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Effect of interphase gap and pulse duration on electrically evoked potentials is correlated with auditory nerve survival

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Abstract

We investigated the effect of pulse duration (PD) and interphase-gap (IPG) on the electrically-evoked auditory brain stem response (EABR) and viiith nerve compound action potential (ECAP) of deafened guinea pigs in order to test the hypothesis that the extent of change in these neural responses is affected by the histological status of the auditory nerve. Fifteen guinea pigs were deafened by co-administration of kanamycin and furosemide. Animals were acutely implanted with an 8-band electrode array at 1, 4 or 12 weeks following deafening. EABR and ECAP input/output functions were recorded in response to charge balanced biphasic current pulses. We determined the change in current required to equalize; (i) the EABR amplitude when the duration of the current pulse was doubled (104 to 208 μ s/phase); and (ii) the EABR and ECAP amplitudes when the IPG was increased from 8 μ s to 58 μ s using a 104 μ s/phase current pulse. Following the completion of each experiment the cochleae were examined quantitatively for spiral ganglion neuron survival. As expected, the current level required to evoke an EABR with equal amplitude was lower when the animal was stimulated with current pulses of 208 compared with 104 μ s/phase. Moreover, the current level required to evoke EABR/ECAPs with equal amplitude was lower when current pulses had an IPG of 58 versus 8 μ s. Importantly, there was a reduction in the magnitude of this effect with greater neural loss; the reduced efficacy of changing both PD and IPG on these electrically-evoked potentials was statistically correlated with neural survival. These results may provide a tool for investigating the contribution of auditory nerve survival to clinical performance among cochlear implant subjects.

Keywords

neural degeneration; deafness; electrical stimulation; cochlear implant; neural prostheses; EABR; ECAP

Introduction

Degenerative changes in the peripheral auditory system as result of a sensorineural hearing loss include the relatively rapid loss of the peripheral process of the spiral ganglion neuron (SGN), more gradual demyelination of SGN soma and at least part of its central axon (Hardie and Shepherd, 1999; Leake and Hradek, 1988; Spoendlin, 1984), and ultimately degeneration of the SGN (Hardie and Shepherd, 1999; Hinojosa and Marion, 1983; Leake and Hradek,

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1988; Nadol et al., 1989; Otte et al., 1978; Shepherd and Javel, 1997). The rate and extent of these changes depend on factors including etiology and the duration of deafness, and show large variation in the clinical population (Felix and Hoffmann, 1985; Nadol, 1997; Nadol et al., 1989). Given that SGNs are the target neurons for cochlear implants, large variations in the number of surviving neurons could contribute to the large variability evident in the auditory performance across cochlear implant subjects (Skinner et al., 2002; Skinner et al., 1994).

The biphasic current pulse is the most common current waveform used for cochlear implants because it is considered electrochemically safe (Brummer and Turner, 1977; Rose and Robblee, 1990). Two principal temporal parameters of this kind of pulse are pulse duration (PD) and interphase gap (IPG) - the duration of the zero-current portion which lies between the two phases of the stimulus. Changing either of these temporal parameters can evoke changes in the auditory response. These changes can be detected using both electrophysiological and psychophysical techniques. Increasing PD decreases the neural threshold of auditory nerve fibers (Hartmann et al., 1984; Parkins, 1989; Parkins and Colombo, 1987; Shepherd and Javel, 1999; van den Honert and Stypulkowski, 1984). Psychophysical studies also describe a reduction in detection thresholds with increased PD (Pfungst et al., 1991), as well as increases in the dynamic range (Shannon, 1985; Zeng et al., 1998). Measurements of the perceptual effects of varying PD have shown that the current change required to maintain the same loudness when pulse duration is doubled varied between -2 and -5.9 dB across subjects (McKay and McDermott, 1999). This value was correlated with the absolute levels of stimulation, i.e. subjects with higher stimulus levels had values closer to zero than -6 dB that the equal-charge value would predict. Furthermore, the value was correlated with duration of profound deafness - subjects with a longer duration of deafness had values closer to zero, implying that the effect of changing PD is correlated with neural survival. Support for this hypothesis was provided by a study by Miller et al., (1995b), who measured the changes in electrically evoked auditory brainstem response (EABR) threshold with changes in PD in deafened guinea pigs over time. They reported that the strength-duration curves became shallower over time, i.e. PD changes resulted in smaller changes in threshold current, presumably reflecting increased neural degeneration.

