the stimulating electrodes is used (Seluakumaran et al. 2008a). Precise placement at the point of lowest facial nerve threshold at least ensures that the electrodes are placed between the facial genuae. Provided current strengths are kept below a critical amount, and the electrodes are not advanced deeper into the brain stem, selective olivocochlear activation can be achieved. In guinea pig, it appears that placement of the electrodes slightly rostral to the lowest facial nerve threshold point maximizes the possibility of selective activation of MOC axons (Seluakumaran et al. 2008a).

Ideally, this approach needs an independent method of verification, and this can be obtained by monitoring field potentials in the IC. If shocks to the floor of the ventricle are kept well below the strength that elicits measurable field potential responses in the IC, this provides additional assurance that major ascending tracts have not been activated as well as the MOCS axons (Seluakumaran et al. 2008a). Despite these precautions however, it cannot be ruled out that some unintended activation of non-olivocochlear tracts occurs. The large "onset chopper" neurons whose axons form a commissural pathway between the two cochlear nuclei may be especially prone to this problem. In a detailed study of the responses of onset chopper neurons to midline electrical stimulation in guinea pig (Mulders et al. 2007), it has been found that even at shock strengths that do not activate the axons of other major output neurons of the cochlear nucleus, some onset choppers show clear evidence of antidromic activation, indicating that their large-diameter myelinated axons in the intermediate acoustic stria may have lower thresholds than other axons to shocks intended to activate only MOCS axons.

A final technical consideration is that electrical stimulation in the brain stem is likely to activate a variety of motor pathways, including those innervating the middle ear muscles. Activation of these motor pathways, by generating masking noise and by affecting middle ear sound conduction, can confound the results and hence paralysis of skeletal muscle, elimination of middle ear muscle contraction, and artificial ventilation are obligatory requirements in all such studies.

10.2.2 Early Work

Reference has already been made to the pioneering study of Desmedt (1962), who recorded field potentials in response to acoustic clicks from brain stem, midbrain, and cortex and measured the effects of electrical stimulation of the olivocochlear axons at the floor of the IVth ventricle, in cats. Comis and Whitfield (1968) were the first to study the effects of electrical stimulation of the SOC on activity of single cochlear nucleus neurons. Unlike all subsequent studies, they used a ventral

approach to the SOC, instead of selectively activating the olivocochlear fibers at the floor of the IVth ventricle. The aim of these authors was in fact not to stimulate the MOCS (the division of the olivocochlear efferents into medial and lateral components was not well known until the mid-1970s), but instead, to activate a separate non-olivocochlear projection from the SOC to the CN. However, the placement of their stimulating electrodes deep within the SOC makes it likely that at least part of the olivocochlear projection was activated in their experiments, although no monitoring of effects in the cochlea was performed. These authors found numerous examples of neurons in both ventral and dorsal subdivisions of the CN that were excited by SOC stimulation. They used local iontophoretic injection of atropine to demonstrate that this excitation was probably cholinergic. Despite the substantial limitations of this early study, it does provide the first single-neuron evidence suggesting that olivocochlear activation might not result in exclusively inhibitory effects in central nuclei.

In a remarkably complete study in decerebrate cats, Starr and Wernick (1968) used electrical stimulation of the olivocochlear fibers at the floor of the IVth ventricle (Fig. 10.2). Importantly, these authors verified the correct placement of the stimulating electrodes by monitoring effects on the cochlear compound action potential and cochlear microphonic, although these effects were not routinely quantified. They reported a variety of effects of olivocochlear stimulation on both spontaneous and sound-evoked activity in all major subdivisions of CN. Approximately 50% of neurons showed no change, and about equal numbers showed either an increase or a decrease in spontaneous firing. Many neurons also showed complex and long-lasting temporal patterns of spontaneous firing change as a result of olivocochlear stimulation that appeared to be rather different from the small, short-lasting drops in spontaneous rate seen in primary afferent fibers (Wiederhold 1970; Wiederhold and Kiang 1970). Complex excitatory and inhibitory effects were also observed when tone-evoked responses were examined. Some neurons could show different effects depending on tone level, something that the authors noted was not observed in primary afferents. Importantly, these authors also showed that changes in spontaneous activity were still observed in about 40% of CN neurons after destruction of the ipsilateral cochlea, eliminating all peripheral effects of olivocochlear stimulation. Although it was not stated explicitly by the authors, this latter observation presumably applied to neurons in the dorsal subdivision of CN, because all spontaneous firing in the ventral CN is probably dependent on input from the cochlea (Koerber et al. 1966). Regardless, this result clearly implicated olivocochlear collateral pathways in the effects observed in CN neurons. Starr and Wernick speculated that in the intact system, direct olivocochlear actions in the CN and the effects of peripheral afferent suppression interacted within complex central circuitry to generate the diversity of central effects seen.