Increasing IPG results in a reduction in the threshold of auditory nerve fibers. For example, using bipolar stimulation and 100 μ s/phase current pulses, increasing the IPG from 0 to 100 μ s will systematically reduce the threshold of auditory nerve fibers by 1 dB or more; for IPGs in excess of 100 μ s, the neural threshold evoked for biphasic pulses approaches the threshold of the responses evoked via a monophasic pulse (Shepherd and Javel, 1999). Consistent with this electrophysiological study is the recent demonstration of significant reductions in behavioral thresholds obtained from human implantees with increasing IPG (Carlyon et al., 2005). Importantly, varying IPG also influences the perception of suprathreshold percepts such as loudness when measured psychophysically. For example, an exponential increase in current level is required to maintain equal loudness when the IPG is reduced from 100 μ s to 8.4 μ s (McKay and Henshall, 2003). This effect of IPG on loudness depends on the current intensity and pulse duration. It is greater at near threshold levels and for shorter pulse durations (26 μ s compared to 52 μ s). We predict, therefore, that for patients with greater neural survival, in which a response to a pulse train is probably carried by many neurons at low spike probabilities, the effect of varying IPG will be greater than for patients that have few surviving SGNs.

We therefore studied the effects of increasing PD and IPG on the amplitude of both the EABR and the electrically-evoked compound action potential (ECAP) of guinea pigs with different levels of auditory nerve survival. Aspects of this research have been previously presented in abstract form (Prado-Gutierrez et al., 2004).

Methods & Materials

Experimental design

Deafened animals were randomly placed into one of three groups that were studied at 1 (n=5), 4 (n=5) or 12 (n=5) weeks following the deafening procedure. Each animal was anesthetized with an intramuscular (im) injection of ketamine (60 mg/kg) and xylazine (3.8 mg/kg) and its temperature maintained at 37 ± 1 °C.

Experimental subjects

Fifteen adult guinea pigs [mean weight = 578.1g; SD = 178.5g] were used in this experiment. All animals had otoscopically normal tympanic membranes and normal hearing determined by the click-evoked auditory brainstem response (ABR; threshold ≤ 38 decibels peak equivalent sound pressure level [dB p.e. SPL re 20 μ Pa]). The present study was performed under approval of the Royal Victorian Eye and Ear Hospital's Animal Research and Ethics Committee, and conformed to the guidelines of the National Health and Medical Research Council of Australia.

Auditory brainstem responses

ABRs were recorded differentially using stainless-steel needle electrodes (vertex positive; neck negative; thorax ground). Computer generated rectangular pulses of 100 μ s duration were presented to a loud speaker placed 10 cm from the pinna of the test ear in order to generate rarefaction clicks (Hardie and Shepherd, 1999). Threshold was determined monaurally for both ears; auditory input to the contralateral ear was blocked using an ear mold compound (Otoform®). The system was calibrated so that at this distance the maximum sound intensity at the pinna was 98 dB p.e. SPL. Click stimuli were presented at 33 per second and the recordings were amplified by 10^5 and bandpass filtered (150 Hz-3 kHz). The output of the filter was fed to a 10 bit analogue-digital converter (ADC) and sampled at 20 kHz for 12.5 ms following the stimulus onset. Five hundred responses were averaged for each recording and stored for subsequent analysis. A programmable attenuator controlled stimulus intensity; two recordings were made at each intensity. Threshold was defined as the smallest click amplitude required to evoke a response within a latency window of 2.25-3.25 ms following stimulus onset for both responses (wave III of the ABR). All recordings were made in a sound attenuated, electrically shielded room.

Deafening

Animals were anaesthetized using ketamine and xylazine dose rates described above. They were bilaterally deafened by co-administration of kanamycin (300 mg/kg) delivered subcutaneously and furosemide (150 mg/kg) delivered intravenously (Gillespie et al., 2003). The extent of the hearing loss was evaluated using click-evoked ABRs one week following this procedure. Only animals with a hearing loss greater than 93 dB p.e. SPL (i.e. a threshold increase of > 55 dB) were used in the present study.

Surgery

Guinea pigs were acutely implanted with an eight-ring intracochlear electrode array manufactured by Cochlear Ltd. Anesthesia was induced with ketamine (60 mg/kg; im) and xylazine (3.8 mg/kg; im), and atropine sulfate (0.06 mg/kg; im) was administered to decrease mucosal secretions. Supplemental doses of the anesthesia were administered during surgery at a level sufficient to maintain the animal in an areflexic state. The animal was placed in a stereotaxic frame and the right cochlea was surgically exposed via a post auricular approach. The round window was carefully incised and the electrode array inserted into the scala tympani to a depth of 6 electrodes (4.5 mm) and the round window was covered with muscle.

Electrical stimulation

Biphasic current pulses were generated under computer control using a Laura™ Max Speech Processor (Cochlear Ltd) coupled via a radio-frequency link to a Nucleus® 24RE receiver-stimulator. The receiver-stimulator was connected to the intracochlear electrode array. Current pulses were delivered to the most apical bipolar electrode pair of the array using the most apical electrode as a cathode for the first phase of the current pulse.

EABR recordings

EABRs were recorded differentially using stainless-steel needle electrodes (vertex positive; neck negative; thorax ground). The electrical stimulus consisted of charge balanced biphasic current pulses. Either PD (104 or 208 μ s/phase with a fixed 8 μ s IPG) or IPG (8 or 58 μ s with fixed 104 μ s/phase current pulses) were systematically varied. The current pulses were presented at 33 per second and the scalp recorded response amplified by 100 dB, the electrical artifact was removed using a sample-and-hold circuit, and the signal band-pass filtered (150 Hz-3 kHz). The output of the filter was digitized using a 10-bit ADC sampling at a rate of 20 kHz for 12.5 ms following the stimulus onset. Five hundred presentations were averaged for each recording. Two sets of recordings were made at each current level and current amplitude was reduced to levels below threshold. Threshold was defined as the smallest current level required to evoke a peak-trough response amplitude of >0.25 μ V for wave III of the EABR, i.e. within a latency window of 1.5-2.5 ms following stimulus onset for both responses. Supra-threshold EABR amplitudes were also measured from the peak of wave III to the following trough. Stimulus intensity was varied from below threshold to 1.75 mA. Input-output functions were constructed by plotting mean response amplitude of the two recordings against current amplitude. EABRs were recorded in an electrically shielded room.

ECAP

ECAP recordings were only used to study the effects of changing IPG (8 or 108 μ s with 104 μ s/phase current pulses); stimulus artifact in ECAP recordings were too prolonged to allow recordings in response to long pulse duration stimuli (e.g. 208 μ s/phase). Using a forward masking paradigm (Brown et al., 1990; Charlet de Sauvage et al., 1983; Lai and Dillier, 2000), ECAPs were obtained via the Neural Response Telemetry® (NRT) system within the Nucleus® NPE software (Cochlear Ltd). As with the EABR measurements, the stimulation electrodes used to evoke the ECAP were the most apical bipolar pair on the electrode array. The stimuli consisted of 104 μ s/phase biphasic pulses with an IPG of 8 or 58 μ s. For a given intensity, each stimulation series had 100 presentations with a repetition rate of 33 Hz.

The neural responses were differentially recorded using an electrode pair in the basal most part of the cochlea, with the most apical electrode of the pair the positive recording electrode. ECAP responses were recorded for each type of stimulus from below threshold intensity to 1.75 mA. NRT threshold was defined as the smallest current level required to evoke a peak-trough response amplitude of ≥ 5 μ V for the descending part of wave P1 of the ECAP responses (see Fig. 4). One recording was made at each current level and current amplitude was reduced to levels below threshold. Input-output functions were constructed by plotting the mean P-N response amplitude within the 300-600 μ s time window, against current amplitude. ECAPs of acceptable quality were recorded in nine of the 15 animals in this study.