By demonstrating the presence of excitation as well as inhibition, and by showing effects in the absence of intact cochlear efferent innervation, these two initial studies in CN provided the first evidence that effects of olivocochlear activation in central nuclei are not always readily predictable from the established effects in the cochlea. However, in neither of the studies were stringent attempts made to rule out activation

of non-olivocochlear pathways, nor was particular attention paid to the relationship between the effects seen and neuronal response type classification.

10.2.3 Recent Studies in CN and IC

In a series of recent studies in guinea pig and rat, the effect of olivocochlear activation on single CN and IC neurons has been investigated in some detail, both in quiet and in the presence of background noise (Mulders et al. 2002, 2003, 2008; Seluakumaran et al. 2008a, b). The studies in guinea pig employed the necessary precautions to reduce the likelihood of confounding factors described in Sect. 10.2.1. In addition, quantitative comparison was made of the peripheral effects of MOCS stimulation (assessed by cochlear action potential suppression) and the changes in central neuron responses.

The overall results of these studies can be summarized by stating that in both of these higher centers, about 50% of neurons show MOCS effects on responses to CF tones in quiet and in noise backgrounds, which are similar to those described in primary afferents, while the remainder show a variety of effects that are not normally observed in primary afferents.

10.2.3.1 Effects in Quiet

In quiet, MOCS stimulation causes a rightward shift in the input–output curve to CF tones with little or no change in maximum firing rate in a variety of different response types in both CN and IC (schematically illustrated in Fig. 10.4). These effects are qualitatively predictable from the effects on primary afferents. Attempts to quantify the degree of rightward shift in comparison to the peripheral neural sensitivity changes in the same animals are complicated by the fact that the peripheral effect is based on the change in compound action potential generated at the onset of the test tone, whereas the single-neuron input–output curves are generated from spike counts collected over the duration of the entire 50-ms tone bursts. In many such cases, however, the central and peripheral threshold shifts appear to be roughly equivalent.

In ventral and posteroventral CN, in which single neuron classification is considerably more standardized than in the IC, it can be stated with some confidence that such classic MOCS effects are seen in primary-like neurons, and all classes of chopper neurons, including onset choppers. In the IC, neurons classified on the basis of their input–output curves as “monotonic” and “nonmonotonic” also showed these classic effects.

However, not all neurons show such simple, predictable effects. In some CN neurons, strong suppression of firing is seen across the full range of CF tone intensities employed (Fig. 10.5c, d). Although some small suppression of maximum discharge rate can be seen in a proportion of primary afferents, it is not as strong as

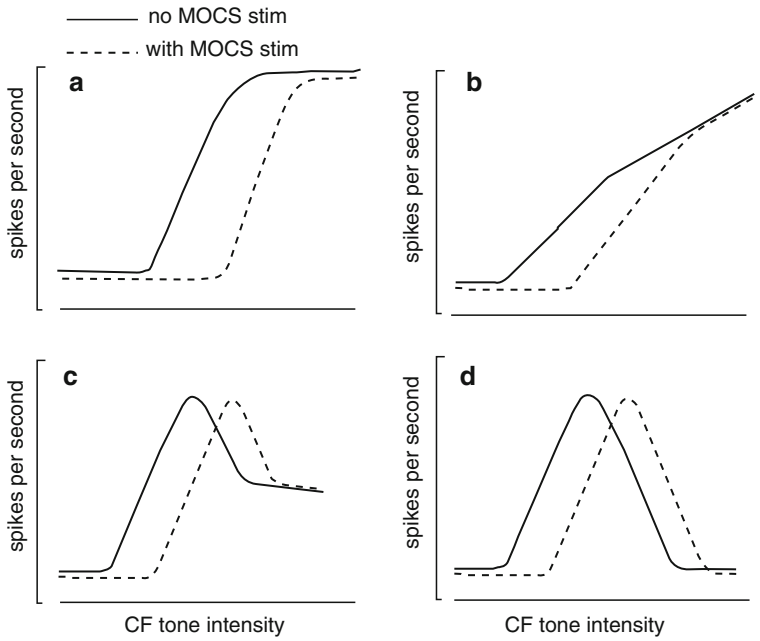

Fig. 10.4 Schematic examples of CF input–output curves of CN and IC neurons in quiet background illustrating effects of MOCS activation that resemble effects seen in primary afferents (i.e. rightward shift with little or no change in maximum discharge rate; compare with Fig. 10.1a). (**a**, **b**) saturating and nonsaturating types of monotonic input–output curves commonly found in CN and IC. (**c**, **d**) nonmonotonic types of input–output curves found in IC. Note that shapes of input–output curves are schematic only and do not accurately depict diversity of types seen in each central structure

that seen in these central nervous system neurons, implying that an additional inhibitory mechanism is present. In agreement with this notion, in animals in which removal of peripheral MOCS action is achieved either by intracochlear perfusion of the efferent blocker strychnine or destruction of OHCs, some CN neurons still showed inhibition and rightward shifts of their input–output curves caused by MOCS activation (Mulders et al. 2002).

A small number of transient and sustained choppers in CN show increases in maximum discharge rate, despite a rightward shift in their input–output curves (Fig. 10.5a). This appears to be similar to the level-dependent changes reported by Starr and Wernick (1968) and contrasts with the effects on primary afferents. In a small number of transient and sustained choppers, CF input–output curves are not altered at all by MOCS stimulation (Fig. 10.5e), even though measurement of cochlear responses shows the presence of substantial suppression of the peripheral afferent neural response to the same tone frequencies. These latter results imply the existence of centrally mediated excitation that offsets the effects of peripheral suppression.

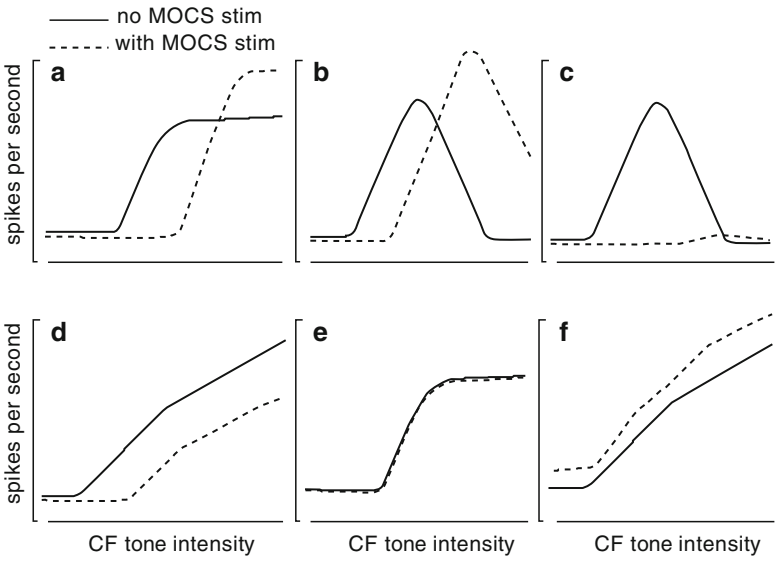

Fig. 10.5 Schematic examples of input–output curves of CN and IC neurons in quiet background illustrating effects of MOCS activation that differ from those seen in primary afferents. (**a**, **b**) rightward shift with increase in maximum rate; (**c**) inhibition that is much stronger than seen in primary afferents, (**d**) rightward shift accompanied by; substantial drop in maximum rate (**e**), no change despite presence of peripheral threshold change; (**f**) increase in firing rate across extent of input–output curve. Note that shapes of input–output curves are schematic only and do not accurately depict diversity of types seen in each central structure

Direct evidence of excitation in input–output curves of CN neurons by MOCS stimulation was less common in these more recent guinea pig studies compared to the earlier reports of Starr and Wernick (1968) and Comis and Whitfield (1968) in the cat. Mulders et al. (2002) reported that onset-like neurons and other neurons whose responses were not classifiable showed a leftward shift (increased responsiveness) in their CF input–output curves, and in some cases, elevations of spontaneous firing rates were also observed (Fig. 10.5f). However, a more recent study (Mulders et al. 2008) with more stringent cell classification failed to reveal obvious leftward shifts in input–output curves, or increases in spontaneous firing rates in any response types, including well classified onset chopper neurons.

In the IC, effects of MOCS stimulation on single neuron responses have been reported only in the central nucleus contralateral to the cochlea to which test sounds are presented (Seluakumaran et al. 2008a). Typical afferent-like effects in quiet are commonly observed for various response types differing in the shape of their input–output curves (Fig. 10.4a, c, d). However, as in CN, a range of other effects are seen. Some neurons show marked reduction in maximum firing rate as well as rightward shifts in their input–output curves (Fig. 10.5c, d). In some cases, the degree of rightward shift of the input–output curve was far greater than the threshold change of the cochlear nerve action potential, again implying the existence of

additional inhibitory mechanisms operating on central neurons. As in the CN, other neurons exhibited large increases in maximum rate, at the same time as rightward shifts in their input–output curves (Fig. 10.5a, b). No instances were seen in this nucleus of direct excitatory effects near threshold (leftward shifts in input–output curves).