Histology

At the conclusion of each acute experiment the animal was euthanized with an overdose of Lethobarb (150 mg/kg) and transcardially perfused with heparinized, phosphate buffered (pH=7.35) 0.9% saline solution followed by phosphate buffered 4% paraformaldehyde solution. The cochleae were harvested, decalcified in a solution of 4% EDTA/

paraformaldehyde, dehydrated, embedded in resin and serially sectioned at 2 μm . Sections every 126 μm were stained with haematoxylin and eosin. SGN densities for the basal most three cochlear turns were measured from five randomly selected mid-modiolar sections. Each cochlear turn was identified and the cross-sectional area of Rosenthal's canal was measured using NIH Image (<http://rsb.info.nih.gov/niH-image/>). All neurons with a nucleus were then counted and SGN density (cells/mm^2) determined. A single observer performed all these measurements using appropriate blind techniques. The mean SGN density for each cochlea was calculated from the SGN densities measured across these three cochlear turns. The cochleae from one four week deafened animal were not processed for histology.

Data analysis

All EABR and ECAP amplitudes were normalized to the largest response in each input/output function. In all cases, exponential functions were fitted to the resultant curves. Statistical analysis was performed using nonlinear regression tests ($r^2 > 0.95$, $p < 0.05$). The mean current difference required to equalize the EABR/ECAP response amplitude for both the PD and IPG series was calculated for each animal. These mean values for each evoked potential were calculated from the mean current offset between the two response growth functions (two PDs or two IPGs) across a normalized amplitude range of 0.2 to 0.8. A correlation between mean current offset and SGN density was tested using a parametric Pearson Correlation Test.

Results

Effect of pulse duration on the auditory evoked potentials

Figure 1 illustrates representative EABRs from animals with different durations of deafness stimulated with biphasic current pulses of 104 or 208 μs /phase (IPG was fixed at 8 μs). For both pulse durations, the amplitude of the EABR increased with an increase in stimulus intensity. However, the threshold of the evoked potential was consistently lower and the response amplitude larger for a given supra-threshold current level for the 208 compared with the 104 μs /phase current pulse. These results were observed in all animals, independent of the duration of deafness, although for a given pulse duration the EABR of the animals with longer durations of deafness typically had higher thresholds and lower response amplitudes.

The normalized EABR input/output function obtained with both PDs had a similar shape, however, the wider PD consistently shifted the function to the left (Fig. 2). That is, the intensity required to evoke an EABR at a given amplitude was lower when the pulse duration was longer.

Effect of IPG on EABRs & ECAPs

Increasing IPG from 8 to 58 μs , while keeping PD fixed at 104 μs /phase, consistently resulted in lower EABR and ECAP thresholds together with a concomitant increase in their response amplitudes for a given supra-threshold stimulus intensity (Figs. 3 & 4). While the effect of increasing IPG on EABR and ECAP thresholds and input/output functions were similar to that observed with increasing PD, the extent of this shift was less than the effect of doubling the PD (Fig. 5).

Spiral ganglion histology

All cochleae examined showed no evidence of surviving inner or outer hair cells. The SGN density decreased with the duration of deafness (e.g. Fig. 6). However, there was some variability in SGN survival across animals having the same duration of deafness. For this reason we examined the relationship between SGN density and our electrophysiological data statistically.

Effect of SGN density on PD and IPG

The intensity difference required to evoke EABRs of equal amplitude when pulse duration was increased from 104 to 208 μ s/phase was statistically correlated with SGN density (Fig. 7a; $p < 0.05$). In addition, the current change needed to equalize both EABR and ECAP amplitudes when IPG was increased from 8 to 58 μ s was statistically correlated with SGN survival (Fig. 7b&c respectively; $p < 0.05$).

Discussion

This work presents evidence based on electrically-evoked potentials demonstrating a reduction in thresholds and a shift toward lower current levels in input/output functions with an increase in the PD or IPG of the biphasic current pulse. These findings are consistent with previous single unit (Parkins, 1989; Parkins and Colombo, 1987; Shepherd and Javel, 1999; van den Honert and Stypulkowski, 1984) and psychophysical studies in experimental animals (Miller et al., 1999; Pfindt et al., 1991; Smith and Finley, 1997), and implant subjects (McKay and McDermott, 1998; McKay and McDermott, 1999; McKay and Henshall, 2003).