10.2.3.2 Effects in Background Noise

The picture with regard to effects of MOCS stimulation in the presence of background masking noise is equally complex, both in CN and IC. However, a key point is that in many neurons, antimasking effects are seen that are qualitatively similar to those observed in primary neurons (Fig. 10.6). As in primary afferent neurons, the net effect is a significant restoration of the neurons' output dynamic range, with an accompanying improvement in measures of signal discrimination (Mulders et al. 2008; Seluakumaran et al. 2008b). In many instances, this improvement in output dynamic range is achieved, as it is in primary afferents, by a reduced background firing to the noise and increased maximum discharge rate. However, an interesting variant is seen in IC (Fig. 10.7a), in which some neurons under masked conditions shift their input–output curve dramatically to the right but do not show the usual increase in background firing (Fig. 10.7a). These neurons have zero or very low spontaneous firing rates under both quiet and masked conditions. Nonetheless, in these neurons, MOCS stimulation still dramatically improves the maximum discharge rate.

A notable exception to the antimasking effect of MOCS stimulation in CN is the onset chopper neuron category, in which MOCS stimulation appears to have either no effect on masked input–output curves or in fact causes a further rightward shift

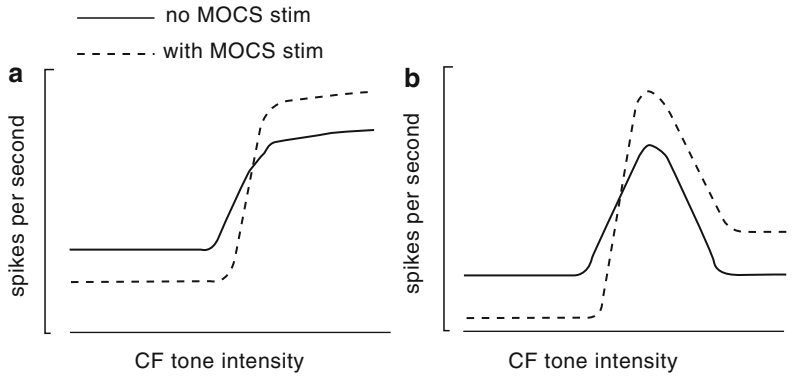

Fig. 10.6 Schematic examples of monotonic and nonmonotonic input–output curves of CN and IC neurons in presence of continuous background noise illustrating effects of MOCS activation that resemble effects seen in primary afferents (i.e., restoration of output dynamic range by drop in basal firing and increase in maximum rate; compare to Fig. 10.1b)

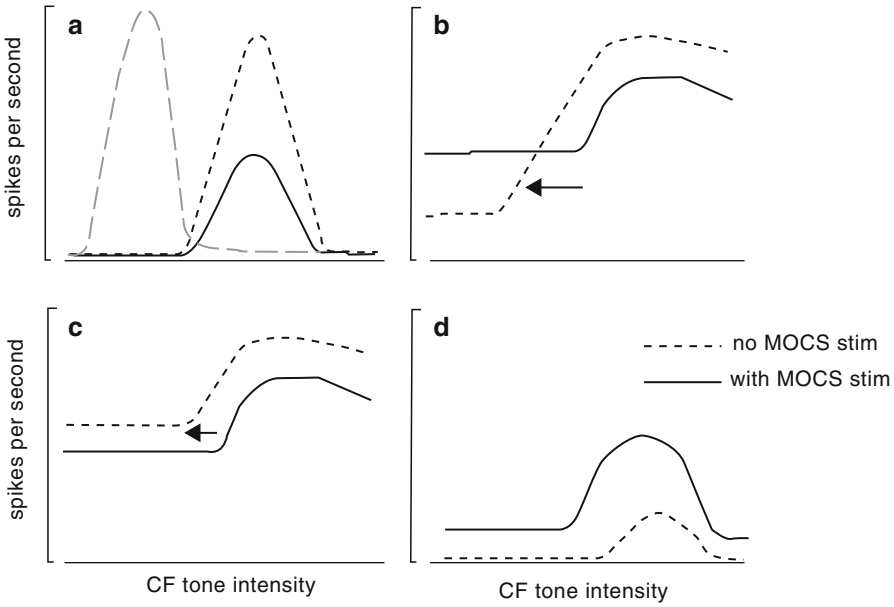

Fig. 10.7 Schematic examples of input–output curves of CN and IC neurons in presence of background noise illustrating effects of MOCS activation that differ from those seen in primary afferents. *Coarse dashed line* in (**a**) shows input–output curve in unmasked condition (quiet background) for comparison with masked condition (*fine dashed line*). (**a**) Nonmonotonic neuron in IC. Note release from masking despite no basal firing to masker; (**b**) improvement in threshold caused by leftward shift of curve and drop in basal firing rate; (**c**) improvement in threshold caused by leftward shift accompanied by overall elevation in firing rate; (**d**) increased suppression, that is, lack of antimasking effect

and reduction in firing rate. Examples of this phenomenon are also seen in IC (notably in neurons with nonmonotonic input–output curves) in which MOCS stimulation causes a further deterioration in masked responses, rather than an antimasking effect (Fig. 10.7d). Other variants are also seen in both central nuclei, such as increases in both background and maximum rate, and reductions in background rate without changes in maximum rate.

A finding of considerable interest is the fact that in both CN and IC, examples have been found (Fig. 10.7b, c) of neurons whose input–output curves to CF tones in the presence of background noise are shifted to the left by MOCS stimulation, that is, their thresholds to tones were actually improved. This novel effect was seen in transient and sustained chopper neurons of CN and in IC neurons with CF input–output curves showing varying degrees of nonmonotonicity. It is distinct from the classic antimasking effect which, although it expands a neuron's output dynamic range by lowering background firing rate and restoring maximum rate, is not accompanied by any substantial leftward shift of the CF input–output curve (Fig. 10.1b).

10.2.4 In Vivo Evidence for MOCS Collateral Involvement in Novel Central Effects

A critical issue in understanding how effects of MOCS activation on central neurons differ from those observed in the primary afferent neurons concerns the cellular targets and action of the MOCS collaterals. Collateral branches of MOCS axons have been described within the SOC itself, but nothing is known about their role in modifying activity of interneurons in this important brain stem region (Brown et al. 1988; Brown 1993). Most detailed studies have focused on the collaterals that terminate in the CN (Brown et al. 1988, 1991; Winter et al. 1989; Benson and Brown 1990; Benson et al. 1996) and see Brown, Chap. 2). In the CN, MOCS collaterals are thought to terminate primarily on large multipolar neurons (although these are not the only targets in the cochlear nucleus). The MOCS collateral terminals on cochlear nucleus neurons have been shown to exhibit ultrastructural features typical of excitatory synapses. As a consequence, it has been suggested that these collaterals may be excitatory in their action in the cochlear nucleus, in contrast to the overall suppressive effects of the peripheral MOCS terminals on cochlear neural output. As such, these collaterals are possible candidates for generating reported excitatory effects of MOCS stimulation on cochlear nucleus neurons, and they may also explain the presence of central neurons that show no suppression despite the presence of peripheral MOCS-mediated suppression.

As mentioned previously, Starr and Wernick (1968) and Mulders et al. (2002) combined extracellular single neuron recording in CN with various methods of eliminating cochlear effects of the MOCS. Acute perfusion of the cochlea with strychnine to block the OHC receptors for the efferent neurotransmitter (Mulders et al. 2002) is an especially powerful technique because it permits normal sound-evoked responses to be studied and enables the effects on the same CN neuron to be observed with and without peripheral MOCS-mediated suppression. Although many cochlear nucleus neurons showed no residual effects of MOCS stimulation after elimination of peripheral suppression, numerous examples were found of clear persistent excitation or inhibition in a range of chopper and onset neuron types as well as a number of unclassifiable neurons. Such effects must presumably be mediated by MOCS collaterals, although it is not possible with such methods to conclude whether the effects are direct or multisynaptic in origin.

Another approach to the problem of isolating the effects of MOCS collaterals has been to make intracellular recordings from cochlear nucleus neurons and to search for evidence of direct synaptic events (excitatory postsynaptic potentials [EPSPs] and inhibitory postsynaptic potentials [IPSPs]) as a result of MOCS stimulation. Presumably if such events are observed, they must originate from an action of the MOCS collaterals on CN neurons, rather than being indirectly mediated through MOCS action on the cochlea. Using this method in rat CN, Mulders et al. (2003) observed EPSPs in onset neurons. Examples were also found of inhibitory events (IPSPs) in chopper neurons. This study was limited by the fact that peripheral measures of the effectiveness of MOCS stimulation were not made, and because of uncertainty about the precise classification of neuronal response type.