Importantly, the present study demonstrated a statistically significant correlation between the change in current intensity required to evoke equal amplitude EABR/ECAPs for two different PDs or IPGs with auditory neural survival. That is, the extent of the decrease in response threshold and the shift in the input/output function towards lower current levels with an increase in PD or IPG is significantly reduced in cochleae with greater SGN loss. These findings may provide a non-invasive technique for quantifying the extent of SGN loss in cochlear implant subjects.

Previous research in the auditory system has studied the effect of increasing PD on the auditory response (Parkins, 1989; Parkins and Colombo, 1987; Shepherd and Javel, 1999; van den Honert and Stypulkowski, 1984). Biphasic current pulses of longer duration require smaller currents than shorter pulses to evoke an EABR of a given intensity. If the neural membrane were a perfect integrator, one would expect the response growth functions to be offset by 6 dB (a halving of current for a doubling of PD). However electrophysiological studies have consistently shown that this effect is < 6 dB (Abbas and Brown, 1991; Miller et al., 1995a; Parkins and Colombo, 1987; Shepherd et al., 2001; van den Honert and Stypulkowski, 1984), implying that the neural membrane can be considered a leaky integrator. That is, a longer pulse containing the same charge as a shorter pulse will be less efficient than the shorter pulse in eliciting a response. The present results are consistent with these previous electrophysiological data; doubling the PD led to an offset of between 3.1 to 5.2 dB (re 1 μ A).

While the majority of psychophysical data (McKay and McDermott, 1999; Miller et al., 1995b; Smith and Finley, 1997) also report strength-duration slopes of < 6 dB per doubling, two papers have reported > 6 dB changes as PD is doubled (Miller et al., 1995a; Pfindt et al., 1991). Indeed, Miller and colleagues (1995a) described a difference between an electrophysiological (-5.25 dB/doubling) versus psychophysical measure (-6.18 dB/doubling) in the same animals, suggesting that there is possibly a central mechanism of stimulus integration in addition to that occurring at the auditory nerve (Miller et al., 1995a).

The values for the offset in current to equalize EABR or ECAP when IPG was increased from 8 to 58 μ s ranged from 0.3-2.5 dB in the present study. This range is similar to the range in human implantees for the offset required to equalize loudness (McKay and Henshall, 2003). For biphasic stimulation, the function of the second phase is to balance the charge delivered by the first phase, in order to decrease the level of direct current induced by the stimulus (Huang et al., 1999; Robblee and Rose, 1990). When the total charge delivered by the first phase is close to threshold, spike initiation can occur a short time after the end of the phase

(van den Honert and Mortimer, 1979). Increasing the IPG delays the beginning of the second (hyperpolarizing) phase of the stimulus, thereby increasing the probability of spike initiation.

The correlation of SGN density with the effects of PD and IPG observed in the present study may be due to several factors. One of these may be the alteration in charging characteristics of neurons which have suffered partial degeneration. Following deafness, reduction in SGN density is accompanied by demyelination of the remaining neurons, and degeneration of the peripheral processes, leading to an increase in threshold to electrical stimulation using bipolar electrodes (Hardie and Shepherd, 1999; Shepherd and Javel, 1997; Shepherd et al., 2004). One consequence of neural demyelination is an increase in the time constant (τ) of the neural membrane (Koles and Rasminsky, 1972; Tasaki, 1955). Therefore, neurons in long-term deafened animals may need a longer time to reach the threshold potential for initiation of an action potential than neurons in short-term deafened animals.

A second possible mechanism underlying the correlation of SGN density and the effects of PD and IPG is more directly related to neural density differences. In animals with high SGN density, there will be many more neurons activated by each current pulse. As well as directly resulting in a reduction in threshold, higher SGN density will lead to an average reduction in the spike probabilities of activated neurons. That is, for the same overall neural response, the case of high neural density will have many more neurons activated by a biphasic pulse, but a higher proportion of these neurons will be closer to their individual thresholds.

The ECAP morphologies in the present study did not show the prominent initial negative peak that is typically observed in these responses. While it is clear that a strong negative peak is characteristic of most ECAP recordings, the morphology of the ECAP is dependent on several factors including (i) recording site (intracochlear vs nerve trunk); (ii) electrode configuration (monopolar vs bipolar); and (iii) stimulus polarity. Positive peaked ECAPs like those described in this manuscript have been reported by a number of investigators recording from a variety of sites (Brown, 1994; Miller et al., 2004).