The latency of both excitatory and inhibitory events was surprisingly long (in excess of 3 ms in most cases, and occasionally two sequential EPSPs were seen in response to single midline electrical stimuli. These data suggest that the effects seen may have been indirect, mediated by MOCS collateral action on neurons other than those being recorded from.

In a more recent study Mulders et al. (2007) used extracellular recordings with stringent classification of neuronal response type and tight control over MOCS stimulation site and current strength. An action potential collision technique was used in an attempt to differentiate between antidromically generated action potentials and ones generated by excitatory synaptic input (MOCS collateral input). In about 50% of onset chopper neurons the results were compatible with direct synaptic excitation by orthodromic activation of MOCS collaterals. However, the fact that in the remaining onset chopper neurons the results of collision assays were compatible with antidromic activation of onset chopper axons in the intermediate acoustic stria highlights the difficulty of precise and selective activation of MOCS axons. The results of all such studies should probably be regarded with some caution, as it is probably impossible to completely rule out antidromic activation of recurrent pathways in the central nuclei.

Whether or not the action of MOCS collaterals in CN and SOC has significant upstream consequences for activity in structures such as the IC has not been intensively investigated. In one study (Seluakumaran et al. 2008a), systemic injection of gentamicin was used to eliminate MOCS effects in the cochlea and the responses of IC neurons to MOCS stimulation was recorded. No residual effects were seen, but the small sample size and the possibility that gentamicin might have central as well as peripheral effects means that this result is far from conclusive.

10.3 In Vitro Studies

The issue of MOCS collateral action has also been addressed using brain slice recording methods. Fujino and Oertel (2001) studied the effects of bath application of cholinergic agonists and antagonists on patch-clamped CN neurons in slices of mouse brain stem. They found that so-called D-stellate cells (named for their morphology and dorsally directed axons) were not affected by drugs presumed to activate the postsynaptic receptors associated with cholinergic MOCS collaterals. D-stellate neurons in brain slices are believed to correspond to onset chopper neurons classified by their in vivo properties, and this result suggests that the multipolar cell targets of MOCS collaterals are not onset choppers. In addition, Fujino and Oertel (2001) found that so-called T-stellate cells, presumed to correspond to sustained and transient chopper in vivo response categories, were strongly excited by the same pharmacological agents. These data are seemingly at variance with the available in vivo evidence for MOCS collateral action on onset type neurons, but there are many possible explanations for such discrepancies. For example, bath application of cholinomimetics may not be physiologically equivalent to synaptic release of acetylcholine by MOCS collaterals at specific synapses. It might also be

that D-stellate cells in the mouse are not the analog of onset chopper neurons defined by physiological criteria in other species. With regard to the excitatory effects on T-stellate cells, it is possible that these neurons receive input from other cholinergic pathways such as the direct SOC to CN pathway (Sherriff and Henderson 1994) that was the presumed subject of investigation by Comis and Whitfield (1968). This pathway would not be activated by MOCS stimulation in the intact animal at the floor of the IVth ventricle, but its postsynaptic receptors would be accessible to bath application of cholinomimetics.

10.4 Mechanisms of Nonclassic MOCS Effects in Central Neurons

The diverse effects of MOCS stimulation seen in central nuclei may have several explanations. The presence of MOCS collaterals in the cochlear nucleus that may be excitatory or inhibitory on subpopulations of neurons obviously creates a substrate for modifying the effects of reduced afferent input. Examples of neurons in which frank excitation is seen, or in which no rightward shift in I/O curves occurs despite a reduction in peripheral sensitivity, may be the result of a direct excitatory action of these collaterals, counteracting the effects of peripheral suppression. Similarly, suppression that exceeds that usually seen in primary afferents might also be explained by an inhibitory effect of collaterals. These effects need not be mediated by direct collateral input to the neurons from which recordings are being made, because the complexity of interneuronal circuitry in central nuclei also means there is a large repertoire of possible indirect effects as well.

In addition to possible collateral action, however, other factors need to be considered when seeking explanations for the complex central effects of MOCS activation. The response properties of many neurons in CN and IC are derived from an integration of multiple inputs from widespread cochlear regions. These inputs can be either excitatory or inhibitory, presumably with differing synaptic weights and different dependence on acoustic stimulus intensity and frequency. In addition, the method of MOCS stimulation employed in the in vivo studies excites many MOCS axons that collectively innervate a large length of the organ of Corti. Central neurons receiving very restricted place-specific afferent input from the peripheral receptor might be expected to exhibit similar MOCS-mediated effects to primary afferents. However, neurons that integrate widespread input from across the cochlea might be expected to exhibit more complex effects depending on how MOCS stimulation alters the balance of excitatory and inhibitory inputs under a given set of stimulus conditions. Further, MOCS-mediated effects in the periphery are themselves dependent on the acoustic stimulus frequency and intensity. Suppression of primary neural output at CF will be greatest for low-level stimulation because of the saturation of the OHC active process at higher stimulus levels. An additional factor is that MOCS effects on primary afferent neural sensitivity are maximum near CF for off-CF frequencies that are more and more distant from the tuning curve tip,

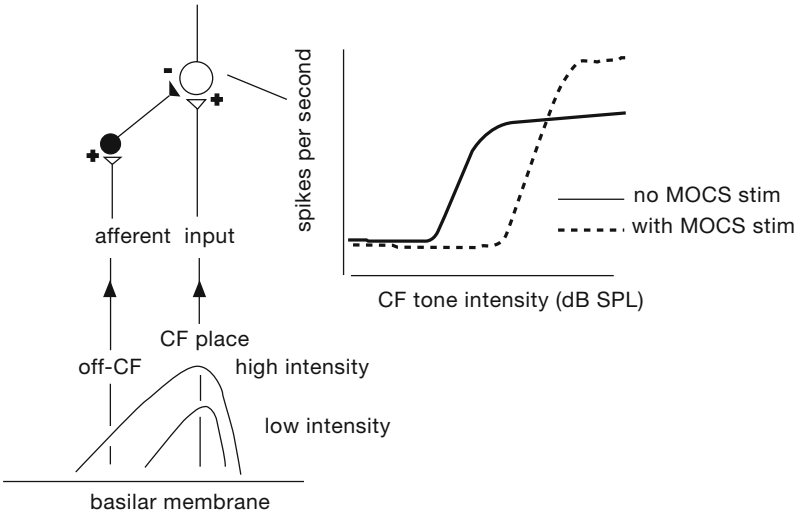

Fig. 10.8 Schematic representation of a possible simple circuit to explain effect of MOCS activation on input–output curve of a single central neuron in quiet background such as that illustrated in Fig. 10.5a. Inhibitory interneuron shown in black. Positive and negative signs indicate excitatory and inhibitory synapses

MOCS effects are reduced because these responses are relatively uninfluenced by the OHC active process.

Figure 10.8 attempts to provide one illustration of how some of these factors might interact in central circuitry to produce nonclassic effects on CF input output curves. In this example, a central neuron receives excitatory CF input and inhibitory input from adjacent off-CF cochlear regions. The neuron's firing rate at low stimulus levels is dominated by the excitatory CF input, but at high levels of a CF tone firing rate will be determined by a combination of inhibition and excitation as the excitation pattern on the basilar membrane spreads to recruit the off-CF region. MOCS stimulation will produce inhibition of the response at low levels of the CF tone (rightward shift of input–output curve) but at high levels, this effect will become less significant because of the saturation of the OHC active process at CF. At the same time, however, MOCS stimulation could release the neuron from off-CF inhibition, providing the off-CF regions that provide the inhibition are still sufficiently close to the tuning curve tip to be subject to MOCS effects. The result would be an increase in firing rate at high tone levels.

Similar logic might be used to model other types of central neural responses to MOCS stimulation. Detailed modeling would be especially challenging in the case of responses in the presence of masking noise, but it could reveal useful information not only about the mechanism of the diverse central MOCS effects, but also about central afferent circuitry in general. One striking example is provided by neurons that show a marked restoration of the maximum discharge rate (see, e.g., Fig. 10.7a) as a result of MOCS stimulation even though the masking noise itself does not cause an increase in background firing rate (albeit there is a marked

rightward shift in threshold induced by the masker). The release from masking must be, in these cases, due to some other factor than a MOCS-induced reduction in background firing rate, because this is not elevated by the masker. One possibility is that the masking in these cases is not dominated by peripheral events, but by central inhibitory effects activated by the masker and that MOCS stimulation selectively turns off this inhibition.

10.5 Behavioral Experiments

Several studies have attempted to elucidate the role of central connections of the MOCS using a combination of behavioral measurements and manipulations of the MOCS system, either pharmacologically or by genetic modification. The focus in these studies has been on signal detection in noise. In early studies (Pickles and Comis 1973; Pickles 1976b), indwelling cannulae were used to infuse a blocker of acetylcholine receptors into the cochlear nucleus of awake cats. Tone thresholds in masking noise were markedly more elevated than absolute thresholds, suggesting that a cholinergic pathway in the cochlear nucleus is involved in antimasking. Such experiments, however, provide no proof that it is the olivocochlear collaterals that are involved, because, as already mentioned, there are other cholinergic pathways from SOC to CN.