Finally, the present findings have implications for the fitting of cochlear implants to profoundly deaf patients. Large variations in the number of surviving neurons could contribute to the large variability evident in the auditory performance across cochlear implant subjects (Skinner et al., 2002; Skinner et al., 1994). We have shown that the effects of changes in PD and IPG on auditory evoked potential amplitudes were correlated with SGN density in deafened guinea pigs. The measurement of similar effects on electrically-evoked potentials in humans may provide a valuable tool to assess SGN survival in this clinical population. Knowledge of SGN survival would be useful when choosing the likely optimal electrode geometry and processing strategy for fitting, and would facilitate research which investigates the effects of SGN survival on perception with a cochlear implant.

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Abbreviations

ADC, analog to digital converter; EABR, electrically-evoked auditory brainstem response; ECAP, electrically-evoked compound action potential; Hz, Hertz; IPG, interphase gap; PD, pulse duration; SGN, spiral ganglion neuron; SPL, sound pressure level.

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Figure 1.

Representative EABRs obtained from guinea pigs deafened for 1 (a & b), 4 (c & d) and 12 weeks (e & f), illustrating responses evoked to current pulse durations of 104 (a, c, e) and 208 μ s/phase (b, d, f). The stimulus intensity (in mA) is illustrated for each response. In all cases in these recordings the IPG was fixed at 8 μ s. The positive peak of wave III is illustrated in (a), while threshold is indicated by “T”. The blanking pulse (~ 0.9 ms) at the start of each recording effectively eliminates wave I of the EABR in these responses. This prolonged blanking pulse was necessary to eliminate both the direct electrical artifact and artifact generated by the radio frequency link between the speech processor and the receiver-stimulator. Scale bar = 20 μ V.

Figure 2.

Typical EABR input/output functions obtained using biphasic current pulses of 104 and 208 μ s duration (IPG was fixed at 8 μ s). The data have been normalized to the largest response in each input/output function. In this example the animal was studied one week after deafening. 208 μ s/phase $\circ$; 104 μ s/phase $\bullet$.

Figure 3.

Representative EABRs obtained from guinea pigs deafened for 1 (a & b), 4 (c & d) and 12 weeks (e & f), illustrating responses evoked by 104 μ s/phase current pulses with an IPG of 8 μ s (a, c & e) or 58 μ s (b, d & f). The stimulus intensity (in mA) is illustrated for each response. The positive peak of wave III is illustrated in (a), while threshold is indicated by "T". Scale bar = 20 μ V.

Figure 4.

Representative ECAPs recorded from guinea pigs deafened for 1 (a, b), 4 (c, d) and 12 weeks (e, f), illustrating responses evoked in response to 104 μ s/phase current pulses with an IPG of 8 μ s (a, c, e) or 58 μ s (b, d, f). The stimulus intensity (in mA) is illustrated for each response. The blanking time, used to avoid the stimulus artifact at the onset of each recording, varied in this figure (a, 293 μ s; b, 343 μ s; c, 293 μ s; d, 367 μ s; e, 293 μ s; f, 314 μ s). The positive peak P1 is illustrated in (a), while threshold is indicated by "T".

Figure 5.

EABR (a) and ECAP (b) input/output functions to 8 and 58 μ s IPG obtained from one animal studied one week after deafening. Responses were obtained using biphasic current pulses of 104 μ s/phase. Note the similar response for both the EABR and ECAP to the increase in IPG. Again, the data have been normalized to the largest response in each input/output function. 58 μ s IPG $\circ$; 8 μ s IPG.

Figure 6.

Representative cochlear morphology illustrating turn 3 (a & b), turn 2 (c & d) and turn 1 (e & f) of an animal deafened for a period of 1 week (a, c, e respectively) and 4 weeks (b, d, f respectively). Mean SGN densities for each animal in this study were determined and correlated with our evoked potential data. Scale bar=100 μ m

Figure 7. Change in current required to generate an equal amplitude response as a function of SGN density for (a) PD recorded using EABR; (b) IPG recorded using EABR; (c) IPG recorded using ECAP. In all cases the extent of change in response amplitude by manipulating PD or IPG reduced significantly with SGN loss.