More recent studies (May et al. 2002) have used transgenic knockout mice lacking a crucial subunit of the peripheral intracochlear acetylcholine receptor (α9 nicotinic acetylcholine receptor). Such animals could still perform as well as normal animals in detection and discrimination of tones in noise. MOCS collateral pathways to CN have recently been shown to remain intact in such animals (Brown and Vetter 2009), and one interpretation of the result is therefore that the collaterals contribute substantially to antimasking, independent of any peripheral action of the MOCS. May et al. suggest that this might be mediated through excitatory collateral effects on chopper-type neurons corresponding to the T-stellate cell category described in mouse CN slices. Some caution needs to be exercised in the interpretation of these and similar studies because of a number of concerns that are well discussed by May et al. (2002). In particular, it has recently been reported that the design of behavioral testing regimens that incorporate substantial training components may permit animals to recruit other mechanisms for enhancing signal detection in noise, possibly obscuring initial effects of loss of components of MOCS action (May et al. 2004).

10.6 Functional Significance

The first and arguably most important result that emerges from the studies discussed in this chapter is that despite the complexities of central circuitry and the presence of MOCS collaterals, many central neurons, both in CN and IC, exhibit effects of MOCS stimulation that are very similar to those reported in primary afferents.

This is especially significant with regard to the antimasking effects in the presence of background noise. This phenomenon, which forms the main basis for theories of peripheral MOCS involvement in signal discrimination in background noise, had previously been demonstrated only in primary afferents. A new element is the finding that in addition to the classical release from masking by which MOCS stimulation extends the output dynamic range, a number of central neurons also show real improvements in their masked tone thresholds. These results together strengthen the case for MOCS involvement in enhancement of signal detection and discrimination in noisy environments.

The functional significance of the many other "nonclassic" effects that differ from those seen in primary afferents is unclear and must remain speculative at this stage. The finding that in some neurons, MOCS stimulation in quiet background causes no change in their CF input–output curves even though peripheral sensitivity is reduced at the same frequency, is intriguing. This seems to represent a form of "efference copy" in which central sensitivity is adjusted to compensate for peripheral sensitivity changes caused by MOCS activation. By comparing activity between such neurons and others with rightward shifts in their input–output curves, the brain could deduce that firing rate changes were not the result of a change in acoustic stimulus intensity. Further study will be required to determine which neuronal categories show such sensitivity adjustments.

Excitatory effects in which sensitivity to tones in quiet is increased are also intriguing. It is conceivable that such effects could serve to enhance responses of some neural populations to important signals in selective attention tasks, while inhibitory effects might operate to reduce responses of other neural classes to the same stimuli. The coarse mode of MOCS stimulation employed in these studies is perhaps not well suited to unraveling such mechanisms.

The particular case of onset choppers is, at one and the same time, interesting and confusing. In CN, these are the only neurons in which the traditional form of MOCS stimulation appears to reduce further the sensitivity to CF tones in the presence of background noise. Onset choppers are believed to generate broadband inhibition in the cochlear nuclei, and this MOCS effect may serve to reduce the inhibitory action of these cells on other neural populations. The purpose of such reduced inhibition is, however, unclear. However, other in vivo evidence suggests that single shocks to MOCS, in contrast to the long trains of shocks traditionally used, can cause excitatory effects in onset choppers (Mulders et al. 2003, 2007; Seluakumaran et al. 2008b). Such short-acting excitation of onset choppers could enhance their postulated role in some forms of release from masking (Pressnitzer et al. 2001; Verhey et al. 2003).

10.7 Summary

Forty years of research has provided solid evidence that the effects of MOCS activation on central neurons are complex and diverse. In many cases, sensitivity reduction in quiet and antimasking in noise are observed, in a manner qualitatively

predictable from the effects of MOCS on primary afferent responses. However, in many other neurons, effects are seen that are not readily predictable from the peripheral action of the MOCS. These effects may be variously explained by complex interactions within the ascending neuronal network, by MOCS collateral action separate from the peripheral effects, or by a combination of both.

Despite this work, important questions remain. Although more recent work has used various neuronal classification schemes, there is still no clear picture of how tightly the diverse MOCS effects are segregated according to neuronal response type. The effects of more naturalistic activation of the MOCS need to be investigated, in contrast to activation of the entire efferent bundle with shock trains. The precise action of the central collaterals of the MOCS is still unclear, as is the physiological identity of their cellular targets. For this matter to be clarified, the apparent conflict between results obtained with different methodologies needs to be resolved.

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